UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

INSTITUTO DE CIÊNCIAS BÁSICAS DA SAÚDE

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS BIOLÓGICAS: BIOQUÍMICA

TESE DE DOUTORADO

Caracterização gênica do modelo de células diferenciadas SH-SY5Y e o potencial uso para estudo do papel da toxicidade sistêmica no transtorno bipolar

BIANCA WOLLENHAUPT DE AGUIAR

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"Por vezes sentimos que aquilo que fazemos não é senão uma gota de água no mar.

Mas o mar seria menor se lhe faltasse uma gota".

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SUMÁRIO

APRESENTAÇÃO

A presente tese de doutorado está organizada em três partes, conforme a seguir:

Parte I: Resumo, *Abstract*, Introdução e Objetivos;

Parte II: Resultados apresentados na forma de 03 artigos científicos publicados e 01 capítulo com introdução, metodologia, resultados e discussão referente a artigo científico em preparação;

Parte III: Discussão, Conclusões, Perspectivas e Referências bibliográficas.

Além disso, a seção de Anexos compreende: 1) lista de figuras; 2) lista de tabelas 3) artigo de revisão realizado durante o período do doutorado; 4) artigo científico com resultados obtidos a partir desta tese; 5) reportagem referente ao capítulo quatro desta tese publicado no site *EurekAlert*; 6) capítulo de livro aceito para publicação e 7) dados complementares referentes ao capítulo três desta tese.

Os trabalhos que compõem esta tese foram desenvolvidos entre os anos de 2012 e 2016 em dois laboratórios: Laboratório de Bioquímica Celular (laboratório 24), no Departamento de Bioquímica da Universidade Federal do Rio Grande do Sul, sob orientação do Prof. Dr. Fábio Klamt e no Laboratório de Psiquiatria Molecular, localizado no Centro de Pesquisas Experimentais do Hospital de Clínicas de Porto Alegre, sob orientação do Prof. Dr. Flávio Kapczinski.

PARTE I

INTRODUÇÃO E OBJETIVOS

RESUMO

O transtorno bipolar (TB) é caracterizado como um grave transtorno psiquiátrico, que apresenta curso crônico com notável prejuízo cognitivo e funcional nos pacientes. Nesta tese, através de duas revisões avaliamos as alterações de marcadores periféricos de estresse oxidativo, neurotrofinas e inflamação presentes em pacientes com TB e discutimos o envolvimento destes na toxicidade sistêmica, bem como uma possível associação destas alterações com as disfunções cognitivas e funcionais apresentadas pelos pacientes ao longo do transtorno. Neste sentido, muitos estudos têm sido realizados buscando compreender a fisiopatologia do TB, no entanto, para o estabelecimento de um modelo *in vitro* é necessário ter um modelo celular adequado e um desafio que possa mimetizar a fisiopatologia da doença. Neste contexto, não há na literatura, até o momento, um modelo adequado que compreenda toda a complexidade dos sintomas do TB, por isso o objetivo geral desta tese consistiu na caracterização gênica do modelo *in vitro* de diferenciação celular da linhagem de neuroblastoma humano SH-SY5Y, induzido por ácido retinóico, e a busca por um modelo experimental para a avaliação da toxicidade sistêmica apresentada pelos pacientes com TB. O modelo de diferenciação foi avaliado através da técnica de microarranjo, onde verificamos que nas células diferenciadas há maior expressão de processos biológicos envolvidos no desenvolvimento neuronal, enquanto nas células indiferenciadas observamos maior expressão de processos biológicos relacionados a proliferação e manutenção celular. Ainda, genes relacionados a função sináptica e a síntese dopaminérgica estavam mais expressos nas células diferenciadas. Estes achados contribuem para a validação de um modelo de origem humana, de fácil manuseio e que apresenta perfil neuronal; auxiliando assim no estudo de doenças que acometem o sistema nervoso central, dentre elas o TB. Para avaliar o perfil de toxicidade no soro de pacientes bipolares, tratamos as células SH-SY5Y diferenciadas com soro de pacientes com TB, tanto em estágio inicial quanto avançado do transtorno. Como resultado, verificamos que o soro dos pacientes em estágio avançado apresenta maior toxicidade quando comparado ao soro de indivíduos controles por causar uma diminuição da viabilidade celular e uma diminuição na densidade de neuritos. Analisados em conjunto, os achados desta tese apontam para um novo modelo *in vitro* para analisar a fisiopatologia do TB, bem como o efeito de medicações e vias metabólicas envolvidas. Além disso, corroboram com dados prévios da literatura de que perifericamente os pacientes apresentam um índice de toxicidade relevante quando comparado a indivíduos controles e que este índice estaria relacionado a progressão do transtorno.

ABSTRACT

Bipolar disorder (BD) is characterized as a serious psychiatric disorder that presents chronic course with remarkable cognitive and functional impairment. In this thesis, we analyzed in two reviews the changes in peripheral markers of oxidative stress, neurotrophins and inflammation, discussing their involvement in systemic toxicity, as well as a possible association of these changes with the cognitive and functional impairment presented by BD patients throughout the disorder. In this sense, many studies have been performed seeking to understand the pathophysiology of this illness. Moreover, research on BD and drug development is hampered by the lack of suitable *in vitro* models. To counteract this, many attempts to explore patient-derived samples have been undertaken, resulting in partial reproduction of disease aspects. However, still does not exist in the literature a suitable model to understand the complexity of the BD symptoms. Therefore, the aims of this thesis was to evaluate the differential gene expression of the cell differentiation model of human neuroblastoma cell line SH-SY5Y, induced by retinoic acid, and the search for an experimental model for the evaluation of systemic toxicity in patients with BD. The differentiation model was assessed by microarray analysis and we found that the differentiated cells had increased expression of biological processes involved in neuronal development, while undifferentiated cells showed higher expression of biological processes related to cellular proliferation and maintenance. Also, genes related to the synaptic function and dopaminergic synthesis were more expressed in differentiated cells. These findings contribute to the validation of a cellular model from human source, easy handling and featuring neuronal profile; thereby aiding in the study of diseases that affect the central nervous system, including BD. In order to evaluate the toxicity profile in serum of bipolar patients, differentiated SH-SY5Y cells were treated with sera of BD patients in early and late stages of the disorder. As a result, for the first time in the literature, it has been verified the potential neurotoxicity of bipolar patients serum directly in human cells with a neuronal profile and we found that the serum of patients at late stage would present higher toxicity when compared to the control sera, causing a decrease in cell viability and a reduced neurite outgrowth density. Taken together, the findings of this thesis point to a new *in vitro* model to analyze the pathophysiology of BD, as well as the effect of medications and metabolic pathways involved in this disorder. Moreover, corroborate previous peripherally data found in the literature where patients would have a toxicity index compared to control subjects and that this index would be related to the progression of the disorder.

Lista de Abreviaturas

Bcl-2 = Célula-B de linfoma 2, do inglês *B-cell lymphoma 2*

BDNF = Fator neurotrófico derivado do cérebro, do inglês *brain-derived neurotrophic factor*

BHE = Barreira hemato-encefálica

CID-10 = Classificação Internacional das Doenças

DMEM = Meio para cultivo celular, do inglês *Dulbecco's Modified Eagle Medium*

DSM-IV = Manual Diagnóstico e Estatístico de Transtornos Mentais, 4ª edição, do inglês *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*

FAST = Escala Breve de Funcionamento, do inglês *Functioning Assessment Short Test*

GR = Glutationa Redutase

GR = receptor de glicocorticoide, do inglês *glucocorticoid receptor*

GST = Glutationa *S*-Transferase

HDRS = *Hamilton Depression Rating Scale*

HPA = Hipotálamo-Pituitária-Adrenal

IDO = Indoleamina 2,3-dioxigenase

IL-2 = Interleucina 2

IL-4 = Interleucina 4

IL-6 = Interleucina 6

IL-10 = Interleucina 10

KYN = Quinurenina

KYNA = Ácido cinurênico

MTT = Do inglês, *3- (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide*

NAA = N-acetil-aspartato

NMDA = N-metil D-Aspartato

OMS = Organização Mundial da Saúde

PET = Tomografia por emissão de pósitrons

QUIN = Ácido quinolínico

ROS = Espécies reativas ao oxigênio, do inglês *reactive oxygen species*

SFB = Soro Fetal Bovino

SNC = Sistema Nervoso Central

TB = Transtorno Bipolar

TBARS = Substâncias reativas ao ácido tiobarbitúrico, do inglês *Thiobarbituric acid reactive substances*

TDO = Triptofano 2,3-dioxigenase

TNF-α = Fator de Necrose Tumoral alfa, do inglês *tumor necrosis factor alpha*

USA = Estados Unidos, do inglês *United States of America*

YMRS = *Young Mania Rating Scale*

1. INTRODUÇÃO

1.1 Transtorno bipolar

O transtorno bipolar (TB) é uma doença psiquiátrica grave que apresenta curso crônico e recorrente com altas taxas de morbidade e mortalidade (Muller-Oerlinghausen et al., 2002) trazendo prejuízos cognitivos e funcionais significativos para o paciente (Baune and Malhi, 2015). É caracterizado por alternâncias de episódios de humor, com sintomas que incluem períodos de mania, hipomania, psicose ou depressão, intercalados com períodos de bem-estar relativo, denominados eutimia (Grande et al., 2016). O curso clínico é variável para cada paciente; raramente apresentam um único episódio de humor, possuindo taxas de recaída para um novo episódio que podem chegar a mais de 70% em cinco anos (Price and Marzani-Nissen, 2012). Segundo dados da Organização Mundial da Saúde (OMS), o TB é considerado a sexta maior causa de incapacitação do mundo na faixa etária entre 15 e 44 anos (Lopez and Murray, 1998), apresentando uma prevalência de 2,4 % na população mundial (Merikangas et al., 2011).

De acordo com a Classificação Internacional das Doenças (CID-10) da OMS e o Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM-V) da Associação Americana de Saúde, o TB é classificado em quatro subtipos: TB tipo I, TB tipo II, ciclotimia e TB sem outra especificação. Os principais sintomas correspondem a alterações no humor, cognição e comportamento, embora suas intensidades sejam variáveis entre os pacientes (tabela 1). O TB tipo I representa a forma mais prevalente do transtorno, sendo caracterizado pela ocorrência de episódios maníacos ou mistos e episódios depressivos, enquanto o TB tipo

II caracteriza-se pela presença de episódios hipomaníacos e episódios depressivos. A ciclotimia corresponde a sintomas hipomaníacos e depressivos que não fecham critérios para TB tipo II e ausência de episódios de depressão maior (Price and Marzani-Nissen, 2012). O TB não apresenta predileção por raça, sexo ou etnia. Embora possa ocorrer em qualquer idade, a ocorrência do primeiro episódio em pessoas mais jovens do que 25 anos é mais comum, sendo 18 anos a idade média de início dos sintomas no TB I e 22 anos no TB II (Merikangas et al., 2007).

Tabela 1. Sinais e sintomas para o diagnóstico do Transtorno Bipolar.

Sintomas
Menor necessidade de sono por alguns dias sem se sentir cansado; Perturbações do sono (por exemplo, trabalho por turnos; viagens, mudança de estação, especialmente primavera e outono) que dispara um evento de mania ou hipomania; Depressão atípica: hipersonia, aumento do apetite, psicose, culpa patológica, humor lábil; Pensamentos rápidos que impedem o início do sono; Irritabilidade, impulsividade, irracionalidade; Mudanças de humor (mudanças irregulares de baixa para alta).
Histórico Familiar
Parente com transtorno bipolar; Vários parentes com qualquer um dos seguintes: depressão, obsessivo compulsivo, déficit de atenção / hiperatividade, ansiedade, transtorno do pânico; Histórico familiar em várias instâncias de suicídio, prisão, abuso de drogas ou álcool.
Histórico pessoal
Vários divórcios; Episódios anteriores de depressão, especialmente com o início precoce (idade 13 anos ou mais jovens) ou variabilidade sazonal; Nenhuma resposta a três ou mais ensaios antidepressivos; Problemas legais ou financeiros; Tentativa de suicídio; Abuso de álcool ou drogas; Perda de emprego recorrente; Intolerância a um antidepressivo, esteroides, ou outro medicamento, especialmente se causou agitação ou mania; Episódios anteriores de mania ou hipomania.

Fonte: adaptado de Price e Marzani-Nissen*. Bipolar Disorders: a review*. *Am Fam Physician*; 2012.

Os episódios maníacos caracterizam-se por uma euforia ou elevação de humor (expansivo ou irritável), com duração mínima de uma semana que deve estar associado a pelo menos três dos seguintes critérios (quatro, se humor irritável): redução da necessidade de sono, distratibilidade, sentimentos de grandiosidade, pressão por falar, fuga de ideias, agitação psicomotora, comportamento excessivo e voltado para atividades prazerosas que apresentam grande potencial para consequências dolorosas. As alterações de humor devem ser suficientemente graves a ponto de causar prejuízo tanto no âmbito ocupacional quanto social do indivíduo e os sintomas não devem ser consequência de efeitos fisiológicos ou de uma condição médica geral e nos casos que requerem a hospitalização o diagnóstico independe da duração do episódio (Association, 2013; Price and Marzani-Nissen, 2012).

Os episódios hipomaníacos assemelham-se ao episódio maníaco pelos sintomas e critérios do humor elevado apresentados anteriormente, mas caracteriza-se como um episódio sem sintomas psicóticos ou sintomas que possam causar danos ou colocar em perigo a vida de um indivíduo ou a do próprio paciente, difere-se também em relação à duração do episódio que se apresenta com uma duração mínima de quatro dias (Association, 2013; Price and Marzani-Nissen, 2012).

No caso dos episódios depressivos, o diagnóstico é definido pela presença de pelo menos cinco dos seguintes sintomas (tendo no mínimo duas semanas de duração): perda de interesse ou prazer nas atividades do cotidiano, humor deprimido, distúrbios de peso (perda ou ganho significativo de peso) ou apetite, distúrbios do sono (insônia ou hipersonia quase todos os dias), alterações psicomotoras (agitação ou retardo), perda de energia, sentimentos

de inutilidade ou culpa excessiva, dificuldade de concentração, indecisão e pensamentos de morte e/ou ideação suicida. O humor deprimido ou perda de interesse deve ser um dos sintomas, mas com a inclusão de critérios compostos (por exemplo, inutilidade ou culpa), o diagnóstico de depressão pode ser satisfeito por diversas variantes, e os episódios podem ser qualificados por outras características associadas - por exemplo, pós-parto, padrão sazonal, com melancolia ou sintomas psicóticos (Association, 2013; Price and Marzani-Nissen, 2012).

A etiologia do TB ainda não foi completamente esclarecida. Contudo, sabe-se que fatores genéticos, bioquímicos, psicodinâmicos e sócio-ambientais estariam envolvidos, sendo considerado um transtorno de causa multifatorial (Miller, 2006). Evidências indicam que alterações na neuro-imagem estrutural e funcional, no aumento da atividade pró-inflamatória, estresse oxidativo e alterações em vias neurotróficas estariam associados à fisiopatologia do TB (Langan and McDonald, 2009). O tratamento do TB é baseado no manejo dos episódios agudos e no tratamento de manutenção como meio de prevenção para diminuir a ocorrência de novos episódios de humor. Lítio e valproato de sódio são os estabilizadores de humor considerados padrão-ouro para o tratamento do TB (Yatham et al., 2013; Grande et al., 2016).

1.2 Progressão e estadiamento no TB

A fisiopatologia do TB ainda não está totalmente elucidada, mas evidências apontam para a importância do caráter sistêmico deste transtorno, por levar a alterações em diferentes

níveis: molecular, celular e de expressão gênica. Ainda, além do sistema nervoso central, sabe-se que há o acometimento imunológico, endócrino e cardiovascular, com alterações bioquímicas relevantes (revisado no capítulo um e dois desta tese). Considera-se que essas alterações bioquímicas podem desempenhar um papel causal nas alterações verificadas no SNC dos pacientes; o que tem sido chamado de toxicidade sistêmica (Kapczinski et al., 2010). Cada vez mais evidências sugerem que o transtorno bipolar pode apresentar um curso progressivo (Post et al., 2012) indicando que o prognóstico de pacientes com TB estaria diretamente relacionado com desfechos clínicos desfavoráveis, tais como: menor capacidade de resposta ao tratamento, especialmente ao lítio, e terapia cognitivo-comportamental, pior desfecho na psico-educação familiar, maiores taxas de comorbidade, maior comprometimento funcional, aumento da disfunção cognitiva, e um risco aumentado de suicídio e hospitalização (Fries et al., 2012).

Neste contexto, modelos de estadiamento têm sido propostos para classificar os pacientes conforme o estágio de progressão do TB (Kapczinski et al., 2009; Berk et al., 2011; Muneer, 2016). Basicamente, os pacientes são classificados em estágio I a IV, segundo os sintomas de humor, disfunção cognitiva e funcional, bem como pelo padrão de recorrência dos episódios e a gravidade dos sintomas clínicos (ver tabela 2). Novos modelos para o estadiamento têm surgido visando aprimorar cada vez mais o entendimento da fisiopatologia deste transtorno, como o estudo de Mwangi e colaboradores (2016) que sugere a realização de um estadiamento utilizando biomarcadores neuro-anatômicos como um dos critérios (Mwangi et al., 2016).

Estudos mostram que pacientes em estágios iniciais do TB apresentam melhor desfecho clínico do que aqueles com múltiplos episódios (Kapczinski et al., 2008). Neste contexto, há diversos estudos evidenciando diferenças significativas entre pacientes em estágios inicial e tardio da doença em diferentes aspectos, dentre eles: **1)** diferenças neuro-anatômicas, como aumento do volume dos ventrículos em pacientes com múltiplos episódios de TB em comparação com aqueles que tiveram apenas um episódio (Strakowski et al., 2002), alterações no volume do hipocampo em pacientes em estágios tardios do TB (Cao et al., 2016); **2)** funções cognitivas, mostrando que a neurotoxicidade de episódios repetidos podem contribuir para uma disfunção sustentada em várias áreas do funcionamento psicossocial (Rosa et al., 2012); **3)** marcadores inflamatórios, tendo sido relatado a interleucina (IL)-6 e o fator de necrose tumoral alfa (TNF-alfa) estando aumentados em pacientes em fases inicial e tardia, enquanto a IL-10 só foi aumentada na fase inicial da doença; **4)** marcadores neurotróficos, como os níveis séricos de BDNF que encontram-se diminuídos na fase tardia do TB, quando comparados com pacientes na fase inicial da doença (Kauer-Sant'Anna et al., 2009); **5)** parâmetros de estresse oxidativo, onde estudos sugerem aumento de lipoperoxidação, avaliado pelos níveis de substâncias reativas ao ácido tiobarbitúrico (TBARS) nos pacientes em estágio tardio, mas não em pacientes na fase inicial e controles, bem como alteração na atividade das enzimas Glutationa Redutase (GR) e Glutationa *S*-Transferase (GST) em pacientes em fase tardia em comparação com aqueles na fase inicial do TB (Andreazza et al., 2009).

Tabela 2. Características clínicas dos diferentes estágios do TB.

Estágio	Características clínicas
Latente	Em situação de risco para o desenvolvimento de TB, presença de histórico familiar. Sintomas de humor ou ansiedade, sem critérios mínimos para o diagnóstico de TB.
I	Períodos bem definidos de eutimia sem sintomas psiquiátricos evidentes.
II	Os sintomas em períodos inter-episódicos estão relacionados principalmente a comorbidades.
III	Acentuado prejuízo na cognição e funcionamento.
IV	Incapazes de viver autonomamente devido ao comprometimento cognitivo e funcional.

Fonte: Adaptado de Kapczinski et al.*Clinical implications of a staging model for bipolar disorders*. *Expert Rev Neurother* 9:957-966., 2009.

Episódios agudos no TB já foram associados com toxicidade sistêmica e prejuízos cognitivos (Kapczinski et al., 2010; Grande et al., 2012) e evidências sugerem que esses efeitos possam ser cumulativos, sendo sutis após o primeiro episódio, mas mais pronunciados após múltiplos episódios (Magalhaes et al., 2011). Dessa forma, nota-se que o TB se caracteriza como uma doença progressiva causando alterações bioquímicas que podem ser avaliadas tanto no sistema nervoso central (SNC) como na periferia. Neste contexto, cada vez mais estudos têm procurado elucidar a fisiopatologia do TB visando evitar os danos que os episódios de humor recorrentes causam no paciente, pois sabe-se que dentre os pacientes com o TB, as taxas de suicídio são maiores que as taxas da população em geral (Angst et al., 2002), o que enfatiza a necessidade pela busca de marcadores capazes não somente de melhor entender a progressão do transtorno e, assim, evitá-la, como também com o propósito de se buscar terapias alternativas e inovadoras para os pacientes.

1.3 Alterações neuro-anatômicas no TB

Em relação à neurobiologia, estudos de ressonância magnética e neurofuncionais sugerem alterações no circuito que compreende o córtex pré-frontal, o sistema límbico e os núcleos da base, os quais podem estar associados à fisiopatologia do TB, pois se pressupõem serem estas regiões as responsáveis pela modulação do comportamento (Bearden et al., 2001; Strakowski et al., 2012). Achados mostram a diminuição no volume do córtex pré-frontal subgenual e córtex pré-frontal dorsolateral (Brambilla et al., 2002; Lopez-Larson et al., 2002), bem como uma alteração no tamanho do terceiro ventrículo (Strakowski et al., 1993; Hauser et al., 2000), do ventrículo lateral (Figiel et al., 1991) e um aumento do volume do estriado em pacientes bipolares comparados a controles saudáveis (Aylward et al., 1994). Ainda, evidências sugerem que o TB está associado com volumes reduzidos de estruturas do lobo temporal medial, como amígdala e hipocampo tanto em adolescentes quanto em adultos (Blumberg et al., 2003).

O TB também está associado a déficits cognitivos, envolvendo áreas do sistema límbico e do córtex pré-frontal responsáveis pela modulação da emoção. O padrão de déficits de atenção em pacientes bipolares é mais consistente com uma disfunção no córtex órbitofrontal, estruturas temporais subcorticais e mediais, e porções do córtex parietal posterior (Javadapour et al., 2010). Déficits na memória de trabalho também sugerem anormalidades no córtex órbitofrontal, córtex cingulado anterior, estriado, tálamo e estruturas temporais mediais (Adler et al., 2004). Estes achados corroboram com os dados encontrados nos estudos de ressonância magnética, tomografia computadorizada, e de neuro-imagem

funcional (ressonância magnética funcional e tomografia por emissão de pósitrons -PET) que apontam para alterações significativas do córtex pré-frontal e de estruturas subcorticais e mediais, componentes do sistema límbico anterior que modulam o comportamento, e parecem estar envolvidos no transtorno bipolar (Strakowski et al., 2005; Strakowski et al., 2012; Cao et al., 2016).

Estas mudanças morfológicas sugerem uma disfunção na plasticidade e resiliência celular. Neste contexto, aumentam as evidências que sistemas de sinalização responsáveis pela regulação da plasticidade e sobrevivência celular, possam estar alterados em pacientes com transtornos de humor (Hashimoto et al., 2004; Maletic and Raison, 2014).

1.4 Modelos Experimentais para o estudo do TB

Os modelos experimentais constituem uma importante ferramenta na investigação da fisiopatologia do TB (Einat et al., 2003). Contudo, devido à complexidade dos sintomas, até o momento não há um modelo experimental específico para a pesquisa do TB, pois cada modelo experimental apresenta vantagens e desvantagens, sendo necessário ao pesquisador escolher a melhor abordagem, conforme seu objetivo de estudo. Neste contexto, tem se estabelecido diferentes modelos *in vivo*, *in vitro* e *post-mortem* que têm sido utilizados com sucesso relativo para o avanço das pesquisas no TB (Harrison et al., 2016). Dentre os modelos *in vivo*, o modelo animal de mania consiste em um dos mais estudados (Logan and McClung, 2016) utilizando desde animais geneticamente modificados a indução farmacológica, como no caso da *D*-anfetamina (Stertz et al., 2014) e ouabaína (Valvassori et al., 2016), com o

objetivo de mimetizarem no animal o episódio de mania, característico do TB. Pesquisas recentes tem apontado para o desenvolvimento de modelos animais que identifiquem e permitam a alternância de episódios maníacos e depressivos, o que seria um grande avanço para os estudos da neurobiologia do TB (Young and Dulcis, 2015).

Em relação aos estudos *post-mortem*, mesmo que haja dificuldades inerentes quanto à obtenção do tecido, estes têm se mostrado essenciais para identificar alterações neuropatológicas em pacientes com TB. Investigações neste campo têm geralmente analisado concentrações ou atividades específicas de determinados constituintes, tais como: enzimas, metabólitos intermediários, cofatores e neurotransmissores (Johnston-Wilson et al., 2000). Neste contexto, a determinação da expressão gênica e proteica em estados normais e patológicos do SNC tem sido de grande importância para a compreensão da neurobiologia do TB (Konradi et al., 2012).

Quanto aos modelos *in vitro*, a cultura de células se tornou um importante recurso para a pesquisa científica do TB. Atualmente, existem diversos modelos celulares que possibilitam a realização de estudos funcionais, bioquímicos e moleculares, além da análise de alvos farmacológicos no TB (Viswanath et al., 2015). Dentre os tipos de cultura celular, temos o cultivo primário e as linhagens celulares. Quando as células são diretamente obtidas de um tecido humano ou animal, temos a cultura celular primária; nesse sentido, estudos com células periféricas de pacientes com TB, como os linfócitos, indicaram aumento da apoptose e alteração na resiliência celular nestes pacientes (Fries et al., 2013; Pfaffenseller et al., 2014). Já as linhagens celulares são células imortalizadas que adquiriram a capacidade de se

multiplicar indefinidamente. Comparadas às culturas primárias, experimentos empregando células de linhagens tendem a oferecer maior reprodutibilidade (Masters, 2000). Neste contexto, a linhagem de células de neuroblastoma humano SH-SY5Y tem sido muito utilizada para a pesquisa de doenças como o câncer e mais recentemente tem recebido destaque no estudo de doenças que afetam o SNC, como Parkinson e Alzheimer (Lopes et al., 2010; Schonhofen et al., 2015), devido a sua capacidade de diferenciação em neurônios, proporcionando assim, um modelo mais adequado para estudar doenças que afetam o SNC, como o TB (Chiocchetti et al., 2016).

A terapia celular é um dos mais recentes modelos para o estudo de doenças que afetam o SNC e consiste na administração de células saudáveis em um tecido lesado, o qual seria estimulado a um processo de regeneração. Neste sentido, as células tronco mesenquimais (CTMs) têm emergido como uma potencial ferramenta terapêutica para o TB por serem capazes de se diferenciar tanto em células mesodermais (osteoblastos, condrócitos, adipócitos) quanto em outros tipos celulares não mesodérmicos, como hepatócitos e células neurais (Krabbe et al., 2005; Giordano et al., 2007 e revisado no artigo Colpo, Ascoli e Wollenhaupt-Aguiar et al., 2015 que segue como anexo 3 desta tese).

Outro modelo relevante e recente para o estudo de transtornos psiquiátricos surgiu em 2007, onde a partir de fibrosblastos foi possível gerar células-tronco embrionárias através de reprogramação genética. Estas células têm sido denominadas como células-tronco de pluripotência induzida ou pela sigla *iPS* (do inglês *induced pluripotent stem cells*). O processo de reprogramação se dá através da inserção de vírus contendo 4 genes: oct-4, sox-

2, Klf-4 e c-Myc; estes se inserem no DNA da célula adulta (por exemplo: fibroblastos) e reprogramam o código genético. Com esta reprogramação as células voltam ao estágio de uma célula-tronco embrionária e possuem características de autorrenovação e a capacidade de se diferenciarem em qualquer tecido (Kim et al., 2016). Estudos têm sido realizados com pacientes bipolares (O'Shea and McInnis, 2016), como o de Chen e colaboradores (2014) que avaliaram a via de sinalização do cálcio em neurônios diferenciados a partir de *iPS* de pacientes bipolares (Chen et al., 2014).

Com base nestes estudos, nota-se que existem diferentes modelos experimentais e cada modelo contribui para o avanço das pesquisas sobre o TB, possibilitando desde o teste de novos fármacos e busca pelo entendimento do mecanismo de ação dos já estabelecidos, bem como no estudo das alterações neurobiológicas e fisiopatológicas e vias de sinalização envolvidas a novas tecnologias e novos tratamentos para o manejo dos episódios de humor. Nesse sentido, espera-se que a integração dos dados obtidos nos diferentes modelos experimentais permitirá revelar importantes conhecimentos sobre a etiologia, fisiopatologia e tratamento do TB no futuro. Nesta tese, em relação ao modelo experimental, nosso enfoque será no modelo *in vitro* de diferenciação celular da linhagem de neuroblastoma humano SH-SY5Y, que será abordado nos capítulos 3 e 4.

1.5 Alterações celulares no TB

O TB é caracterizado pela existência de diversos alvos celulares e moleculares associados não só com a sua fisiopatologia, mas também com o seu perfil terapêutico. A

maior parte destes alvos têm sido mostrados regular criticamente a plasticidade e a resiliência celular (Soeiro-de-Souza et al., 2012).

A plasticidade celular que corresponde a capacidade de sofrer e manter alterações, é essencial para o bom funcionamento do nosso sistema nervoso. Esta capacidade de mudança permite aos organismos se adaptar a alterações complexas em ambos os seus ambientes: internos (como em organelas celulares: disfunção mitocondrial e estresse do retículo endoplasmático) e externos (como alteração na expressão de receptores de membrana e excitotoxicidade); o que consiste em um recurso fundamental para a sobrevivência e reprodução (Schloesser et al., 2008). Além da evidente necessidade de mecanismos de adaptação significativos na aprendizagem e memória, bem como na homeostase fisiológica, todos os complexos fenômenos comportamentais -incluindo humor e emoção- são processos dinâmicos que dependem da plasticidade de circuitos neurais. A base biológica desta capacidade de adaptação engloba um conjunto diversificado de mecanismos celulares e moleculares que tem sido denominado neuroplasticidade (Schloesser et al., 2008). A neuroplasticidade é um termo que representa as alterações nas cascatas de sinalização intracelular e de regulação de genes, modificações de número e força sináptica, alterações na liberação de neurotransmissores, modelagem da arquitetura dendrítico e axonal e, em algumas áreas do SNC, a geração de novos neurônios (McClung and Nestler, 2008).

Recentemente, estudos tem associado transtornos de humor com comprometimentos estruturais e funcionais relacionados com a neuroplasticidade em várias regiões do SNC, como uma diminuição de estruturas cerebrais em consequência de uma redução da

conectividade celular devido a disfunções na neuroplasticidade (Soeiro-de-Souza et al., 2012; Berk et al., 2011; Manji et al., 2000). Em adição, fármacos psicotrópicos comumente usados para tratar estas condições, têm como alvo moléculas e cascatas de sinalização envolvidos no controle da neuroplasticidade (Machado-Vieira et al., 2009).

Neste contexto, a resiliência celular é definida como a capacidade de uma célula para se adaptar a diferentes insultos que são causados pelo ambiente, o que pode ser exacerbado (ou atenuado) por certos fatores herdados ou desenvolvidos (Manji and Duman, 2001). Além disso, estudos tem colocado a resiliência celular como um mecanismo para tratar o TB, sugerindo que a perda de plasticidade celular pode ser devido à perda de fatores tróficos ou de sobrevivência, juntamente com mecanismos adicionais, como alterações em cascatas de sinalização intracelulares (Schloesser et al., 2008). Assim, a análise da resiliência celular pode ser realizada através de uma variedade de mecanismos, incluindo (mas não exclusivamente) neurotróficos, de sobrevivência, receptores de glicocorticoides (GR) e vias de sinalização (Hunsberger et al., 2009). Os fatores neurotróficos, inicialmente identificados como moduladores de crescimento e diferenciação neuronal, foram atualmente considerados como reguladores críticos da plasticidade e resistência celular em neurônios adultos e na glia (Manji et al., 2000). Neste contexto, a ativação de vias neuroprotetoras e neurotróficas foi também associada aos efeitos terapêuticos dos estabilizadores do humor (Manji and Duman, 2001). Com base nestas evidências, pode-se inferir que a resposta celular a uma devida disfunção está diretamente relacionada ao tipo e ao nível do estímulo, sendo assim, seria a capacidade adaptativa da célula a responsável por ativar diferentes vias de resposta, dentre

elas pode-se destacar a resposta ao estresse oxidativo, as proteínas de choque térmico e de proteínas mal enoveladas. Caso estas respostas não sejam suficientes para cessar a disfunção, a célula pode vir a ativar vias de morte celular (Uribe and Wix, 2012).

Neste contexto, estudos têm verificado alterações na plasticidade e resiliência celular em diferentes processos celulares no TB. O íon de cálcio (Ca^{2+}) é um mensageiro intracelular que controla diversas funções biológicas críticas no SNC humano, tais como: influência na síntese e liberação de neurotransmissores e cascatas de segundo mensageiro, afetando assim a ativação da plasticidade, sinalização intracelular, metabolismo energético e consolidação sináptica (Kato, 2008). Assim, a disfunção na regulação das cascatas do Ca^{2+} interfere diretamente na atividade mitocondrial e do retículo endoplasmático e tem um papel crítico na neuroplasticidade e sobrevivência celular. Alterações específicas à canal operado por armazenamento de cálcio, funcionamento do retículo endoplasmático, e a absorção de cálcio mitocondrial foram descritos estarem alterados em células linfoblastóides transformadas de pacientes com TB (Kato et al., 2003).

Ainda, diminuição na atividade do complexo I da cadeia respiratória mitocondrial e na fosforilação oxidativa foi verificada em pacientes com TB (Stork and Renshaw, 2005); expressão de Bcl-2 – proteína associada a membrana com importante função neuroprotetora e anti-apoptótica – foi verificada estar alterada em pacientes com TB e se mostrou ser revertida com tratamento com lítio e valproato (Chen et al., 1999). Estudos em células mononucleares de pacientes com TB indicaram uma disfunção na resposta ao estresse do retículo endoplasmático nos pacientes quando comparados ao grupo controle,

indicando uma menor resiliência celular nos pacientes (So et al., 2007; Pfaffenseller et al., 2014); fator neurotrófico derivado do cérebro (BDNF), tem sido verificado estar diminuído no soro de pacientes com TB (Scola and Andreazza, 2015) e revertido com tratamento com lítio (Rybakowski, 2014). O lítio também mostrou aumentar concentrações cerebrais de N-acetilaspartato (NAA) - um marcador de viabilidade e integridade neuronal (Moore et al., 2000), que já foi descrito estar diminuído no córtex frontal de pacientes com TB (Sassi et al., 2005); em leucócitos de sangue periférico de pacientes eutímicos foi verificada diminuição do número de cópias do DNA mitocondrial (mtDNA) quando comparada ao grupo controle (Chang et al., 2014). Ainda, alterações em fatores apoptóticos tem sido verificado em pacientes, como o aumento da atividade apoptótica em células periféricas (Fries et al., 2013) e presença de dano ao DNA (Andreazza et al., 2007); e já foi descrito que as células do neuroepitélio olfatório de pacientes com TB seriam altamente vulneráveis à morte celular (McCurdy et al., 2006). Neste sentido, estudos com soro de pacientes bipolares em cultura de células mononucleares periféricas de controles saudáveis mostraram que o soro dos pacientes seria capaz de induzir uma maior porcentagem de apoptose comparado ao soro de controles (Herberth et al., 2011), e em cultura de células endoteliais o soro dos pacientes induziu aumento de atividade pró-apoptótica comparado ao soro do grupo controle (Politi et al., 2008). Em conjunto estes achados sugerem que o soro de pacientes bipolares apresentaria um caráter tóxico quando comparado ao soro de indivíduos controles.

2. OBJETIVOS

2.1 Objetivo geral

O objetivo geral desta tese foi realizar a caracterização gênica do modelo de diferenciação celular da linhagem de neuroblastoma humano SH-SY5Y, induzido por ácido retinóico e buscar por um modelo experimental para a avaliação da toxicidade sistêmica apresentada pelos pacientes com transtorno bipolar nos diferentes estágios do TB.

2.2 Objetivos específicos

- Revisar e discutir a toxicidade sistêmica, com foco em neurotrofinas, inflamação e estresse oxidativo como biomarcadores periféricos de atividade da doença e os mecanismos biológicos associados, a partir de dados da literatura.

- Revisar e discutir a associação entre as alterações nos marcadores neurotróficos, inflamatórios e de estresse oxidativo com alterações cognitivas nos pacientes com TB.

- Caracterizar o modelo de diferenciação celular por ácido retinóico das células SH-SY5Y, através da técnica de microarranjo, para corroborar com os achados bioquímicos anteriores do grupo que indicam que este protocolo de diferenciação é adequado para o estudo de doenças que afetam o SNC, por permitir a diferenciação de células de neuroblastoma humano em células com perfil neuronal.

- Utilizando o modelo celular proposto, avaliar a toxicidade sistêmica presente no soro de pacientes bipolares comparados a indivíduos controles, pareados por sexo e idade, e nos diferentes estágios do TB, através da capacidade do soro em causar alterações na morfologia, na viabilidade celular e na densidade de neuritos.

PARTE II

MÉTODOS E RESULTADOS

3. ARTIGOS CIENTÍFICOS

3.1 CAPÍTULO 1

Neurotrophins, inflammation, and oxidative stress as illness activity biomarkers in bipolar disorder

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EXPERT REVIEWS

Neurotrophins, inflammation and oxidative stress as illness activity biomarkers in bipolar disorder

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Recent studies highlight the presence of systemic toxicity as an integral dimension of bipolar disorder pathophysiology, possibly linking this mood disorder with other medical conditions and comorbidities. This review summarizes recent findings on possible peripheral biomarkers of illness activity, with a focus on neurotrophins, inflammation and oxidative stress. The possible mechanisms underlying the systemic toxicity associated with acute episodes in bipolar disorder are also discussed. Finally, the authors outline novel therapies that emerge from this new research and the assessment of multiple biomarkers as a potential approach to improving management strategies in bipolar disorder.

Keywords: bipolar disorder • endoplasmic reticulum stress • glial dysfunction • illness activity • inflammation • mitochondrial dysfunction • neurotrophins • novel therapies • oxidative stress • peripheral biomarkers • systemic toxicity

Bipolar disorder (BD) is a severe chronic illness in which recurrent episodes of mania and depression alternate with periods of clinical remission (euthymia). BD has been commonly associated with significant disability, morbidity, and premature mortality [1,2]. The recurrence of acute episodes and illness progression often translate into worse long-term outcomes, for example, higher rates of clinical comorbidities, functional and cognitive impairments and lower responsiveness to treatment [3–6]. Moreover, patients with BD are at higher risk for developing a wide range of medical conditions, including cardiovascular and cerebrovascular disease, neurological disorders and metabolic syndrome [7].

One of the hypotheses that has been proposed to explain the mechanisms underlying the heavy medical burden and cumulative damage related to BD is the allostatic load theory [8–10]. According to this theory, the chronic activation of mechanisms to restore homeostasis after stressful conditions leads to wear-and-tear in the body and brain that has been called allostatic load [8,11]. These events are vital adaptive functions, but they may also promote maladaptive effects on brain plasticity, as well as on metabolic, immune, and cardiovascular pathophysiology, whenever mediators are excessive in number or remain active [12]. Recently, the allostatic load paradigm has been incorporated into a new concept of neuroprogression in BD, described as a pathological brain rewiring process-taking place when clinical and cognitive deterioration is observed as a result of disease progression [13]. In this sense, there is a growing interest in understanding the systemic pathophysiological mechanisms that contribute to dysfunction resulting from multiple mood episodes in BD, and especially in identifying the pathways associated with allostatic mediators involved in neuroprotection, oxidative stress and inflammation.

Within this scope, several studies have been performed to detect peripheral biomarkers that could work as indicators of cellular impairment and toxicity in patients with BD [14,15]. Different biomarkers could be associated with illness activity (indicating whether the illness is active or in remission), illness neuroprogression, or both. Of note, systemic markers have already been implicated in BD as mediators of allostasis [8,13,16]. These studies may be important in improving our understanding of illness activity

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and progression, and also in providing insights for new approaches to treatment and biomarkers.

The aim of the present communication is to review current evidence available on possible biomarkers of illness activity in BD. Special attention will be given to neurotrophins, inflammation and oxidative stress, as well as to the possible mechanisms whereby these metabolic routes are activated in acute mood episodes. Finally, the authors will outline emerging therapeutic opportunities in the field of BD. For recent reviews on the role of systemic pathophysiology and neuroprogression in BD, please see the reports of Grande *et al.* [9] and Fries *et al.* [17].

Peripheral biomarkers in bipolar disorder

There is considerable interest in incorporating biomarkers into psychiatry [18], using them as biological indicators to more accurately assess psychiatric conditions. A biological marker or biomarker is a feature that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention (National Institutes of Health Definition Working Group, 2001) [19]. Biomarkers may be genes, proteins or other molecules, as well as morphological characteristics identified on the basis of physiological or biological mechanisms.

In addition to improving diagnosis, biomarkers could assist in predicting illness prognosis and the potential risk of developing a disorder, with valuable applications in monitoring illness status and responses to a therapeutic intervention or management strategy [20]. Moreover, biomarkers could help discover new therapeutic targets and are likely to contribute to uncover illness mechanisms in complex psychiatric disorders [21]. Particularly in BD, biomarkers may become useful tools in detecting illness activity associated with different mood states (a state marker) or in identifying specific features of the long-term course of illness (a trait marker) [22].

Only validated biomarkers can be used in the clinical setting. In other words, in order to be used clinically, a biomarker has to prove it is accurate, has high sensitivity and specificity for the expected outcome, is highly reproducible in standardized, cost effective, fast assays, is minimally invasive and acceptable to the patient, and also that it provides a clinically relevant result, with easily interpretable information [20]. Among the strategies adopted for biomarker discovery and application in BD, a great interest in peripheral biomarkers is observed: certain proteins found in peripheral blood may be transported through the blood–brain barrier and enter the CNS [23]. For instance, proteins of the neuregulin (NRG) family, that could enhance myelination of neurites, and brain-derived neurotrophic factor (BDNF) could enter the spinal cord and brain by a saturable receptor-mediated mechanism [24,25]. A recent study has found a correlation between cerebrospinal fluid and plasma BDNF levels in drug-naive, first-episode psychotic subjects [26].

This approach, using peripheral biomarkers, has several advantages, including easy collection, low cost, wide availability and feasibility for large-scale studies. Several peripheral markers have been studied as mediators of allostasis in BD [8,13]. Studies have focused primarily on biological pathways related to neuroplasticity in BD, including the role of neurotrophins, inflammation, oxidative stress and underlying processes.

Neurotrophins

Neurotrophic factors are small-secreted proteins that act in a range of biological functions related to interaction with different receptors, their local distribution and transport in the CNS [27]. Nerve growth factor was the first neurotrophin to be identified, by Levi-Montalcini in 1966. After that, several studies have discovered other neurotrophins, such as BDNF, glial cell-line derived neurotrophic factor (GDNF), neurotrophin 3 and neurotrophin 4/5 (NT-4/5), all playing major roles in synaptic plasticity, dendritic arborization, and neuronal connectivity. In addition, all have been shown to be altered in BD, as will be discussed below [8,28].

BDNF is the most abundant and widely distributed neurotrophin in the CNS and also the most studied one; current studies show that an altered expression of BDNF contributes to several disorders, including BD. A correlation between serum BDNF levels and other markers of CNS injury has also been suggested [29,30]. Moreover, a growing body of evidence points towards a relationship between peripheral BDNF levels and illness activity in BD.

Serum BDNF has been found to be reduced in BD during manic and depressive episodes when compared with euthymic patients and healthy controls, even in drug-free patients [31–34]. In unmedicated manic children and adolescents, a decrease in both mRNA levels of lymphocyte-derived BDNF and protein levels in platelets has been found in relation to healthy controls [35]. Despite some discrepancies between studies [15,36–39], meta-analyses have been performed to measure the effect size of differences in BDNF levels between patients in different mood states and controls [40,41]. The latest of these meta-analyses demonstrated that peripheral BDNF levels decrease during manic and depressive states and those patients who have experienced more episodes present lower BDNF levels.

In this context, the discrepancies found in the peripheral levels of BDNF could be associated with the difference on the methodology used in these studies. Further, this could be related to a study that verified that patients at different stages of the illness differ in the BDNF levels, showing changes in the late stages but not in early stages of illness compared with controls [42]. In addition, another study observed that BDNF levels were inversely related with age and length of illness [43]. Taken together, these findings suggest that the toxicity and cognitive impairment observed in patients with BD would be related to the number of episodes; each new episode would lead to further damage and therefore lower levels of BDNF [44].

Regarding treatment, mood stabilizers have been shown to increase BDNF levels [40]. Patient recovery from a manic episode after treatment with lithium has been associated with an increase in serum BDNF levels [45]. In the same vein, Rybakowski and Suwalska found that excellent lithium responders showed higher plasma BDNF levels compared with non-responders, and similar

levels compared with controls [46]. Other data have shown a significant increase in BDNF levels after lithium monotherapy for the management of manic episodes, suggesting a direct role of the regulatory effects of lithium on BDNF levels in mania [47]. A very recent open-label longitudinal trial in previously medication-free patients measured serum BDNF sequentially for 16 weeks. Relevantly, BDNF levels tended to increase with treatment, but only in patients acutely depressed at baseline. Those in manic or mixed episodes, in turn, showed a decrease in BDNF levels in the first weeks of treatment. These results suggest that manic and mixed episodes may be particularly toxic compared with depression, perhaps requiring a longer treatment time for BDNF to return to its baseline levels [9]. All these studies describing an important role of BDNF in the pathophysiology of BD have led to further research into novel targets of this neurotrophin, in addition to the already known therapeutic action of mood stabilizers.

Changes in other neurotrophic factors have also been reported in patients with BD, such as increased serum neurotrophin 3 levels during manic and depressive episodes compared with euthymic patients and healthy controls [48,49] and increased serum NT-4/5 levels in patients versus healthy controls, regardless of symptomatic state [50]. A recent work found increased GDNF plasma levels in euthymic patients compared with manic patients and healthy controls [51], although another study observed increased levels of GDNF in manic and depressive patients but not in euthymic patients when compared with control group [52]. Moreover, a previous study had found decreased serum levels of GDNF in patients during mania and depression, and increased levels after remission [53]. In line with this, a study has shown decreased levels of GDNF in remitted patients [54]. Taken together, these findings reinforce the implication of GDNF in the BD pathophysiology, but with a still unclear role. Additional evidence is needed to assess whether peripheral levels of GDNF are correlated with CNS levels of the neurotrophin [55].

Inflammation

Over the past few years, the number of publications focusing on immunological abnormalities involved in the pathophysiology of BD has grown substantially. Immune disturbances have been related to the severity and recurrence of mood episodes [42], illness progression [56,57], high rates of comorbidities [56] and drug effects [58,59].

Overall, mood episodes have been characterized as pro-inflammatory states [22], based on findings that show increased peripheral levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, during depressive episodes, and of IL-2, IL-4, IL-6 and TNF-α in mania when compared with euthymic patients and healthy subjects [60–62]. A recent review and meta-analysis has found that, during mania, patients show increased levels of TNF-α, soluble TNF receptor type 1 (sTNF-R1) and soluble IL-2 receptor (sIL-2R) when compared with healthy subjects, and high levels of sTNF-R1 and TNF-α when compared with euthymic patients [63]. Another recent meta-analysis has found that manic patients show increased TNF-α and sIL-2R levels and a trend toward higher sTNF-R1 concentrations when compared with euthymic patients, in addition to increased IL-1 receptor antagonist (IL-1RA) and a trend toward higher IL-6 levels when compared with healthy controls. Increased IL-10 levels were also found in patients in depression versus controls, however not reaching significance between acute phases. Finally, some cytokines, such as IL-1RA, have shown altered levels during euthymia compared with controls [64].

An aberrant inflammatory gene expression signature has also been demonstrated in monocytes from patients with BD; some of them were related to the cytokines most commonly correlated with BD, namely, TNF and IL-6 [65]. In this study, mRNA expression of chemokine ligand 2 and MAPK-6 was found to be significantly greater in monocytes during manic and depressive episodes. In addition, IL-6, PTX3, and cell survival/apoptosis signaling genes *EMP1* and *BCL2A1* were overexpressed during the depressive phase compared with euthymic patients, suggesting a differentiated activation of the inflammatory response system. The study mentioned above showed that the inflammatory state in monocytes from patients is familial, which means that similar results were found in the offspring of these patients, but the study did not evaluate the possible interaction between the existence of an aberrant proinflammatory gene expression signature and environmental factors. In a follow-up study, Padmos *et al.* have shown that the pro-inflammatory activation of monocytes in monozygotic and dizygotic twins is most likely due to shared environmental factors [66]. In the same direction, this group showed that schizophrenic patients also present an inflammatory activation of monocytes. This signature is such like the one found in patients with BD, an upregulation of ATF3, DUSP2, EGR3 and MXD1, and differs of BD signature in PTPN7 and NAB2 [67].

However, this increased inflammatory signature at the transcriptomic level has not been demonstrated at the protein level in patients with BD. In addition, Herberth *et al.* identified altered expression of seven pro-inflammatory and five pro-/anti-inflammatory protein analytes in the serum of euthymic patients [68]. This serum was used to treat peripheral blood mononuclear cells and was observed to decrease cell viability, pointing to an increased inflammatory response and likely cell death in the immune system of patients with BD.

In accordance with the aforementioned abnormalities, adolescents with BD have also been shown to present some type of immune disturbance. Preliminary findings obtained in a sample of adolescents with BD have indicated an association between severity of manic symptoms and high-sensitivity C-reactive protein (hsCRP), as well as a negative association between serum IL-6 and BDNF protein levels [32]. In the same vein, Padmos *et al.* demonstrated that the offspring of patients with BD also had an altered expression of inflammation-related genes [65].

Changes mentioned above serve as a source of information on the biological bases of BD, however these changes have not been found every time when tested and the same cytokines are not always implicated. Therefore, the use of inflammatory markers as biomarkers for predicting prognosis is still limited, but these findings could point to targets for treatment and monitoring of these patients in order to improve their quality of life.

The origin of immunological imbalance in BD is still unknown. However, some studies have pointed to factors such as sleep and circadian rhythm alterations, stress, immune activation by retrovirus infection or autoimmune dysfunction [69], unhealthy lifestyle, long-term exposure to drugs and some specific mechanisms that should be the focus of further studies [70,71].

Patients with BD are known to be at a higher risk of developing medical comorbidities, including cardiovascular disease, metabolic syndrome and diabetes [32,72,73]. The main connection between these disorders seems to be the presence of chronic systemic inflammation, or high levels of the inflammatory markers mentioned above. In fact, it is precisely because of the growing evidence suggesting chronic mild inflammation in the periphery and brain of patients with BD [60,74,75] that BD has been referred to as a multisystemic inflammatory disease by some authors [56,76].

A major confounding factor present in almost all studies designed to investigate inflammation in BD is the exposure of patients to drugs. Some studies have proposed that lithium can restore the inflammatory imbalance observed in BD [77]. Guloksuz *et al.* found a correlation between lithium response and TNF-α levels, where patients with a poor response to lithium showed increased serum TNF-α levels [78]. Further studies are needed to elucidate the relationship between inflammatory markers, treatment and the development of medical comorbidities in BD.

Oxidative stress

A growing body of evidence has demonstrated that oxidative stress plays an important role in the pathophysiology of BD [79–81]. Oxidative stress is defined as an imbalance between oxidant and antioxidant agents, potentially leading to cellular damage. Decreased levels of antioxidants or an increased production of pro-oxidants will result in an oxidative stress state, ultimately causing damage to macromolecules such as lipids, proteins (receptors and enzymes), carbohydrates and DNA [82].

The CNS is particularly vulnerable to oxidative injury, due to high oxygen consumption and hence the generation of free radicals, and also because of the relatively low antioxidant capacity of this structure [83]. Increased neuronal oxidative levels may have deleterious effects on signal transduction, plasticity and cellular resilience [84]. The antioxidant system is the major line of defense against oxidative stress, and can be divided into the enzymatic system, comprising the key enzymes superoxide dismutase (SOD), catalase and glutathione peroxidase (Gpx), and the nonenzymatic system [85]. The most important nonenzymatic cellular antioxidant and redox-regulator is glutathione (GSH), the brain's dominant antioxidant [86].

Under physiological conditions, mitochondria are a major source of free radicals (oxidants), produced in electron transport chain complexes [87]. In BD, the prevalent hypothesis is that a greater burden of oxidative stress is generated as a result of a disturbed mitochondrial function [13]; this hypothesis has been supported by postmortem studies reporting alteration in mitochondrial complex I activity [88] and decreased levels of GSH [89] in the prefrontal cortex of patients. Mitochondrial dysfunction in BD will be reviewed in another section.

Clinical studies have demonstrated systemic alterations in diverse oxidative stress parameters and antioxidant enzymes in patients with BD. Some of these changes have been related to mood episodes. For instance, Andreazza *et al.* reported that SOD activity is increased during manic and depressive phases, but not in euthymia [90]. This finding was confirmed by Machado-Vieira *et al.* [33] who showed increased SOD activity in unmedicated manic patients, as well as by Kunz *et al.* [91] who also reported increased SOD activity in acute phases of BD, but not during euthymia. However, others studies have shown decreased SOD activity in acute phases of BD and in the euthymia [92–94]. Furthermore, Raffa *et al.* did not found differences in the SOD levels in patients when compared with healthy controls [95]. Catalase activity was also decreased in euthymic patients [90,94,95], but increased in medication-free patients during mania [33]. These results suggest that alteration in antioxidant enzymes can change due the treatment and the phases of the illness.

An increased frequency of DNA damage possibly caused by oxidative stress has been shown in patients with BD and was correlated with severity of depression and manic symptoms [96]. Conversely, a meta-analysis investigating markers of oxidative stress in BD showed that thiobarbituric acid reactive substance, a marker of lipid peroxidation and nitric oxide, a reactive nitrogen species, were significantly elevated in all phases of BD [79], suggesting a relevant role of these parameters as possible biomarkers of illness traits.

Parenthetically, evidence from preclinical, clinical and epidemiological studies suggests a benefit for adjunctive antioxidant compounds in BD [97]. *N*-acetylcysteine, for instance, proved safe in two randomized trials as an adjuvant to mood stabilizers [98–100]. Preliminary data also suggest clinical effects of antioxidant compounds in mania and depression, and a particularly strong effect in patients with comorbid medical conditions [100,101].

Mechanisms underlying cellular alterations & toxicity in bipolar disorder

Mechanisms leading to reduced resilience to stressful conditions associated with acute episodes in BD probably involve cell signaling pathways and organelles that are typically responsible for maintaining cellular homeostasis, for example, the mitochondrion and endoplasmic reticulum (ER), and could affect cells from both the periphery and the CNS, for example, neurons and glial cells. Basic research experiments have significantly contributed to the understanding of these mechanisms, partially explaining the toxicity related to cumulative mood episodes in BD. In this section, the authors attempt to summarize some of the mechanisms underlying toxicity in BD.

Mitochondrial dysfunction & the role of chronic stress

A growing body of evidence has suggested a key role of mitochondrial dysfunction in BD [102]. Impaired energy metabolism, alterations in respiratory chain complex enzymes, altered levels of

cytoplasmic calcium, and downregulation of mitochondria-related genes are some of the abnormalities reported [102]. In addition, several postmortem, imaging, and genetic studies have pointed to an association between mitochondrial dysfunction and BD [103]. Mean cerebrospinal fluid lactate concentrations are significantly higher in patients when compared with controls, which indicates increased extra-mitochondrial and anaerobic glucose metabolism and is consistent with impaired mitochondrial metabolism in BD [41]. More recently, a decrease in attachment of hexokinase 1 to the outer mitochondrial membrane in postmortem brain parietal cortex tissue of individuals with BD has been reported, associated with increased activity of an alternative anaerobic pathway of glucose metabolism [104]. In the same vein, alterations in mitochondrial shape and distribution could be one of the underlying causes of energy dysfunction in BD, as shown in the prefrontal cortex of postmortem brains and in peripheral cells from patients with BD [103]. The role of mitochondrial dysfunction in BD is further supported by studies reporting that known mood stabilizers and antidepressants can enhance mitochondrial function [102,105,106]. For instance, lithium has been shown to stimulate the activity of mitochondrial respiratory chain enzymes at clinically relevant concentrations [107].

To a greater extent, abnormalities may be associated with the consequences of chronic exposure to stress, which seems to play a role in the pathophysiology of BD [108]. The stress hormone axis, more commonly known as the hypothalamic–pituitary–adrenal axis, is clearly altered in mood disorders, as suggested by the high number of patients with BD that inefficiently suppress cortisol release on the dexamethasone suppression test [109]. This deficiency of the hypothalamic–pituitary–adrenal axis results in a feed-forward production of cortisol in response to stress and in a decreased ability to return to resting levels once stress exposure is ceased [110]. As a consequence, patients with BD in the three phases of the disorder present similarly increased levels of cortisol, higher than those observed in controls [111]. These increased cortisol levels may have important long-term consequences in patients. For instance, *in vitro* and animal model studies have shown that chronic stress and chronic exposure to glucocorticoids can induce mitochondrial dysfunction, causing reductions in oxygen consumption, mitochondrial membrane potential, and calcium holding capacity and ultimately leading to apoptosis [112,113]. Glucocorticoids may also aggravate inflammation and induce toxicity in the CNS, making neurons less capable of removing glutamate from the synapse and quenching free radicals [114]. In addition, neuronal toxicity and damage could be generated by an increase in synergists of inflammation, oxidative stress and mitochondrial dysfunction [115].

Altogether, the authors hypothesize that some of the impairments in mitochondrial functions in patients with BD are induced and further stimulated by chronic stress. As a consequence, dysfunctional mitochondria are likely to impair cellular resilience to environmental stimulus, ultimately inducing activation of caspases and apoptosis. Once dead, these cells may end up releasing immunostimulatory molecules and therefore induce alterations in inflammatory markers. These alterations may be then responsible for detrimental effects on peripheral cells, possibly inducing apoptosis and completing a vicious cycle of peripheral toxicity and reduced cellular resilience.

ER stress

The ER plays a central role in Ca^{2+} storage and signaling, and also in the synthesis, folding and quality control of secretory and membrane proteins [116]. Alterations in the ER luminal environment, such as changes in the redox state and in calcium homeostasis, nutrient deprivation, or defects in protein post-translational modifications, may affect the function of this organelle and subsequently result in accumulation of unfolded proteins. This condition is known as ER stress, and the cellular response to this condition is called unfolded protein response (UPR), an adaptive physiological process in which cells activate protective mechanisms to restore homeostasis in the ER. Prolonged ER stress (e.g., when UPR is not sufficient to restore the balance) leads to cell death [117,118].

Some studies have suggested an involvement of UPR dysfunction in the pathophysiology of BD. For instance, a decreased response of XBP1 (a transcription factor that induces the expression of ER chaperones) and CHOP (a transcription factor that induces ER stress-induced apoptosis) was found in lymphoblastoid cells from patients exposed to two ER stress inducers [119]. Other findings have confirmed these results, reporting a reduction in stress-induced splicing of XBP1 and in the expression of GRP94 (another ER chaperone) in patients with BD [120]. Moreover, pharmacological evidence suggests that mood stabilizer valproate modulates ER stress response [121–123]. In a recent study, lymphocytes from patients with BD, in contrast to healthy controls, failed to induce UPR-related proteins and presented higher cell death levels in response to *in vitro*-induced ER stress, suggesting that this dysfunctional response to ER stress may reflect an increased cellular susceptibility [124].

Taken together, these findings suggest that patients with BD show a dysfunctional ER stress response, inappropriate and insufficient to maintain homeostasis. This impaired response to ER stress may be related to several neural function impairments reported for these patients, given that UPR components are also involved in neural development and plasticity, maturation and transport of several receptors and calcium signaling [125–127].

The ER is closely linked with mitochondria, both morphologically and functionally; Ca^{2+} exchange is possibly the main way of communication between both organelles [128]. ER-derived Ca^{2+} signals modulate mitochondrial bioenergetics. As a result, alterations in ER–mitochondria interactions, such as changes in cellular Ca^{2+} levels, influence the regulation of cellular metabolism and could cause mitochondrial dysfunction, metabolic imbalance and ultimately lead to cell death [129]. Of note, changes in intracellular calcium levels are a consistent finding in BD [130].

Harmful crosstalk between both organelles has also been shown to be involved in oxidative damage [131]. Taking into consideration the prolonged ER stress and mitochondrial dysfunction observed in BD, the disruption of ER–mitochondria interactions may

potentially be responsible for metabolic alterations and peripheral toxicity associated with the disorder. ER stress may also be related to neurotrophic pathways [132,133] that may contribute to maintaining oxidative damage and systemic inflammation in BD, as these processes are intimately interrelated [134,135].

Glial alterations

In 1858, Rudolf Virchow described glial cells as a connective tissue that binds nervous elements together [136]. As we know today, the role of these cells goes far beyond: glial cells are functional components of the nervous system. Sometimes called neuroglia, some of their functions include maintaining homeostasis (astrocytes), forming myelin (oligodendrocytes), and providing support and protection for neurons in the brain (microglia). Glial cells are capable of responding to changes in the cellular and extracellular environment, and, possibly through a glial network, have communication skills that complement those of the neurons [136]. Given the fact that these cells play an important role in the CNS, it is natural to think that they will also play an important role in the establishment and development of neurological disorders. Indeed, several studies have demonstrated alterations in glial cells in psychiatric disorders, including a decreased glial density in the amygdala of patients with major depression [137] and upregulation of extracellular matrix proteins in astrocytes of the amygdala and entorhinal cortex of schizophrenic patients [138]. More directly in BD, the results in the last 5 years are scarce.

Histological observations as well as imaging studies support findings of myelin abnormalities and glial alterations in BD [125]. Oligodendrocytes express transferrin, an iron mobilization protein that acts as a trophic and survival factor for neurons and astrocytes, pointing to another important function of oligodendrocytes in addition to myelination [139]. A postmortem study has shown that transferrin is underexpressed in the internal capsule of patients with BD; in contrast, two astrocyte-associated genes (*GFAP* and *ALDH1L1*) showed higher mean levels in all brain regions [140]. These results could indicate an impaired functioning of oligodendrocytes and some degree of astrocytosis (increase in astrocyte markers). Another study has reported that astroglial and microglial markers (glial fibrillary acidic protein, inducible nitric oxide synthase, c-fos and CD11b) were significantly upregulated in the postmortem frontal cortex of patients with BD, in particular the IL-1 receptor (IL-1R) cascade involved in microglial activation [141]. Microglia are the brain resident macrophages, which become activated in response to tissue damage or brain infections [142]. Moreover, the fact that neuregulin (*NRG*), a gene involved in oligodendrocyte development and myelination of the CNS, is located at one of the genetic loci for BD [143] is another indicator that glial alterations deserve further attention. In fact, it is possible that glial dysfunction in BD could result in abnormal neuronal–glial interactions, as already reported for mania [144].

We speculate that the abnormalities described above could be interrelated, affecting cellular resilience and function both in the periphery and in the brain of patients with BD. In line with previous hypotheses [8], there is likely a set of complex, interacting processes occurring in BD that could lead to cell endangerment and be related to the toxicity found in patients during acute episodes [15]. In order to better understand the mechanisms underlying toxicity in BD, further studies addressing the association between these processes and mood states are required.

Novel therapies for bipolar disorder

In light of the pathways known to be implicated in illness activity, novel therapies can be designed and proposed for a better management of BD. Thinking of the more immediate future, interesting alternatives may involve adjuvant therapies that act on the pathways mentioned in this review [14,15]. Some of these agents, with antioxidant, anti-inflammatory and neuroprotective effects, will be described in more detail below.

N-acetylcysteine (NAC), a precursor of GSH, has been shown, in both basic and clinical studies, to attenuate oxidative stress, modulate inflammation and act on neurogenesis and glutamatergic and dopaminergic pathways [59,99]. Supplementation of conventional treatment for BD with substances that act on oxidative stress has been investigated in clinical trials. NAC treatment adjunctive to usual medication for BD in the maintenance phase significantly improved depressive symptoms, quality of life and functioning in a double-blind, randomized, placebo-controlled trial with large effect sizes [99]. A secondary exploratory analysis revealed that adjunctive NAC showed promising effectiveness for participants with a syndromal diagnosis of bipolar depression [100]. More recently, a double-blind, randomized, placebo-controlled trial investigating the maintenance effects of NAC failed to find significant differences in recurrence or symptomatic outcomes during the maintenance phase [98]. Further randomized trials assessing adjunctive NAC for BD are required to more reliably determine the effect size of this treatment approach.

In addition to influencing the redox state, the neuroprotective properties of NAC may be associated with its ability to induce neurogenesis, which is likely related to mitochondria-protective mechanisms [145]; also, the modulating effects of NAC on inflammation [146] may be fundamental for its efficacy as a mood-stabilizing agent, considering the already described relevance of systemic inflammation in BD pathophysiology [15]. Therefore, even though very few studies have investigated the use of anti-inflammatory agents as an adjunct therapy for BD, inflammatory pathways seem to be another group of potential new therapeutic targets for the development of more effective treatments for BD. Conventional mood stabilizers have been described to have effects on both pro- and anti-inflammatory cytokines [78,147]. Among anti-inflammatory drugs, cyclooxygenase-2 (COX-2) inhibitor celecoxib was studied in a double-blind, randomized, placebo-controlled study as an adjunct in the treatment of patients with BD during depressive or mixed episodes. Treatment with celecoxib was associated with a more rapid improvement of depressive symptoms after 1 week compared with placebo, but the difference was statistically significant only for subjects who completed the full 6-week trial. This

finding suggests a potential antidepressant effect of COX inhibitors [58]. In this context, studies have demonstrated that mood stabilizers approved for the treatment of BD decrease expression of markers of the rodent brain arachidonic metabolic cascade, and reduce excitotoxicity and neuroinflammation-induced upregulation of these markers [148]. Recent papers demonstrating neuroinflammation, excitotoxicity [141] and upregulated arachidonic acid metabolism [149] in the postmortem brain of patients with BD support the hypothesis of altered arachidonic acid cascade in BD.

Another compound currently under investigation is minocycline, a tetracycline antibiotic that crosses the blood–brain barrier and has shown antioxidant, anti-inflammatory and neuroprotective effects [150]. Given that these pathways overlap with the pathophysiological mechanisms observed in BD, the use of minocycline has been pointed out as a potential adjunctive treatment. More specifically, minocycline inhibits microglia-mediated release of proinflammatory cytokines IL-1b, TNF-α, IL-6 and p38, and promotes the release of anti-inflammatory cytokine IL-10 [151]. It is also an effective scavenger of reactive oxygen species and protects against glutamate-induced excitotoxicity [152]. Case reports of individuals with psychiatric disorders have shown benefits of minocycline treatment for the severity of symptoms. Currently, a clinical trial is testing the efficacy of minocycline and/or aspirin in the treatment of bipolar depression and evaluating the anti-inflammatory effects of these compounds [153].

Supplementation with ω-3 polyunsaturated fatty acids (ω-3 PUFAs) has also been considered a potential new treatment for BD, as these fats have shown neuroprotective and antioxidant capacity in animal models [154]. A recent review of clinical trials using nutraceuticals in combination with standard treatment for BD has shown that ω-3 PUFAs improved bipolar depression symptoms [155]. The BDNF signaling pathway is one of the possible mechanisms of action by which ω-3 PUFAs mediate mood regulation in patients with BD [156]. Further double-blind, placebo-controlled, randomized clinical trials with long follow-up periods and adequate power-effect sizes are needed before we can gain a better understanding of this relationship and of the therapeutic role of ω-3 PUFAs in BD.

Neurotrophic factors are emerging as promising therapeutic targets in BD. Lithium, the classical mood stabilizer, has been shown to be effective in restoring peripheral BDNF levels in patients with BD [40,47]. In this sense, studies that attempt to prevent, treat and reverse molecular impairments are interesting therapeutic avenues for novel and improved therapies in BD [157]. In particular, delivery of neurotrophic factors from biomaterial scaffolds seems to be a promising area of research for the treatment of any disorder affecting the CNS. This drug delivery system allows to control the site and time of release of therapeutic agents, ensuring that biologically active agents, for example, neurotrophic factors, will be transported to the desired location to help treat a disorder [158]. In a recent review, the advantages and challenges associated with different drug delivery systems were evaluated, and the possibility to combine drug delivery systems with gene therapies was raised, suggesting that the drug delivery device could be adjusted to provide a controlled release of neurotrophic factors [159].

Regarding the mechanisms of action of the mood stabilizers traditionally used for the treatment of BD (lithium and valproic acid), hypothesis involving pathways discussed in this review are often highlighted. A recent work has reviewed preclinical findings showing that these drugs, in addition to other roles, regulate the transcription and expression of factors involved in neuroprotective, neurotrophic and anti-inflammatory effects. Moreover, oxidative stress pathways and cell survival signaling cascades may further underlie beneficial actions of these already established treatments [160].

In summary, the identification of specific therapeutic targets commonly modulated by these drugs may reveal new avenues for the effective use of add-on therapies, with the primary aim of treating acute mood episodes and preventing their recurrence.

Peripheral biomarkers & illness activity in bipolar disorder

As discussed above, an increasing body of evidence points to changes in neuroplasticity, oxidative stress and inflammation pathways in BD, mainly during mood episodes. However, these peripheral biomarkers have usually been investigated individually, contrary to the proposal that single biomarkers are unlikely sufficient to identify complex disorders. Rather, research should be geared towards sets of biomarkers, reflecting different processes implicated in a given condition [18,20].

To evaluate these biomarkers simultaneously, Kapczinski *et al.* conducted an *en bloc* assessment of a set of targets related to oxidative stress, neurotrophins and inflammation, all previously described as individual biomarkers of mood episodes in BD. The results demonstrated significant correlations among most biomarkers, which were then used to extract a systemic toxicity index. Patients in manic and depressive episodes showed higher systemic toxicity than euthymic patients and healthy controls, but lower systemic toxicity was seen when compared with patients with sepsis ('positive' control group for extreme peripheral illness; Figures 1 & 2) [14,15].

The findings above associating acute episodes with significant systemic toxicity in BD corroborate the idea that BD can be seen as a multisystemic illness of which peripheral pathophysiology is a major component [1]. However, these data alone are unable to explain how peripheral changes correlate with brain changes. The brain coordinates all physiological processes and is therefore sensitive to systemic damage [12]. Of note, central and peripheral pathophysiology could be connected in pro-oxidant states [161], possibly via changes in blood–brain barrier permeability. Peripheral toxicity has been shown to significantly alter brain oxidative stress [162]. Indeed, as mentioned above, there may be a link between inflammation, oxidative stress and neuroplasticity pathways in BD. For instance, inflammation has been demonstrated to cause oxidative stress through activation of calcium-dependent proteins and direct inhibition of the mitochondrial electron transport chain [163]. Changes in oxidative status, in

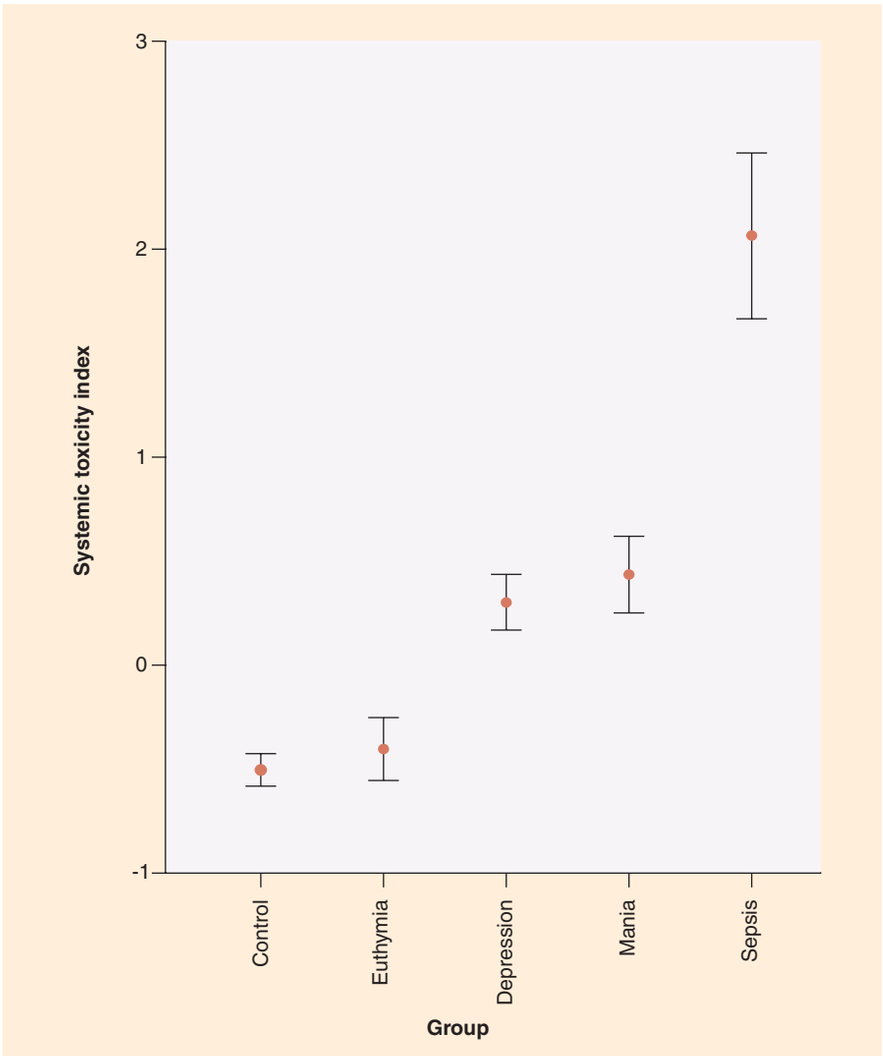

Figure 1. Systemic toxicity index to assess peripheral changes in mood episodes. To evaluate the peripheral toxicity associated with illness activity in patients with bipolar disorder, Kapczinski et al. conducted an en bloc assessment of a set of targets related to oxidative stress, neurotrophins and inflammation, all previously described as individual biomarkers of mood episodes. These peripheral biomarkers were measured in different acute mood states and in healthy subjects. Moreover, they also were evaluated in patients with sepsis ('positive' control group for extreme peripheral illness) with the aim of highlighting the relevance of potential changes between groups. More specifically, the biomarkers assessed were neurotrophins (brain-derived neurotrophic factor, neurotrophin-3), oxidative stress markers (protein carbonyl content, thiobarbituric acid reactive substances, and total reactive antioxidant potentials) and inflammatory markers (IL-6, IL-10 and TNF-α). The results demonstrated significant correlations among most biomarkers, which were then used to extract a systemic toxicity index. Patients in manic and depressive episodes showed higher systemic toxicity than euthymic patients and healthy controls; however, it was lower when compared with patients with sepsis. Figure reproduced with permission from [15].

turn, may be mechanistically associated with the reduced levels of BDNF observed in patients during acute mood episodes [164].

In summary, peripheral biomarkers have been consistently demonstrated to differentiate between patients with BD in manic or depression episodes and euthymic subjects. Whereas changes in one single biomarker usually have small effect sizes, the assessment of multiple biomarkers, especially primary mediators, could be a practical approach to improving diagnostic strategies and promoting earlier interventions [16,18].

Expert commentary

This review highlights the systemic toxicity related to acute mood episodes in BD and discusses possible mechanisms underlying these processes. Clinical and preclinical research gives overall support to the view of illness episodes as toxic to multiple elements in the body. Regarding the use of peripheral biomarkers as means for assessing illness activity, promising candidates at the moment can be subsumed in three main general areas: oxidative stress, inflammation and neurotrophins, in particular BDNF. These three groups do not yet meet the empirical characteristics of a traditional biomarker; however, they are relevant inasmuch as they provide information on the pathophysiology of BD and on illness activity. The assessment of systemic toxicity through a set of peripheral biomarkers may facilitate understanding of the body and brain damage associated with recurrent mood episodes and of the way it affects illness management.

Perhaps the most relevant upshot of having validated illness activity biomarkers would be the identification of biological features that indicate either the onset of an episode before specific symptoms occur or the lingering of illness activity despite an apparent response. Another potential application could be the detection of early response, before symptom resolution. Peripheral biomarker alterations in an acute mood episode could follow three different patterns, all of which would be powerful tools in guiding therapy (Figure 3).

Regarding new therapeutic strategies, preliminary evidence supports a role for novel adjunctive therapies in modulating neurotrophic, inflammatory, oxidative and apoptotic processes. Potential neuroprotective agents are currently available, but further clinical trial data are needed, as is information regarding which subgroups would benefit most from such interventions. Furthermore, in view of the high comorbidity rates observed in BD, there has been a push towards understanding the mechanisms underlying acute toxicity and illness activity. This perspective is the rationale behind an approach where the validation of

novel biological indicators will enhance the clinical strategies traditionally employed.

Five-year view

Well-documented studies evaluating potential peripheral biomarkers in BD have reported disturbances in inflammatory, neurotrophic, and oxidative stress markers in patients versus healthy individuals. However, pertinent questions remain about the translational applications of biomarkers in BD within the next years. It is expected that, in the future, translational approaches will be applied to the diagnosis and treatment of BD, using peripheral biomarkers to predict outcomes and identify high-risk individuals. This could guide the planning of more personalized clinical strategies and help monitor treatment interventions. In addition, a better understanding of illness activity mechanisms could advance the development of novel and more effective treatments. If changes in biomarkers can be reversed with treatment, we could ultimately consider that some pathological mechanisms are alterable, and thus allow interventions and secondary prevention (especially of the deleterious effects associated with multiple episodes).

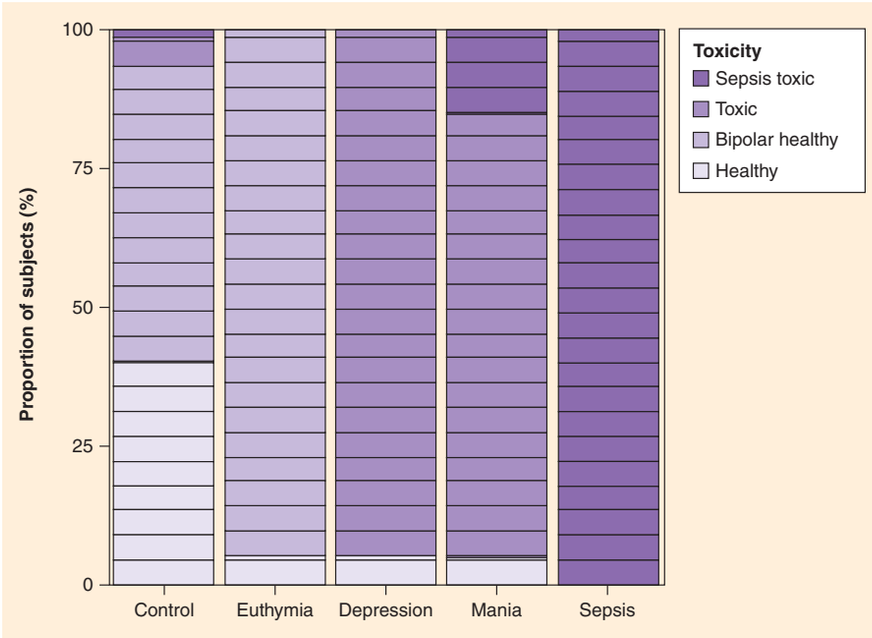

Figure 2. Peripheral biomarkers and illness activity in bipolar disorder. The graph shows the proportion of study subjects classified into four different categories: the category deemed most toxic, including all septic patients, was named 'sepsis toxic'. The less toxic category, which contained mostly healthy controls, was termed 'healthy'. The category that had serum biomarker levels in the toxic direction and included the patients in mood episodes was called 'toxic'. The last category was intermediary in terms of serum biomarkers and mostly contained euthymic patients, and was termed 'bipolar healthy'. Figure reproduced with permission from [14].

Future studies assessing biomarkers in large-scale, prospective cohorts (for an increased statistical power) and testing candidate biomarkers for sensitivity and specificity (to address overlaps with related disorders) will be quite valuable in determining the applicability of these biological markers in different rigorous scientific approaches [22]. In the past few years, much research has been undertaken to better understand individual biological markers related to the pathophysiology of BD; in the 5 years to come, an important direction will be measuring and comparing several biomarkers together, that is, not only the levels of each biomarker but also the correlations between them. Of note, several of these systemic toxicity mechanisms do not seem to be unique to BD, but may also be present in other psychiatric disorders presenting alterations related to illness activity (in cases of acute episodes followed by euthymia, such as in major depressive disorder or schizophrenia). However, the combination of peripheral alterations may differ between pathologies. For instance, neurotrophic alterations seem to go in an opposite direction in schizophrenia compared with BD [165]. In addition, inflammatory markers are different among different diagnosis and populations, which suggests peculiar means of activation of inflammation associated with specific disorders [166–168].

The common limitations of clinical studies will become an even more pressing issue in the investigation of more rigorous biomarkers for BD. For instance, until now, most research has been conducted with chronic patients treated for BD at tertiary care centers. Therefore, further studies, with other groups of patients with BD and other medical and psychiatric conditions, are required to increase the representativeness of the findings and to evaluate the effects of long-term medication use. In addition, studies conducted in community samples will be interesting to study individuals that are not usually seeking treatment at these healthcare facilities, thus avoiding a selection bias. Finally, among the clinical samples to be investigated, children, adolescents and young adults with BD are a group of great interest: evaluation of peripheral biomarkers in these individuals could contribute to a better understanding of primary illness changes [74] and some neurodevelopmental aspects, focusing on early interventions and, especially, on prevention attitudes.

Longitudinal studies will be able to confirm mood state-related findings and the hypothesis that these indices of peripheral abnormalities are related to course of illness, cognitive/functional impairment, and medical burden. Prospective studies assessing a set of measures, in turn, will be relevant to determine whether these peripheral biomarkers of illness activity may predict course of illness or medication response. In either way, the utility of these biomarkers will have to be validated via assessment of peripheral biological changes following specific therapies, for example, with anti-inflammatory or antioxidant agents [70,169], and treatment efficacy will have be evaluated based on mental health outcomes. If the biological changes suspected to occur during mood episodes are confirmed, novel

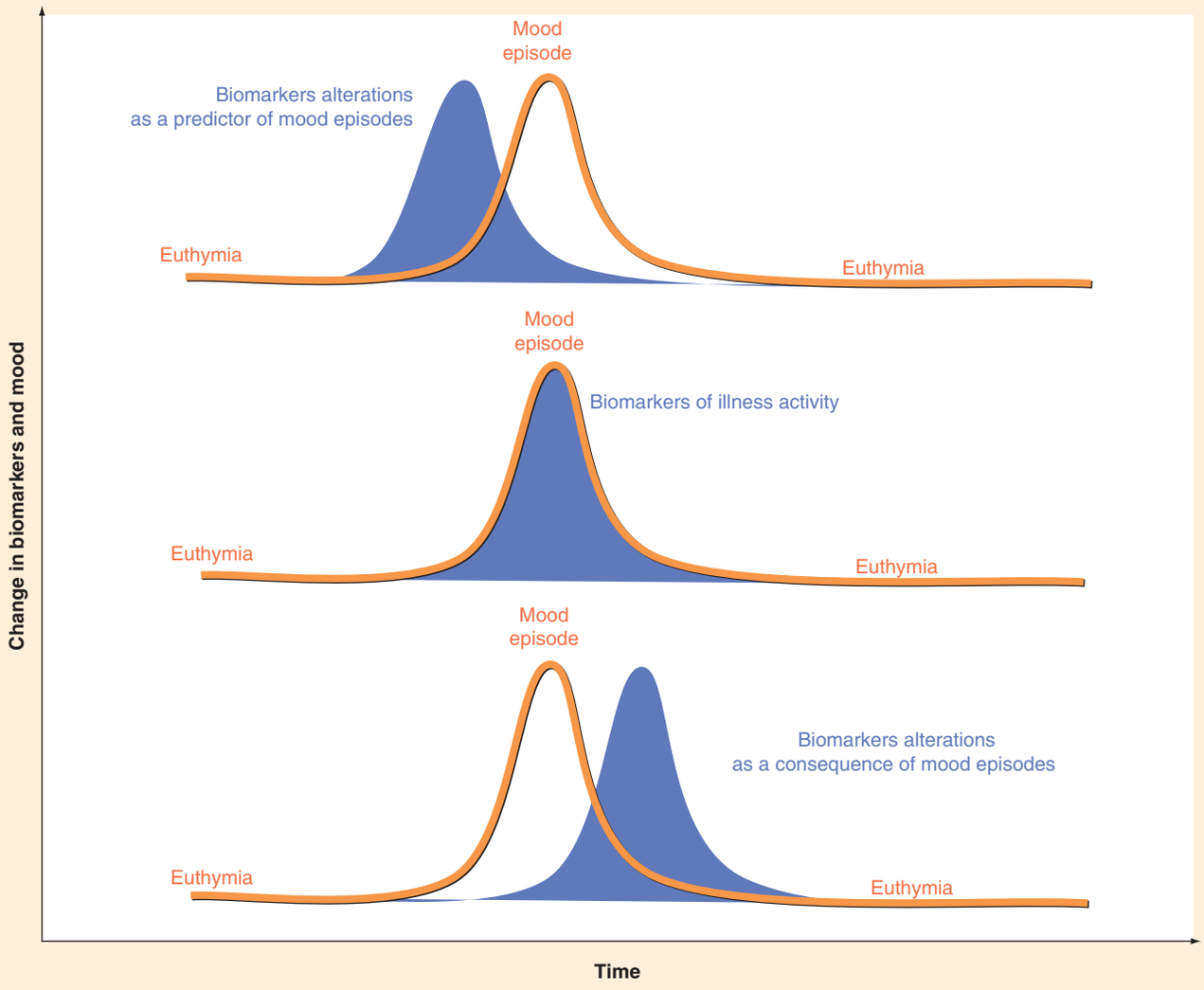

Figure 3. Peripheral biomarker alterations in an acute mood episode (mania or depression) could follow three different patterns. First, biomarkers could change before the beginning of a mood episode, showing a potential to predict these events. In this case, biomarkers would have a major therapeutic potential: they could help plan/implement early interventions and prevent/monitor treatment response. Second, biomarker changes could occur concomitantly with mood episodes, reflecting illness activity. In this case, they would be a useful tool in supporting clinical decisions for a better management of acute episodes. Finally, biomarkers could change after a mood episode, that is, because of it, which could contribute to improve our understanding of the pathophysiology of bipolar disorder. This assessment could be useful as a surrogate of pharmacological efficacy, predicting response to treatment of an acute episode after therapy initiation. The alteration patterns of biomarkers and their temporal relationship with mood episodes in bipolar disorder remain unknown.

treatment strategies should involve agents that act on pathways related with illness activity in BD. These findings could be useful not only to develop a more efficient, personalized approach to treat mood symptoms, but also to understand and perhaps revert biological changes associated with the illness, potentially bringing psychiatry into a new era of preventive psychopharmacology.

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Key issues

- The recurrence of acute mood episodes in bipolar disorder (BD) often translates into several worse outcomes; for example, higher rates of clinical comorbidities, functional and cognitive impairments and decreased responsiveness to treatment.
- There is a growing interest in understanding the pathophysiological mechanisms that contribute to dysfunction resulting from multiple mood episodes in BD, especially those pathways involved in neuroprotection, oxidative stress and inflammation.
- Among neurothophins, consistent evidence suggests a possible role of brain-derived neurotrophic factor in the pathophysiology of BD: brain-derived neurotrophic factor levels are reduced during manic and depression episodes, and treatment with mood stabilizers is able to increase its levels.
- Mood episodes in BD have been characterized as pro-inflammatory states based on findings reporting alterations in the levels of cytokines and their receptors and an aberrant inflammatory gene expression.
- Several studies have demonstrated systemic alterations in diverse oxidative stress parameters in patients during mania or depression; for example, increased lipid peroxidation and nitric oxide levels and alterations in antioxidant enzymes superoxide dismutase and catalase.
- Mechanisms leading to reduced resilience associated with acute episodes probably involve organelles typically responsible for maintaining cellular homeostasis, for example, the mitochondrion and endoplasmic reticulum (ER), and could affect cells from both the periphery and the CNS, such as neurons and glia.
- A growing body of evidence suggests a key role of mitochondrial dysfunction in BD, including impaired energy metabolism, alterations in respiratory chain complex enzymes, altered levels of cytoplasmic calcium and downregulation of mitochondria-related genes. Patients with BD also seem to show a dysfunctional ER stress response, failing to stimulate an appropriate or sufficient response to maintain homeostasis under stress situations.
- Glial dysfunction and activation of a proinflammatory process by the release of damage-associated molecular patterns, as well as disruption of ER–mitochondria interactions, may be responsible for metabolic alterations and peripheral toxicity in BD.
- In light of the pathways known to be implicated in illness activity, novel therapies can be proposed for a better management of acute mood episodes and to prevent their recurrence. These could include adjuvant therapies with antioxidant, anti-inflammatory and neuroprotective agents.
- The assessment of systemic toxicity through a set of peripheral biomarkers may facilitate understanding of the body and brain damage associated with recurrent mood episodes and of the way how it impacts illness management.

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3.2 CAPÍTULO 2

Inflammatory mediators of cognitive impairment in bipolar disorder

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Review

Inflammatory mediators of cognitive impairment in bipolar disorder

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ABSTRACT

Objectives: Recent studies have pointed to neuroinflammation, oxidative stress and neurotrophic factors as key mediators in the pathophysiology of mood disorders. Little is however known about the cascade of biological episodes underlying the cognitive deficits observed during the acute and euthymic phases of bipolar disorder (BD). The aim of this review is to assess the potential association between cognitive impairment and biomarkers of inflammation, oxidative stress and neurotrophic activity in BD.
Methods: Scopus (all databases), Pubmed and Ovid Medline were systematically searched with no language or year restrictions, up to November 2013, for human studies that collected both inflammatory markers and cognitive data in BD. Selected search terms were bipolar disorder, depression, mania, psychosis, inflammatory, cognitive and neurotrophic.
Results: Ten human studies satisfied the criteria for consideration. The findings showed that high levels of peripheral inflammatory-cytokine, oxidative stress and reduced brain derived neurotrophic factor (BDNF) levels were associated with poor cognitive performance. The BDNF *val66met* polymorphism is a potential vulnerability factor for cognitive impairment in BD.
Conclusions: Current data provide preliminary evidence of a link between the cognitive decline observed in BD and mechanisms of neuroinflammation and neuroprotection. The identification of BD specific inflammatory markers and polymorphisms in inflammatory response genes may be of assistance for therapeutic intervention.

1. Introduction

The mood symptoms of bipolar disorder (BD) are more often than not accompanied by verbal and working memory deficits (Bearden et al., 2006; Diwadkar et al., 2011), poor sustained attention (Glahn et al., 2007) and reduced executive functioning (Quraishi and Frangou, 2002; Najt et al., 2007; Ancin et al., 2010). Cognitive deficits persist during the euthymic phase of BD (Robinson et al., 2006; Malhi et al., 2007) which suggests that cognitive dysfunction may not be attributable to mood disturbance. In the last decade an increasing number of papers have emphasized the roles of inflammation, oxidative stress and related cellular degeneration in the pathophysiology of mood disorders (Miller et al., 2011; Carey et al., 2013; Turner, 2013). It is however still unclear whether these mechanisms are associated with the risk of developing cognitive impairment in patients diagnosed with BD.

BD is characterized by high peripheral levels of pro-inflammatory agents, such as interleukins (in particular IL-6, IL-2R, IL-1beta), tumour necrosis factor (TNF-α) and cellular TNF-α receptors (TNFR1) (Barbosa et al., 2011), and elevated pro-oxidative C-reactive protein (CRP) concentrations (Kapczinski et al., 2011; Kunz et al., 2011; Gimeno et al., 2009; Myint et al., 2009). This increase in the peripheral inflammation is likely to be associated with elevated neuroinflammation. Indeed cytokines penetrate the brain via leaky regions (e.g. choroid plexus) and are associated with the increased expression of pro-inflammatory eicosanoids (prostaglandin 2 – PGE_2), nitric oxide (NO) (Capuron and Dantzer, 2003), TNF-α, IL-1β, reactive oxygen species as well as monocytes and

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Glossary

ACC	Anterior cingulate cortex
AMPH	D-amphetamine
ATP	adenosine triphosphate
BBB	Brain blood barrier
BD	Bipolar disorder
CAT	Catalase
CANTAB	Cambridge Neuropsychological Test Automated Battery
CPT	Continuous performance test
CRF	Corticotropin-releasing factor
CRP	C-reactive protein
DNA	Deoxyribonucleic acid
ELR	excellent lithium responders
ERK	Extracellular signal-regulated kinase
FAB	Frontal Assessment Battery
FEP	First episode psychosis
FTT	Finger tapping test
GABA	Gamma-Aminobutyric acid
GPx	Glutathione peroxidase
GR	Glutathione reductase
GSH	Glutathione (GSH)
HC	Healthy control
HPA	Hypothalamic-pituitary-adrenal
IL	Interleukin
INF-α	Interferon-α
LPS	Lipopolysaccharide
MDA	Malondialdehyde
MDD	Major Depression Disorder
MINI	Mini International Neuropsychiatric Interview
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
Na + K + ATPase	Sodium–potassium adenosine triphosphatase pump
NFkB	Nuclear factor-kappa B
NGF	Nerve growth factor
NO	Nitric oxide
NMDA	N-methyl-D-aspartic acid
NOS	Reactive nitrogen species
NPSH	Non-protein thiols
NT-3/NT-4	Neurotrophin 3 or 4
O&NS	Oxidative and nitrosative stress
PANSS	Positive and negative syndrome scale
PET	Positron emission tomography
PG	Prostaglandins
PhSe2	Diphenyldiselenide
RAVLT	Rey's Auditory Verbal Leaning Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
ROS	Reactive oxygen species
sACC	Subgenual anterior cingulate cortex
SB	Sodium butyrate
fMRI	functional magnetic resonance imaging
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
sMRI	structural magnetic resonance imaging
SOD	Superoxide dismutase
SSRI	Selective serotonin reuptake inhibitors
TAS	Total anti-oxidant status
TBARS	Thiobarbituric acid reactive substances
TNF	Tumour necrosis factor
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test

macrophages in the brain (Capuron and Dantzer, 2003; Minagar and Alexander, 2005; Blank and Prinz, 2013) (Fig. 1). Alongside the increase in peripheral inflammation, BD has been associated with a decrease in brain-derived neurotrophic factor (BDNF) levels (Cunha et al., 2006; Bourne et al., 2013). Neurotrophins, such as BDNF, are a group of secreted proteins that are essential for neuron survival and synaptic functioning (Ichim et al., 2012; Huang and Reichardt, 2001; Buckley et al., 2007; Jiang et al., 2009).

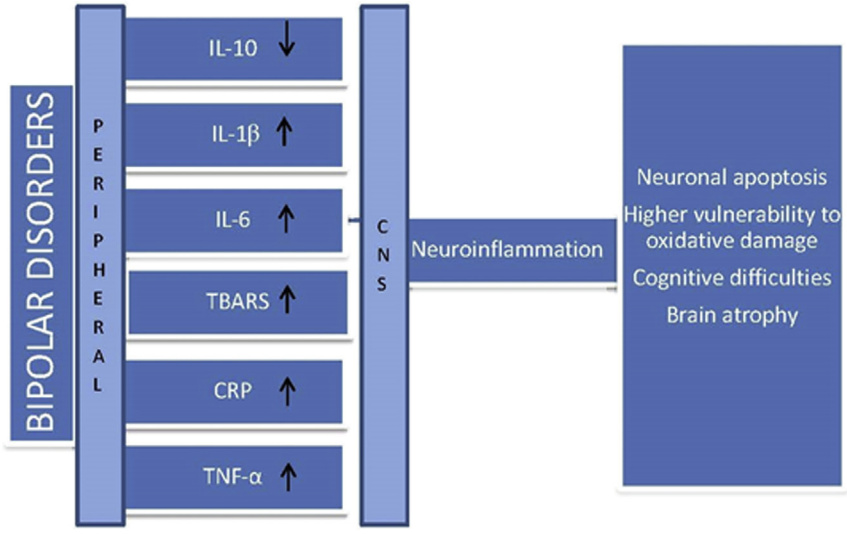

Fig. 1. Bipolar disorders are characterized by elevated levels of peripheral pro-inflammatory cytokines such as interleukins (IL-6, IL-2R, IL-1beta), tumour necrosis factor (TNF-α) and oxidative stress (Thiobarbituric acid reactive substances – TBARS and C-reactive protein – CRP). Pro-inflammatory agents enter the central nervous system (CNS) via the blood brain barrier, activate the brain inflammatory signal and release inflammatory agents, monocytes and macrophages in the brain. Exposure to pro-inflammatory substances and reactive oxidative substances is associated with neuronal damage and loss of brain function.

Clinical and preclinical evidence suggest that multiple mood episodes disrupt the homeostasis between inflammatory mechanisms, oxidative processes, and neuroprotective mechanisms, such as BDNF, and lead to neuronal death (apoptosis) (Fries et al., 2012; Berk et al., 2011). This cycle of events is defined as "neuroprogression" and has been linked to an increase in the individual's vulnerability to psychological stress, brain atrophy and ultimately cognitive impairment (Berk et al., 2010; Kapczinski et al., 2008). The concept of "staging" has been applied to the pathophysiology of BD to explain the progressive decline in mental health, psychosocial functioning and cognitive performance over the course of the disease (Gama et al., 2013; Frodl and Amico, 2013; Kapczinski et al., 2009).

Accordingly, neuroimaging studies show that individuals diagnosed with BD exhibit a significant loss of gray matter volume and white matter integrity, which is likely related to inflammatory processes such as apoptosis, cellular shrinkage, alterations in neurogenesis and reduced gliogenesis (Czéh and Lucassen, 2007). Recent neuroimaging studies have also identified a significant cortical atrophy and enlargement of the ventricles in individuals who experienced multiple mood episodes as compared to gender and age-matched healthy individuals (Pfaffenseller et al., 2012; Strakowski et al., 2012). Furthermore, an inverse relationship between gray matter volumes and length of illness has also been reported (Brambilla et al., 2001; Frey et al., 2008).

In summary, chronic inflammation may lead to structural brain abnormalities and cognitive deficits in individuals diagnosed with BD. However, to date, this hypothesis has not been systematically reviewed. Thus, the purpose of this review is to assess the potential association between cognitive impairment and biomarkers of inflammation, oxidative stress and neurotrophic activity in individuals diagnosed with BD.

2. Literature search

Scopus (all databases), Pubmed and Ovid Medline were systematically searched with no language or year restrictions, up to November 2013, for research articles addressing the relationship between bipolar disorder, inflammation and cognition. Selected search terms were 'bipolar disorder', 'depression', 'mania', 'psychosis', 'inflammatory', 'cognitive' and 'neurotrophic' as occurring either anywhere in the article (for Pubmed and Ovid Medline) or in the case of PUBMED, in the title, abstract or keywords only. The search engines listed above were chosen because of their well-established accuracy and exhaustive search across multidisciplinary fields such as psychology, nutrition, biochemistry and medicine (Moher et al., 2009). Inclusion was restricted to studies with clinical populations with a diagnosis of BD, studies were cognitive functioning was assessed using pen and paper or computerized cognitive batteries, and where inflammatory markers or polymorphisms of inflammatory genes using blood or other tissues were quantified. Excluded studies included those using animal models, clinical populations with neurological and cardiovascular diseases, children, adolescents, pregnant or lactating mothers. Exclusion criteria was defined by the following considerations. Cognition is affected by a range of neurochemical mechanisms and cardiovascular parameters. During pregnancy and lactation, a number of physiological changes take place and this physiological state could affect cognitive performance. Finally, since the nervous system of children, and adolescents is still developing, the relationship between inflammation and cognition in children cannot be equated to that observed in a mature central nervous system. All data were extracted by a single, non-blinded, reviewer (IB) to determine if studies met inclusion criteria and, in cases where this information was not provided in abstracts, full texts were obtained. All papers identified were published in English. No papers were identified prior to 2003. Duplicates, review articles and articles not fulfilling the search criteria were removed (Fig. 2).

3. Quality evaluation

Since there is no official instrument for the evaluation of observational studies in psychiatry and inflammation we conducted a quality evaluation based on the Centre for Reviews and Dissemination (CRD) Hierarchy of evidence (Cochrane, 2003) and a revised version of Ibrahim and colleague's quality evaluation scale (Ibrahim et al., 2012). The CRD Hierarchy of evidence ranks study designs in descending order of strength: 1. Experimental studies, 2. Quasi experimental studies, 3. Controlled observational studies, 3a. Cohort studies, 3b. Case control studies, 4. Observational studies without control groups, 5. Expert opinion based on theory, laboratory research or consensus. The quality evaluation scale was composed of 6 items: 1) The clinical sample was representative of the target population, 2) The control group was appropriately matched (e.g. by age, gender) to the clinical sample 3) The authors conducted sample size calculations and/or power analyses 4) The study used well-established measures of inflammation 5) The study used well-established measures of cognitive functioning 6) The authors reported confidence intervals and/or effect sizes of their findings. Each item was scored one point if the criterion was satisfied. The overall quality score was calculated by adding the scores of all items.

4. Study characteristics

We identified ten published clinical studies exploring the association between peripheral pro-inflammatory cytokines, oxidative markers, neurotrophins and cognitive performance in individuals diagnosed with BD. Two studies collected peripheral measures of oxidative stress (CRP, RBANS) and peripheral pro-inflammatory cytokine measurements (IL-18, TNF). Eight studies examined the relationship between BDNF levels or polymorphism and cognitive functioning (see Table 1). All studies were observational in nature and did not involve any anti-inflammatory and/or antioxidant treatments. Cognitive performance in all studies comprised of traditional pen-and-paper tests and computerized cognitive batteries. Table 1 summarizes the study characteristics.

5. Results of identified studies

5.1. Pro-inflammatory cytokines, markers of oxidative stress and cognitive functioning

Peripheral serum CRP expression was negatively correlated with performance scores of immediate memory, language, and attention, on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in a study involving 107 individuals diagnosed with BD. The authors interpreted these results as indicating that oxidative damage negatively affects cognitive functioning in BD patients. However, as this study did not include a control population it is unknown whether the relationship between CRP expression and cognitive performance is specific to individuals diagnosed with BD, or whether it may also be observed in healthy controls (Dickerson et al., 2013).

Peripheral serum expression of the pro-inflammatory cytokine, TNF-α, was found to be negatively correlated with accuracy on the delayed memory component on the Rey Auditory Verbal Learning Test (RAVLT), in a study consisting of 54 medicated individuals diagnosed with euthymic (absence of a depressive or manic cycle) BD type I. Furthermore, the expression of two soluble TNF receptors

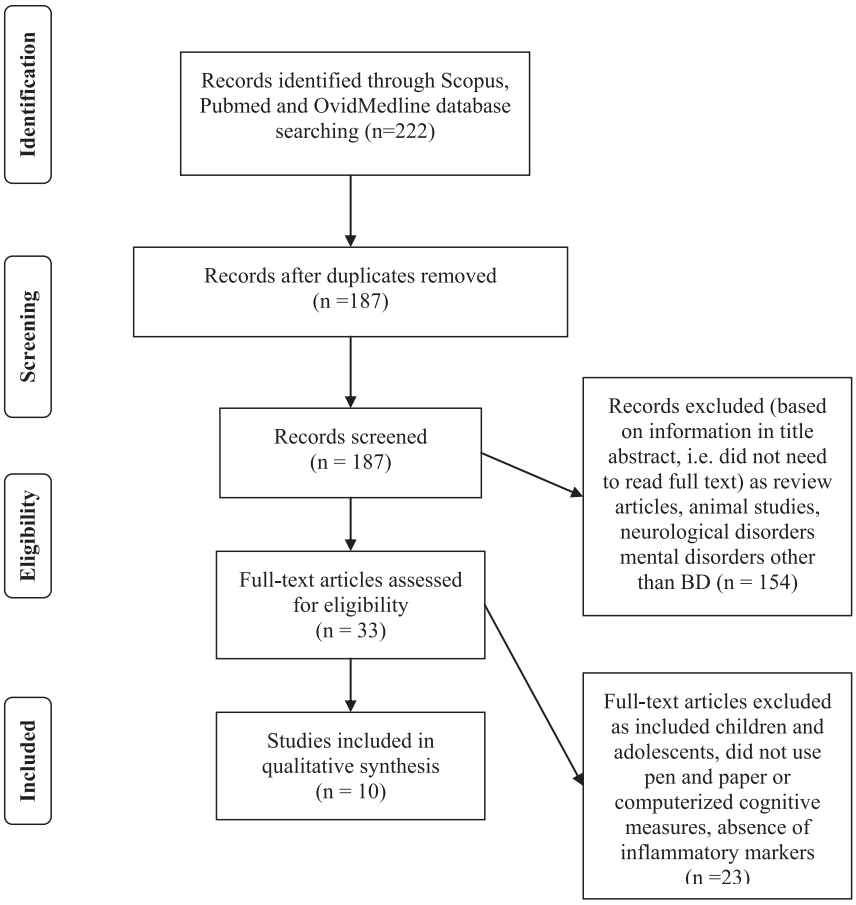

Fig. 2. PRISMA flowchart (Moher et al., 2009) showing the filtering process used to select the 10 studies included in the systematic review of studies investigating inflammatory markers and cognition in bipolar disorder.

(sTNFr1 and sTNFr2) was higher in euthymic BD individuals as compared to healthy controls (Doganavsargil-Baysal et al., 2013). It is noteworthy that BD patients and healthy individuals did not differ in terms of TNF-α levels. The authors concluded that this result may have been related to the fast degradation of TNF-α in peripheral tissues (Doganavsargil-Baysal et al., 2013). Further, the elevated production of sTNF receptors may explain why cognitive deficits persist during the euthymic phase of BD (Pattanayak et al., 2012; King et al., 1996). Given that previous research shows that the production of sTNF receptors is catalyzed by TNF-α (Grassi-Oliveira et al., 2009), it is however unclear why the levels of sTNF receptors did not correlate with cognitive performance in Doganavsargil-Baysal et al.'s study (Doganavsargil-Baysal et al., 2013).

At present, research regarding the relationship between inflammatory response and cognitive performance in BD is extremely limited. The above studies however provide preliminary evidence of the negative effects of pro-inflammatory and oxidative processes on high-order cognitive abilities such as memory, attention and executive functioning.

5.2. Neurotrophins and cognitive functioning

In one study, middle-aged euthymic BD patients were found to have higher peripheral BDNF expression than gender-matched healthy individuals. However, there was no significant correlation between BDNF expression and the Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) scores (Barbosa et al., 2012). This negative finding may be due to the type of tests used to measure cognitive functioning. Indeed the MMSE and the FAB provide a short and generic assessment of age-related cognitive decline (e.g. in Alzheimer's and fronto-temporal dementia) but are not sufficiently sensitive to detect mood-related cognitive changes (Gluhm et al., 2013; Boban et al., 2012). Furthermore, since the participants of this study were relatively young ($M \pm SD$: 50.88 ± 9.11 years), they likely exhibited a high level of accuracy on these tests.

Dias et al. (2009) found that serum BDNF levels positively correlated with accuracy on a verbal fluency task in individuals diagnosed with BD. It is important to emphasize that, contrary to the findings of Barbosa et al., Dias et al. found no difference in BDNF expression between euthymic BD and healthy individuals, in peripheral blood samples (Dias et al., 2009). Participants in this study were medicated, which may have influenced BDNF expression and confounded results. In particular, valproate-treated participants had higher BDNF levels, and lithium-treated participants lower BDNF levels, when compared with non-medicated healthy volunteers (Dias et al., 2009). Additionally, this study involved individuals with euthymic BD. While previous research shows that BDNF expression can fluctuate during manic and depressive episodes (Cunha et al., 2006; Goldstein et al., 2011), previous research demonstrated that, during the euthymic phase of BD, BDNF expression is comparable to that of healthy volunteers (Fernandes et al., 2011).

Consistent with Dias et al.'s study (2009), Chou et al. did not find any difference in plasma BDNF expression between euthymic BD and healthy controls. Furthermore, in the clinical sample there was

Table 1
Summary of studies that explored changes in inflammatory and oxidative stress biomarkers, and cognitive measures in individuals with bipolar disorder; BD = Bipolar disorder, HC = Healthy control.

Citation	Subject description (diagnosis, gender (M/F)	Age (Years)	Design	Duration of illness (years)	Antipsychotic/ mood stabilizer medication (Yes or No)	Cognitive measures	Inflammatory biomarker	Statistics	Outcome +Evidence of a link between inflammation and cognition −no evidence of a link between inflammation and cognition
Oxidative stress and cytokines									
Dickerson et al. (2013) *Journal of Affective Disorders*	107 BD (31/76)	36.3 ± 13.4	Observational study	≈20 years	Yes	Repeatable Battery for the Assessment of Neuropsychological status (RBANS) Wechsler Adult Intelligence Scale (WAIS III), Trail Making Test	Serum CRP	Logistic regression	+Lower RBANS scores in the High CRP group compared to the Low CRP group
Doganavsargil-Baysal et al. (2013) *Human Psychopharmacology*	54 euthymic BDI (18/36) 18 HC (5/13)	BD: 39.46 ± 11.62 HC: 38.33 ± 10.80	Observational study	≈13 years	Yes	Wisconsin Card Sorting Test (WCST), Rey's Auditory Verbal Leaning Test (RAVLT)	Serum TNF	Spearman's correlation, *t*-test	+BD have higher levels of sTNFr1 and sTNFr2 than HC +BD exhibit lower cognitive performance on WCST and RAVLT than HC +sTNFr2 levels correlate positively with illness duration
Neurotrophin									
Aas et al. (2013) *Progress in Neuro-psychopharmacology*	249 BD (122/127) and 476 HC	BD: 20–40 HC: 34.79 ± 10.25	Observational study	Not provided	Yes	California Verbal Learning test, letter number sequencing, digit span forwards/backwards, Color Word Interference test, verbal fluency, block design, matrix reasoning, vocabulary	BDNF gene (not specified whether serum or plasma)	Regression model	+*val/met* BDNF gene carriers are more vulnerable to childhood trauma sequels, have smaller hippocampal volumes and larger ventricles
Barbosa et al. (2012) *Journal of Affective Disorders*	25 euthymic BD (8/17) vs 25 HC (11/14)	BD: 50.88 ± 9.11 HC: 48.04 ± 7.08	Observational study	27.88 ± 11.8	Yes	Mini-Mental State Examination and Frontal Assessment Battery	Plasma BDNF	Mann–Whitney *U* test, Spearman's correlation	+Higher BDNF in the BD than HC −No correlation between BDNF and executive functioning
Chou et al. (2012) *Journal of affective disorders*	23 BD (6/17) and 33 HC (12/21)	HC: 37.6 ± 7.8 BD: 36.5 ± 8.9	Observational study	5.7 ± 4.68	Yes	Go/No-Go task of the test for attentional performance, Memory (Wechsler Memory scale – III), Word list, Face test, Color trail test, Wisconsin card sorting test	Plasma BDNF	*t*-test, ANCOVA, correlation	−no difference in BDNF levels between BD and HC +reduced face recognition and accuracy on the WCST in BD compared to HC
Dias et al. (2009) *Bipolar disorders*	65 euthymic BD (24/41), 50 HC	BD: 37.8 ± 10.51 HC: 33.6 ± 9.66	Observational study	13.3 ± 8.78	Yes	Wechsler Memory Scale, Wechsler Intelligence Scale for adults revised	Serum BDNF	*t*-test, ANOVA,	−No difference in BDNF levels between BD and HC +Positive correlation between BDNF levels and verbal fluency in BD and HC
Rybarkowski et al. (2003) *Bipolar disorder*	54 BD I (18/36)	BD: 18–72 (mean 46 years)	Observational study	16 ± 12	Yes	Wisconsin Card Sorting Test	Whole blood BDNF gene	*t*-test	+the *val/val* BDNF polymorphism exhibits better cognitive functioning than the *val/met* genotype +the *val* allele was associated with an earlier onset of illness

Rybarkowski et al. (2006) *Psychiatry and Clinical Neurosciences*	111 BD (37/74) 160 HC (gender ratio N/A)	BD: 43.4 ± 13.7 HC: 32.9 ± 11.5	Observational study	N/A	Wisconsin Card Sorting Test, N-back test	Whole blood BDNF gene	*t*-test, ANOVA	+The percentage of correct reactions to the N-back test and accuracy on WCST was higher in the *val/val* group compared with *val/met* and *met/met*
Rybakowski and Suwalska (2010) *International Journal of Neuropsychopharmacology*	60 BD (25/35) 60 HC (25/35)	BD: 52.6 ± 10.2 HC: 52.1 ± 13.6	Observational study	22.2 ± 10.8	Yes	CANTAB	Plasma BDNF level	Mann–Whitney/ Kruskal–Wallis ANOVA	+BD have lower BD have poorer cognitive performance and lower BDNF plasma levels than HC +No difference in plasma BDNF levels between ELR and HC
Tramontina et al. (2009) *Revista Brasileira de Psiquiatria*	64 BD I (14/50)	BD I: 42.3 ± 11.1	Observational study	N/A	Yes	Wisconsin Card Sorting Test	BDNF gene (not specified whether serum or plasma)	Mann–Whitney's *U* analysis, ANCOVA	−The percentage of non-perseverative errors was higher in the *val/val* group −No association between *met* allele and cognitive functioning

no significant correlation between BDNF expression and cognitive performance (Chou et al., 2012). Since the mean illness duration was shorter (6 years) than that in Dias et al.'s study (13 years) it could be hypothesized that illness duration counteracts the beneficial effects of BDNF on cognitive performance. In another study poor lithium responders were found to have lower BDNF levels compared to healthy controls. By contrast, excellent lithium responders (ELR) exhibited BDNF levels comparable to those of healthy controls, and performed better than non-ELR on all tasks of the Cambridge Neuropsychological Test Automated Battery (CANTAB), in particular the spatial working memory task (Rybakowski and Suwalska, 2010). Thus, it could be hypothesized that high BDNF levels counteract the cognitive decline observed in BD.

Previous research has focused on the relationship between the genotype of BDNF and cognitive functioning. In particular, studies have associated the BDNF *val66met* polymorphism with BD symptomatology. In this BDNF gene variation the *valine (val)* allele is replaced by the methionine *(met)* allele at codon 66 (Craddock et al., 2005). In the present review, we identified one study showing that *met* carriers diagnosed with BD have smaller hippocampi volumes and larger ventricles than *val/val* carriers. Moreover, *met* carriers were seen to encounter more difficulties in verbal fluency and working memory tasks than the *val/val* group (Aas et al., 2013).

Additionally, Rybakowski et al. found that individuals with a BDNF *val66met* polymorphism developed BD type 1 approximately 11 years earlier than *val/val* carriers and performed more poorly on a test of executive functioning (Wisconsin Card Sorting Test – WCST) (Rybakowski et al., 2003). A few years later Rybakowski et al. found that the *val/val* genotype was associated with higher accuracy on the N-back and WCST tests when compared with *val/met* and *met/met* genotypes (Rybakowski et al., 2006).

By contrast, another identified study, by Tramontina et al. found that *val/val* carriers diagnosed with BD type I made more perseverative errors than *val/met* and *met/met* participants. Thus the *met* allele was not seen to be associated with cognitive impairment in this study (Tramontina et al., 2009), possibly due to the heterogeneous ancestry of Tramontina et al.'s participants (European, Amerindian and African) as compared to the more homogenous European ancestry of participants involved in Rybakowski's study. Alternatively, other factors such as the age of onset of the disease and the severity of BD may have blunted the differences between *met* and *val* carriers, however the influence of these variables were not explored.

Overall, current findings provide initial evidence of an association between decreased BDNF levels and a high risk of cognitive decline in BD. Furthermore, the BDNF *val66met* polymorphism appears to be a potential risk factor for cognitive impairment in BD.

6. Quality evaluation: findings

The quality and reliability of the 10 studies included in this review are shown in Table 2. The CDR hierarchy of evidence was estimated to be 3–4, as the current studies are not randomized cross-sectional studies with and without a control group. Given the observational nature of the studies, the current findings provide little information on trends over time and do not investigate possible causality link between inflammation and cognitive impairment in bipolar disorder. Further, investigators were not blinded to the case/control status of their participants. This raises the possibility that the knowledge of the diagnosis may have affected their testing style and cognitive evaluation. The clinical populations were recruited in hospital settings and their diagnosis was based on well-established clinical scales such as the SCID (First

Table 2
Quality assessment of the 10 studies included in the review. The Overall Quality Score was calculated by adding scores of items 1 to 6; CRD levels are: 1. Experimental studies, 2. Quasi-experimental studies, 3. Controlled observational studies, 3a. Cohort studies, 3b. Case control studies, 4. Observational studies without control groups, 5. Expert opinion based on theory, laboratory research or consensus; BD = Bipolar disorder, HC = healthy control.

Citation	Overall quality score (1–6)	CRD Hierarchy of evidence (levels 1–5)	Sample size $N < 30$ small $N = 30–50$ medium $N > 50$ large	Item 1 Representative sample	Item 2 Matched control groups	Item 3 Power analysis/Sample size calculation	Item 4 Adequate assessment of inflammation	Item 5 Adequate measure of cognition	Item 6 Confidence intervals (CI) or effect size (ES)
Criterion is fulfilled = 1 Criterion is not fulfilled = 0									
Dickerson et al. (2013)	4	4	Large, 107 BD	1, patients were recruited in a psychiatric health care program, diagnosis was based on SCID	0, No HC	0	1	1	1, CI, no ES
Doganavsargil-Baysal et al. (2013)	6	3	Small/Medium 54 BDI 18 HC	1, patients were recruited in an outpatient psychiatric clinic, diagnosis was based on DSM-IV TR	1, HC matched by age, gender, educational level	1	1	1	0, No CI, Estimated ES = 1
Aas et al. (2013)	3	3	Large 249 BD 476 HC	1: Patients recruited in hospitals, diagnosis based on DSM-IV criteria.	0, HC not demographically matched	0	1	1	0, No CI/ES
Barbosa et al. (2012)	4	3	Small, 25 BD 25 HC	1, patients recruited in an out/inpatient psychiatric clinic, diagnosis based on Mini International Psychiatric inventory	1, HC matched by age and gender	0	1	1	0, No CI/ES
Chou et al. (2012)	4	3	Small 23 BD 33 HC	1: patients were diagnosed based on DSM-IV criteria.	1, age-matched HC	0	1	1	0, No CI/ES
Dias et al. (2009)	3	3	Medium 65 BD 50 HC	1, patients diagnosed based on DSM-IV criteria and Mini International Psychiatric inventory	0, HC not demographically matched	0	1	1	0, No CI/ES
Rybakowski et al. (2003)	3	4	Medium 54 BD I	1: Outpatients recruited in hospitals, diagnosis based on DSM-IV criteria.	0, No HC	0	1	1	0, No CI/ES
Rybakowski et al. (2006)	3	3	Large 111 BD 160 HC	1: inpatients recruited in hospitals, diagnosis based on DSM-IV criteria.	0, Not matched	0	1	1	0, No CI/ES
Rybakowski and Suwalska (2010)	4	3	Large 60 BD 60 HC	1: Patients attending an outpatient lithium clinic, diagnosis based on DSM-IV criteria -SCID	1, age and gender-matched HC	0	1	1	0, No CI/ES
Tramontina et al. (2009)	4	4	Medium 64 BD I	1: outpatients recruited in a hospital setting, diagnosis based on DSM-IV criteria.	0, No HC	1	1	1	0, No CI/ES

et al., 2012) and the Mini International Neuropsychiatric inventory (Sheehan et al., 1997) which indicates that the clinical profile of the samples is a reliable representation of the bipolar illness. All studies used well-accepted techniques to estimate inflammatory markers (e.g. ELISA assays) and widely used measures of cognitive functioning (e.g. Repeatable Battery for the Assessment of Neuropsychological Status). It could therefore be concluded that the current results provide an accurate description of the cognitive functioning and inflammatory response in BD patients. While the average sample size was satisfactory as it ranged from medium to large ($N \geq 30$), only two studies reported estimating the sample size based on power analyses. As a result, some of the studies may be underpowered and report misleading findings. In addition, the lack of information on the effect sizes and the confidence intervals of the statistical analyses limit the evaluation of the size of the experimental effects of the findings. Other methodological flaws include the absence of a control population in three studies and inadequate matching of the control population to the clinical population in six studies. Moreover, given the current trend for overrepresentation of positive studies in medicine and hard sciences (Turner, 2013), it is possible that a number of unpublished studies did not find any link between inflammation and cognition in bipolar disorder.

7. Discussion

This review aimed to examine the literature exploring the relationship between the cognitive deficits seen among individuals diagnosed with bipolar disorder, and markers of inflammation, neurotrophins and oxidative damage. Thus, we conducted a systematic search of the human literature on inflammation and cognition in BD. It is important to emphasize that this is a novel approach as previous reviews have linked inflammation with mood symptoms, but have not explored the relationship between peripheral markers of inflammation and cognitive impairment.

We identified 10 observational studies. Of these studies 2 investigated the relationship between pro-inflammatory cytokines (TNF-a) and markers of oxidative stress (CRP) and 8 investigated the relationship between the neurotrophin BDNF, and cognitive functioning. The results of these studies indicate that the cognitive deficits observed in individuals diagnosed with BD appear to be associated with an increased inflammatory state and a decrease in the neurotrophic factor, BDNF. Despite the limited number of studies in this field and their heterogeneity in terms of cognitive outcome measures, these studies provide preliminary evidence that an elevated inflammatory state negatively affects frontotemporal cognitive abilities such as memory, attention and executive functions, and indicate a need for further investigation.

Consistent with previous research (Berk et al., 2010), we identified one study showing that individuals diagnosed with BD have reduced hippocampi volumes and larger ventricles. Importantly, this was associated with more difficulties in verbal fluency and working memory tasks (Aas et al., 2013). Previous authors have speculated that systemic toxicity and cognitive dysfunction are directly related to the number of episodes suffered by the patient (Kapczinski et al., 2009) and that peripheral cytokine and BDNF expression could be potential markers of illness progression, thus corroborating the "staging" hypothesis of BD (Kauer-Sant'Anna et al., 2009). However, as all the studies identified in the present systematic review were observational in nature, there appears to be no research regarding the relationship between inflammatory markers and changes in cognitive measures over the course of the BD. A longitudinal design study could be a suitable approach to explore the relationship between peripheral biomarkers of inflammation, oxidative stress and neurotrophic activity. This type of design may also help clarify the relationship between biomarkers and cognitive impairment at different phases of the disease.

None of the reviewed studies investigate the relationship between oxidative stress, mitochondrial dysfunction and neuroprogression. However, a number of studies using animal models of mania have observed increased levels of reactive oxygen species (ROS), a marker of mitochondrial dysfunction (Murphy, 2013). One study demonstrated increased lipid peroxidation, and a high number of free radical, superoxide in submitochondrial particles of the prefrontal cortex and hippocampus (Diwadkar et al., 2011). A second study showed that repeated amphetamine exposure, which induces manic symptomatology in animal models, increases levels of anti-oxidant enzymes, superoxide dismutase (SOD) and catalase (CAT), in regional specific manner, in the prefrontal cortex, hippocampus and striatum (Glahn et al., 2007). The authors interpreted these results to reflect an imbalance between SOD and CAT expression, potentially indicative of a predisposition to the generation of ROS (Frey et al., 2006a, 2006b). Increased oxidative stress has been associated with abnormalities in the glutamatergic system and neuronal apoptosis. Neuronal apoptosis has been hypothesized to be a progressive process that begins at synaptic terminals and dendrites and continues to the cell body via apoptotic cascades (Mattson, 2000; Mattson et al., 1998). The dynamic of neuronal cell death mechanisms may underlie the decline in neurocognitive function observed over the course of the bipolar illness. Additionally, clinical research indicates that BD is characterized by low levels of brain energy metabolites such as creatine and high lactate and glutamate-related metabolite concentrations, which are clinical markers of mitochondrial dysfunction (Haas et al., 2007), as assessed using magnetic resonance spectroscopy (MRS) (Strakowski, 2012). Lactate accumulation may indicate a shift to anaerobic glycolytic mechanisms, possibly due to inadequate energy production within the mitochondria (Strakowski, 2012; Gigante et al., 2012). Anaerobic glycolysis produces less adenosine triphosphate (ATP) molecules than aerobic glycolysis, and reduced ATP production could lead to cerebral hypometabolism, brain dysfunction and eventually cognitive impairment (Minuzzi et al., 2011).

A further limitation of the studies reviewed here is that they differ with respect to the estimation of the peripheral levels of inflammatory biomarkers. Indeed, as illustrated in Table 1, the majority of the studies measured the expression of cytokines, BDNF and antioxidants in serum, plasma, or whole blood cells (a combination of serum, plasma and erythrocytes). For instance, since plasma cells have a short turnover (Slifka et al., 1998), they may be ideal to measure acute inflammation (e.g. infection), but may not reflect a state of chronic inflammation. Erythrocytes and whole blood cells (which have a turnover of approximately 12 weeks) (Katan et al., 1997) may therefore be better indices of inflammatory markers in cell membranes and possibly the brain tissue. Further, previous studies have shown that aminoacids and carbohydrate levels differ significantly between plasma and serum (Malhi et al., 2007; Pace et al., 2007). In particular, BDNF levels are higher in serum compared to plasma (Ibrahim et al., 2012; Pace et al., 2007; Watson et al., 2012). The latter result is probably due to the release of BDNF from platelets to serum during the coagulation process (Ibrahim et al., 2012). Hence, finding of studies using serum BDNF levels may not be comparable to those of studies using plasma BDNF levels. Quality evaluation of the current studies reveals some methodological concerns in terms of research design and statistical analyses, as earlier discussed. Hence, caution should be taken in the interpretation of the data presented in this systematic review, regarding the relationship between inflammation and cognition in bipolar disorder.

Surprisingly, none of the studies identified investigated the relationship between the inflammatory response and the hypothalamic-pituitary-adrenal (HPA) axis activation. Indeed a number of mood disorders present with abnormalities in the HPA axis, such as increased levels of cortisol and corticotropin-releasing factor (CRF) (DeBattista and Belanoff, 2006). A potential explanation for the abnormal HPA axis activity is that pro-inflammatory cytokines disrupt the glucocorticoid function and lead to glucocorticoid resistance, characterized by cortisol and CRF hypersecretion. In turn, glucocorticoid resistance initiates pro-inflammatory mechanisms and reduces peripheral BDNF levels (Pace et al., 2007; Mackin et al., 2007). Both glucocorticoid resistance and inflammation have been associated with depressed mood and cognitive difficulties (Pace et al., 2007). It is notable that in medicated BD patients the glucocorticoid receptor antagonist, mifepristone improves mood and spatial working memory, and to a lesser extent, verbal fluency and spatial recognition (Watson et al., 2012; Young et al., 2004). In particular, the improvement in spatial memory appears to be related to the cortisol response to mifiprestone, not mood changes (Watson et al., 2012). It could be speculated that mifiprestone inhibits the proinflammatory response by regulating the HPA-axis activity, however this remains unknown as these studies did not collect inflammatory markers. Taken together these findings provide a strong rationale for the development of trials investigating the synergistic role of the inflammatory response and the HPA-axis function in the pathophysiology of BD.

In conclusion, research in the field of cognition and inflammation in BD is still in its infancy and additional work is needed to understand how pro-inflammatory processes affect brain function and induce cognitive impairment. The identification of inflammatory markers and polymorphisms in inflammatory response genes underlying cognitive decline will have important implications for the development of new therapies targeting chronic inflammatory conditions such as BD.

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Contributors

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Conflict of interest

Dr Bauer, Dr Pascoe and Dr Wollenhaupt-Aguiar have no conflicts of interest.

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3.3 CAPÍTULO 3

Caracterização gênica do modelo de diferenciação da linhagem de neuroblastoma humano SH-SY5Y com ácido retinóico

Introdução

A linhagem celular de neuroblastoma humano SH-SY5Y tem sido muito utilizada no estudo de vias moleculares e bioquímicas envolvidas na fisiopatologia de várias doenças, dentre elas: Niemann-Pick**,** Parkinson e Alzheimer (Chatterjee et al., 2015; Xie et al., 2015; Ferrante et al., 2016). No entanto, essas células possuem características proliferativas e se apresentam em um estágio precoce de diferenciação, caracterizado pela baixa expressão de marcadores neuronais (Langdon, 2004). Dessa forma, muitos estudos têm sido realizados com o objetivo de estabelecer condições ideais para a diferenciação de células SH-SY5Y proliferativas em células com perfil neuronal com características morfológicas e bioquímicas de neurônios catecolaminérgicos maduros (Lopes et al., 2010; Schonhofen et al., 2015); sabendo que este protocolo busca a obtenção de células de origem humana e com características neuronais, diminui-se assim as limitações inerentes ao uso de células tumorais e possibilita um modelo mais adequado *in vitro* para o estudo de doenças que afetam o sistema nervoso central, como o TB.

Por análises bioquímicas, sabe-se que o modelo de diferenciação com ácido retinóico e diminuição do soro fetal bovino (SFB) para 1%, por sete dias, leva ao aumento de marcadores neuronais relevantes: TH (tirosina hidroxilase - enzima chave na síntese de dopamina), NeuN (marcador nuclear específico para neurônio) e NSE (enolase neurônio-específica), bem como a redução de marcadores de células indiferenciadas, como a nestina (Constantinescu et al., 2007). Contudo, na caracterização do modelo ainda há uma lacuna quanto a mudanças na expressão gênica destas células. Por isso, visando avançar no estabelecimento e caracterização do modelo de diferenciação proposto por Lopes e colaboradores (2010), neste estudo procuramos analisar as alterações na expressão gênica das células proliferativas e diferenciadas, reforçando assim este modelo como um modelo de diferenciação neuronal, contribuindo como mais uma ferramenta para a pesquisa de doenças que afetam o SNC por ser de origem humana e de fácil acesso, comparada aos modelos experimentais já existentes.

Metodologia

- Cultivo de células SH-SY5Y e diferenciação neuronal

As células proliferativas da linhagem de neuroblastoma humano SH-SY5Y (adquirida da ATCC, *USA*) foram cultivadas em meio DMEM/F12 (1:1) suplementado com 10% de soro fetal bovino (SFB), 2 mM de glutamina, 100 μg/μL de gentamicina e 0,25 μg/mL de anfotericina B e mantidas em um ambiente umidificado com 5% de CO_2 a 37°C.

A diferenciação celular é induzida com a diminuição do SFB no meio de cultivo a 1% acrescido de 10 μM de ácido retinóico durante 7 dias, com troca de meio a cada três dias. Depois desse protocolo, as células adquirem características morfológicas e bioquímicas de neurônios dopaminérgicos, com aumento de marcadores neuronais, diminuição da proliferação celular, alteração da morfologia da célula para um formato mais estrelado e aumento da densidade de neuritos, como previamente descrito por Lopes e col. (2010). Mais recentemente, nosso grupo também padronizou o protocolo de diferenciação colinérgica, que difere do primeiro pela adição da neurotrofina BDNF (10 nM) ao meio de cultura a partir do quarto dia de diferenciação (Figura 1).

- Extração e purificação de RNA e Análise de Microarranjo

Para a realização do microarranjo foi realizado o protocolo de diferenciação acima descrito com objetivo de avaliar o perfil de expressão gênica das células SH-SY5Y em quatro grupos experimentais (Figura 1):

1) células proliferativas (‘*Proliferative*’);

2) células diferenciadas com ácido retinóico por 4 dias (‘*4d Differentiation’*);

3) células diferenciadas com ácido retinóico por 7 dias (‘*7d Differentiation’*);

4) células diferenciadas com ácido retinóico por 7 dias e com adição de BDNF a partir do 4º dia de diferenciação (‘*BDNF Differentiation’*).

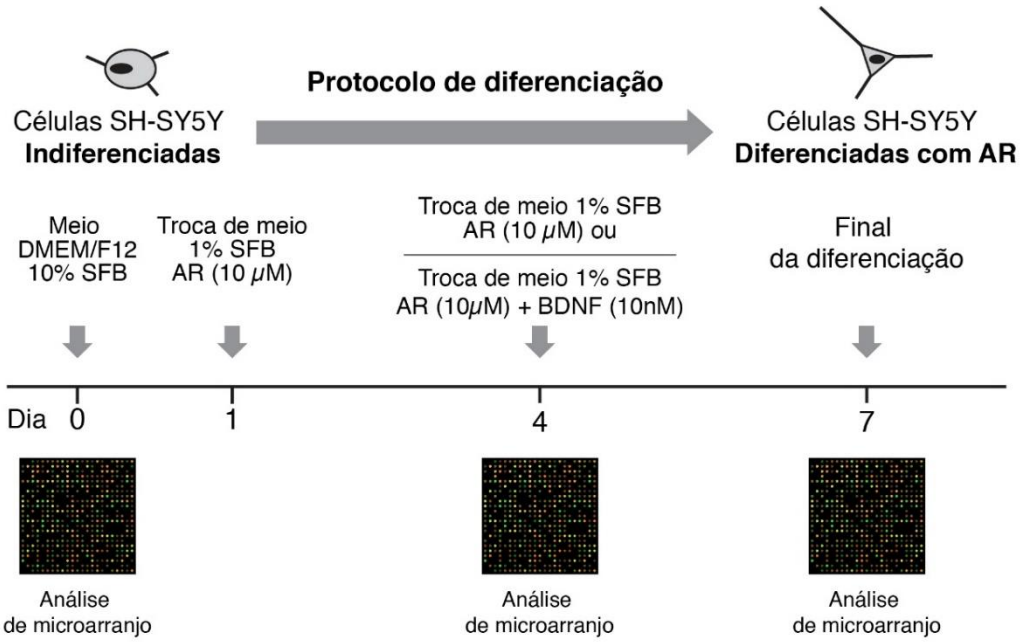


Figura 1. Esquema do protocolo de diferenciação das células SH-SY5Y. No dia 0, as células indiferenciadas foram cultivadas em meio DMEM/F12 contendo 10% de soro fetal bovino (SFB). Após 24 horas (dia 1), o meio de cultivo anterior foi removido e adicionado meio fresco contendo 1% de SFB e 10 µM de ácido retinóico (AR) (meio de diferenciação). Após três dias (dia 4), o meio de diferenciação foi substituído por meio fresco, que pode ser meio contendo somente AR (para diferenciação dopaminérgica) ou meio contendo também 10 nM de BDNF (para diferenciação colinérgica). No dia 7, as células SH-SY5Y estão diferenciadas e prontas para a realização dos experimentos de interesse. Neste caso, as células foram coletadas para as análises de microarranjo em quatro condições diferentes do protocolo: dia 0 = células proliferativas; dia 4 = células diferenciadas com AR por quatro dias; dia 7 = células diferenciadas com AR por sete dias; e dia 7 = diferenciadas com AR/BDNF por sete dias.

No total, obteve-se 16 amostras para o microarranjo e para cada amostra, utilizou-se 10 milhões de células para a extração de RNA. As amostras de RNA foram obtidas seguindo o protocolo de extração por *TRIzol Reagent* (*Life Technologies*) e purificação e tratamento com DNA*se* utilizando kits comerciais da *Qiagen* (*Qiagen 74104 RNeasy Mini Kit* e *Qiagen 79254 RNase-Free DNase Set*, respectivamente). As amostras de RNA foram quantificadas com o uso de *NanoDrop* (*Thermo*) com rendimento final mínimo de 100 ng/µL e armazenadas em freezer – 80°C para posterior análise por microarranjo. A integridade do RNA foi avaliada através de eletroforese em gel de agarose para observação das bandas ribossomais 28S e 18S e confirmada por eletroforese capilar (*Bioanalyzer Agilent*).

A técnica de microarranjo foi realizada utilizando o chip *GeneChip® PrimeView™ Human Gene Expression Array* da empresa Affymetrix, conforme orientações do fabricante. Resumidamente, a partir de 100 ng de RNA total, é gerado RNA complementar (RNAc) amplificado e biotinilado. Após purificação e fragmentação, 10 µg de RNAc foram hibridizados por 16 horas a 45ºC no *GeneChip Human PrimeView* (*Affymetrix*), e estes então foram lavados e marcados na estação *Affymetrix Fluidics Station 450*. Para o passo final, os chips foram escaneados usando o *GeneChip® Scanner 3000 7G* (*Affymetrix*).

- Análise dos dados do microarranjo

Primeiramente, foi realizado o controle de qualidade da extração de RNA, o processamento para hibridização, a marcação com fluorescência e a aquisição dos dados que foram avaliados e os dados brutos processados por bio-informata utilizando o pacote do

Bioconductor em ambiente R. Os dados processados foram submetidos a um repositório público de dados de genômica funcional (*Gene Expression Omnibus* - GEO).

Análise de componentes principais (PCA analysis)

A análise de Componentes Principais (do inglês, *Principal Component Analysis* - PCA) é uma técnica matemática utilizada para enfatizar as variações entre as amostras. Consiste em uma transformação linear ortogonal que transforma os dados para um novo sistema de coordenadas de forma que a maior variância dos dados fica ao longo da primeira coordenada (chamado de primeiro componente – PC1), a segunda maior variância fica ao longo da segunda coordenada (PC2), e assim por diante. Essa análise visa encontrar padrões em dados de elevada dimensão para expressar estes dados de modo a realçar as suas semelhanças e diferenças, facilitando assim sua visualização (Lyra WS, 2010).

Análise de expressão diferencial e Análise de enriquecimento de processos biológicos

A análise dos genes diferencialmente expressos foi realizada no pacote *limma* do software *Bioconductor* (Gentleman et al., 2004), para avaliar as vias que foram moduladas diferentemente pelo processo de diferenciação das células. Essa análise foi realizada na comparação entre o fenótipo das células proliferativas e o fenótipo das células diferenciadas com ácido retinóico por sete dias (diferenciação dopaminérgica - *7d Differentiation*). Nessa comparação, os grupos de genes diferencialmente expressos em cada fenótipo foram divididos usando uma métrica logarítimica (logFC), conforme os níveis de expressão. Então,

os grupos de genes separados dessa maneira foram utilizados para identificar os processos biológicos enriquecidos por fenótipo, pela análise de enriquecimento de grupos de genes (GSEA) usando o *Gene Ontology* (GO). O GO é um projeto de bioinformática colaborativo criado para unificar a representação de genes e produtos gênicos em todas as espécies que permite, por exemplo, a interpretação funcional de dados experimentais através de análise de enriquecimento (Consortium, 2008). O domínio do GO utilizado neste estudo refere-se aos processos biológicos, que podem ser definidos como conjuntos de eventos moleculares com início e fim definidos. Assim, considerando o grupo de genes diferencialmente expressos em cada fenótipo (células proliferativas e diferenciadas), a análise de enriquecimento identificou quais processos biológicos do GO estão significativamente representados neste conjunto de genes, e assim enriquecidos para um determinado fenótipo.

Resultados

Análise de componentes principais (PCA analysis)

O microarranjo foi realizado com sucesso em todas as amostras e foi incluído na base de dados do GEO, sob número GSE71817 (Figura 2). Após a normalização dos dados, foi verificado através da análise de componente principal (PCA) a distribuição das amostras segundo os dois principais componentes da variância (no caso, proliferativas e diferenciadas). Por ser uma ferramenta de análise exploratória a PCA permitiu revelar a existência ou não de amostras anômalas, de relações entre as variáveis medidas e de relações

ou agrupamentos entre amostras (Lyra WS, 2010), permitindo assim verificar a consistência dos grupos amostrais. Como demonstrado na Figura 3, as células proliferativas e diferenciadas estão em uma distribuição oposta indicando existir uma diferença de expressão gênica entre os grupos.

Com base no resultado obtido com o PCA e conforme os objetivos desta tese, focamos a partir desta análise nas diferenças de expressão entre as células proliferativas e diferenciadas 7 dias com ácido retinóico (AR-diferenciadas). Caso a distribuição dos grupos na análise de PCA se apresentasse semelhante, indicaria que provavelmente entre os grupos não haveria diferenças significativas na expressão gênica.

Análise de expressão diferencial e Análise de enriquecimento de processos biológicos

Nesta análise, foi possível notar que há processos biológicos bem distintos em cada fenótipo estudado (proliferativas e AR-diferenciadas)[1]. Verificamos assim, que no grupo de células proliferativas o grupo de genes mais enriquecidos estavam relacionados a processos biológicos de ciclo celular e proliferação celular, enquanto que no grupo de células AR-diferenciadas, o grupo de genes mais enriquecidos estavam relacionados a processos biológicos envolvendo desenvolvimento neuronal.

[1.] As tabelas completas contendo todos os processos biológicos de cada um dos fenótipos estudados: AR-diferenciadas (tabela 3) e proliferativas (tabela 4), por serem muito extensas seguem no anexo 7, ao final desta tese.

Na Figura 4, temos a representação dos fenótipos associados a seus processos biológicos e a critério de ilustração organizamos um quadro contento quatro processos biológicos envolvidos em cada fenótipo e sua disposição na representação geral. Também foi possível notar que um mesmo gene poderia estar presente em mais de um processo biológico, o que auxiliaria na identificação dos genes que seriam mais relevantes em cada fenótipo (Figura 5).

Estas análises foram possíveis graças ao GO; pois devido à dificuldade de se interpretar genes individuais em uma lista de genes importantes, recentemente têm-se centrado na descoberta de caminhos biológicos ao invés da função individual do gene. Nesse sentido, o GO (http://www.geneontology.org) reflete os agrupamentos de genes com base na função molecular, processo biológico, ou estrutura celular / organela. Consequentemente, a interpretação dos grupos GO diferencialmente expressos geralmente é mais simples do que a apresentação de uma lista de genes estatisticamente significativos, e mais robusta, diminuindo as possiblidades de conclusões errôneas que podem surgir de artefatos do microarranjo (Lee et al., 2008).

Discussão

Para a caracterização gênica do protocolo de diferenciação das células SH-SY5Y utilizamos a técnica de microarranjo e análises de bioinformática. A tecnologia de microarranjo forneceu a possibilidade de analisar os níveis de expressão de milhares de genes simultaneamente. Neste trabalho, buscamos analisar as diferenças de expressão gênica entre amostras de células SH-SY5Y proliferativas e AR-diferenciadas.

Para a pesquisa sobre doenças que afetam o SNC a escolha do modelo experimental é decisiva e os modelos *in vitro* geralmente são realizados com células neuronais de espécies diferentes tendo como uma limitação a falta de um modelo humano para estudar os mecanismos moleculares envolvidos na fisiopatologia destas doenças, o que ocorre devido à dificuldade para reproduzir as características fisiológicas e bioquímicas complexas de um neurônio dopaminérgico humano *in vitro*. Neste contexto, muitos estudos têm utilizado a linhagem de células SH-SY5Y diferenciadas, tendo na literatura diferentes protocolos utilizando o ácido retinóico (AR) como fator de diferenciação com tempos e concentrações diferentes, quer isoladamente, ou em combinação com outros agentes, tais como fatores de crescimento e neurotrofinas (Pahlman et al., 1995; Encinas et al., 2000; Constantinescu et al., 2007). O ácido retinóico, associado a diminuição do SFB, causa mudanças na morfologia e conduz a parada do ciclo celular, levando ao aumento das características neuronais e dopaminérgicas das células (Lopes et al., 2010).

Estudos evidenciam que as células SH-SY5Y AR-diferenciadas expressam marcadores dopaminérgicos diversos, incluindo a tirosina hidroxilase (enzima chave na síntese de dopamina) e o transportador de dopamina (DAT – do inglês *dopamine transporter*). Enquanto, no estado indiferenciado (proliferativo), as células são neuroblastos imaturos que mantêm características de células-tronco e proliferam de forma agressiva por um longo período de tempo. No entanto, existem poucos estudos sobre as diferenças entre as células SH-SY5Y indiferenciadas e AR-diferenciadas (Presgraves et al., 2004; Luchtman and Song, 2010).

Nosso grupo tem utilizado o protocolo de diferenciação com AR proposto por Lopes e colaboradores (2010), buscando caracterizar este protocolo como um modelo *in vitro* adequado para estudar doenças que afetam o SNC, bem como para analisar a neurotoxicidade de compostos (Schonhofen et al., 2015). Por isso, neste estudo conseguimos avaliar que após o protocolo de diferenciação, por sete dias com ácido retinóico, as células proliferativas se tornam células diferenciadas expressando genes envolvidos na diferenciação neuronal, corroborando assim com os achados de bioquímica e morfologia anteriormente analisados pelo nosso grupo e que já indicavam que ao final deste protocolo de diferenciação teríamos células com comportamento neuronal (Lopes et al., 2010).

Sendo assim, nossos achados indicam uma diferença relevante nos fenótipos estudados: células SH-SY5Y indiferenciadas e AR-diferenciadas; onde as células indiferenciadas apresentaram baixa expressão de genes relacionados à função sináptica e elevada taxa de proliferação. Por outro lado, as células SH-SY5Y AR-diferenciadas

apresentaram características de um fenótipo neuronal, onde na avaliação por processos biológicos verificamos genes associados ao desenvolvimento do sistema nervoso, neurogênese, diferenciação e desenvolvimento neuronal, organização e transmissão sináptica, desenvolvimento dendritico, transporte e secreção de neurotransmissores e nas análises de enriquecimento, verificamos uma maior expressão da maquinaria molecular responsável pela função sináptica.

Com a adição das análises de expressão gênica, temos um modelo que foi verificado a nível bioquímico, morfológico e molecular. Juntos, estes achados evidenciam que o referido protocolo de diferenciação tem potencial para se tornar de grande utilidade como mais um modelo experimental *in vitro* para o estudo dos transtornos que acometem o SNC por ter o diferencial de ser de origem humana. Como perspectiva deste trabalho, vamos seguir com a validação do microarranjo através da técnica de PCR em tempo real dos genes diferencialmente expressos no grupo de células proliferativas e no grupo de células AR-diferenciadas, visando assim confirmar os dados de bioinformática analisados até o momento.

Figuras e legendas

Figura 2. Página do banco GEO. Esta figura ilustra o depósito dos dados realizado no GEO, permitindo que os dados encontrados neste estudo sejam de domínio público, sob número GSE71817. (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE71817, página acessada em 08/04/2016).

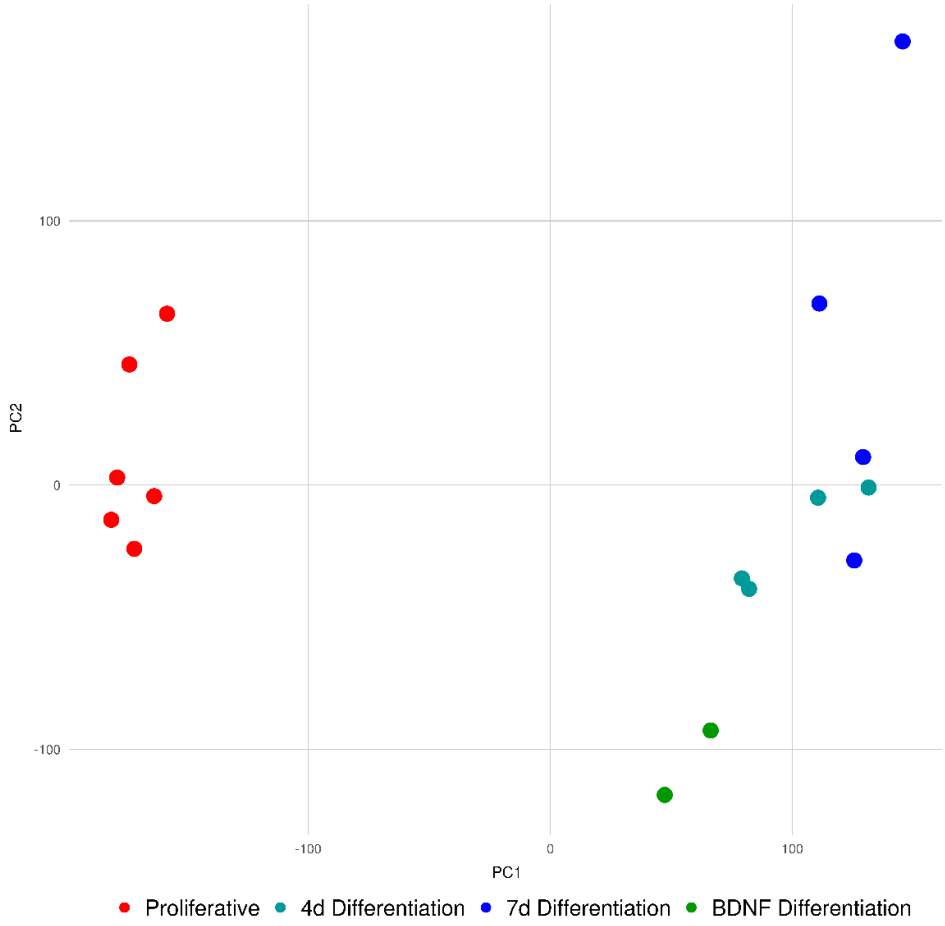
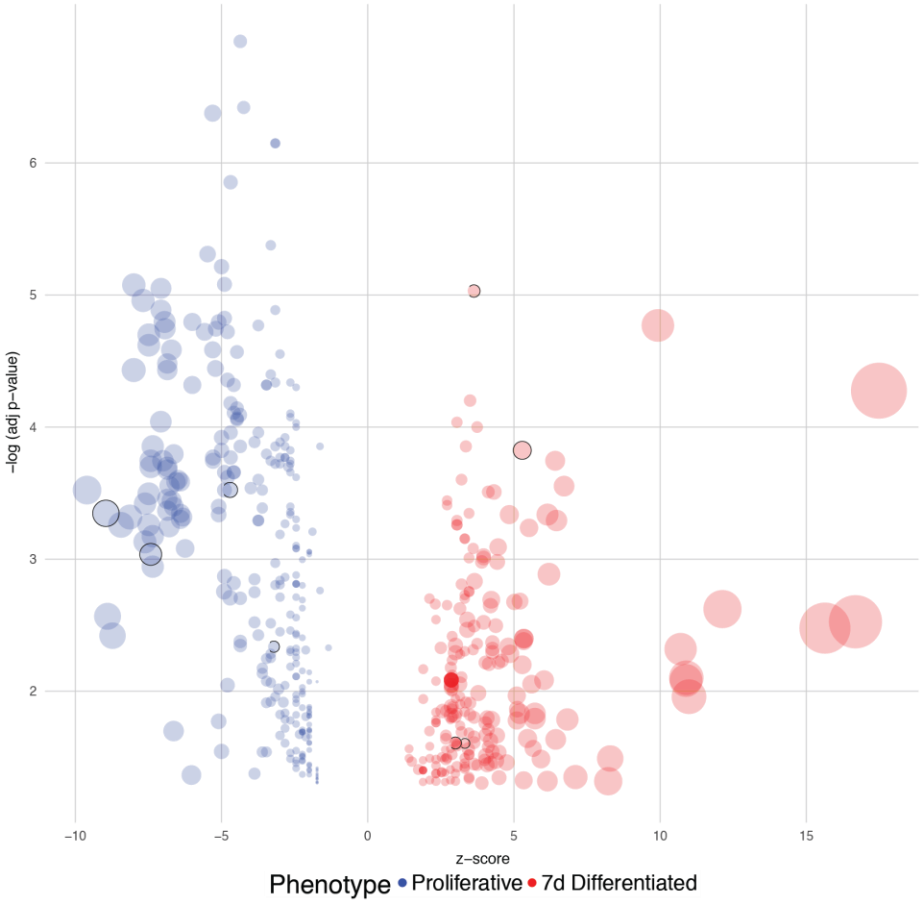


Figura 3. Análise de PCAs. Análise foi realizada com os quatros grupos experimentais: células proliferativas (‘*Proliferative’*); células diferenciadas com ácido retinóico por 4 dias (‘*4d Differentiation’*); células diferenciadas com ácido retinóico por 7 dias (‘*7d Differentiation’*) e células diferenciadas com ácido retinóico por 7 dias com adição de BDNF a partir do 4º dia de diferenciação (‘*BDNF Differentiation’*).



ID	Description
7d Differentiated	
GO:0050808	Synapse organization
GO:0007268	Synaptic transmission
GO:0042391	Regulation of membrane potential
GO:0001505	Regulation of neurotransmitter levels
Proliferative	
GO:0008283	Cell proliferation
GO:0044237	Cellular metabolic process
GO:0009058	Biosynthetic process
GO:0051726	Regulation of cell cycle

Figura 4. Análise dos processos biológicos em células proliferativas e AR-diferenciadas. Neste gráfico temos a representação dos fenótipos (proliferativa ou AR-diferenciada) associados a seus

processos biológicos. No eixo Y temos os grupos de genes distribuídos conforme o enriquecimento, enquanto no eixo X temos a separação pelos fenótipos. Cada círculo representa um processo biológico, onde o diâmetro dos círculos é diretamente proporcional ao número de genes associados a este processo biológico. Os círculos contornados em preto no gráfico representam os processos biológicos indicados no quadro.

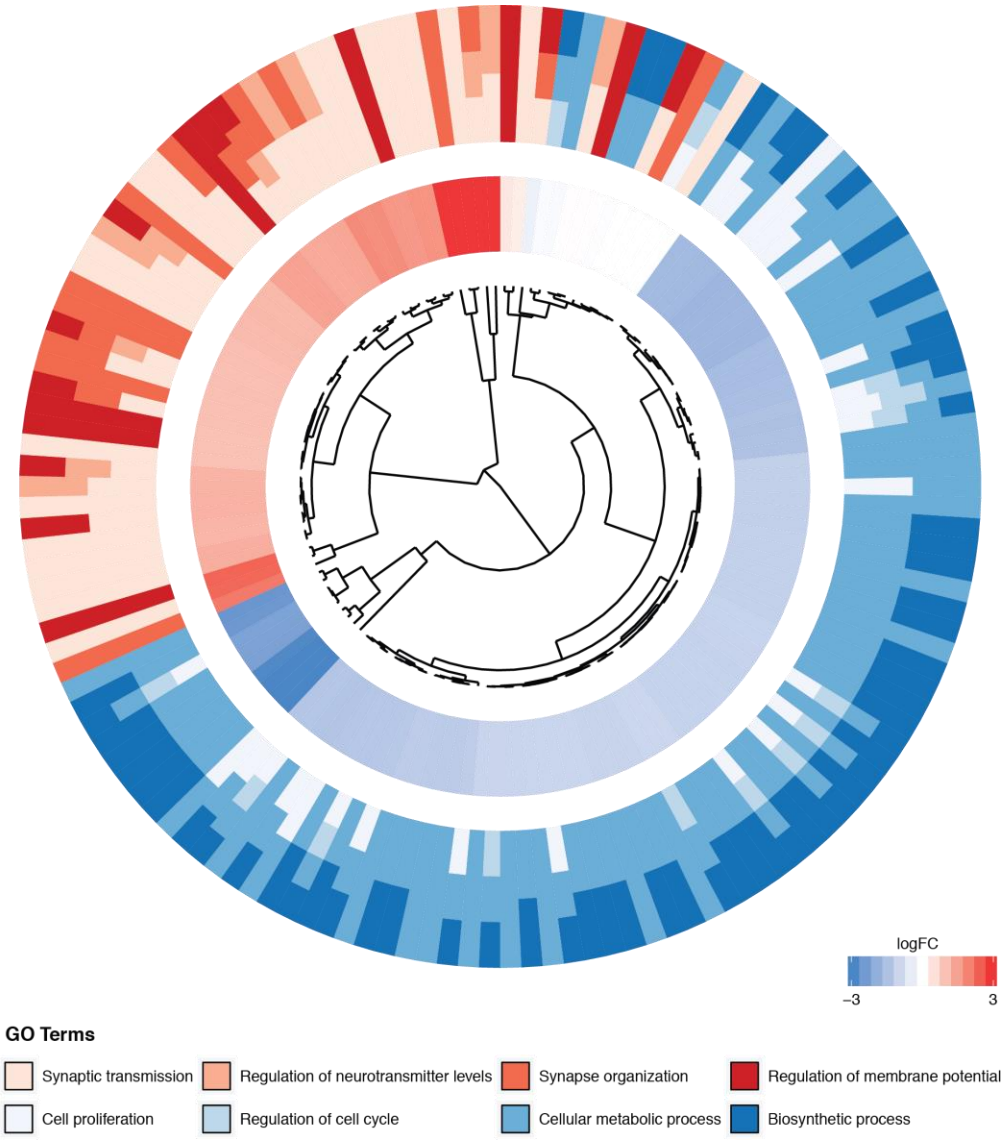


Figura 5. Análise dos genes e processos biológicos associados ao grupo de células diferenciadas por 7dias com ácido retinóico. Nesta análise é possível verificar a relação dos genes (círculo interno) em cada processo biológico destacado (círculo externo). A representação do logFC indica a expressão do gene no microarranjo (em vermelho maior expressão, azul menor expressão). Os processos biológicos mostrados neste gráfico são referentes ao grupo de células diferenciadas por 7dias com ácido retinóico.

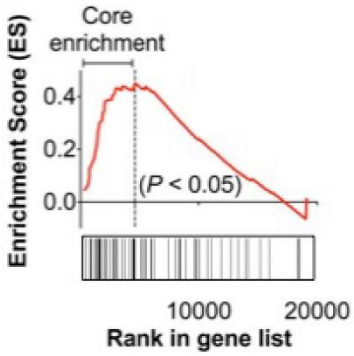
RESULTADOS SUPLEMENTARES

Além destes achados, a análise deste microarranjo originou um artigo original que discute as alterações gênicas entres os fenótipos proliferativa e AR-diferenciadas por sete dias com ácido retinóico, com enfoque em ciclo celular, função sináptica e dopaminérgica. Este artigo segue, por completo, no anexo 4 desta tese.

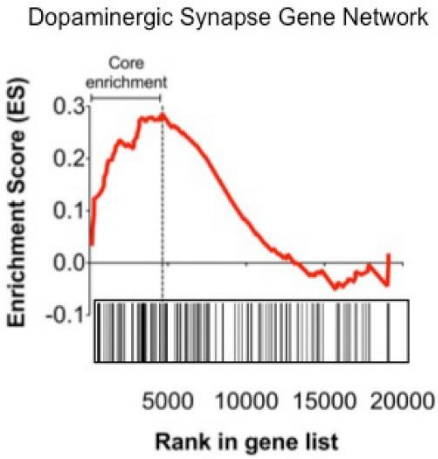
A análise de enriquecimento, GSEA (*Gene Set Enrichment Analysis*) foi utilizada para identificar os genes que individualmente contribuíram para a alteração global dos níveis de expressão observada nas células AR-diferenciadas, sendo assim, observou-se um enriquecimento significativo do conjunto de genes compreendendo os componentes da vesícula sináptica (Figura 6a), sinapse e síntese dopaminérgica (Figura 6b). Também foi possível verificar que os genes PKA, MAPK, CaMKII e PP2A, principais reguladores da atividade da TH (enzima responsável pela síntese de dopamina), estavam associados com o fenótipo neuronal. Além destes, a expressão dos genes DRD2 e SLC18A1 associados a função sináptica e do GCH1, associado a síntese de dopamina também estavam mais

relacionados ao grupo de células AR- diferenciadas (Figura 6c). Ainda, verificou-se que a proliferação celular está reduzida nas células AR-diferenciadas quando comparadas as células indiferenciadas, durante o protocolo de diferenciação (Figura 6d).

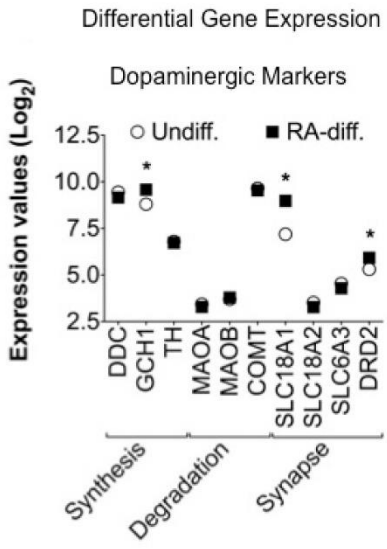
a)



b)



c)



d)

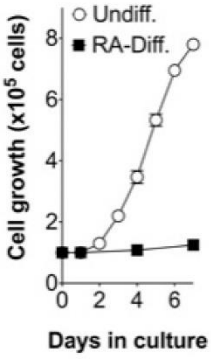


Figura 6. Comparativo do fenótipo neuronal (AR- diferenciadas) e indiferenciado das células SH-SY5Y. a) análise de enriquecimento utilizado para identificar os genes que contribuem individualmente para as alterações globais nos níveis de expressão em células AR-diferenciadas envolvendo a rede de genes da vesícula sináptica e, **b)** envolvendo componentes de sinapse e síntese dopaminérgica. **c)** análise dos níveis de expressão diferencial de marcadores pré-sinápticos dopaminérgicos em células indiferenciadas e AR-diferenciadas. **d)** taxas de proliferação em cada fenótipo analisado, indicando a diminuição da proliferação em células com fenótipo neuronal, em comparação com as células indiferenciadas.

3.4 CAPÍTULO 4

Reduced neurite density in neuronal cell cultures exposed to serum of patients with bipolar disorder

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Rapid Communication

RAPID COMMUNICATION

Reduced Neurite Density in Neuronal Cell Cultures Exposed to Serum of Patients with Bipolar Disorder

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Abstract

Background: Increased inflammatory markers and oxidative stress have been reported in serum among patients with bipolar disorder (BD). The aim of this study is to assess whether biochemical changes in the serum of patients induces neurotoxicity in neuronal cell cultures.
Methods: We challenged the retinoic acid-differentiated human neuroblastoma SH-SY5Y cells with the serum of BD patients at early and late stages of illness and assessed neurite density and cell viability as neurotoxic endpoints.
Results: Decreased neurite density was found in neurons treated with the serum of patients, mostly patients at late stages of illness. Also, neurons challenged with the serum of late-stage patients showed a significant decrease in cell viability.
Conclusions: Our findings showed that the serum of patients with bipolar disorder induced a decrease in neurite density and cell viability in neuronal cultures.

Keywords: bipolar disorder, neurite density, RA-differentiated SH-SY5Y cells, systemic toxicity

Introduction

Bipolar disorder (BD) affects about 2% of the world's population, with sub-threshold forms affecting up to a further 2% (Merikangas et al., 2007). The course of BD is highly variable, and a subset of patients seem to present a progressive course associated with brain changes (Cao et al., 2016) and functional impairment (Rosa et al., 2014). Nonetheless, the molecular foundations for this illness progression are just beginning to be explained. It is known that brain-derived neurotrophic factor

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(BDNF) serum levels were decreased in the late-stage of BD when compared to those at an early stage of the illness (Kauer-Sant'Anna et al., 2009). Moreover, altered cellular resilience was reported in late-stage patients (Pfaffenseller et al., 2014). In addition, patients at a late stage of illness present increased levels of C-C motif ligand 11 (CCL11) and decreased levels of CXCL827 chemokines (Panizzutti et al., 2015). However, what is not known is how these abnormal peripheral blood markers may lead to, or be involved with, brain changes in BD.

In 2011, our group hypothesized that impairments in neuroplasticity of BD patients may be translated into shrinkage of the brain structures by reducing neurites and intercellular connections in the neuronal network (Berk et al., 2011). We also suggested that the aforementioned biochemical changes may play a causal role in this scenario, which has been called the systemic toxicity (Kapczinski et al., 2010). Recently, several studies reported reductions in the volume of the left hippocampi (Cao et al., 2016) and frontal cortices of patients with late-stage BD (Abe et al., 2015). These findings are in line with the pioneering work of Strakowski and colleagues (2002), which reports increased ventricle volumes in multiple-episode patients with BD compared to those who had only one episode. However, the causal role of the abnormal peripheral blood markers on neuronal cells of the patients with late-stage BD has not been investigated yet.

In the present study, we used an *in vitro* approach with the retinoic acid (RA)-differentiated human cell line SH-SY5Y exposed to serum of bipolar patients. The differentiated human neuroblastoma cell line, SH-SY5Y, has been used as an experimental model to assess molecular and biochemical pathways involved in the pathophysiology of brain disorders (Lopes et al., 2010) and for neurotoxicological experiments in developmental and mature neurons (Schonhofen et al., 2015). This model has the advantage of being derived of human cells, displaying neuronal morphology, and neuronal markers (as high neurite density, tyrosine hydroxylase, dopamine transporter) during RA-differentiation (Lopes et al., 2010).

Therefore, the aim of the present study was to assess whether biochemical changes in serum of patients with BD could induce neurotoxicity in neuronal cell cultures.

Methods

The Ethical Committee of the Hospital de Clínicas de Porto Alegre (HCPA) approved the study (application number: 12–0102). All subjects had signed the informed consent.

Subjects

We recruited 12 patients with BD from the Bipolar Disorders outpatient clinic of the HCPA. We also selected six healthy controls matched by age and gender from the blood donation center of HCPA. They had no previous history of psychiatric illness as well as no history of psychiatric or neurologic disorders in first-degree relatives. Inclusion criteria were euthymic subjects with BD type 1 according to the DSM-IV and aged between 18 and 60 years. Exclusion criteria were a history of autoimmune diseases or a history of chronic infection/inflammatory disorders, as well as any severe systemic disease or use of immunosuppressive therapy.

Assessments

Subjects were evaluated through a socio-demographic history form. Axis-I diagnoses and clinical and functioning characteristics were assessed using the Structured Clinical Interview for DSM-IV axis-I Disorders (SCID-I) and Functioning Assessment Short Test (FAST), respectively, which were administered by trained staff. Current dimensional mood symptoms were assessed with the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) and the Young Mania Rating Scale (YMRS; Young et al., 1978). Euthymia was defined by the HDRS score < 8 and YMRS score < 5.

The patients were classified in stages I to IV, based on functional impairment, as well as patterns of episode recurrences and severity of clinical features (Kapczinski et al., 2009). Patients were stratified in early-stage (stage I or II) or late-stage (stage III or IV) of BD. Of note, we used the same staging criteria of previous studies from our group (Fries et al., 2013; Pfaffenseller et al., 2014).

Sample Collection

Four milliliters of blood were collected from each subject by venipuncture into a free-anticoagulant vacuum tube. After withdrawal, the blood was centrifuged at 3000 g for 10 minutes and the serum was stored at -80°C until assayed.

Cell Culture and Treatment

The neuronal differentiation of human neuroblastoma SH-SY5Y cells were performed in accordance with the protocol established by Lopes and colleagues (2010). The neuronal differentiation is induced by reducing the fetal bovine serum (FBS) in the culture medium at 1% plus 10 µM all-trans retinoic acid (Enzo Life Sciences, Inc.) for seven days. At the end of this protocol, the cells acquire the morphological and biochemical characteristics of mature, differentiated neurons. After the neuronal differentiation protocol, the cells were treated with inactivated serum (56°C for 30 min) of controls and bipolar patients (1%) for 24 h. The cells treated with FBS were used as the control group for the experiment.

Cell Viability

Cell viability was evaluated by the quantification of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction to a blue formazan product by cellular dehydrogenases, as previously described (Mosmann, 1983). The cells were seeded in 12-well plates and 24-well plates at a density of 160 000 and 80 000 cells/well, respectively. After treatment, the medium was discarded and MTT (0,5 mg/mL; Sigma-Aldrich) was added to each well and the plate were incubated for 1 h at 37°C. Then, the MTT was discarded, and dimethyl sulfoxide was added to solubilize the formazan crystals. Absorbance was determined at 560 and 630 nm in a SoftMax Pro Microplate Reader (Molecular Devices). Data were expressed as percentage of experimental control group of three independent experiments.

Immunofluorescence

The immunofluorescence was performed using anti-βIII tubulin antibody (Alexa 488-conjugated; Sigma-Aldrich) and with Nuclear dye Hoechst 33342 (0.25 µg/µL; Sigma-Aldrich). Randomly selected images were captured using an EVOS Floid Cell Imaging Station (Thermo Fisher Scientific Inc.) and analyzed with Nikon Imaging Software (NIS), the NIS- elements. The neurite density was assessed using the AutoQuant Neurite software (implemented in R program) and expressed as arbitrary units (AU) as described previously (Schonhofen et al., 2015).

Statistical Analysis

Statistical analyses were performed using the SPSS 18.0 software (SPSS Inc.). The normality of data distribution was assessed using

the Shapiro–Wilk test. Data are expressed as mean ± standard deviation (SD) with a *t*-test and one-way ANOVA used where appropriate (n = 6). *P* values < 0.05 were considered significant.

Results

There was no difference in age and gender among patients at early- and late-stage BD and healthy controls. Moreover, illness duration and medication status were not different between patients at early and late stages (Table 1). We performed a RA-differentiation protocol of SH-SY5Y cells and replaced the fetal bovine serum (FBS) with the serum of bipolar patients and control subjects (Figure 1A) and assessed neurite density and cell morphology using immunofluorescence (Figure 1B). We found a reduction in the neurite density of RA-differentiated SH-SY5Y cells treated with the serum of patients with BD compared to healthy controls (p = 0.0153). Furthermore, when the effect of the serum of patients at a late stage were compared to the serum of the control group, we also found a significant reduction in neurite density (p = 0.0089). There was no difference when the serum of patients at the early stages was compared to healthy controls (Figure 1C). There was no difference between the serums of patients and controls in cell viability analysis. However, higher serum neurotoxicity was found to be attributed to late-stage patients, leading to a significant decrease in cell viability compared to the serum of both early-stage patients (p = 0.0290) and healthy control subjects (p = 0.0075; Figure 1D).

Discussion

The present study showed that the serum of patients at a late stage induced a significant reduction of neurite density and a decrease in the cell viability compared to the serum of healthy controls. In addition, the serum of patients at a late stage caused a significant decrease in the cell viability compared to those at an early stage. Besides, we presented a potential new model for the study of illnesses that affect the central nervous system as BD, where it would be possible to evaluate the molecular and biochemical changes featured in BD.

Previously, a study reported the neurotoxic effect of the serum of patients with BD in human endothelial cells by inducing apoptosis (Politi et al., 2008). Moreover, another study showed that the serum of euthymic patients with BD had detrimental effects on peripheral blood mononuclear cells function (Herberth et al., 2011). To our knowledge, however, our work was the first to evaluate the effect of serum of patients at different stages of BD in cellular parameters using human neuronal cells. Our findings corroborate the hypothesis that patients with BD might have a loss of neuronal connectivity leading to neuroplasticity and cellular resilience impairments (Rajkowska, 2002). Thus, they suggest that the serum of patients with BD, mainly those at the late stage of the illness, may contain chemicals that could be toxic and alter neural cells, as proposed by the systemic toxicity hypothesis (Kapczinski et al., 2010). Specifically, our previous work showed that mood episodes are associated with peripheral changes in inflammation, oxidative stress, and neurotrophin markers (Kapczinski et al., 2010). In this sense, the cumulative damage caused by the recurrent mood episodes may explain why the serum of patients at a late stage is more neurotoxic than of patients at an early stage.

Moreover, these findings add to the notion of neuroprogression. The term neuroprogression has been proposed as the pathological rewiring of the brain that takes place in parallel with the clinical and neurocognitive deterioration in the course of BD (Berk et al., 2011). This hypothesis may explain why some patients with BD have a progressive course associated with a shortening of inter-episodic intervals, functional and cognitive impairment, treatment refractoriness, and suicide attempts (Merikangas et al., 2007; Rosa et al., 2014).

In addition, there was no difference between groups in illness duration (Table 1). This finding corroborates current staging models in BD, where the number of episodes and functioning impairments are more relevant to the definition of stages than length of illness (Kapczinski et al., 2014).

Our study has some limitations. First, there is a question as to what extent neuronal cell line experiments reflect what actually happens *in vivo*. Addressing this issue, a recent study proposed a model wherein transient or persistent disruption of blood-brain barrier integrity is associated with decreased central nervous system protection and increased permeability of proinflammatory and oxidative stress substances from the peripheral blood into the brain in patients with BD (Patel and Frey, 2015). Also, a positron emission tomography scan study reported that there is neuroinflammation in the brain of patients with BD (Haarman et al., 2014). Second, the sample size is small. Third, the patients were on medication, which could potentially change the serum biological markers. However, we observed that 24 h treatment with different medications has no detrimental effects in the cell viability in our study (data not shown). Moreover, there was no difference between medication status between patients at the early and late stages (see Table 1). Future research with drug-free patients would be important to evaluate the effect of drugs in this model. Finally, studies with large sample sizes are also needed to replicate our findings.

Table 1. Clinical and Demographic Characteristics of Controls and Euthymic Patients at Early vs. Late Stages of Bipolar Disorder

Euthymic patients	Early (n = 6)	Late (n = 6)	Control (n = 6)	*p*
Age (years)	48.2 ± 4.7	49.0 ± 5.0	48.8 ± 5.1	0.904[a]
Gender (male/female)	2/4	2/4	2/4	1.00[b]
Duration of illness	24.3 ± 11.29	21.5 ± 5.6	n/a	0.595[c]
Number of episodes	5.67 ± 3.5	15.83 ± 7.02	n/a	0.010[c]
Medications (%)				
Mood stabilizers	83.3%	50%	n/a	0.545[d]
Antidepressants	16.6%	0%	n/a	1.00[d]
Atypical antipsychotics	16.6%	33.3%	n/a	1.00[d]
Typical antipsychotics	0%	16,6%	n/a	1.00[d]
Benzodiazepines	16.6%	0%	n/a	1.00[d]

[a]analysis of variance, data expressed as mean ± standard deviation; [b]chi-square test; [c] independent-samples *t*-test, data expressed as mean ± standard deviation; [d]Fisher's Exact Test. n/a = not applicable.

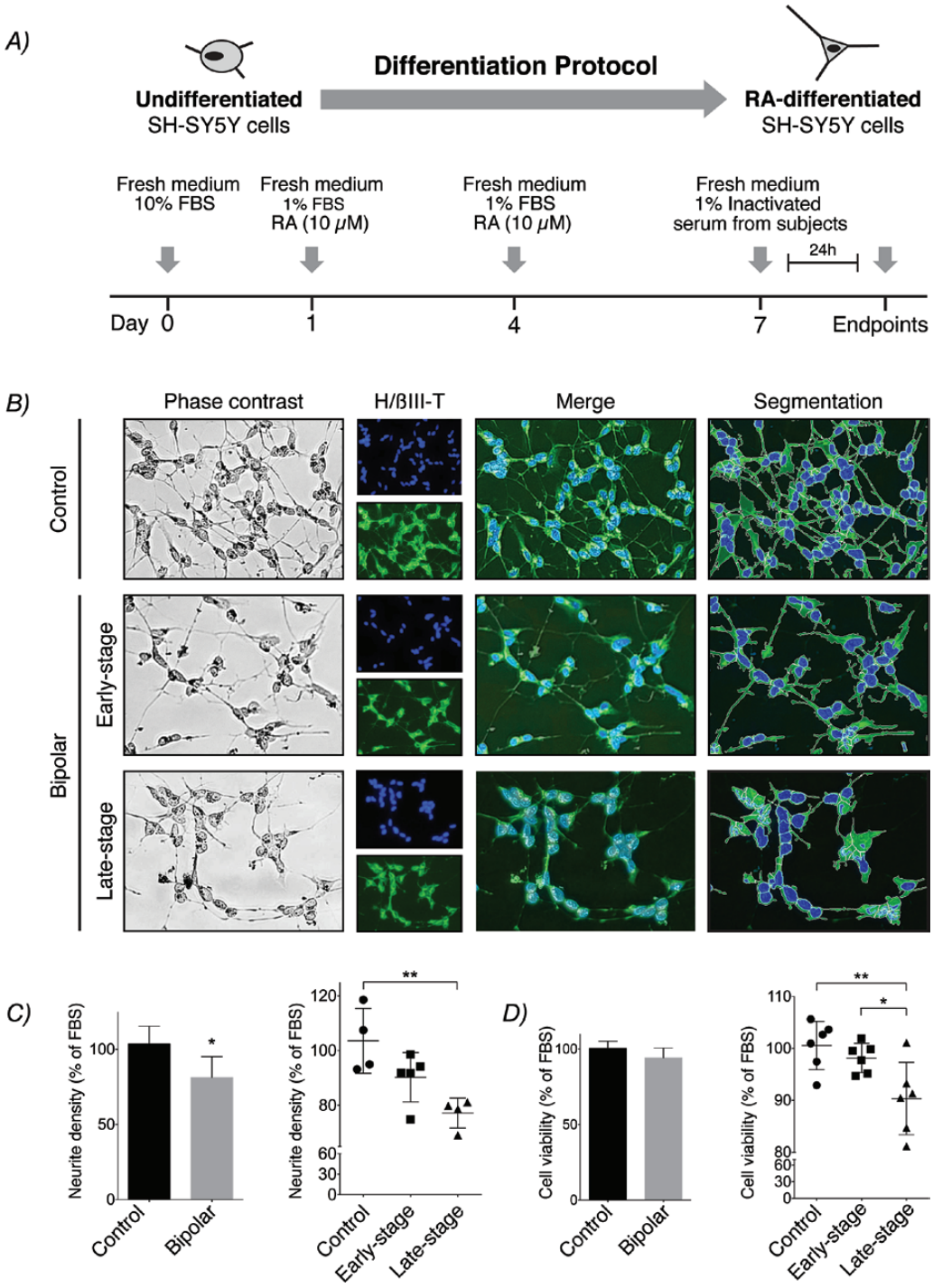

Figure 1. Protocol design, neurite density, and cell viability of retinoic acid (RA)-differentiated SH-SY5Y cells challenged with bipolar disorder (BD) serum. (A) RA differentiation protocol of human SH-SY5Y cells. At day 0, the exponentially-growing proliferative SH-SY5Y cells (ATCC) were cultured in Dulbecco's Modified Eagle Medium (DMEM) / F12 (1:1) medium supplemented with 2 mM glutamine, 100 µg/µL gentamycin, and 0.25 mg/mL amphotericin B and containing 10% fetal bovine serum (FBS) and maintained in a humidified atmosphere with 5% CO2 at 37°C. After 24 hours (day 1), the previous medium was removed and a fresh medium containing 1% of FBS and 10 µM of RA (differentiation medium) was added. Three days later (day 4), the differentiation medium was replaced by a fresh one. At day 7, SH-SY5Y cells were ready to perform the experiments of interest. The medium was replaced by fresh medium with 1% of serum of bipolar patients and controls, instead of FBS. The treatment lasted 24 h, when the endpoints were analyzed. (B) Representative phase contrast and fluorescent images of human RA-differentiated SH-SY5Y cells labeled with nuclear dye Hoechst 33342 (H) and anti-βIII tubulin (βIII-T) treated with the serums of bipolar patients and controls. Merge is the combination of phase contrast, H, and βIII-T images for analysis in the AutoQuant neurite software. Representative neurite segmentation shows the neurite density per cell body, identified by the AutoQuant neurite software. (C) Neurite density analysis. Comparison between bipolar patients and the control group ($p = 0.0153$) and between late-stage patients and controls ($p = 0.0089$) showed statistical differences. (D) Cell viability analysis. Comparison between bipolar patients and the control group did not show a statistical difference. However, when comparing the late-stage group of patients to the control group ($p = 0.0075$) and late- and early-stage patients ($p = 0.0290$) there was a statistical difference. Fetal bovine serum (FBS) was considered as 100% of cell viability. Data are presented as mean ± standard deviation. A *t*-test and one-way ANOVA were performed when appropriate. *Significant differences were considered when $p < 0.05$. **Significant differences were considered when $p < 0.01$.

In summary, we analyzed the effect of exposure to the serum of patients with BD in human cells differentiated into neuron-like cells. Our results showed neurotoxic activity in the serum of BD patients, particularly late-stage patients. In addition, we developed a new experimental model using neuronal RA-differentiated human cell cultures.

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Statement of Interest

Drs Wollenhaupt-Aguiar, Pfaffenseller, de Saraiva Chagas, Castro, Passos, and Klamt have no declaration of interest. Dr Kapczinski has received grants or research support from AstraZeneca, Eli Lilly, Janssen-Cilag, Servier, NARSAD, and the Stanley Medical Research Institute; has been a member of speakers' boards for AstraZeneca, Eli Lilly, Janssen, and Servier; and has served as a consultant for Servier. Dr Kauer-Sant'Anna is on speaker/advisory boards for, or has received research grants from, NARSAD, Stanley Medical Research Institute, CNPq-Universal, CNPq/INCT-TM, FIPE-HCPA, and Novartis.

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RESULTADOS SUPLEMENTARES

Neste experimento também testamos diferentes fármacos utilizados no tratamento do TB: o estabilizador de humor valproato de sódio e o antipsicótico atípico clozapina, com o objetivo de analisar o efeito da medicação na cultura de células AR-diferenciadas. Como resultado preliminar, verificamos que as medicações não alteraram a morfologia nem a viabilidade celular (analisada pela técnica de MTT) e ainda foram capazes de prevenir os danos causados pelo composto 6-hidroxidopamina (6-OHDA), que possui uma estrutura similar a dopamina e assim, alta afinidade pelos transportadores de dopamina; uma vez dentro da célula, a 6-OHDA se acumula no citosol, sofre auto-oxidação não enzimática levando a formação de radicais livres, como peróxido de hidrogênio (H_2O_2) e p-quinonas (Blandini et al., 2008). Essa neurotoxina também inibe a atividade do complexo I mitocondrial devido ao aumento na geração de espécies reativas (Inden et al., 2006; Lehmensiek et al., 2006; Chin et al., 2008). Dessa forma, a 6-OHDA leva a diminuição da viabilidade neuronal (Jordan et al., 2004).

Como perspectivas pretendemos replicar estes achados e analisar os efeitos de outros fármacos relevantes na clínica do TB, como o lítio. Além disso, utilizar como insulto celular o soro dos pacientes em tratamentos com as medicações, visando avaliar a capacidade neuroprotetora destes fármacos e tendo como desfechos iniciais alterações na densidade de neuritos, morfologia e viabilidade celular. Também seria de grande relevância buscar identificar qual (ou quais) compostos presentes no soro dos pacientes com TB seria o

responsável pelas alterações verificadas neste capítulo, o que poderia vir a auxiliar no desenvolvimento de novas terapias para o tratamento do TB.

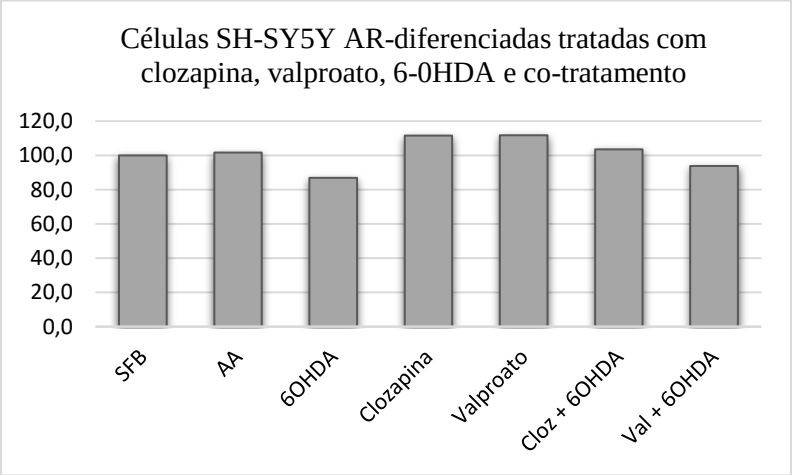

Figura 7. Avaliação da viabilidade Celular após tratamento com fármacos e insulto com 6-OHDA. As células AR-diferenciadas foram tratadas com clozapina (30µM) ou valproato de sódio (100 µg/mL) no último dia de diferenciação. Após 24h, foi adicionado o composto 6-OHDA (15 µM) e mantido por mais 24h. Após este período as células foram submetidas ao protocolo de MTT para avaliação da viabilidade celular. Grupo de células que não sofreu interferência (mantidas em soro fetal bovino – SFB) foram utilizadas como controle. Os dados foram expressos como percentagem do grupo de controle experimental. Cada tratamento foi realizado em triplicata. AA = ácido ascórbico, composto utilizado na solubilização da 6-OHDA.

PARTE III

DISCUSSÃO, CONCLUSÕES E PERSPECTIVAS

4. DISCUSSÃO

O transtorno bipolar é uma doença psiquiátrica de curso crônico e grave, com grande impacto na sociedade; estudos indicam que cerca de um terço dos pacientes com TB realiza uma tentativa de suicídio ao longo da vida (Novick et al., 2010), apresentando alta taxa de mortalidade associada as tentativas de suicídio (Osby et al., 2001). Estes achados, juntamente com a complexidade dos sintomas, demonstram a importância da pesquisa nesta área. O TB tem sido caracterizado nos últimos anos, não somente como um transtorno de alterações a nível de sistema nervoso central, mas também com alterações periféricas importantes (Berk et al., 2011). Neste contexto, cada vez mais estudos têm sido realizados buscando compreender a sua fisiopatologia, a qual não está completamente esclarecida.

No capítulo um desta tese, realizamos uma revisão da literatura visando compreender e sumarizar as principais alterações bioquímicas presentes nos pacientes com TB, com foco em inflamação, estresse oxidativo e neurotrofinas. Discutindo a possibilidade de estes serem potenciais biomarcadores da atividade do transtorno, abordando a toxicidade sistêmica e a neuroprogressão no TB, e por fim, propondo novas terapias para o tratamento do TB. No capítulo dois desta tese, mantemos o foco nestas alterações visando uma possível associação entre estas alterações bioquímicas e disfunção cognitiva nestes pacientes. Com estas revisões foi evidenciado o caráter sistêmico do TB, onde diversos estudos ao longo dos anos têm indicado o envolvimento de marcadores bioquímicos na fisiopatologia do TB, os quais vamos

abordar nos próximos parágrafos associando a neurobiologia e buscando assim discutir a sua relevância para o TB.

Estresse oxidativo

Nas revisões foi possível verificar um desequilíbrio do sistema redox no TB, caracterizado pelo o aumento do estresse oxidativo, através, por exemplo, do dano lipídico e proteico, e de uma menor atividade de enzimas antioxidantes. O resultado deste desequilíbrio é a formação excessiva de radicais livres, denominados espécies reativas ao oxigênio (ROS, do inglês *reactive oxygen species*). Estas espécies reativas também podem ser geradas por células inflamatórias ativadas, como macrófagos e microglia, sendo assim, estresse oxidativo e inflamação estão inextricavelmente interligados. Em concentrações fisiológicas, as espécies reativas ao oxigênio desempenham funções importantes no SNC (Nayernia et al., 2014). Por outro lado, o excesso de ROS pode causar excitotoxicidade ao glutamato e alterar a atividade mitocondrial (Morris and Berk, 2015). A disfunção mitocondrial, por sua vez, leva ao aumento da regulação do receptor de NMDA, aumentando ainda mais o estresse oxidativo, o que resulta em um processo celular prejudicial e autossustentável.

Estudos indicam que os radicais superóxido e hidroxil, produtos do estresse oxidativo, seriam capazes de induzir resistência ao cortisol através da alteração no receptor de glicocorticoide (um dos fatores mais importantes na resposta ao cortisol, se ligando ao hormônio no citosol e transportando-o para o núcleo, onde funciona como um fator de transcrição). Desregulação do eixo hipotalâmico-pituitário-adrenal (HPA) por ROS, por sua

vez, provoca uma resposta pró-inflamatória com o aumento dos níveis circulantes de citocinas pró-inflamatórias (Ventriglio et al., 2015). Estudos também indicam que atividade excessiva de ROS seria responsável pelo aumento da permeabilidade da barreira hemato-encefálica através da liberação de metaloproteinases de matriz e posterior degradação de proteínas de adesão celular, levando a neuro-inflamação e aumento da apoptose em neurônios (Gu et al., 2011).

Inflamação

Na revisão que compõe o capítulo dois, encontramos aumento dos níveis periféricos de citocinas pró-inflamatórias, tais como a interleucina (IL)-6 e fator de necrose tumoral alfa (TNF-α), durante episódios depressivos, e de IL-2, IL-4, IL-6, e TNF-α na mania, quando comparado com pacientes eutímicos e indivíduos saudáveis.

O estresse é um componente importante do TB e sugere-se que o estresse constante nos pacientes com TB levaria a ativação do eixo hipotalâmico-pituitário-adrenal (HPA) com aumento da secreção de cortisol; além disso, há estimulação do eixo medular simpato-adrenal com o aumento dos níveis circulantes de epinefrina e norepinefrina (Jones and Thomsen, 2013). Estes hormônios do estresse atuam via receptores de membrana, afetando a transcrição de genes que codificam citocinas através da diminuição da inibição do fator nuclear-kappa B (NF-kB) e das vias de transdução de sinal inflamatórias como fator ativador da proteína-1 (AP-1), fatores de ativação de transcrição (JAK-STAT), e proteína cinase ativada por mitogéno (MAPK) (Miller et al., 2008). As células do sistema imune inato (por

exemplo, monócitos, macrófagos e linfócitos T) secretam moléculas de citocinas pró-inflamatórias, quimiocinas e moléculas de adesão celular que se difundem para o cérebro e ativam a microglia, causando neuroinflamação, seguida por ativação do eixo HPA (Barbosa et al., 2014). A secreção contínua de hormônios do estresse levaria a um meio com baixo grau inflamatório, porém constante, que estaria diretamente relacionado a neuroprogressão, bem como predispõe a alterações cardiovasculares e metabólicas, que são frequentemente encontradas nesses pacientes.

A ativação do sistema imune estaria assim relacionada com neuro-inflamação através da ativação da microglia, que exerce uma função central em vias neuro-inflamatórias (Stertz et al., 2013). Um estudo recente de imagem de tomografia por emissão de pósitrons (PET) verificou aumento de atividade microglial e neuro-inflamação no hipocampo direito e uma tendência semelhante no hipocampo esquerdo de pacientes com TB tipo I (Haarman et al., 2014).

Neste contexto, é importante ressaltar que a inflamação sistêmica está diretamente relacionada com a ativação dos macrófagos periféricos e aumento da produção de citocinas pró-inflamatórias no SNC. As citocinas Th1 ativam a enzima microglial triptofano 2,3-dioxigenase (TDO) e a indoleamina 2,3-dioxigenase (IDO), deslocando o catabolismo da quinurenina microglial (KYN) na direção do ácido quinolínico (QUIN). Este desequilíbrio entre QUIN e a síntese de ácido cinurênico (KYNA) promove a susceptibilidade microglial ao estresse que pode estar relacionado à recorrência de novos episódios de humor e baixa resposta ao tratamento (Dantzer et al., 2008). Sendo assim, este meio pró-inflamatório

observado em pacientes bipolares pode promover um aumento da permeabilidade da barreira hemato-encefálica, conduzindo a um recrutamento massivo e infiltração de marcadores inflamatórios a partir da periferia para o cérebro, desencadeando a ativação e proliferação da micróglia (Ascoli et al., 2016). Como os macrófagos periféricos, a microglia ativada promove a secreção de citocinas inflamatórias, amplificando a resposta inflamatória, resultando em disfunções de rede neural com consequente impacto sobre os sintomas de humor, cognição e resposta ao tratamento. Por isso, novas estratégias que normalizem as vias imuno-inflamatórias poderiam proporcionar oportunidades terapêuticas benéficas para o tratamento do TB (Ascoli et al., 2016).

Neurotrofinas

Nos estudos avaliados no capítulo dois e três desta tese é possível verificar que os níveis periféricos do fator neurotrófico derivado do cérebro (BDNF) estariam diminuídos durante os episódios de humor e os pacientes que sofreram mais episódios apresentariam níveis menores de BDNF comparado com pacientes que tiveram menor número de episódios ao longo da vida (Fernandes et al., 2015). Devido a sua relevância, o BDNF tem sido evidenciado como um possível biomarcador periférico para o TB. Dentre as neurotrofinas, o BDNF recebe maior destaque no TB, por ser a mais abundante e exercer importante função na plasticidade sináptica, na formação de conectividade sináptica e na sobrevivência neuronal (Park and Poo, 2013), possui também papel importante durante o desenvolvimento cerebral, através da regulação do desenvolvimento do circuito neural, orientação e crescimento axonal e na formação e maturação das sinapses (Cohen-Cory et al., 2010).

Essa combinação de função tanto de regulação neuronal como de estrutura sináptica coloca o BDNF como um regulador essencial dos processos celulares que fundamentam o comportamento e a cognição. Estudos sugerem existir uma relação entre o BDNF e áreas específicas do cérebro envolvidas na atenção e cognição, tais como: hipocampo, córtex frontal e amígdala (Radka et al., 1996). Galloway e colaboradores (2008) mostraram que o BDNF desempenha um papel importante na memória de trabalho do córtex pré-frontal. Nesse sentido, evidências indicam que o BDNF desempenha também um papel importante na aprendizagem e memória. Estudos em modelo animal têm relacionado os níveis de BDNF com o desempenho em tarefas cognitivas, enquanto a administração de BDNF mostrou melhorar o desempenho animal durante o teste labirinto aquático de Morris (também chamado *Morris Water Maze* - que visa avaliar a capacidade de aprendizagem espacial e memória) (Messaoudi et al., 1998). Em contrapartida, a privação de BDNF endógeno nos ventrículos laterais levou a um comprometimento da memória e da aprendizagem espacial em ratos adultos, no mesmo teste (Mu et al., 1999).

Na revisão da literatura realizada no capítulo dois, foi verificada uma associação entre altos níveis periféricos de citocinas pró-inflamatórias, estresse oxidativo e níveis diminuídos de BDNF com pior desempenho cognitivo em pacientes com TB. Ainda, o polimorfismo *Val66Met* do gene do BDNF se mostrou ser um potencial fator de vulnerabilidade para o comprometimento cognitivo no TB. Estes achados reforçam a importância da investigação de biomarcadores periféricos para o TB, conforme foi discutido no capítulo um.

Nesse contexto, na busca pelo entendimento da fisiopatologia do TB, muitos modelos experimentais têm sido utilizados; contudo há uma grande dificuldade em se encontrar um modelo ideal que represente toda a complexidade dos sintomas e alterações bioquímicas presentes no TB, principalmente em modelos *in vitro*. No capítulo três desta tese, abordamos a caracterização gênica do modelo experimental *in vitro* de diferenciação das células SH-SY5Y com ácido retinóico. Nossos achados apontaram para fenótipos com diferenças específicas entre as células SH-SY5Y indiferenciadas e AR-diferenciadas. Nos quais as células indiferenciadas apresentaram características típicas de um fenótipo tumoral, com a morfologia epitelial, baixa expressão de genes relacionados à função sináptica e elevada taxa de proliferação. Por outro lado, as células SH-SY5Y AR-diferenciadas apresentaram características de um fenótipo neuronal, com baixas taxas de proliferação, marcada morfologia neuronal e uma maior expressão da maquinaria molecular responsável pela função sináptica. Assim, estes resultados permitiram preencher uma lacuna previamente existente na caracterização deste modelo. Com os achados verificados nesta tese, podemos inferir que este modelo de diferenciação acrescenta a literatura a possibilidade de se obter células com perfil neuronal dopaminérgico de origem humana.

O TB é uma condição médica complexa cuja etiologia envolve fatores genéticos e epigenéticos atuando ao lado de estressores ambientais que juntos determinariam a expressão do transtorno (Pregelj, 2011). Atualmente, é considerada uma doença que interfere em múltiplos sistemas, ou seja, que não somente afeta o funcionamento do cérebro, mas também resulta em comorbidades físicas relevantes, como doença cardiovascular, diabetes *mellitus*,

distúrbios de imunidade, e disfunção endócrina (McElroy, 2004). Estudos genômicos não conseguiram detectar um único gene para explicar a incidência do TB, reforçando a hipótese de que é uma condição poligênica, onde os genes envolvidos interagem com estressores da vida levando a uma desregulação nos mecanismos biológicos e homeostáticos do organismo (Goes, 2016). Nesse sentido, evidências de estudos com gêmeos e familiares reforçam a importância do componente genético para o TB envolvendo múltiplos genes e modos complexos de hereditariedade (Smoller and Finn, 2003; Frey et al., 2007). Nos últimos anos, ligação genética, estudos casos controle e estudos de desequilíbrio investigaram potenciais genes candidatos dentro do sistema dopaminérgico que podem conferir susceptibilidade para o desenvolvimento de TB, bem como influenciar na eficácia das terapias farmacológicas (Cousins et al., 2009). Os esforços de pesquisa nos últimos anos têm revelado que a desregulação de vias bioquímicas específicas atua de forma orquestrada na patogênese do TB. Caracterizado por uma disfunção na sinalização de glicocorticoides (Belvederi Murri et al., 2016), no desequilíbrio imunológico-inflamatório (Bhattacharya et al., 2016), aumento do estresse oxidativo (Siwek et al., 2016), anormalidades no metabolismo do triptofano (Toker et al., 2010), alteração na função das mono aminas, ácido gama-aminobutírico (GABA), glutamato (Kugaya and Sanacora, 2005; Douma et al., 2014), vias de sinalização de segundo mensageiro (Ascoli et al., 2016) e dano ao DNA (Andreazza et al., 2007). Alterações de receptores dopaminérgicos em regiões específicas do cérebro, assim como variações no gene do transportador de dopamina (DAT) têm sido sugeridos estarem associados a maior suscetibilidade para o desenvolvimento do TB (Pantazopoulos et al., 2004). Dentro deste contexto, a desregulação da dopamina tem sido proposta como um

modelo para a mania e para depressão no TB (Berk et al., 2007b). Evidências apontam que a neurotransmissão excessiva de dopamina estaria relacionada ao desenvolvimento dos sintomas maníacos em pacientes com TB (Vawter et al., 2000; Kapczinski et al., 2008). Classicamente, hiperatividade comportamental induzida por psico-estimulantes tem sido utilizada para mimetizar a mania em modelos animais (Walz et al., 2008; Stertz et al., 2014). Além disso, evidências indicam que o precursor da dopamina, L-dopa, (van Praag and Korf, 1975), assim como agonistas dopaminérgicos, tais como pramipexol e bromocriptina poderiam induzir a mania (Silverstone, 1984; Yatham, 2005). Em contrapartida, déficits de dopamina têm sido associados a sintomas depressivos (Berk et al., 2007b). Em conjunto, estes estudos indicam que alterações no sistema dopaminérgico estariam relacionadas aos mecanismos neuroquímicos no TB. Sendo assim, a avaliação gênica do modelo de diferenciação das células SH-SY5Y em células com perfil de neurônios dopaminérgicos acrescenta a literatura um modelo *in vitro* de origem humana que pode vir a auxiliar no avanço das pesquisas sobre a fisiopatologia, busca por fármacos e testes de novas terapias dos transtornos que acometem o SNC, dentre eles o TB.

No quarto e último capítulo desta tese, associamos os achados dos três primeiros capítulos. Assim, utilizamos o modelo celular de diferenciação das células SH-SY5Y, que foi caracterizado por expressão gênica como um modelo de diferenciação em células com perfil neuronal, no capitulo três, com o objetivo de avaliar a toxicidade sistêmica dos pacientes bipolares, a qual foi descrita e revisada nos capítulos um e dois.

A utilização do soro de pacientes com TB em cultura celular já foi realizada em outros dois estudos (Politi et al., 2008; Herberth et al., 2011), contudo esta foi a primeira vez em que foi avaliado em células de origem humana com perfil neuronal e analisado nos diferentes estágios do TB. Nesse sentido, sabe-se que o paciente bipolar apresenta alterações bioquímicas ao longo da vida e um grande corpo de evidências aponta para a neuroprogressão no TB. As alterações nos marcadores biológicos periféricos no TB parecem ocorrer ao longo de duas vias distintas, a primeira seria a toxicidade sistêmica que estaria associada aos episódios agudos, os estados alostáticos. Enquanto a segunda, estaria sendo demonstrada à medida que o TB progride através dos danos cumulativos, relacionado assim com a neuroprogressão (Grande et al., 2012).

Nesse sentido, a teoria da carga alostática que representa a gravidade dos sintomas apresentados pelos pacientes ao longo dos anos, fornece uma ligação teórica entre sintomas, aparentemente separados, como a disfunção cognitiva, alteração na funcionalidade e as alterações bioquímicas que ocorrem em pacientes com TB, onde um evento estressor levaria a ocorrência de um episódio de humor, este irá causar alterações periféricas e centrais no paciente, ao passar dos anos e do número de episódios, estas alterações vão se acumulando, causando como consequência uma diminuição da capacidade de adaptação (resiliência) do paciente, tornando-o mais suscetível a novos episódios, formando assim um ciclo que culminaria com um pior prognóstico clínico (ver figura 8). Este seria caracterizado por um maior tempo e número de internações (da Costa et al., 2015), episódios recorrentes (Kessing et al., 2004), tentativas de suicídio (Forty et al., 2014), menor responsividade à medicação

(Swann et al., 1999), bem como a uma disfunção cognitiva e funcional acentuada (Rosa et al., 2014). Ou seja, a carga alostática se refere à visão cumulativa e multissistêmica do custo fisiológico que é necessário para a adaptação; exemplificando, seriam situações em que mediadores de alostase não são desligados quando o estresse é prolongado, ou não estão ativos de forma adequada durante um estresse ou quando são usados em excesso devido ao estresse constante (McEwen, 2006).

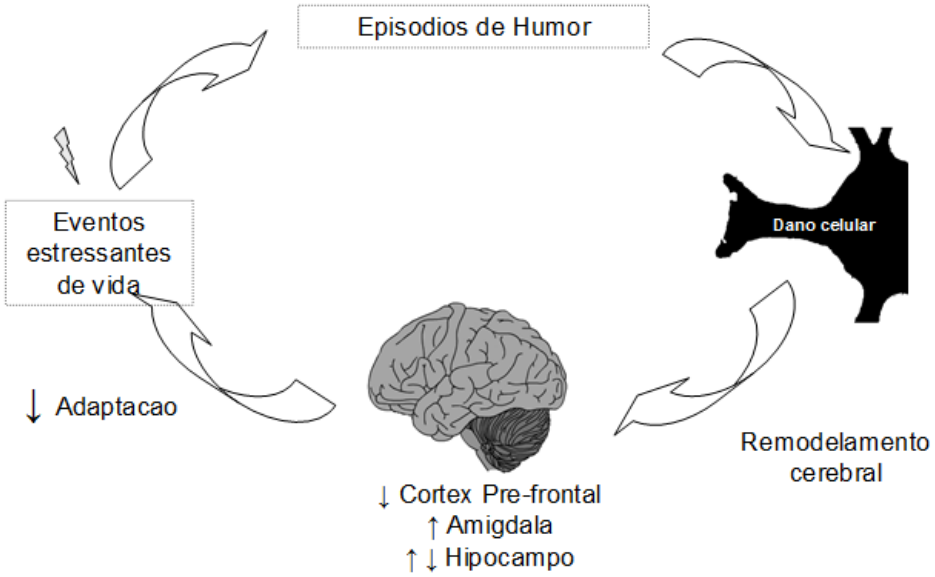

Figura 8. **Representação esquemática da teoria da carga alostática para explicar o dano causado por múltiplos episódios nos pacientes com TB**. O estresse ambiental e os episódios de humor recorrentes estariam associados à diminuição dos níveis de neurotrofinas, como o BDNF, aumento de estresse oxidativo e disfunção inflamatória. Estas alterações estariam associadas a uma maior propensão ao dano celular, o que, por sua vez, levaria a um remodelamento cerebral e consequente alteração nas regiões criticamente envolvidas na regulação do humor. Tais alterações,

por consequência, diminuiriam a capacidade de adaptação ao estresse (menor resiliência), resultando em maior vulnerabilidade à ocorrência de novos episódios agudos de humor (Modificado de Kapczinski et al., 2008).

As alterações bioquímicas que ocorrem ao longo dos anos nos pacientes com TB até pouco tempo eram avaliadas de forma individual, tendo sido Kapczinski e colaboradores (2010) quem pela primeira vez organizou um índice de toxicidade sistêmica para estas alterações periféricas presentes no TB (inflamação, estresse oxidativo e neurotrofinas), avaliando em soro de pacientes em episódios agudos de mania e depressão, e em pacientes eutímicos e controles. Como resultado, foi verificado que os episódios agudos seriam mais tóxicos que os períodos de remissão (eutimia) e estes mais tóxicos quando comparados ao grupo controle. Assim, a toxicidade sistêmica relacionada aos episódios poderia ocorrer devido a uma acumulação de processos ativos e passivos de comprometimento celular relacionados com a incapacidade de se estabelecer mecanismos compensatórios adequados para lidar com os desafios ambientais (Kapczinski et al., 2010).

Todos estes resultados são consistentes com a noção de que a toxicidade se acumularia durante o curso do TB, atuando assim no aumento da carga alostática e levando ao comprometimento de mais sistemas de regulação nos pacientes com TB. A disfunção cognitiva e o comprometimento funcional, por exemplo, seriam o resultado da toxicidade sistêmica gerada pelos episódios de humor. Nesse contexto, a resposta ao estresse, a atuação dos neurotransmissores catecolaminérgicos, a alteração nos sistemas inflamatórios,

neurotrófico e de estresse oxidativo seriam os mediadores da alostase nos pacientes com TB (Figura 9).

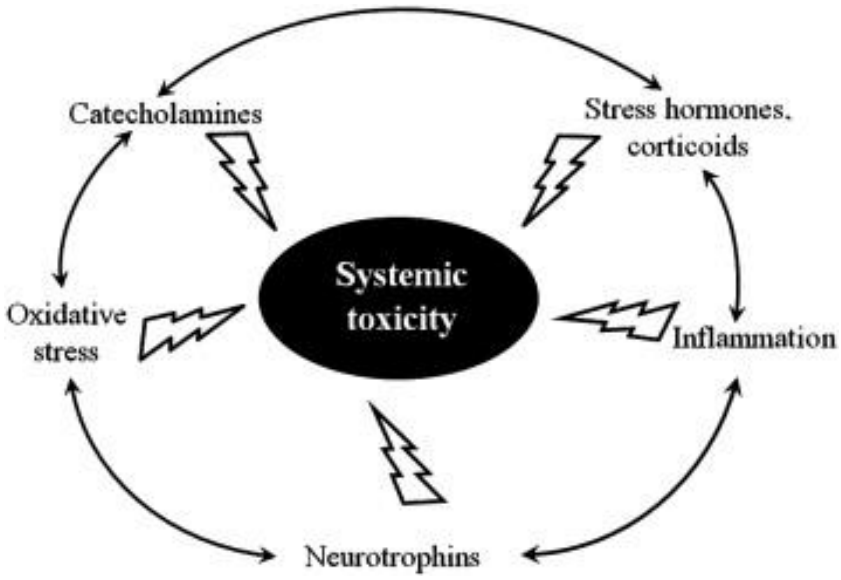

Figura 9. **Representação da rede de mediadores de alostase envolvidos na toxicidade sistêmica**. Os hormônios do estresse, os corticóides, as catecolaminas, o estresse oxidativo, os fatores inflamatórios e neurotrofinas são indicados como marcadores que apresentam um papel significativo na toxicidade sistêmica (figura extraída do artigo Grande et al., 2012).

Neste contexto, é relevante ressaltar que em doenças que apresentam curso progressivo, se torna interessante a avaliação de modelos de estadiamento, pois estes podem ser extremamente úteis para permitir uma avaliação mais específica das necessidades dos pacientes em cada estágio. Para o TB já há diferentes modelos para o estadiamento (Berk et al., 2007c; Berk et al., 2007a; Kapczinski et al., 2009; Mwangi et al., 2016), basicamente um paciente nos estágios iniciais teria um melhor prognóstico clínico, ou seja, menor gravidade

dos sintomas clínicos, possivelmente poucos episódios de humor e baixa alteração cognitiva e funcional, enquanto um paciente em estágios mais avançados do TB, já apresentaria considerável declínio cognitivo e funcional, maior número de episódios, menor resposta à medicação, assim como maior gravidade dos sintomas clínicos. Além disso, muitos estudos de neurobiologia e de marcadores periféricos têm demonstrado alterações conforme o estágio do TB. Pacientes com muitos episódios de humor apresentam maior redução do volume cerebral quando comparado a pacientes que tiveram um menor número de episódios (Strakowski et al., 2002). Citocinas pró-inflamatórias, como TNF-alfa e IL-6 estariam aumentadas nos estágios iniciais e tardio do TB em relação aos controles, enquanto os níveis de BDNF diminuíram na fase tardia, mas não no estágio inicial, enquanto os níveis da citocina anti-inflamatória IL-10 diminui nos pacientes em estágio tardio no TB (Kauer-Sant'Anna et al., 2009). Estes achados demonstram a importância do estadiamento no TB, permitindo avaliar de forma mais específica os diferentes aspectos deste transtorno; o que no futuro pode vir a auxiliar no esclarecimento da sua fisiopatologia, bem como possibilitar o desenvolvimento de terapias específicas para os diferentes estágios do TB.

Com base nessas evidências e ainda, considerando os aspectos relativos à progressão do TB, nós dividimos os pacientes em dois estágios, estágio inicial e estágio tardio, conforme o modelo de estadiamento clínico proposto anteriormente pelo nosso grupo (Kapczinski et al., 2009); com o objetivo de avaliar a capacidade neurotóxica do soro dos pacientes bipolares nos diferentes estágios do TB.

Assim, os achados indicados no capitulo quatro, sugerem a presença de toxinas no soro de pacientes em estágio tardio, podendo conduzir a alterações em células neuronais.

No entanto, ao discutirmos os efeitos de alterações periféricas no SNC, surge o questionamento sobre a capacidade destas alterações se relacionarem efetivamente com as células do SNC. Neste sentido, muitos estudos têm sido feitos investigando a barreira hemato-encefálica em pacientes com transtornos de humor (Viet Tran et al., 2006; Patel and Frey, 2015; Ascoli et al., 2016).

A barreira hemato-encefálica é responsável pela regulação das trocas entre o SNC e a periferia, tendo como funções principais proteger o cérebro de substâncias tóxicas presentes no sangue, garantir o fornecimento de nutrientes oriundos dos tecidos para o cérebro, além de filtrar compostos nocivos do cérebro de volta para a corrente sanguínea (Patel and Frey, 2015). Portanto, para a manutenção da homeostase do SNC é essencial que barreira hemato-encefálica esteja intacta e funcional. Nesse sentido, estudos apontam que durante uma inflamação crônica, ocorre o aumento de citocinas pró-inflamatórias, estas poderiam atuar aumentando a permeabilidade microvascular, levando a migração dos leucócitos para o parênquima cerebral (Frank et al., 2015; Weber et al., 2015). Essa infiltração desencadeia a ativação de citocinas e a liberação de metaloproteinases de matriz (MMP) intensificando tanto a permeabilidade da barreira-hemato encefálica como a inflamação no SNC, através da ativação glial (Ascoli et al., 2016).

Sabendo que aumento de marcadores inflamatórios e de estresse oxidativo estão fortemente associados a fisiopatologia do TB, estudos tem buscado explicar a relação entre as alterações periféricas e centrais verificadas nos pacientes com TB. Neste contexto, uma das hipóteses mais recentes é a proposta por Patel e Frey (2015), ilustrada na Figura 10, onde uma maior permeabilidade na barreira hemato-encefálica estaria associada com menor proteção e, posteriormente, maior afluxo de material inflamatório e de estresse oxidativo da periferia para o cérebro de indivíduos com TB. Em contrapartida, estudos tem relatado que os estabilizadores do humor utilizados no tratamento do TB, tais como lítio e valproato, poderiam inibir a função das metaloproteinases e atenuar assim a disfunção da barreira hemato-encefálica (Yu et al., 2013).

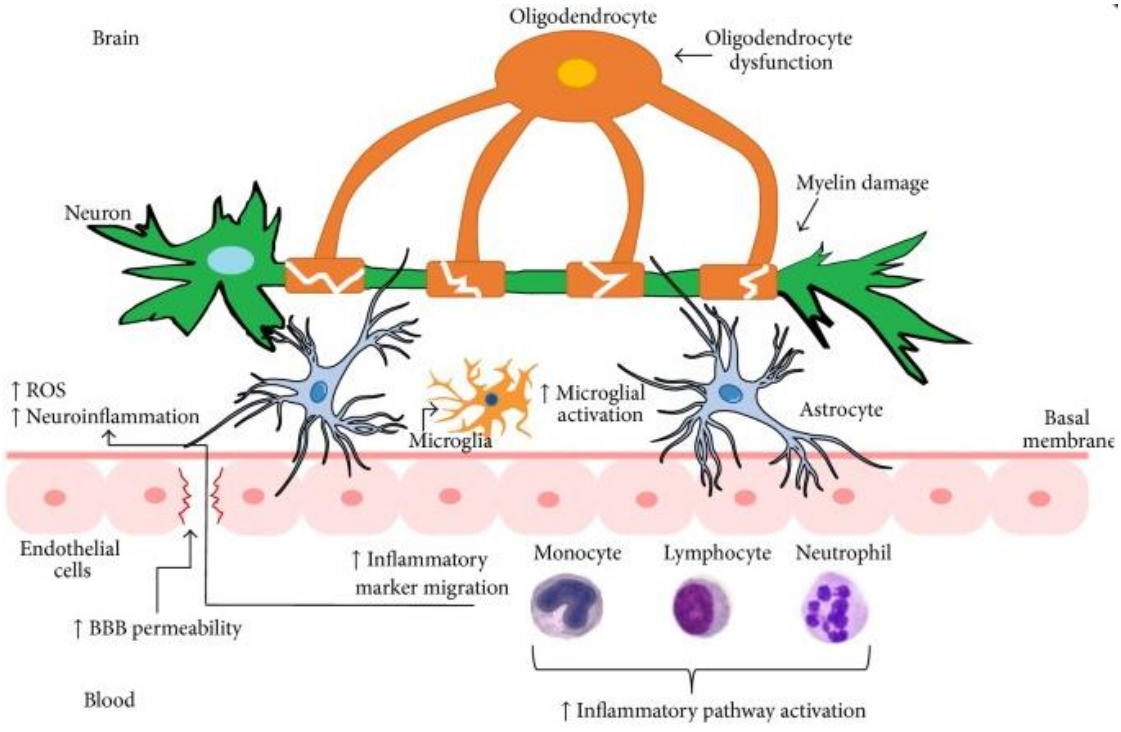

Figura 10. **Proposta de modelo de perturbação na barreira hemato-encefálica (BHE) no transtorno bipolar**. Aumento da permeabilidade da BHE através das células endoteliais (rosa) e da membrana basal (rosa escuro) podem facilitar o aumento da migração de moléculas inflamatórias no cérebro. Ativação das células microgliais (laranja claro) e um aumento de espécies reativas de oxigênio (ROS) iria amplificar os processos neuroinflamatórios e, finalmente, induzir danos na bainha de mielina, quer diretamente através de oxidação lipídica / protéica ou indiretamente, através de disfunção em oligodendrócitos (laranja escuro). (Figura extraída do artigo Patel e Frey, 2015).

Sendo assim, nossos resultados apontam para um novo modelo experimental em que seria possível avaliar as alterações moleculares e bioquímicas presentes no transtorno bipolar, auxiliando, assim, na pesquisa deste transtorno, podendo ser um grande avanço para a investigação científica nesta área. Ainda, estes achados auxiliam na caracterização da toxicidade sistêmica em pacientes com TB, indicando a presença de compostos tóxicos no soro de pacientes bipolares capazes de levar a uma disfunção neuronal. Além disso, estes resultados corroboram a hipótese de que pacientes com TB apresentariam uma diminuição na conectividade neuronal (Zarate et al., 2006; Kapczinski et al., 2008; Magioncalda et al., 2015) sendo pela primeira vez analisado por ensaios de imunofluorescência e bioinformática.

Por fim, mesmo que a utilidade de biomarcadores em transtornos psiquiátricos ainda sejam limitadas, biomarcadores, incluindo os mediadores de alostase, mostram ser uma ferramenta útil que pode vir a auxiliar e guiar o tratamento do TB.

5. CONCLUSÕES

Com base nos assuntos abordados nos dois primeiros capítulos desta tese, podemos concluir que a toxicidade sistêmica no TB envolve uma série de mecanismos biológicos, como alteração em fatores neurotróficos, inflamatórios e de estresse oxidativo. Também foi possível verificar uma associação entre as alterações periféricas (aumento de perfil inflamatório, de estresse oxidativo e diminuição dos níveis da neurotrofina BDNF) com pior desempenho cognitivo nos pacientes com TB, conforme avaliado através de dados da literatura.

Em relação ao capítulo três, verificamos que o modelo de diferenciação das células SH-SY5Y, com ácido retinóico por sete dias, apresenta uma expressão gênica com perfil neuronal. O que juntamente com os achados anteriores do nosso grupo indica que este modelo seria adequado para estudar transtornos que acometem o SNC, por ser inovador ao trazer um modelo celular de origem humana, de fácil manuseio e com perfil neuronal verificado por análises de expressão gênica.

Nos testes *in vitro*, realizados no capítulo quatro, avaliamos que o soro dos pacientes bipolares seria capaz de causar toxicidade em células com perfil neuronal e ao analisar os diferentes estágios do TB, verificamos que pacientes em estágio tardio apresentam maior toxicidade, levando a diminuição da viabilidade celular, quando comparado a pacientes em estágio inicial e ao grupo controle. Ainda, que o soro de pacientes bipolares mostrou ser

capaz de reduzir a densidade de neuritos quando analisados em cultura de células de perfil neuronal, sendo ocasionado, principalmente, pelos pacientes em estágio tardio, indicando que o soro de pacientes neste estágio teria um composto tóxico capaz de levar a diminuição da conectividade neuronal.

Sendo assim, os achados dos testes do soro de pacientes bipolares em cultura, corroboram com dados da literatura que sugerem que o paciente bipolar em estágio tardio teria uma diminuição da conectividade neuronal, possivelmente estando assim relacionado as alterações de cognição e funcionalidade que se encontram mais proeminentes em pacientes em estágio avançado do TB.

6. PERSPECTIVAS

Como perspectiva dos achados dessa tese, iremos realizar a validação do microarranjo realizado, visando confirmar os dados de bioinformática já analisados. A validação da técnica de microarranjo será realizada por expressão gênica através da técnica de PCR em tempo real, onde os dez genes que se mostraram estar mais expressos em cada modelo (proliferativa e AR-diferenciadas) serão analisados.

Outro ponto importante, seria a realização de estudos longitudinais com pacientes bipolares, estratificados em estágio inicial e tardio do TB, a fim de verificar - em um tamanho amostral maior - os desfechos avaliados nesta tese (viabilidade celular e densidade de neuritos) e suas correlações com sintomas apresentados pelos pacientes ao decorrer do estudo. Assim como, analisar o efeito de outros fármacos neste modelo celular, juntamente com o co-tratamento do soro com as medicações ou potenciais compostos para terapia adjuvante ao tratamento, visando avaliar *in vitro* os efeitos da medicação na toxicidade sistêmica.

Além disso, a realização de estudos com pacientes não medicados seria relevante para o estabelecimento dos possíveis efeitos dos metabólitos sobre as células neuronais. Por fim, avaliar quais compostos estariam presentes no soro dos pacientes, buscando assim identificar qual (ou quais) compostos presentes no soro seriam os responsáveis pela neurotoxicidade.

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Artigo de revisão publicado na revista *Anais da Academia Brasileira de Ciências*, propondo o modelo experimental de terapia celular com células-tronco mesenquimais para o tratamento de transtornos psiquiátricos.

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Mesenchymal stem cells for the treatment of neurodegenerative and psychiatric disorders

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ABSTRACT

Mesenchymal stem cells (MSCs) are multipotent progenitor cells that have the capacity to differentiate into all lineages of mesodermal origin, e.g., cartilage, bone, and adipocytes. MSCs have been identified at different stages of development, including adulthood, and in different tissues, such as bone marrow, adipose tissue and umbilical cord. Recent studies have shown that MSCs have the ability to migrate to injured sites. In this regard, an important characteristic of MSCs is their immunomodulatory and anti-inflammatory effects. For instance, there is evidence that MSCs can regulate the immune system by inhibiting proliferation of T and B cells. Clinical interest in the use of MSCs has increased considerably over the past few years, especially because of the ideal characteristics of these cells for regenerative medicine. Therapies with MSCs have shown promising results neurodegenerative diseases, in addition to regulating inflammation, they can promote other beneficial effects, such as neuronal growth, decrease free radicals, and reduce apoptosis. Notwithstanding, despite the vast amount of research into MSCs in neurodegenerative diseases, the mechanism of action of MSCs are still not completely clarified, hindering the development of effective treatments. Conversely, studies in models of psychiatric disorders are scarce, despite the promising results of MSCs therapies in this field as well.

Key words: Mesenchymal stem cells, treatment, neurodegenerative disease, psychiatric disorders.

INTRODUCTION

Mesenchymal stem cells were first described by Friedenstein as "colony forming units-fibroblastic" due to their ability to generate single cell-derived colonies (Friedenstein et al. 1976). Subsequently, authors have used different names to refer to these structures, and only in the 2000s did the committee of the International Society of Cytotherapy propose the name "multipotent mesenchymal stromal cells". Since then, authors have simply referred to them as

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mesenchymal stem cells (MSCs) (Dominici et al. 2006).

MSCs are multipotent progenitor cells that have the capacity to differentiating into all lineages of mesodermal origin, e.g., cartilage, bone, and adipocytes (Pittenger et al. 1999). Recent studies have shown that MSCs are also able to differentiate into cells from sources other than mesodermal, such as neurons and hepatocytes (Dezawa et al. 2004, Hermann et al. 2004, Perrier et al. 2004, Sato et al. 2005). MSCs have been identified at different stages of development, including adulthood, and in different tissues, such as bone marrow, adipose tissue, bone, lung, liver, teeth, skeletal muscle, amniotic fluid, umbilical cord, and cord blood (Campagnoli et al. 2001, da Silva Meirelles et al. 2006, Erices et al. 2000, Lee et al. 2004).

Three basic criteria have been established by the International Society of Cellular Therapy to determine whether *ex vivo* expanded cells could be considered MSCs; namely: 1) ability to adhere to plastic in cell culture; 2) capacity to differentiate into osteoblasts, adipocytes, and chondrocytes *in vitro*; and 3) expression of specific surface membrane molecules (CD73, CD90, CD105), simultaneous lack of expression of hematopoietic markers (CD14, CD34, CD45) and human leukocyte antigen DR (HLA-DR) (Dominici et al. 2006).

Due to their differentiation, self-renewal, and immune-suppressive abilities, MSCs have received increasing attention from investigators with regard to their potential use as cell therapy in different conditions, including ischemia, diabetes, and even neurological diseases (Drela et al. 2013, Ezquer et al. 2008, Honma et al. 2006, Horwitz et al. 1999, Phinney Prockop 2007). Therapies can consist of the implantation of exogenous cells to the injured site, or the release of trophic factors that will assist in the endogenous regeneration of the injured region (Sohni and Verfaillie 2013).

MIGRATION OF MSCs

Recent studies have shown that MSCs have the ability to migrate to injured sites (Chapel et al. 2003, Wang et al. 2002). MSCs migration mechanisms involve the expression of specific receptors to facilitate reaching the target site, adhering to and infiltrating the damaged organ or tissue. In this line, an important issue in MSCs therapy is the way that cells will reach the site of damage, a process denominated "homing." Therapy effectiveness depend directly on the cells' ability to produce trophic factors, such as growth factors and cytokines that will assist in the regeneration of endogenous cells. For this to occur, correct migration of cells to the injured tissue is of utmost importance. Important factors such as age, number of cell passages, number of cells, and the protocols used for cell delivery are crucial for the migration and homing processes to be successful (Ries et al. 2007, Rombouts and Ploemacher 2003).

So far, the gold standard delivery method in the administration of MSCs is intravenous infusion (Akiyama et al. 2002, Nomura et al. 2005). Notwithstanding, research continues to try to improve homing and migration, with the goal of increasing the number of MSCs capable of reaching the target site and consequently improving MSCs transplantation protocols for specific clinical applications (Cheng et al. 2008, Choi et al. 2010, Gerrits et al. 2010, Grayson et al. 2007, Maijenburg et al. 2011).

MSCs SECRETOME AND PARACRINE ACTIVITY

In addition to their differentiation potential and the migratory properties that enable tissue replacement (Mafi et al. 2011, Quevedo et al. 2009), MSCs have broad immunomodulatory properties (Aggarwal and Pittenger 2005, Menard and Tarte 2013) and paracrine activities (Mureli et al. 2013, Waszak et al. 2012). These characteristics have been associated with the therapeutic effects of MSCs and

have been investigated with a focus on potential clinical applications.

The MSCs secretome includes the molecules released by MSCs in response to injury that directly or indirectly promote repair, e.g., growth factors, cytokines, antioxidants, and extracellular matrix proteins (Chan and Lam 2013, Chen et al. 2008). Some conditions that lead to tissue damage, such as pro-inflammatory or hypoxic stimuli and exposure to apoptotic factors, increase the secretion of specific factors by MSCs, which act on angiogenesis, neurogenesis and regulate neural niche environment, mediating protection and repair processes (Chen et al. 2003, Chen et al. 2002, Rosova et al. 2008).

Evidence has suggested that MSCs have the potential to show paracrine activity even without direct cell contact. For instance, studies have demonstrated that MSCs conditioned medium was able to protect neurons from inflammation in the absence of engraftment, suggesting a neuroprotective effect through secretion of neurotrophic factors even at a distance from the damaged organ (Bai et al. 2012, Uccelli and Prockop 2010). Some of these factors with protective effects have been identified, namely: stem cell-secreted hepatocyte growth factor (HGF), fibroblast growth factor (FGF)-II, brain-derived neurotrophic factor (BDNF), and platelet-derived growth factor (PDGF)-AB (Bai et al. 2012, Constantin et al. 2009, Voulgari-Kokota et al. 2012). MSCs-secreted BDNF and nerve growth factor beta (β-NGF), for instance, have promoted cell resilience and neuritogenesis in co-culture experiments (Crigler et al. 2006). The characterization of MSCs conditioned media has pointed to insulin-like growth factor 1 (IGF-1), HGF, vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGF-β) (Nakano et al. 2010), but other factors involved in the MSCs secretome remain to be identified.

MSCs can also secrete vesicles containing important molecules such as cytokines, in addition to isolated paracrine soluble factors. These vesicles act via paracrine or endocrine signaling, however, their composition and role remain to be established (Biancone et al. 2012, Camussi et al. 2013). Both the soluble factors and these vesicles seem to be essential to the paracrine activity associated with MSCs.

The paracrine effects of MSCs have been studied in different animal models of neurological disorders, e.g., stroke, Parkinson's, Alzheimer's, and Huntington's diseases, and amyotrophic lateral sclerosis, as will be discussed below. The paracrine activity of MSCs could also be related to the immunomodulatory properties of these cells – two functions acting together for brain protection and regeneration (Fig. 1).

MSCs SECRETOME AND IMMUNOMODULATION

An important characteristic of MSCs is their significant immunomodulatory and anti-inflammatory effects. For instance, evidence has shown that MSCs can regulate the immune system by inhibiting the proliferation of T and B cells (Duffy et al. 2011, Franquesa et al. 2012), natural killer (NK) cells (Di Nicola et al. 2002, Spaggiari et al. 2008) and neutrophil apoptosis (Raffaghello et al. 2008). Via this mechanism, MSCs influence the production and secretion of antibodies by B cells, cytokine secretion, and NK cytotoxicity (Aggarwal and Pittenger 2005, Spaggiari et al. 2008). MSCs have also been suggested to inhibit the differentiation of monocytes into dendritic cells and in addition to influencing the roles of these cells (Aggarwal and Pittenger 2005, Ivanova-Todorova et al. 2009).

The mechanisms responsible for the immunosuppressive effects of MSCs have been the focus of several studies, and cell-to-cell contact and soluble factors have been indicated as key elements in this area. Among soluble factors, the following have been highlighted: nitric oxide (Sato et al. 2007), indoleamine 2,3-dioxygenase (Meisel et al. 2004), TGF-β1, HGF (Di Nicola et al. 2002), interleukin-10 (IL-10), prostaglandin E2 (pGe2) (Aggarwal and Pittenger 2005), heme oxygenase-1 (HO1),

IL-6 (Kogler et al. 2005) and soluble HLA-G5 (Selmani et al. 2008). Several studies have suggested that MSCs inhibit inflammatory processes in different disease states (Lee et al. 2009a, Sanchez et al. 2011, van Koppen et al. 2012), contributing to the regeneration of damaged tissues, probably by modulating the immune response.

In summary, the paracrine and immunomodulatory factors present in the MSCss secretome seem to play important roles in establishing an appropriate tissue microenvironment to promote repair in damaged situations justifying research into the therapeutic potential of these cells.

MSCs SECRETOME: CLINICAL APPLICATION

Clinical interest in the use of MSCs has increased significantly over the past few years, especially because of the ideal characteristics of these cells for regenerative medicine. Specifically, MSCs can be obtained from tissues commonly present in clinical situations (e.g., bone marrow, adipose tissue, and umbilical cord blood), they can be expanded in culture for testing purposes and for clinical use, and have low immunogenicity, which is very useful for potential clinical applications (Le Blanc et al. 2003).

However, before MSCs can be used in regenerative medicine, it is essential to understand the biology of these cells and investigate the most appropriate ways to culture and handle them. In addition, it is important to know in detail the properties of the molecules secreted by MSCs, through the characterization of their secretome. In this sense, gene expression, proteomics, and metabolomics have been applied to investigate the potential therapeutic action of new and already known soluble factors secreted by MSCs.

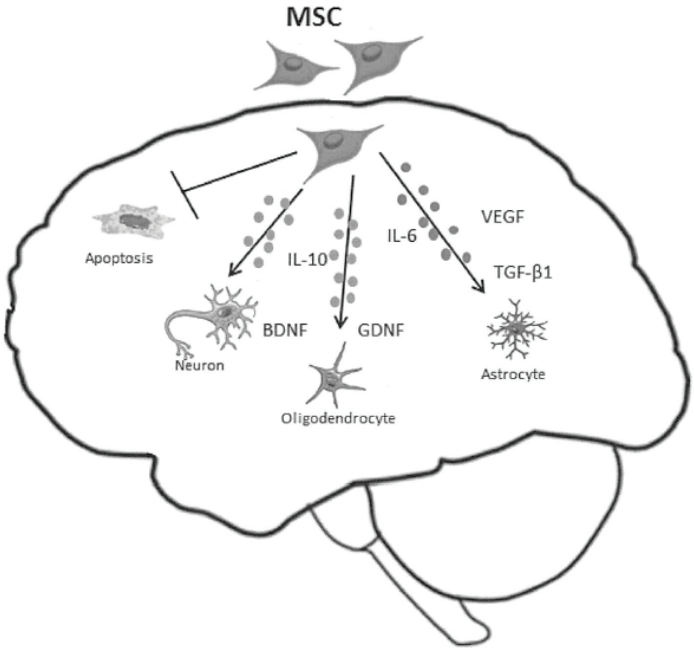

Figure 1 - Schematic figure to show the mechanism of action of MSC in the CNS. The MSC has been described to release neurotrophic factors and anti-inflammatories cytokines (BDNF, GDNF, VEGF, TGF-β1, IL-10, IL-6). These molecules act as an assistant in the nervous tissue regeneration through the activation of neurogenesis, neuroprotection, immunomodulation in astrocyte, oligodendrocyte and neuron. Furthermore can inactivating cell death through apoptosis.

MSCs APPLICATION IN NEURODEGENERATIVE DISEASES

Despite the vast amount of research into neurodegenerative diseases over the past few years, their etiology and pathophysiology are still not completely understood. Moreover, the complexity of these conditions pose difficulties to the development of effective treatments. Inflammation has been identified as a key factor in the pathophysiology of degenerative diseases affecting the central nervous system (CNS). In these pathologies, the primary insult evokes a local inflammation, with reactive astrogliosis, macrophage influx, and cell death generating tissue damage and glial scar formation (Drela et al. 2013). Therefore, immunomodulatory therapies may become a good therapeutic strategy in these cases.

MSCs therapies have shown promising results in neurodegenerative diseases. In addition to regulating inflammation, they can also promote other beneficial effects, such as neuronal growth, a decrease in free radical levels, and reduce apoptosis (Dharmasaroja 2009). Once again, application of MSCs therapies in these scenarios may help reduce all the adverse pathological events caused by neurodegenerative diseases (Table I).

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a devastating and the most common form of dementia, characterized by extracellular amyloid plaques, neurofibrillary tangles, and a progressive loss of neurons and synapses in different brain regions. Patients with AD present memory deficits and cognitive impairment (Ballard et al. 2011). To date, the treatment of AD is only palliative, and involves mainly drugs to increase cerebral acetylcholine levels. MSCs therapy seems to be a very attractive option in this condition (Drela et al. 2013).

Several studies have shown promising results with the use of MSCs in animal models of AD. One study in particular showed that bone marrow-derived MSCs injected intracerebral were effective in reducing accumulation of amyloid-β (Aβ) in the brain of an animal model of AD prepared via direct Aβ injection in the hippocampal dentate gyrus (Lee et al. 2010b). The same group showed that intracerebral transplantation of bone marrow-derived MSCs to amyloid precursor protein and presenilin in double transgenic mice ameliorated cognitive function. Furthermore, mice treated with MSCs showed a decrease in hyperphosphorylated tau protein levels (Lee et al. 2010b). In another study, Lee et al. (2010a) reported that intracerebral injection of human umbilical cord blood-derived MSCs in an acute model of AD, improved cognitive function, reduced levels of neuronal apoptosis, and decreased activation of astrocytes and microglia (Lee et al. 2010a). Injection intracerebral of bone marrow-derived MSCs has also been shown to improve learning and memory in a chemically and age-induced rat model of AD (Babaei et al. 2012). Kim et al. (2012) in turn, evaluated the mechanisms involved in Aβ degradation induced by MSCs. According to that author, soluble intracellular adhesion molecule-1 (sICAM-1) is released by human umbilical cord blood-derived MSCs and acts on microglial cells, inducing the expression of the Aβ-degrading enzyme (Kim et al. 2012).

Recently, one study showed that a single intracerebral injection of MSCs, decreased cerebral Aβ deposition compared with animals treated with phosphate buffered saline (PBS). The expression of dynamin 1 and synapsin 1, two proteins typically decreased in the brains of AD patients, were increased in the brains of AD animals treated with MSCs (Bae et al. 2013).

Even though the results obtained with animal models have been encouraging, findings from clinical studies are not yet available.

PARKINSON'S DISEASE

Parkinson's disease (PD) is an extremely common neurodegenerative illness. This condition is char-

acterized by the progressive loss of dopaminergic neurons in the substantia nigra and a severe decrease in striatal dopamine contents (Jenner 2008). The clinical symptoms of PD include tremor, muscle rigidity, bradykinesia, and postural instability. Existing pharmacological therapies and surgeries can improve clinical symptoms at early stages, but become less effective as the disease progresses (Glavaski-Joksimovic and Bohn 2013). Thus, it is clear that new therapeutic strategies are needed to decrease neuronal loss and slow progression of disease.

MSCs therapy has been considered in PD to replace lost neurons in the substantia nigra with healthy dopaminergic neurons and to avoid neuron loss (Huang et al. 2012). Over the past years, an increasing number of reports have described promising results of MSCs therapy in experimental models of PD. Animals treated with MSCs had the capacity to protect and decrease damage in dopaminergic neurons (Blandini et al. 2010, Danielyan et al. 2011, Li et al. 2001).

Improved behavior has been observed in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) animal model of PD after bone marrow-derived MSCs transplantation (Li et al. 2001). In addition, increased viability and migration of transplanted bone marrow-derived MSCs was observed in lost dopaminergic neurons after the administration of 6-hydroxydopamine (6-OHDA) in an animal model (Hellmann et al. 2006).

MSCs have also been used as a vector for gene delivery in a rat model of PD: cells were transfected with the gene coding for tyrosine hidroxylase (TH), which is the limiting-rate enzyme for dopamine synthesis. The authors reported successful transfer and expression of the TH gene in the rat striatum, as well as clinical improvement (Lu et al. 2005). Experimental studies have shown that MSCs conditioned medium promotes the survival of grafted xenogeneic dopaminergic neurons in affected mice (Shintani et al. 2007). Another study using MSCs intravenously showed a significant decrease in the loss of dopaminergic neurons in rats treated with MG-132, which causes a neurodegenerative disease similar to PD (Park et al. 2008). Furthermore, intravenous injection of MSCs reduced the loss of dopaminergic neurons in models of disease induced by injection of lipopolysaccharide (LPS) into the substantia nigra or by intraperitoneal injection of MPTP (Kim et al. 2009). In another study, treatment with MSCs and pretreatment with glial cell line-derived neurotrophic factor (GDNF) increased the proportion of TH-positive and dopamine-producing cells, resulting in clinical improvement in a 6-OHDA rat model of PD (Dezawa et al. 2004). Yet another study of the same group of authors showed that administration of dopaminergic neuron-like MSCs to the striatum, ameliorated motor function in parkinsonian macaques – a finding that was associated with restoration of the dopaminergic function (Hayashi et al. 2013). Finally, in the same line, intra-striatal injection of MSCs cultured in favorable conditions for neuronal differentiation has been shown to improve clinical symptoms in murine models of PD (Bouchez et al. 2008, Levy et al. 2008). One of the latter studies found comparable efficacy when using undifferentiated MSCs (Bouchez et al. 2008).

Other mechanisms of action of MSCs in PD refer to the immunomodulatory and anti-inflammatory effects of these cells. There is a body of evidence suggesting that inflammation and microglial proliferation are involved in the pathophysiology of PD. One study has demonstrated that MSCs have the capacity to protect dopaminergic neurons from LPS-induced microglial activation and from the production of nitric oxide and tumor necrosis factor alpha (TNF-α) (Kim et al. 2009). Chao et al. (2009) observed that intravenous administration of mouse MSCs, protected dopaminergic neurons from MPTP toxicity and decreased microglial activation (Chao et al. 2009). Those studies reinforce the potential importance of the immunomodulatory effects of MSCs for the treatment of PD.

In humans, only one clinical trial has been conducted, consisting of seven PD patients aged between 22 and 62 years, followed up for a period that ranged from 10 to 36 months. The patients received a single dose of autologous bone marrow-derived MSCs transplanted to the subventricular zone using stereotaxic surgery. Three of the seven patients showed an improvement in symptoms, with a decrease in off/on periods measured using Unified Parkinson's Disease Rating Scale. Two patients also reported subjective improvement of symptoms and reduction in drug dosage (Venkataramana et al. 2010). Further investigation is necessary to confirm the efficacy of this therapy.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease that affects the CNS, characterized by recurrent episodes of axonal lesion and demyelination (Compston and Coles 2002, Hernandez-Pedro et al. 2013). MS is the most common cause of neurological disability in young adults (Chandran et al. 2008). Treatments currently available focus on the immune system, aiming to control the inflammatory process that leads to demyelination (Karussis and Kassis 2008). These therapies are only partially effective, as they are not capable of reversing neuronal damage. Because neurodegeneration is thought to be the cause of the gradual worsening observed in patients with MS, new approaches that promote neuronal repair are needed (Cohen 2013).

Over the last decade, several preclinical studies have demonstrated a great potential of MSCs in the treatment of MS (Gerdoni et al. 2007, Karussis et al. 2010, Zappia et al. 2005, Zhang et al. 2005). The most common animal model of MS is experimental autoimmune encephalomyelitis (EAE), in which immunization with neural antigens derived mainly from myelin, in combination with adjuvants, leads to demyelination, inflammation, and axonal damage in the CNS (Cohen 2013). Zappia et al. (2005) have shown that intravenous injection of MSCs in mice with chronic EAE leads to reduction of demyelination and CNS infiltration by inflammatory cells (Zappia et al. 2005). In that study, MSCs also improved the clinical severity of MS. MSCs were effective when administered at disease onset and peak, but not after disease stabilization. In a study conducted by Zhang et al. (2005), MSCs also caused significant functional improvement when injected intravenously in EAE mice, with some level of engraftment in the CNS. Demyelination significantly decreased, and BDNF cells significantly increased in treated mice, compared to controls (Zhang et al. 2005).

The immunomodulatory activity of MSCs is relevant for the treatment of MS, but it is important to keep in mind that the effects of MSCs are not limited to these properties. MSCs have been shown protect neurons even with very limited evidence of engraftment or transdifferentiation (Morando et al. 2012). MSCs can inhibit pathogenic myelin-specific antibodies, as shown in the study by Gerdoni et al. (2007), where a limited number of labeled MSCs were detected in the CNS of treated EAE mice (Bai et al. 2009, Gerdoni et al. 2007). Many other studies have demonstrated that these cells can modulate peripheral immune response to myelin antigens. Bai et al. (2009) showed that treatment with human bone marrow-derived MSCs, reduced inflammatory T-cells and associated cytokines, and concomitantly increased IL-4-producing type 2 helper (Th2) cells and anti-inflammatory cytokines in treated EAE mice (Bai et al. 2009).

Based on the evidence provided by preclinical studies, a few clinical trials have attempted to demonstrate the safety and efficacy of MSCs in patients with MS (Bonab et al. 2012, Connick et al. 2012, Karussis et al. 2010, Yamout et al. 2010). All those studies were open-label and employed autologous MSCs. Bonab et al. (2012) studied 25 patients with progressive MS unresponsive to conventional treatment recruited to receive a single intrathecal injection of autologous bone marrow-derived MSCs. Therapeutic response was

followed for 12 months, and the authors showed that the clinical course of the disease could be stabilized with no serious adverse effects (Bonab et al. 2012). Another recent clinical trial assessed the neuroprotective effects of intravenous MSCs on optic nerve function and reported improvement after MSCs injection (Connick et al. 2012).

Currently, there are a upcoming clinical trials registered in clinicaltrials.gov aiming to assess the efficacy of MSCs therapies in MS. Although this approach has shown promising results, larger randomized controlled clinical trials are needed to determine treatment feasibility and to elucidate the mechanisms by which this tool can be useful.

HUNTINGTON'S DISEASE

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by a mutation in the huntingtin (*htt*) gene. HD is characterized by neuronal cell loss leading to intellectual decline, movement disorders, and behavioral changes (Lin et al. 2011, Maucksch et al. 2013). The neuropathology of HD manifests in the progressive degeneration of striatal GABAergic neurons. Currently, there is no therapy available capable of interrupting disease progression (Lin et al. 2011, Maucksch et al. 2013).

There is a large interest in the use of MSCs to treat HD, and several preclinical studies have investigated the potential applications of this therapy in animal models. Lee et al. (2009b) showed that human adipose-derived MSCs transplanted into the ipsilateral striatal border of mice transgenic for HD, increased survival, attenuated the loss of striatal neurons, and reduced *htt* aggregates (Lee et al. 2009b). The same study also investigated the effects of human adipose-derived MSCs in cell culture. The authors demonstrated that the cells secreted multiple growth factors, e.g., BDNF, IGF-1, and NGF, among others.

A recent study investigated the effect of the extract of adipose-derived MSCs in a HD mouse model and in neuronal cells. Intraperitoneal injection of the extract improved performance in the rotarod test, used to evaluate motor coordination in rodents and especially sensitive to detect cerebellar dysfunction (Im et al. 2013, Shiotsuki et al. 2010) . Treatment also ameliorated atrophy and mutant *htt* aggregation in the striatum. Neuro2A neuroblastoma cells treated with the same extract showed increased expression of cAMP response element-binding protein (p-CREB) and peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α), which could modify HD progression (Im et al. 2013).

Another two studies have investigated the effects of human MSCs in different mouse models of HD (Lin et al. 2011, Snyder et al. 2010). Both studies demonstrated reduced striatal atrophy after intrastriatal transplantation of human MSCs, suggesting a neuroprotective effect associated with the neurotrophic factors secreted by these cells (Maucksch et al. 2013).

Results reported in studies with animal models are encouraging. However, further studies are required, especially clinical trials, to establish the safety and effectiveness of using MSCs in the treatment of HD.

MSCs APPLICATION IN PSYCHIATRIC DISORDERS

Over the past few years, many studies have focused on immunological abnormalities and the decrease of neurotrophic factors that characterize the pathophysiology of psychiatric disorders. Several studies have shown increased levels of pro-inflammatory cytokines, e.g., TNF-α, IL-6, and IL-2, as well as decreased levels of BDNF, an important neurotrophin for CNS, in severe mental illnesses, such as bipolar disorder, schizophrenia, and major depression (Asevedo et al. 2013, Kapczinski et al. 2011, Kunz et al. 2011, Patas et al. 2013). Furthermore, many studies have shown important cognitive impairment, neuroanatomical alterations and decreased neurogenesis in the hippocampus of patients with affective disorders (Caletti et al.

TABLE I
Summary of the main results using MSCs application in neurodegenerative and psychiatric diseases.

Disease	Model	Route of delivery	Main findings	References
Alzheimer's disease	Animal mode	Intracerebral	Reducing accumulation of amyloid-β (Aβ) in the hippocampal dentate gyrus	Lee et al. 2010b
	Animal model	Intracerebral	Improved cognitive function, reduced levels of neuronal apoptosis, and decreased activation of astrocytes and microglia	Lee et al. 2010a
	Animal model	Intracerebral	Improved learning and memory	Babaei et al. 2012
	Animal model	Intracerebral	Decreased cerebral Aβ deposition	Bae et al. 2013
Parkinson's disease	Animal model	Intracerebral	Increased viability and migration of dopaminergic neurons	Hellmann et al. 2006
	Animal model	Intracerebral	Increased expression of the TH gene in the rat striatum, as well as clinical improvement	Lu et al. 2005
	Animal model	Intravenous	Reduced the loss of dopaminergic neurons in models of disease induced by injection intraperitoneal of MPTP	Kim et al. 2009
	Animal model	Intravenous	Protected dopaminergic neurons from MPTP toxicity and decreased microglial activation	Chao et al. 2009
	Clinical trial	Intra-ventricular	Three of the seven patients showed an improvement in symptoms, with a decrease in off/on periods measured using Unified Parkinson's Disease Rating Scale	Venkataramana et al. 2010
Multiple sclerosis	Animal model	Intravenous	Reduction of demyelination and CNS infiltration by inflammatory cells and improved the clinical severity of MS	Zappia et al. 2005
	Animal model	Intravenous	Functional improvement with some level of engraftment in the CNS and decreased demyelination and increased BDNF	Zhang et al. 2005
	Animal model	Intravenous	Reduced inflammatory T-cells and associated cytokines, and concomitantly increased IL-4-producing type 2 helper (Th2) cells and anti-inflammatory cytokines	Bai et al. 2009
	Clinical trial	Intrathecal	Clinical course of the disease was stabilized with no serious adverse effects	Bonab et al. 2012
	Clinical trial	Intravenous	Improvement in visual acuity and visual evoked response latency	Connick et al. 2012
	Clinical trial	Intrathecal + Intravenous	Functional improvement	Karussis et al. 2010
Huntington's disease	Animal model	Intracerebral	Increased survival, attenuated the loss of striatal neurons, and reduced *htt* aggregates	Lee et al. 2009b
	Animal model	Intraperitoneal	Improved performance in the rotarod test, ameliorated atrophy and mutant *htt* aggregation in the striatum.	Im et al. 2013
	Animal model	Intracerebral	Demonstrated reduced striatal atrophy after intrastriatal transplantation of human MSCs, suggesting a neuroprotective effect associated with the neurotrophic factors secreted by these cells	Lin et al. 2011
Depression	Animal model	Intracerebral	Increased hippocampal neurogenesis and improved depressive behavior	Tfilin et al. 2010

2013, Dranovsky and Hen 2006, Thomas et al. 2007, Torrent et al. 2010, Trivedi and Greer 2013).

In fact, despite the promising contributions of MSCs therapies in psychiatry, few studies have evaluated the effects of MSCs in models of psychiatric disorders. MSCs have the ability to promote neurogenesis and the survival and differentiation of neural cells by expressing neurotrophic factors, e.g., BDNF, NGF, and IGF. Moreover, as a result of their immunomodulatory properties, they can prevent apoptosis and decrease inflammation (Crigler et al. 2006, Yoo et al. 2008).

Tfilin et al. (2010) showed that treatment of an animal model of depression with MSCs, increased hippocampal neurogenesis and improved depressive behavior (Tfilin et al. 2010). Another study evidenced that intra-hippocampal transplantation of MSCs enhanced neurogenesis and did not impair behavioral functions in rats (Coquery et al. 2012). These results are promising and may lead to a novel modality for the treatment of psychiatric disorders. However, more studies are necessary to elucidate the precise mechanisms of action of MSCs in mental illness.

CONCLUSIONS

There are numerous preclinical studies using MSCs transplantation for diseases on the CNS that show promising results. These studies suggest that MSCs act through release of different neurotrophic factors, anti-inflammatories and antiapoptotic factors that can promote recover the injured area and prevent damage in neurodegenerative disorder. However, more clinical studies are necessary to understand the exact mechanism of action of MSCs in neurodegenerative disease and evaluate if the treatment with MSCs could cause side effects in patients. On the other hands, there are a few studies using the MSCs in psychiatric disease, but these studies have demonstrated promising results in depression and suggest that the MSCs can be a new strategy for the treatment of mental disorder. Future studies should be developed to evaluate the most effective routes of administration, dose and source of MSCs for each disease and their therapeutics effects. Thus, this new treatment may became an important therapeutic option for psychiatric patientes that do not respond to conventional treatment.

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RESUMO

Células tronco mesenquimais (CTM) são células progenitoras multipotentes que têm a capacidade de se diferenciar em todas as linhagens de origem mesodérmica, como, cartilagem, ossos, e adipócitos. CTM tem sido identificadas em diferentes fases do desenvolvimento, incluindo a idade adulta e em diferentes tecidos, tais como medula óssea, tecido adipose e cordão umbilical. Estudos recentes têm mostrado que o CTM possui a capacidade de migrar para locais de lesões. Nesse sentido, uma característica importante do CTM são os seus efeitos imunomodulatórios e anti-inflamatórios. Por exemplo, há evidências que as CTM podem regular o sistema imune por inibição da proliferação de células T e B. O interesse clínico no uso das CTM tem aumentado consideravelmente nos últimos anos, especialmente devido as ideais características destas células para a medicina regenerativa. Terapias com CTM têm mostrado resultados promissores em doenças neurodegenerativas, além de regular a inflamação, pode promover outros

efeitos benéficos, por exemplo, o crescimento neuronal, diminuição dos níveis de radicais livres e reduzir a apoptose. No entanto, apesar de muitos estudos em doenças neurodegenerativas, o mecanismo de ação das CTMs ainda não estão completamente esclarecidos, o que dificulta o desenvolvimento de tratamentos eficazes. Por outro lado, estudos em modelos de doenças psiquiátricas são escassos, mas há promissores resultados utilizando CTM nessa área.

Palavras-chave: Células-tronco mesenquimais, tratamento, doença neurodegenerativa, transtornos psiquiátricos.

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ANEXO 4

Artigo científico submetido a revista *Experimental Neurology* que avalia as diferenças entre os fenótipos da linhagem celular SH-SY5Y: células proliferativas e AR-diferenciadas, avaliando, principalmente, a resposta destes fenótipos ao insulto com 6-OHDA.

Dissimilar Mechanism of Action and Dopamine Transporter Dependency of 6-Hydroxydopamine-Induced Neurotoxicity in Undifferentiated and RA-Differentiated SH-SY5Y Cells

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Abstract

Research on Parkinson's disease (PD) and drug development is hampered by the lack of suitable human *in vitro* models that simply and accurately recreate the conditions of the disease. Here we characterize relevant neuronal features to discriminate undifferentiated and retinoic acid (RA)-differentiated SH-SYSY cells, and explored differences between both cell models in response to 6-hydroxydopamine (6-OHDA). RA-differentiated SH-SY5Y cells demonstrated low proliferative rate, pronounced neuronal morphology, high expression of genes related to synapse vesicle cycle and dopaminergic markers. Differences in overall antioxidant defenses were found. Even though RA-differentiated SH- SY5Y cells presented high basal antioxidant capacity and resistance to H_2O_2, they are two-fold more sensitive to 6-OHDA. Dopamine transporter inhibition by 3α-bis-4-fluorophenyl-methoxytropane, and dithiothreitol treatment, a cell- permeable thiol reducing agent, protected RA-differentiated, but not undifferentiated, SH-SY5Y cells from neuronal death caused by 6-OHDA, mimicking a phenomenon described *in vivo* that it is still controversial for *in vitro* models. We demonstrate, for the first time, crucial differences in the 6-OHDA operating action mechanisms in undifferentiated and RA-differentiated SH- SY5Y cells. These will impact our understanding of the pathological mechanisms of PD and the development of new therapies and drugs for the management of the disease.

Keywords: SH-SY5Y, retinoic acid, Parkinson's disease, experimental model, 6-hydroxydopamine, dopamine transporter.

Introduction

Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons in substantia nigra pars compacta (SNpc) and decreased dopamine (DA) innervation in the striatum[1]. Although PD is mainly associated at the cellular level with oxidative stress[2] and mitochondrial dysfunction[3], the functional changes operating during the initial stage of PD remain unknown[4]. These limitations are widely attributed to the lack of reliable human in vitro cell models for studying the molecular mechanisms underlying the pathophysiology of PD[5]. The main cause of this is the difficulty to reproduce the complex physiological and biochemical features of a human dopaminergic neuron in vitro[6].

In this context, the human neuroblastoma cell line SH-SY5Y is the most used in vitro model for modeling dopaminergic neurons[7], mainly because it expresses the catecholamine synthesis machinery[8]. Although SH-SY5Y cells are widely used as an in vitro PD model, they do not express neuronal properties such as a terminal post-mitotic state and the expression of synaptic proteins[5]. Interestingly, the in vitro differentiation of the human SH-SY5Y neuroblastoma cell line into a neuron-like phenotype was established more than 30 years ago. Differentiation protocols commonly use retinoic acid (RA) as a neurotrophin that induces changes in morphology and leads to cell cycle arrest[9]. However, the number of studies addressing the differences between the undifferentiated and RA-differentiated SH-SY5Y cells are few [10–14].

Besides the use of human dopaminergic (neuron-like) cells, it is also necessary to be able to mimic the pathophysiology of PD in order to have a reliable experimental in vitro model for this disorder [15]. For over 40 years, the catecholamine-derived neurotoxin 6-hydroxydopamine (6-OHDA) has been used to induce dopaminergic cell death in several preclinical experimental models of PD[16]. Once inside the neuron, 6-OHDA accumulates in the cytosol where it undergoes non-enzymatic auto-oxidation, resulting in the production of reactive oxygen species and p-quinones, as well as a decrease in antioxidants levels[17,18].

6-OHDA is an analogue of dopamine, which enters the dopaminergic neuron via the dopamine transporter (DAT)[19, 20]. This process is well established in vivo[21], but it is still controversial in in vitro. Previous studies have shown that DAT inhibitors do not

protect SH-SY5Y cells from 6-OHDA toxicity[22]. In contrast to this, they do provide a partial protection against 6-OHDA toxicity towards primary dopaminergic neurons[23]. These controversial findings may be related to the in vitro cellular model used since most of these experiments were performed in cells, including undifferentiated SH-SY5Y cells, which have a low expression level of DAT. In spite of the large amount of data related to this subject, there are no studies showing the role of DAT in mediating 6-OHDA toxicity in RA-differentiated SH-SY5Y cells.

In the present work, we aim to compare gene expression, in undifferentiated and RA-differentiated SH-SY5Y cells, of important networks related to dopaminergic neuron machinery, morphology and redox metabolism. Furthermore, we evaluated the response of both models to 6-OHDA- cytotoxicity. Here, for the first time, we demonstrate the DAT dependency of 6- OHDA-induced cell death in RA-differentiated cells.

Results and Discussion

Neuronal characterization

Neurons are specialized cells that process and transmit information through electrical and chemical signals. Moreover, they are permanently post- mitotic and as such do not undergo cell divisions [24]. Hence, it is important to evaluate whether in vitro models present these relevant features. In order to analyze the neuronal features of undifferentiated and RA-differentiated cells (differentiation protocol described in Fig. 1), we first evaluated the effect of RA treatment upon cell proliferation rates and cell cycle distribution. RA- differentiation was confirmed by the increased expression of tyrosine hydroxylase (TH), neuronal nuclei protein (NeuN), and neuron-specific enolase (NSE), with concomitant decrease in the undifferentiated cell marker nestin, as previously described [12].

Cellular growth, measured using cell counting, showed a significant decrease in the proliferation rates of RA-differentiated cells (Fig. 2a). Previous studies have demonstrated that lowering serum levels in culture medium can cause cell cycle arrest in G1/G0 phase and a decrease in proliferation rates, which combination with RA leads to terminal differentiation of neuroblast cells[25, 26]. In contrast, we observed that decreased

cellular growth in RA-differentiated cells was associated with a decrease in S phase in combination with G2-M arrest (Fig. 2b). This feature is commonly observed in cells treated with brain-derived-neutrophic-factor (BDNF), another important neurotrophin [27].

To further investigate this, we compared gene expression of the cell cycle network in undifferentiated and RA-differentiated cells using microarray analysis and GSEA (Gene Set Enrichment Analysis). No statically significant differences were observed between the two phenotypes (Fig. 2c), which was expected since the gene set network used (KEGG pathways entry hsa04110) covered the cellular machinery related to both cell cycle arrest and proliferation. The genes enriched in RA-differentiated SH-SY5Y cells are summarized in Fig. 2c. These genes are associated with cell cycle arrest, for instance, cyclin- dependent protein kinases (CDK) inhibitors (e.g. p18, p19, p21 and p27) and genes related to G2-M arrest, such as GDD45G and SMAD3 [28].

We next evaluated changes in cell morphology in both cellular models using quantification of neurite density (Fig. 2d,e). A significant increase in neurite density was observed in RA-differentiated cells ($p < 0.0001$), suggesting a change from epithelial (as defined by ATCC for SH-SY5Y cells) [29] to a stellate morphology. The term neurite refers to axons and dendrites extended by neuronal cell lines, and their quantification is an important morphological parameter of neuronal differentiation[5,6]. Hence, the increased neurite density observed in RA-differentiated cells represents a significant advantage of this cellular model, since these structures form synapses and can be used as an endpoint in neurotoxicological evaluations[30].

After morphological characterization, we next analyzed which cellular model possessed the appropriate molecular synapse machinery. One important molecular network are genes involved in synaptic vesicle cycle. Using landscape analysis and GSEA, we observed a significant enrichment of the gene set comprising the synaptic vesicle cycle components (KEGG pathways entry hsa04728) in RA-differentiated, compared to undifferentiated, SH-SY5Y cells ($p < 0.05$) (Fig. 2f,g). Table 1 lists the subset of genes that contribute most to the enrichment result. The synaptic vesicle cycle consists of exocytosis followed by endocytosis and recycle [31]. At first, vesicles are loaded with neurotransmitters, which require the presence of an active transporter along with a proton pump to provides the required pH and electrochemical gradients. Fundamental to

this is the role of H+-ATPase transporters and solute carriers such as SLC18A1, SLC18A3 and SLC17A8[32]. Once the vesicles are loaded, they are tethered near to the release sites, after which vesicles are primed before being ready to undergo fusion. Genes involved in this process include UNC13, RIMS1 and syntaxin[33]. The primed vesicles subsequently undergo fusion processes that are regulated by SNARE proteins, such as SNAP-25, NSF and complexins[34]. Finally, the synaptic vesicles incorporated to the plasma membrane are retrieved by endocytosis, a process which involves many proteins, e.g. dynamins and clathrins[35]. Our results demonstrated that all of these genes were up-regulated in RA-differentiated cells (Fig. 2f,g; Table 1).

Taken together, our data point to highly diverse phenotypes presented by undifferentiated and RA-differentiated SH-SY5Y cells. Undifferentiated cells exhibited characteristics typical of a tumour phenotype, namely epithelial morphology, low expression of genes related to synaptic function and high proliferation rates. In contrast, RA-differentiated SH-SY5Y cells were characteristic of a neuronal phenotype, presenting low proliferation rates, a pronounced neuronal morphology and an enrichment of the molecular machinery responsible for synaptic function.

Dopaminergic characterization

Both cellular phenotypes (undifferentiated and RA-differentiated SH- SY5Y cells) are widely used to study the molecular and cellular mechanisms of PD. Thus, after studying the differences in general neuronal properties, we investigated several dopaminergic features of both cell models. At first, we evaluated global differences in gene expression of the dopaminergic synapse network, using GSEA. Even though we did not find a global significant difference between phenotypes (Figure 3a) – most likely due to this gene set including genes involved in both pre- and post-synaptic processes. PKA, MAPK, CAMKII and PP2A, major regulators of TH activity (rate-limited enzymes of catecholamine synthesis)[36], were all ranked in association with the neuronal phenotype. The complete list of genes significantly enriched in RA-differentiated cells from dopaminergic synapse GSEA is listed in table 2.

Moreover, using differential gene expression analysis, we verified the expression levels of the most common dopaminergic markers derived from SNpc presynaptic

neurons[37]. The genes evaluated were from catecholamine synthesis (DDC, GCH1 and TH), degradation (MAOA, MAOB, COMT), and synaptic function (SLC18A1, SLC18A2, SLC6A3, DRD2). The expression of DR2, GHC and SLC18A1 was significantly increased in RA-differentiated cells as compared to undifferentiated cells (Figure 3b).

Hence, we demonstrated that both phenotypes of SH-SY5Y cells expressed the dopaminergic machinery necessary to produce and release DA. It is well known that neuroblastoma cancers (as the primary tumor that SH- SY5Y cells were isolated from) produce catecholamines[38]. As such, undifferentiated cells are commonly used as PD model. On the other hand, many lines of evidence showed that RA-differentiated cells increase their expression of these dopaminergic markers, such as TH [9,12,13], although other studies have shown no difference in TH expression[11,39]. These discrepancies in the literature might be attributable to the varying differentiation protocols used, since there are differences between them, such as duration, cell densities, serum concentration and differentiation agent (e.g. RA, staurosporine, BDNF)[11–14].

Lastly, DA levels were investigated using an immunohistochemical approach in both SH-SY5Y phenotypes. In Fig. 3c, we confirmed that both models produced DA, as expected. Although we did not directly quantify DA content, qualitative assessment revealed that DA fluorescence signal was increased, suggesting that DA content was significantly higher in RA- differentiated cells (Fig. 3c). Hence, our results show that RA-differentiation of cells increased the expression of pre-synaptic dopaminergic markers, which potentiate the dopaminergic phenotype. As such, RA-differentiated SH-SY5Y cells demonstrate characteristics concordant with dopaminergic neurons and hence are more suitable as an in vitro model of PD.

Antioxidant-related endpoints

Dopaminergic neurons are exposed to a chronic oxidative damage, mostly attributed to the high levels of iron present in SNpc, the hydroxyl radical (HO•) produced by dopamine metabolism[40]. Hence, oxidative stress is thought to causally contribute to the pathogenesis of progressive neurodegeneration observed in PD[2]. Based upon the pivotal importance played by oxidative stress in PD, the endogenous machinery

responsible for the basal enzymatic (an non-enzymatic) antioxidant defenses should be consistently characterized when establishing any relevant in vitro cell model of PD.

To do so, we first evaluated the gene expression levels of the human antioxidant network (according to KEGG pathways) using the GSEA approach. Although there were no globally significant differences between undifferentiated and RA-differentiated cells (Fig. 4a), the expression of a set of antioxidant genes were found to be enriched in RA-differentiated cells. These genes were mostly related to thiol metabolism, such as GLRX and GLRX2 (glutaredoxins), SRN1 (sulfiredoxin), PDIA6 (protein disulfide isomerase) and TMX4 (thioredoxin associated protein) (Fig. 4a). We also verified the expression levels of the antioxidant genes using differential expression as a statistical analysis of microarray data. CAT (catalase), SOD (superoxide dismutase), GPX3 and GPX7 (glutathione peroxidase) were overexpressed in RA-differentiated cell ($p < 0.05$). In contrast, GPX1, GPX2 and GPX6 were overexpressed in undifferentiated SH-SY5Y cells ($p < 0.05$) (Supplementary Fig. 1).

To better characterize these differences in gene expression in vitro, we validated the microarray data by evaluating the activity of several enzymes involved in first line antioxidant defenses (such CAT, SOD, GPx, glutathione reductase – GR, thioredoxin reductase – TrxR, and glutathione-S-transferase – GST) and the levels of non-enzymatic antioxidant defenses (glutathione and reduced thiol levels). We also verified the responses of both cellular models to 6-OHDA and H_2O_2 cytotoxicity (Table 3). Our in vitro validation revealed that: i) both SH-SY5Y phenotypes are extremely dissimilar regarding the overall capacity and the nature of their antioxidant defenses; ii) RA-differentiated cell presented a higher basal antioxidant capacity, which explain their higher resistance against H_2O_2 insult; and iii) RA-differentiated cells were more susceptible to 6-OHDA-cytotoxicity.

Regarding the antioxidant capacity of RA-differentiated SH-SY5Y cells, it is well known that neuronal cells have low levels of antioxidants, thus they are more prone to suffer from oxidative damage when compared to other types of cells[41]. Interestingly, our data showed that the neuronal SH-SY5Y phenotype had a higher overall antioxidant capacity compared to the tumoral phenotype. Even though there is a significant increase in most of the antioxidant activities in RA-differentiated cells, these values are still low

when compared to the human brain (Table 3)[42]. The most intriguing observation was that RA-differentiated SH-SY5Y cells were more resistant to H_2O_2, yet were more susceptible to 6- OHDA cytotoxicity (Table 3), as previously described[12]. Even though 6-OHDA toxicity acts via the induction of oxidative stress, the higher antioxidant capacity observed was not able to protect RA-differentiated cells from the cell death. Therefore, it is possible that 6-OHDA induced cell death via another mechanism in RA-differentiated SH-SY5Y cells.

Although the selectivity of 6-OHDA for dopaminergic neurons reported in in vivo experiments may be due to fact that this toxin is a substrate for the DAT, many lines of evidence obtained from in vitro experiments have shown that this neurotoxin acts extracellularly, where 6-OHDA is rapidly auto-oxidized by molecular oxygen to form the anion superoxide (O2) corresponding p-quinones[22, 43]. Previous studies using undifferentiated SH- SY5Y cells show that 6-OHDA's toxicity is reduced by CAT. Moreover, glutathione, a cell-impermeable thiol, can protect undifferentiated SH-SY5Y cells from 6-OHDA toxicity, and the same study also demonstrated that DAT inhibitors (DATi) failed to decrease 6-OHDA's cytotoxicity [44]. Hence, despite the extensive use of 6-OHDA in both in vivo and in vitro studies, the precise molecular mechanism by which this toxin kills specifically dopaminergic neurons has not been fully elucidated.

In order to investigate the inconsistencies between in vivo and in vitro studies, we first pre-incubated undifferentiated and RA-differentiated cells with two thiol reducing agents, tris(2-carboxyethyl)phosphine (TCEP), a cell- impermeable compound, and dithiothreitol (DTT), a cell-permeable small-molecule, before challenging cells with 6-OHDA (Fig. 4b,d)[45]. Interestingly, no differences were found between both cellular models when TCEP were used to protect cells against 6-OHDA-oxidant insult (Fig. 4c). On the other hand, DTT was able to prevent 60% of 6-OHDA-dependent cytotoxicity in RA-differentiated cells, in contrast to only 24% in undifferentiated cells ($p < 0.0005$) (Fig. 4e). Hence, these data demonstrate, for the first time, significant differences in the mechanism of 6-OHDA's toxicity between undifferentiated and RA-differentiated SH-SY5Y cells, suggesting that, in RA-differentiated cells, part of the oxidative dysfunction caused by 6-OHDA involves the uptake of the neurotoxin (or some metabolite, such as p-quinones) presumably followed by intracellular auto- oxidation.

The role of DAT in 6-OHDA-induced cell death

In order to investigate this, we evaluated the role of DAT in the toxicity induced by 6-OHDA in both cellular models. In vivo, 6-OHDA is imported into the cell by DAT, a classical neuronal dopaminergic marker. DAT is the major regulator of dopamine neurotransmission and is responsible for the re-uptake of dopamine from the synaptic cleft [46]. However, the role played by DAT in in vitro studies is still controversial 22,23,43. Fig. 5a shows an increase in DAT immunocontent in RA-differentiated cells ($p < 0.01$), which is in accord with previous studies [10, 47].

We then investigated whether the inhibition of this transporter interfered in the amount of cell death caused by 6-OHDA. First, we examined this by using molecular docking followed by classical refinement of geometries, how both 3α- bis-4-fluorophenyl-methoxytropane, a DAT inhibitor, and 6-OHDA interacts with DAT (Fig. 5b), and compared the binding energy (EOPT) of those compounds with the corresponding values obtained for DA and p-quinone (see Supplementary Table 1 and 2 for the raw docking data).

In order to evaluate the ability of our procedure to find reliable conformations for ligands in the DAT binding site (PDB ID 4M48)[48], the redocking of nortriptyline was used as input to tune the docking machinery. As the input geometry for all ligands were modeled using quantum methods in vacuum to reach the minima energy conformation, for the sake of comparison the redocking procedure was performed using as input geometry both, the crystallographic nortriptyline data and also a structure generated using quantum geometry optimization methods. The resulting redocking pose using the crystallographic coordinates as input was a little better than the one obtained using the quantum generated structure, producing a RMSD value of 1.1260 and 1.1830 Å, respectively, from the crystallographic data (PDB ID 4M48). Although the results of redocking using distinct inputs differed, this was easily overcome through the use of classical geometry optimization for both resulting poses in the rigid DAT binding site (see Methods). This procedure led both poses to the same final geometry, with an RMSD of 0.7049 and 0.7050 Å from the crystallographic data as depicted in Supplementary Fig. 1. These results convinced us that the achieved parameterization of Autodock 4.0, the methodology applied to generate the ligand structures for docking input, and the post-

docking refinement using a classical method were adequate for the docking of other ligands molecules (such as DA, p-quinone, 6-OHDA and DATi) in the binding site of DAT.

When docked into the binding pocket of DAT, DATi showed similar orientation as observed for nortriptyline with superposition of aromatic rings and orientation of the amine group toward TM1 and TM6 (Fig. 5b). Indeed, the amine group of DATi forms a hydrogen bond with the main-chain carbonyl of Phe319 which is 2.246 Å in length, and sterically prevents Phe319 and TM6a from closing the extracellular gate, a mechanism previously suggested for nortriptyline[48]. Thus, it suggests that 3α-bis-4-fluorophenyl-methoxytropane inhibits DAT by preventing substrate binding and stabilizing the outward-open conformation.

Due to their structural similarities, DA and its metabolite 6-OHDA appear to bind in the same orientation into DAT (Fig. 5b), which to our knowledge is the first demonstration that dopamine, the DATi, p-quinone (one major metabolite of 6-OHDA auto-oxidation) and 6-OHDA, all compete sterically for the same binding site via the spatial blockage of Asp46 residue (Asp79 in DAT from Homo sapiens).

This is pivotal for the interaction of DAT with substrate via a salt bridge with dopamine's amine group (Fig. 5b)[49]. This steric blockage of the same binding site demonstrates a competitive inhibition mechanism of action for DATi. Due to the lower ligation energy of DATi for DAT in comparison to p- quinone and 6-OHDA, but higher for DA, our docking data suggest that DATi blocks completely the interaction of dopamine with DAT, but only partially p- quinone and 6-OHDA (Supplementary Table 1).

Subsequently, we pharmacologically inhibited DAT in both cellular models via pre-incubation with DATi prior to challenging cells with 6-OHDA. Our findings showed that DAT inhibition resulted in a significant decrease in H_2O_2 production and cellular viability only in RA-differentiated cells, with no effect observed in undifferentiated cells (Fig. 5c,e). Fig. 5d,f demonstrated a decrease of approximately 50% in H_2O_2 production and 41% in cellular death caused by 6-OHDA in RA-differentiated SH-SY5Y cells. In contrast, DATi was not able to prevent H_2O_2 generation and cell death caused by 6-

OHDA in undifferentiated SH-SY5Y cells, confirming that the effects observed were specific to RA- differentiated SH-SY5Y cells. Thus, DAT inhibition can protect RA-differentiated cells from the damage caused by 6-OHDA, mimicking a phenomenon described for in vivo experimental models, but still controversial for in vitro models. In contrast, other studies have shown that DATi fail to protect cells against 6- OHDA's neurotoxicity[22, 43, 50]. Most of these studies used cells with low levels of DAT (e.g. undifferentiated SH-SY5Y cells) and high doses of 6-OHDA (e.g. 100 µM), which are not as physiologically relevant as our model presented here. Hence, DAT inhibition can protect RA-differentiated cells from the toxicity of 6-OHDA, which correlates with in vivo experimental models and confirms that 6- OHDA toxicity both in vivo and in vitro occur via the same mechanism.

Conclusion

Undifferentiated and RA-differentiated SH-SY5Y cells are two unique phenotypes which can be distinguished by differences found in cells morphology, cell growth, neuronal and dopaminergic marker expression and redox metabolism. These features may contribute towards two different mechanisms of action for 6-OHDA-cytotoxicty observed in both models. In the neuronal phenotype, we demonstrated DAT dependency in 6-OHDA-induced cell death, which is likely related to their dopaminergic phenotype. Many previous studies have used undifferentiated cells as a PD model to study molecular mechanisms, to test potential drugs for the treatment of this disease and also to evaluate 6-OHDA's mechanisms of action and cellular targets. However, our data demonstrate that undifferentiated cells does not possess neuronal properties, which can create significant bias in such studies, and may have contributed, at least in part, to the limitations in our understanding of PD pathophysiology and, consequently, the lack of potential drugs to treat the disease. Hence, our data support the use of RA-differentiated cells as an in vitro model of PD.

Methods

Chemicals

Chemicals were obtained from Sigma Chemical Co. (St. Louis, MO, USA) unless otherwise stated. RA was obtained from Enzo® (East Farmingdale, NY, USA). Protein concentrations were measured using the Bradford assay[51].

Cell Culture

Human neuroblastoma cell line SH-SY5Y (ATCC, Manassas, VA, USA) was maintained in a 1:1 mixture of Ham's F12 and Dulbeco Modified Eagle Medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Cripion®), 2 mM of glutamine, 100 U/mL of penicillin and 250 µg of amphotericin B in a humidified atmosphere of 5% of CO_2 at 37ºC.

To induce cellular differentiation, cells were seeded at the following densities: 1.8 x 105 cells/well in a 96-well plate, 6 x 104 cells/well in a 24-well plate, 105 cells/well in 12-well plate and 2.5 x 106/well cells in a 75 cm2 flask (~75% of confluence). After 24 hours (day 1), medium was replaced with medium in which the FBS concentration was reduced to 1% and supplemented with 10 µM RA, and incubated for a further 7 days (Fig. 1). At the day 4, the medium was replaced, and at the day 7, cells were used for experiments or treated with neurotoxins/compounds of interest.

It is important to note that successful differentiation depends upon 3 factors: (i) the confluence of the cells in day 1 must be around 75% (higher confluence inhibits neurite outgrowth, and lower confluence leads SH-SY5Y cells to detach); (ii) the cell medium should only be used for a maximum of 2 weeks in order to avoid glutamine decomposition; and (iii) RA must be freshly prepared on the day of the medium replacements (i.e. days 1 and 4). RA stock solutions were prepared in absolute ethanol and the concentration determined using EM(351 nm) = 45000 12.

RNA isolation and microarray assay

Cells were harvested and the RNA was isolated using TRIzol Reagent (Life Technologies) following by purification (Qiagen RNeasy Mini Kit #74 104 and #79 254 - Free RNase DNase Set Qiagen). Microarray analysis wa performed using the chip GeneChip® PrimeView™ Human Gene Expression Array (Affymetrix™). The samples

were collected at the day 0 (undifferentiated cells), day 4 and day 7 (RA-differentiated cells) (Fig 1). Raw data was deposited on GEO repository (GEOID: GSE71817).

Enrichment analysis and expression values

Four genes networks were analyzed in both undifferentiated and RA-differentiated SH-SY5Y cells: synapse vesicle cycle, cell cycle, dopaminergic synapse and antioxidant (extracted from KEGG platform)[52]. GSEA was used to identify genes that contribute to global changes in expression levels in a given microarray dataset comparison. GSEA considers experiments with genome-wide expression profiles from two classes of samples (e.g. undifferentiated vs. 7-day-differentiated cells). Genes were ranked based on the correlation between their expression and the class distinction. Given a prior defined network (e.g. synaptic vesicle cycle), the GSEA determines if the members of these sets of genes are randomly distributed or primarily found at the top or bottom of the ranking[53].

To access the logarithm of gene expression, raw CEL files were analyzed using the R/Bioconductor pipeline. The data was normalized by Robust Multi-array Average (RMA) using the AFFY package, log (base 2) transformed, and batch-corrected with ComBat using the SVA package.

Neurite Density and Dopamine immunoreactivity

Neurite density was analyzed by immunofluorescence using 1:500 anti ßIII-tubulin antibody Alexa 488-conjugated (Abcam®, Cambridge, UK, cat. # ab195887) and Nuclear dye Hoechst 33342 (Thermo Fisher Scientific®, Waltham, Massachussets, USA - 62249 – dilution: 1:2000). The dopamine reactivity was evaluated using an anti-DA antibody (Abcam®, Cambridge, UK, cat. # ab6427- dilution: 1:250) followed by incubation with secondary antibody (Alexa 488-conjugated- Thermo Fisher Scientific®, Waltham, Massachussets, USA- A11008 - dilution: 1:500). Randomly selected images were captured using an EVOS® FLoid® Cell Imaging Station (Thermo Fisher Scientific Inc.) and analyzed with NIS-elements software. Neurite density was assessed using the AutoQuant Neurite software (implemented in R), and expressed as arbitrary units (A.U.)[54].

Cellular growth and cell cycle

DNA composition was measured using propidium iodide (PI), flow cytometry (BD AccuriTM C6 Flow Cytometer, USA). The results were express as percentage of cells in each cell cycle phase (G0/G1, S, G2/M). Cellular proliferation was measured by cell counting using a Neubauer Chamber.

Antioxidant enzymes activities

We evaluated the redox status in both undifferentiated and RA- differentiated SH-SY5Y cells by measuring: reduced thiol and GSH levels as well as the following antioxidant enzymes activities: GPx, CAT, SOD, TrxR, GR, GST as described previously[30].

Cytotoxicity parameters

The cytotoxicity induced by 6-OHDA and H2O2 were analyzed using 3- (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction assay. 6-OHDA was prepared in a 0.1% of ascorbic acid and used fresh. At the end of treatment, cells were washed with PBS and fresh medium containing 0.5 mg/mL MTT was added. Cells were incubated for 1 hour at 37ºC, after which DMSO was added to solubilize the formazan salt. Finally, the absorbances were measured using a microplate reader (SpectraMax® i3 MiniMaxTM 3000 Imaging Cytometer, Molecular Devices, USA) at wavelengths of 560 nm and 630 nm.

Reducing thiol agents experiments

The role of reducing agents in 6-OHDA-cytotoxicity was assessed via pre-treatment with DTT or TCEP in both cell models for 1 hour in 37ºC. Cells were then incubated with the LD50 dose of 6-OHDA[12].

DAT immunocontent and pharmacological inhibition using DATi

Cells were washed with PBS, ressuspended in Tris-buffer (pH 7.0) containing protease inhibitors (Roche®) and lysed by sonication. To evaluate changes in DAT immunocontent during the RA-differentiation process, Western blot analysis was

performed using anti-DAT antibody (Santa Cruz® Biotechnology, Dallas, Texas, USA- dilution: 1:1000). For the loading control, membranes were then stripped and reprobed with rabbit anti-glyceraldehyde-3- phosphate dehydrogenase (GAPDH) antibody (Abcam®, Cambridge, UK, cat. # ab9485- dilution 1:5000).

To investigate the DAT dependency of 6-OHDA-induced cell death in both models, cells were pre-incubated for 30 minutes with 20 µM of the DATi (Sigma®). Following this, cells were exposure to LD50 6-OHDA for 24 hours 12, after which cell viability was assessed using MTT assay. H_2O_2 generation was measured using AmplexRed® (Thermo Fisher Scientific®, Waltham, Massachussets, USA- a12222).

Structural data

The calculations performed in this study have taken full advantage of the X-ray crystal structure of the Drosophila melanogaster dopamine transporter (PDB ID 4M48) at 3.0 Å of resolution 48. The structure was modified in order to replace mutated residues in the crystallographic structure for native ones using Discovery Studio 3.1 package. The protonation state of the receptor was adjusted according to results obtained from the PROPKA 3.1 web server tool 55 and from the Protonation tool in Discovery Studio 3.1 package. The protonation state set up at physiological pH of nortriptyline was accomplished using the Marvin Sketch code version 5.5.0.1 (Marvin Beans Suite – ChemAxon) and the molecular structure was obtained through the addition of a single hydrogen atom to the amine group, with its charge adjusted to +1 (electron charge -1).

Molecular Docking

Molecular docking was performed using Autodock4. To validate the docking protocol adopted in this work we performed the redocking of nortriptyline in the DAT binding site, as describe elsewhere[56] using two distinct input conformations: (i) nortriptyline in its crystallographic conformation, and (ii) nortriptyline at the minimum energy configuration obtained after classical annealing followed by quantum DFT (GGA-TS functional) geometry optimization in vacuum using DMOL3 code. The same procedure described in (ii) was employed to obtain the molecular structures of dopamine, 6-hydroxydopamine, p-quinone and DATi for docking input. Docking was performed 20

times using the Lamarckian genetic algorithm (GA), a GA with 25,000,000 energy evaluations per run, population size set to 150, and a maximum of 27,000 generations per run. Upon completion, a thousand poses were obtained (50 poses per output) and clustered within a RMSD tolerance of 1.0 Å using Autodock Tools[57].

Pose selection and construction of the ligand-DAT complexes

The best results obtained were based upon visual inspection and calculation of energy score. Ligand-DAT complexes were prepared using the crystallographic DAT structure after the removal of nortriptyline. Every complex was classically optimized in two consecutive steps: (i) only hydrogen atoms were free to move during optimization; (ii) all hydrogen atoms and the all atoms of the ligand molecule were free to move during optimization. The classical optimization procedure was performed using the Forcite code with the force field CVFF, the convergence tolerances set to 2 x 10-5 kcal/mol (total energy variation), 0.001 kcal/mol.Å (maximum force per atom), and 1 x 10-5 Å (maximum atomic displacement).

When more than one representative cluster was observed, the best pose of each cluster was classically energy minimized into the binding site of DAT and the score of the selected poses was recalculated, in order to ensure the accuracy of the method, through a classical binding energy calculation (EOPT) as described below:

$$EOPT = EDAT + L - (EDAT + EL) \quad (1)$$

EDAT + L is the total energy of the system formed by ligand bond in DAT; EDAT is the total energy of the DAT alone, while EL is the total energy of the ligand molecule alone.

Molecule Drawing and Images Acquisition

Marvin Sketch code version 5.5.0.1- 2011, ChemAxon, was used to draw the 2D ligands structures and to predict theirs protonation state at physiological pH. The images were prepared using PyMol 1.3 [58].

Statistical Analysis

Data are expressed as means ± S.E.M. of at least 3 independent experiments carried out in triplicate, with Student's t-test and one-way ANOVA used where appropriate ($p < 0.05$) (GraphPad® Software 5.0).

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Competing financial interests statement

The authors declare that they have no competing financial interests.

Figure and Legends

Figure 1: Protocol design of the RA-induced differentiation. At day 0, exponentially growing SH-SY5Y cells were cultured in cell medium containing 10% FBS. After 24 hours (day 1), the medium was removed and fresh medium containing 1% FBS and 10 µM RA (differentiation medium) was added. 3 days later (day 4), the differentiation medium was replaced with fresh differentiation medium. At day 7, SH-SY5Y cells were used in experiments.

Figure 2: Neuronal characterization of undifferentiated and RA-differentiated SH-SY5Y cells: (i) proliferation rates and cell cycle distribution; (ii) morphometric analysis; and (iii) synaptic vesicle network. (a) Cellular growth was performed by cell counting during 7 days in undifferentiated and RA- differentiated cells. (b) Cell cycle analysis was evaluated by propidium iodide (PI) - flow cytometry. Representative image of the cell cycle analysis in undifferentiated cells and RA-differentiated cells, in which results were expressed as percentage of cells in each cell cycle phase (G0/G1, S, G2/M). (c)Enrichment analysis of the cell cycle network in undifferentiated and RA- differentiated SH-SY5Y cells using GSEA, showing the genes upregulated in RA-differentiated cells. (d) Morphological parameter evaluated by tubulin immunofluorescene of undifferentiated and RA-differentiated SH-SY5Y cells. Representative fluorescence microscopy images of undifferentiated and RA-differentiated cells. (e) Quantification of the neurite density per cell body using AutoQuant Neurite software. (f) Expression of synaptic vesicle cycle network in undifferentiated and RA-differentiated SH-SY5Y cells. STRING representation of synaptic vesicle cycle network gene interactions and landscape analysis, generated with ViaComplex® V1.0. Color gradient (Z-axis), demonstrating elevated expression of this network in 7-day-RA-differentiated, compared to undifferentiated, SH-SY5Y cells. P value refers to bootstrap analysis comparing cell lines. (g) Enrichment analysis used to identify the genes that contributed individually to the global changes in expression levels observed in RA- differentiated cells in the syntactic vesicle cycle network. Data are presented as mean ± SD of four independent experiments (n = 4), each carried out in

triplicates. *P < 0.05 (Student's t-test). Transcripts obtained as described in Methods section. Nominal p value of enrichment analysis obtained from GSEA (p < 0.05).

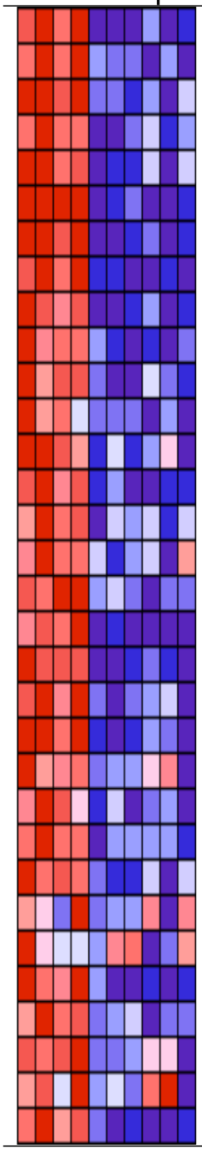
Figure 3: Dopaminergic characterization of undifferentiated and RA-differentiated SH-SY5Y cells (a) Enrichment analysis used to identify the genes that contributed individually to the global changes in expression levels observed in RA-differentiated cells in the dopaminergic synapse network using GSEA. (b) Differential expression levels of pre-synaptic dopaminergic markers in undifferentiated and RA-differentiated cells. (c) Immunocytochemical detection of dopamine. Representative fluorescence microscopy images of undifferentiated and RA-differentiated SH-SY5Y cells. Data are presented as mean ± SD of four independent experiments (n = 4), each carried out in triplicates (n= 4). *P < 0.05 (Student's t-test).

Figure 4: Redox characterization of undifferentiated and RA-differentiated SH- SY5Y cells (a) Enrichment analysis used to identify the genes that contributed individually to the global changes in expression levels observed in RA- differentiated cells in the antioxidant network using GSEA. The table lists the genes upregulated in RA-differentiated cells. (b,c,d,e) The role of thiol-reducing agents in 6-OHDA-induced cell death in undifferentiated and RA-differentiated SH-SY5Y cells. Both cellular models were treated with cell-impermeable (b) and cell-permeable (d) thiol reducing agents, followed by incubation with LD50 concentration of 6-OHDA for 24 hours. Cell viability was evaluated using MTT reduction assay and the results were expressed as a percentage of the control ± SD. Significant differences are expressed by letters, where equal letters represent no significant differences and different letters represent significant differences (P < 0.05) (one-way analysis of variance). (c,e) Analysis of the inhibition of 6-OHDA-induced cell death for each thiol-reducing agent in both cellular models. Data are presented as mean ± SD of four independent experiments (n = 4), each carried out in triplicates. *P < 0.05 (Student's t-test).

Figure 5: Evaluation of the role of DAT in 6-OHDA-induced cell death in undifferentiated and RA-differentiated SH-SY5Y cells (a) Changes in DAT immunocontent (dopaminergic cell marker) in response to RA-differentiation was evaluated using Western blot. Representative densitometric analysis of bands and immunoblot of DAT, using GAPDH as loading control. Results were calculated and

expressed as mean ± SD of densitometric units (n = 4). *P < 0.01 (Student's t-test). (b) Superposition of DATi and 6-OHDA into the binding site of DAT, showing how 6-OHDA is spatially blocked from forming a salt bridge with Asp46. (c) Evaluation of DAT inhibition in the rate of H_2O_2 production, (d) DAT-dependent H_2O_2 generation and (e) cell death in undifferentiated and RA-differentiated SH-SY5Y cells challenged with 6-OHDA. Cells were treated for 30 minutes with DATi prior to incubation with LD50 concentration of 6-OHDA for 24 hours. Cell viability was evaluated using the MTT reduction assay and results were expressed as percentage of untreated cells. Significant differences are expressed by letters, where equal letters represent no significant differences and different letters represent significant differences (P < 0.05) (one-way analysis of variance). (f) DAT-dependent 6- OHDA-induced cell death in both cellular models. Data are presented as mean ± SD of four independent experiments, each carried out in triplicates (n=4). *P < 0.05 (Student's t-test)

Table 1: List of components from synaptic vesicle cycle network significantly enriched in 7-days-RA-differentiated SH-SY5Y cells compared to undifferentiated SH-SY5Y cells.

Heat Map	Gene Symbol	Gene Name
	*SLC18A1*	solute carrier family 18 (vesicular), member 1
	ATP6V1G2	ATPase, H+ transporting, V1 subunit G2
	NSF	N-ethylmaleimide-sensitive factor
	ATP6V0D1	ATPase, H+ transporting, V0 subunit d1
	ATP6V0E2	ATPase, H+ transporting V0 subunit e2
	SNAP25	synaptosomal-associated protein, 25kDa
	ATP6V0E1	ATPase, H+ transporting, V0 subunit e1
	STXBP1	syntaxin binding protein 1
	DNM1	dynamin 1
	ATP6V1C1	ATPase, H+ transporting, V1 subunit C1
	DNM3	dynamin 3
	CPLX3	complexin 3
	CPLX1	complexin 1
	AP2A2	adaptor-related protein complex 2, alpha 2 sub.
	ATP6V0C	ATPase, H+ transporting, V0 subunit c
	RIMS1	regulating synaptic membrane exocytosis 1
	STX3	syntaxin 3
	ATP6V1H	ATPase, H+ transporting, V1 subunit H
	ATP6V1D	ATPase, H+ transporting, V1 subunit D
	AP2B1	adaptor-related protein complex 2, beta 1 sub.
	ATP6V1B2	ATPase, H+ transporting, V1 subunit B2
	CACNA1B	calcium channel, L type, alpha 1B subunit
	SLC18A3	solute carrier family 18 (vesicular), member 3
	AP2M1	adaptor-related protein complex 2, mu 1 subunit
	CLTC	clathrin, heavy chain (Hc)
	SLC17A8	solute carrier family 17, member 8
	ATP6V1G3	ATPase, H+ transporting, V1 subunit G3
	ATP6V1A	ATPase, H+ transporting, V1 subunit A
	CLTA	clathrin, light chain (Lca)
	STX2	syntaxin 2
	UNC13A	unc-13 homolog A (C. elegans)
	ATP6V1E1	ATPase, H+ transporting, V1 subunit E1

Data generated with Gene Set Enrichment Analysis (GSEA) comparing 7-days-RA-differentiated cells (n = 4) *versus* undifferentiated SH-SY5Y cells (n = 6) transcripts obtained as described in Material & Methods section. Nominal *P* value of enrichment analysis obtained from GSEA ($P < 0.05$).

Table 2: List of components from Dopaminergic Synapse Network significantly enriched in 7-days-RA-differentiated SH-SY5Y cells compared to undifferentiated SH-SY5Y cells.

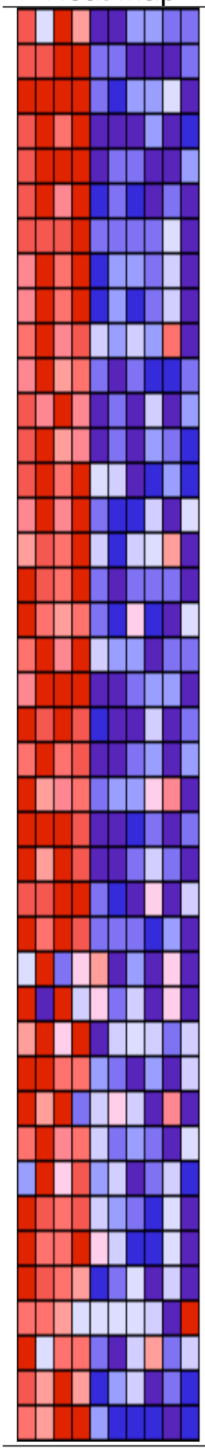
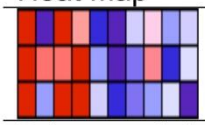
Heat Map	Gene Symbol	Gene Name
	*ITPR2*	inositol 1,4,5-triphosphate receptor, type 2
	CREB5	cAMP-responsive element binging protein 5
	MAOB	monoamine oxidase B
	SLC18A1	vesicular monoamine transporter (family 18), A1
	GNG8	G protein, gamma 8
	GNG7	G protein, gamma 7
	GNG2	G protein, gamma 2
	PPP2R2C	protein phosphatase 2A 55, reg. sub. B gamma
	PPP2R5B	protein phosphatase 2A 56, reg. sub. B, beta
	FOS	c-Fos transcription factor
	DRD2	dopamine receptor 2
	CLOCK	circadian locomotor output cycle kaput
	AKT1	RAC-alpha serine/threonine- protein kinase
	PPP2R5A	protein phosphatase 2A 56, reg. sub. B, alpha
	CREB3L2	cAMP-responsive element binding prot. 3-like 2
	MAPK10	mitogen-activating protein kinase 10
	MAPK9	mitogen-activating protein kinase 9
	ADCY5	adenylate cyclase 5
	PPP2R5C	protein phosphatase 2A 56, reg. sub. gamma
	CREB3	cAMP-responsive element binding protein 3
	GNAQ	G protein (q) subunit alpha
	PRKACA	protein kinase C, catalytic subunit alpha
	CACNA1B	calcium channel, voltage-depend., N, alpha 1B
	GNAS	GNAS complex locus
	KIF5C	kinesin heavy chain isoform 5C
	PLCB4	1-PIP-4,5 phosphodiesterase Beta 4
	CAMK2G	calcium/calmodulin-dependent PK II gamma
	GNGT1	G protein (T) subunit gamma-T1
	PLCB1	1-PIP-4,5 phosphdiesterase Beta 1
	ATF6B	activating transcription factor 6 beta
	PPP2CA	protein phosphatase 2A, cat. sub. alpha
	GNG3	G protein, subunit gamma-3
	PPP2R2D	protein phosphatase 2A 55, reg. sub. B delta
	GNB5	G protein, subunit beta-5
	PPP2CB	protein phosphatase 2A, cat. sub. beta
	MAPK8	mitogen-activating protein kinase 8 (JNK1)
	GNB1	G protein, subunit beta-1
	KCNJ3	K inward-rectifying channel, subfamily J, mem. 3
	MAPK14	mitogen-activating protein kinase 14 (p38)
	GNG12	G protein, subunit gamma-12
	GNAI3	G protein, alpha inhibiting activity 3

Table 2: *Continued…*

Heat Map	Gene Symbol	Gene Name
	*CREB1*	cAMP-responsive element binding protein 1
	GSK3B	glycogen synthase kinase 3 beta
	PRKACB	cAMP-dependent protein kinase, cat. sub. beta

Data generated with Gene Set Enrichment Analysis (GSEA) comparing 7-days-RA-differentiated cells (n = 4) *versus* undifferentiated SH-SY5Y cells (n = 6) transcripts obtained as described in Material & Methods section. Nominal *P* value of enrichment analysis obtained from GSEA ($P < 0.05$).

Figure 1.

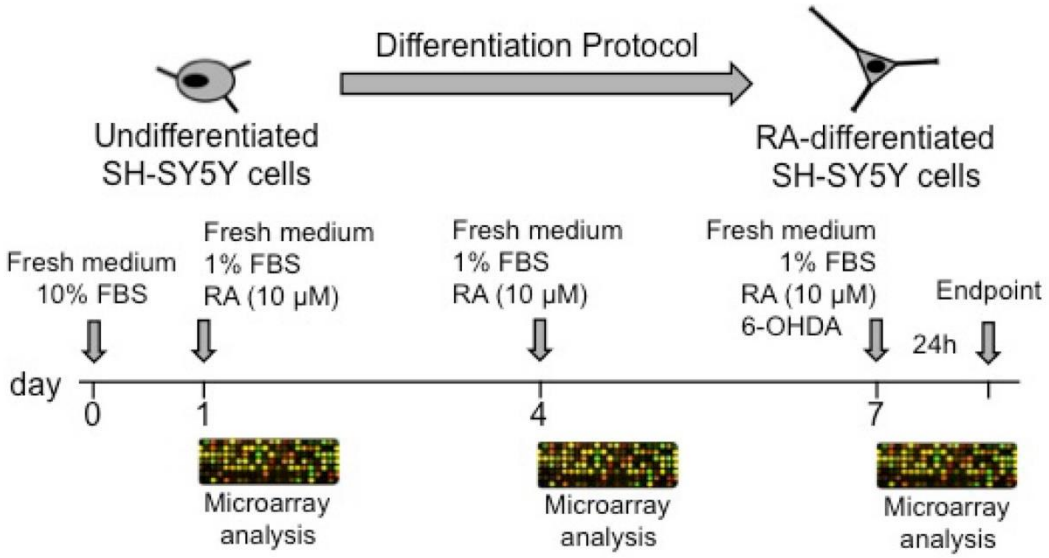


Figure 2.

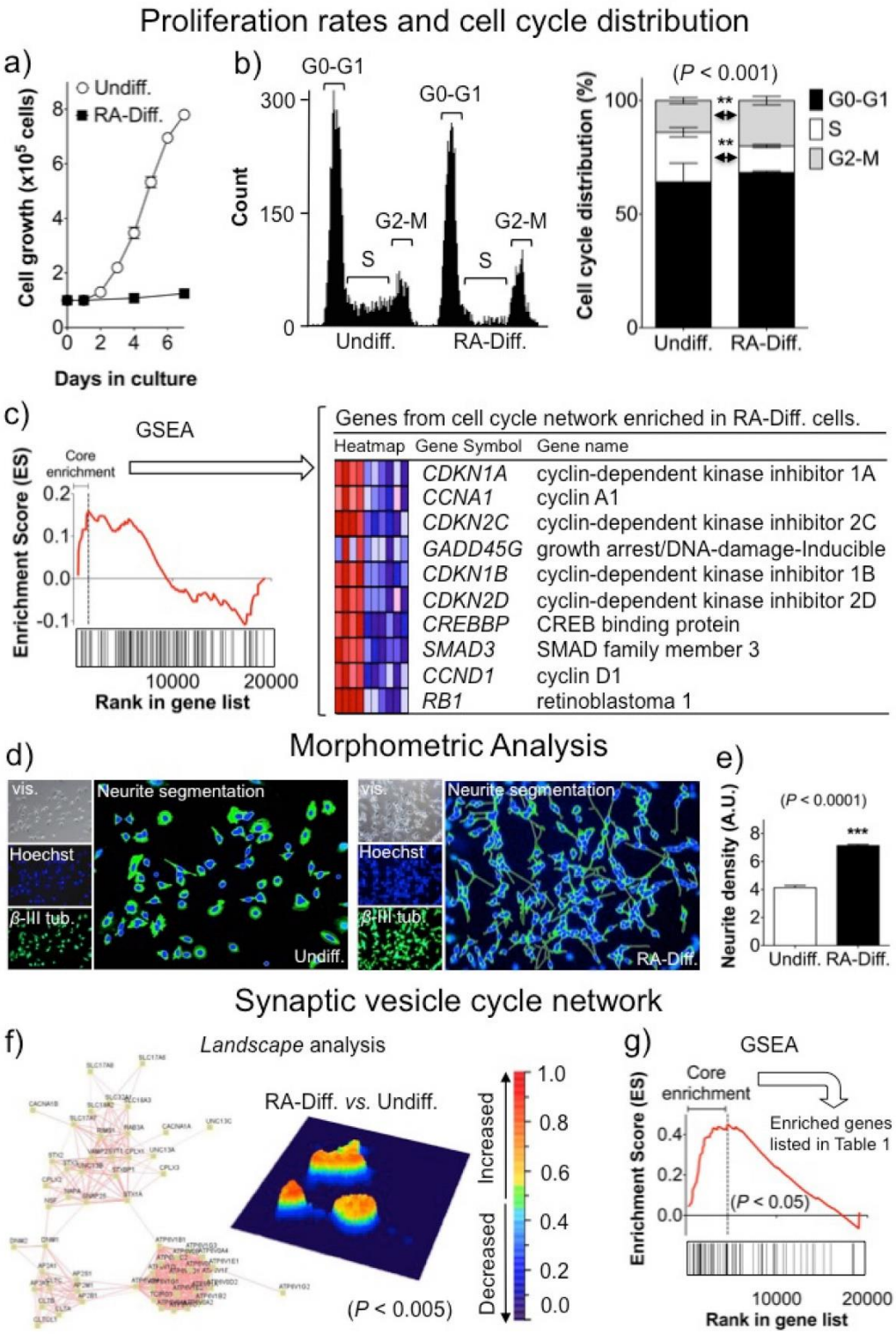

Proliferation rates and cell cycle distribution
a)
Undiff.
RA-Diff.
Cell growth (x10^5 cells)
Days in culture
b)
G0-G1
S
G2-M
Count
Undiff.
RA-Diff.
(P < 0.001)
Cell cycle distribution (%)
G0-G1
S
G2-M
c)
GSEA
Core enrichment
Enrichment Score (ES)
Rank in gene list
Genes from cell cycle network enriched in RA-Diff. cells.
Heatmap Gene Symbol Gene name
CDKN1A cyclin-dependent kinase inhibitor 1A
CCNA1 cyclin A1
CDKN2C cyclin-dependent kinase inhibitor 2C
GADD45G growth arrest/DNA-damage-Inducible
CDKN1B cyclin-dependent kinase inhibitor 1B
CDKN2D cyclin-dependent kinase inhibitor 2D
CREBBP CREB binding protein
SMAD3 SMAD family member 3
CCND1 cyclin D1
RB1 retinoblastoma 1
Morphometric Analysis
d)
vis.
Hoechst
β-III tub.
Neurite segmentation
Undiff.
RA-Diff.
e)
(P < 0.0001)
Neurite density (A.U.)
Undiff. RA-Diff.
Synaptic vesicle cycle network
f)
Landscape analysis
RA-Diff. vs. Undiff.
Increased
Decreased
(P < 0.005)
g)
GSEA
Core enrichment
Enriched genes listed in Table 1
(P < 0.05)
Enrichment Score (ES)
Rank in gene list

Figure 3.

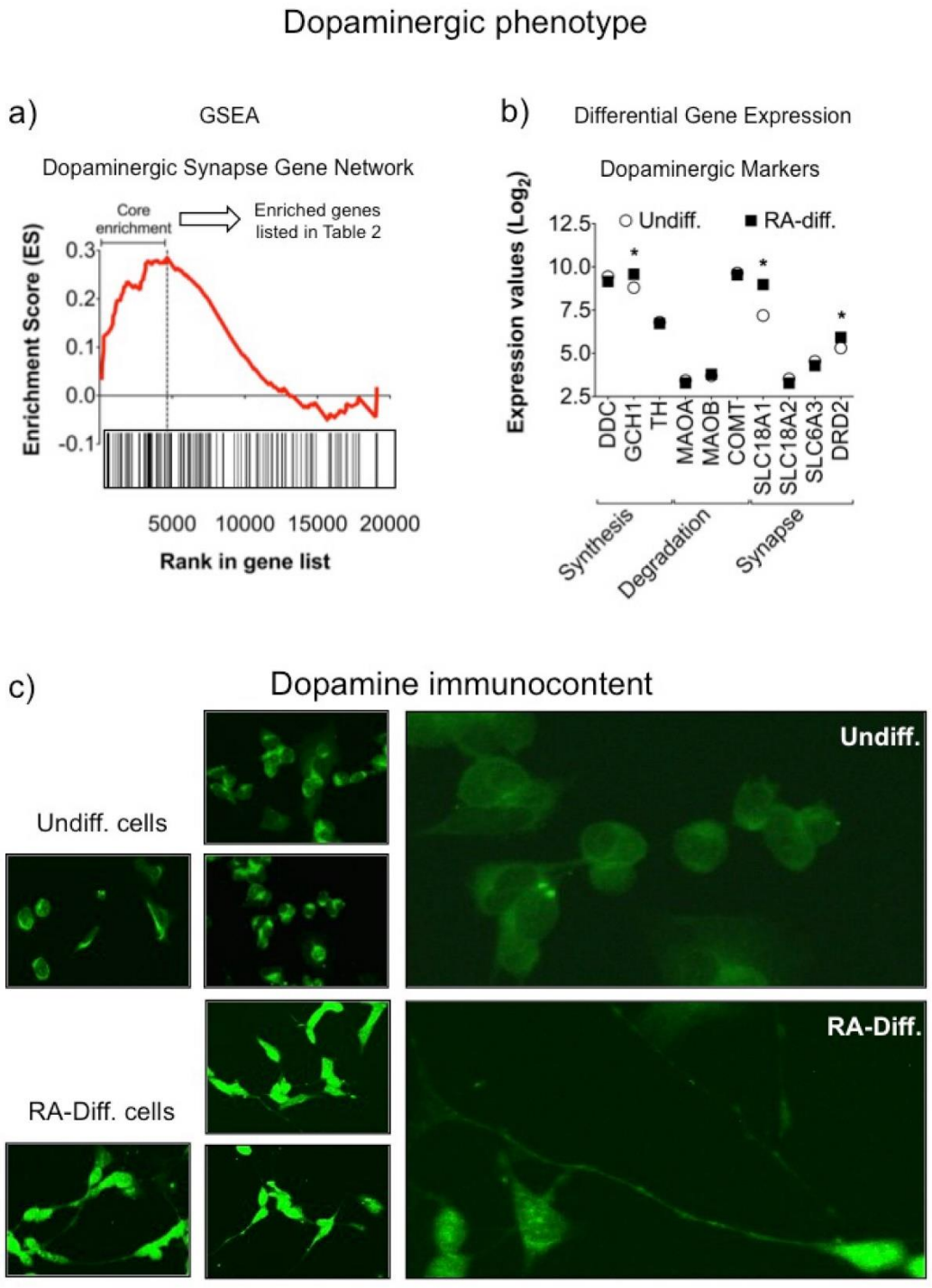

Dopaminergic phenotype
a)
GSEA
Dopaminergic Synapse Gene Network
Core enrichment
Enriched genes listed in Table 2
Enrichment Score (ES)
0.3
0.2
0.1
0.0
-0.1
5000
10000
15000
20000
Rank in gene list
b)
Differential Gene Expression
Dopaminergic Markers
Expression values (Log2)
Undiff.
RA-diff.
12.5
10.0
7.5
5.0
2.5
DDC
GCH1
TH
MAOA
MAOB
COMT
SLC18A1
SLC18A2
SLC6A3
DRD2
Synthesis
Degradation
Synapse
c)
Dopamine immunocontent
Undiff. cells
RA-Diff. cells
Undiff.
RA-Diff.

Table 3. *In Vitro* Evaluation of Redox Parameters in Undifferentiated and 7-days-RA-Differentiated Human SH-SY5Y Neuroblastoma Cells.

	Undifferentiated	RA-Differentiated	Fold change	*P*
Antioxidant enzymes defenses				
CAT (U/mg)	0.43 ± 0.07	**1.43 ± 0.16**	**3.32**	0.046
GPx (U/mg)	2.83 ± 0.50	3.85 ± 0.99	1.36	0.2336
SOD (U/mg)	10.18 ± 4.42	19.52 ± 3.09	1.92	0.0803
GR (nmol/mg)	16.47 ± 1.86	**25.46 ± 1.94**	**1.54**	0.0291
TrxR (nmol/mg)	**23.51 ± 1.59**	11.08 ± 0.54	**0.47**	0.0003
GST (U/mg)	9.96 ± 2.57	**25.31 ± 1.62**	**2.54**	0.0031
Non-enzymatic defenses				
Thiol Levels (nmol/mg)	17.57 ± 3.95	**39.16 ± 3.70**	**2.22**	0.0026
GSH levels (nmol/mg)	**16.39 ± 1.00**	6.96 ± 0.98	**0.42**	0.0008
H_2O_2 production (nmol/min.mg)	**13.05 ± 0.69**	9.57 ± 1.20	**0.733**	0.0094
LD_{50} (μM)				
H_2O_2	573.37 ± 31.52	**740.00 ± 30.55**	**1.29**	0.0024
6-OHDA	**35.00 ± 2.03**	15.00 ± 0.866	**0.42**	0.0001

Data represent mean ± S.E.M. of at least four independent experiments (n = 4). *P* values indicate statistic differences between experimental groups (Student's *t*-test). Abbreviations: CAT, Catalase; GPx, Glutathione Peroxidase; SOD, Superoxide Dismutase; GR, Glutathione Reductase; TrxR, Thioredoxin Reductase, GST, Glutathione-*S*-Transferase; GSH, Glutathione; 6-OHDA, 6-hydroxydopamine.

Figure 4.

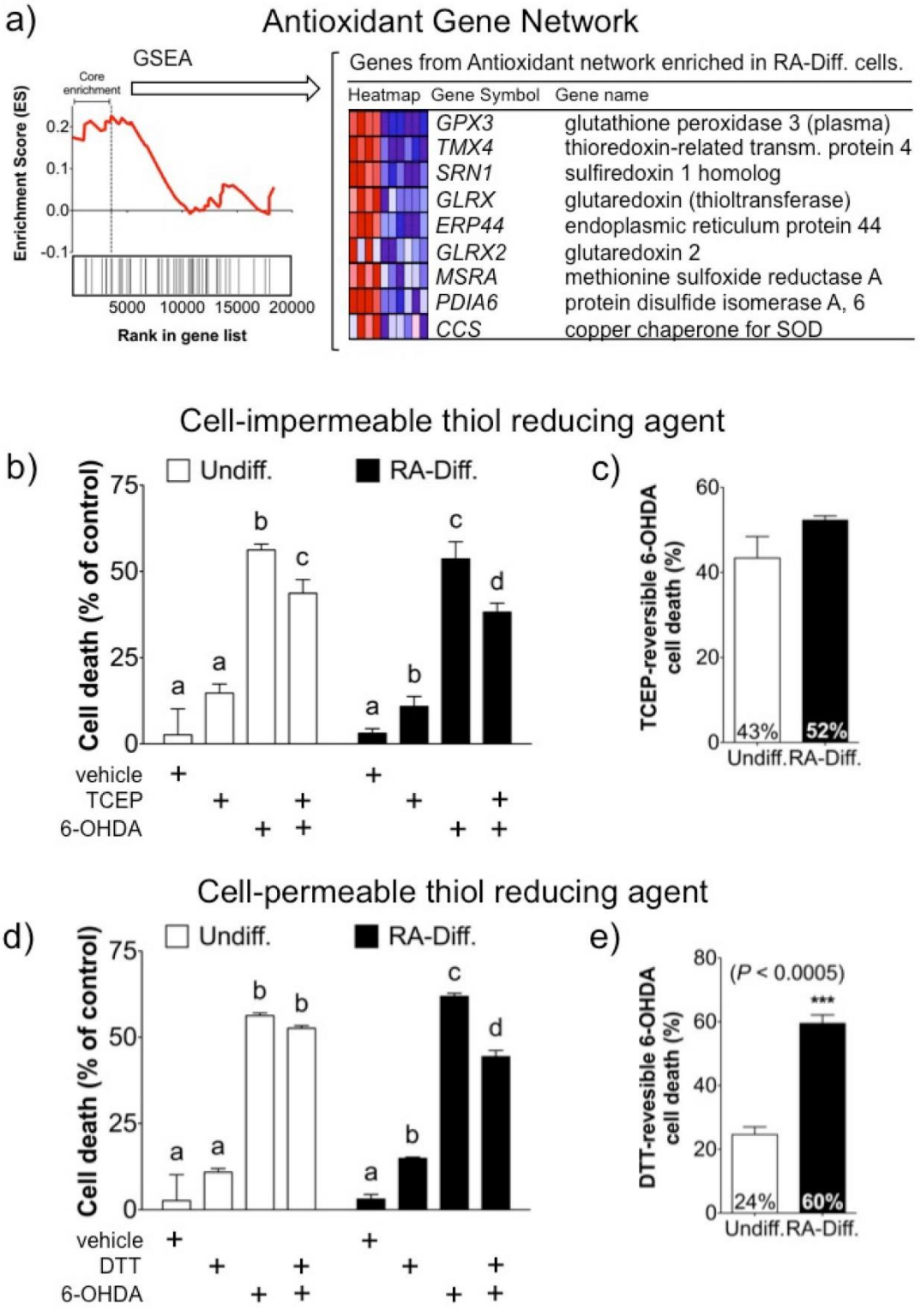
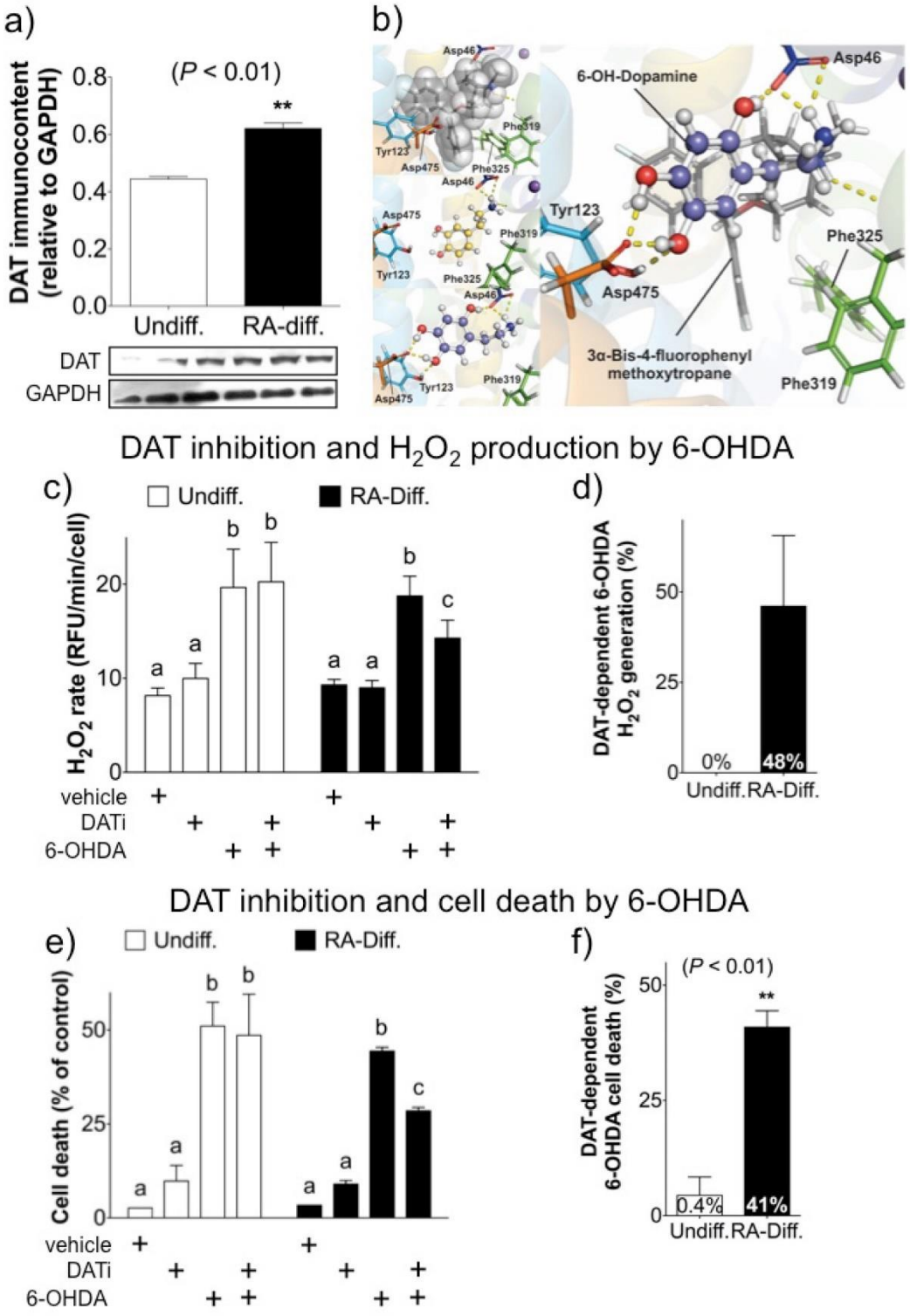

a)
Antioxidant Gene Network
GSEA
Core enrichment
Enrichment Score (ES)
0.2
0.1
0.0
-0.1
5000 10000 15000 20000
Rank in gene list
Genes from Antioxidant network enriched in RA-Diff. cells.
Heatmap Gene Symbol Gene name
GPX3 glutathione peroxidase 3 (plasma)
TMX4 thioredoxin-related transm. protein 4
SRN1 sulfiredoxin 1 homolog
GLRX glutaredoxin (thioltransferase)
ERP44 endoplasmic reticulum protein 44
GLRX2 glutaredoxin 2
MSRA methionine sulfoxide reductase A
PDIA6 protein disulfide isomerase A, 6
CCS copper chaperone for SOD
Cell-impermeable thiol reducing agent
b)
Undiff.
RA-Diff.
Cell death (% of control)
75
50
25
0
a a b c a b c d
vehicle + +
TCEP + + + +
6-OHDA + + + +
c)
TCEP-reversible 6-OHDA cell death (%)
60
40
20
0
43%
52%
Undiff. RA-Diff.
Cell-permeable thiol reducing agent
d)
Undiff.
RA-Diff.
Cell death (% of control)
75
50
25
0
a a b b a b c d
vehicle + +
DTT + + + +
6-OHDA + + + +
e)
DTT-revesible 6-OHDA cell death (%)
80
60
40
20
0
(P < 0.0005)
***
24%
60%
Undiff. RA-Diff.

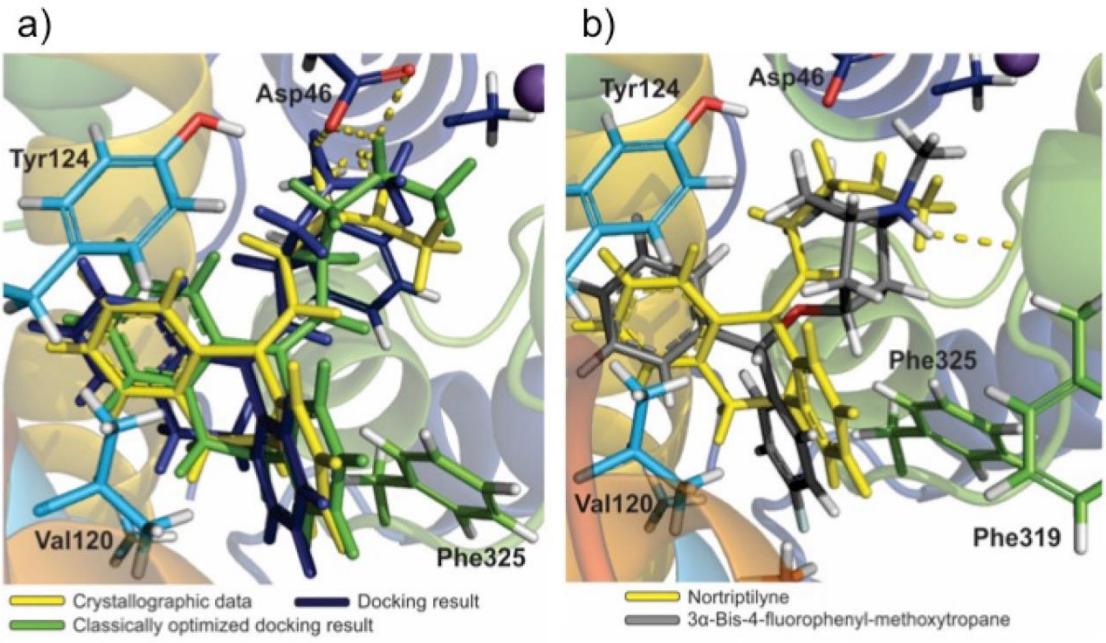
Table 4: Calculated binding interactions with DAT using molecular simulations.

Compounds	*K*i	E_{ATD}	E_{OPT}
Dopamine	22.64	- 6.34	- 81.82
6-Hydroxydopamine	227.72	- 4.97	- 114,74
p-Quinones	122.48	- 5.34	- 96.00
3α-Bis-4-fluorophenyl-methoxytropane	27×10^{-3}	- 10.33	- 90.21

*K*i (inhibition constant) and E_{ATD} (docking binding energy) were obtained from molecular docking using Autodock algorithm. E_{OPT} (optimized binding energy) was calculated after geometry improvements through classical energy minimization of docking solutions. *Ki* is expressed in μM and E in kcal/mol.

Figure 5.


a)
b)
DAT immunocontent (relative to GAPDH)
(P < 0.01)
**
Undiff.
RA-diff.
DAT
GAPDH
6-OH-Dopamine
Asp46
Tyr123
Asp475
Phe325
Phe319
3α-Bis-4-fluorophenyl methoxytropane
DAT inhibition and H2O2 production by 6-OHDA
c)
Undiff.
RA-Diff.
H2O2 rate (RFU/min/cell)
vehicle
DATi
6-OHDA
d)
DAT-dependent 6-OHDA H2O2 generation (%)
0%
48%
Undiff.
RA-Diff.
DAT inhibition and cell death by 6-OHDA
e)
Cell death (% of control)
f)
DAT-dependent 6-OHDA cell death (%)
0.4%
41%



Supplementary Figure 1: a) Redocking of nortriptilyne in the binding pocket of DAT to tune the docking machinery using the crystallographic ligand conformation (Penmatsa et al., 2013). Nortriptilyne at crystallographic coordinates is represented in yellow, redocking using crystallographic conformation is represented in blue and refined redocking result using classical energy minimization procedure is shown in green. The resulting structure is representative of a cluster containing 991 out 1000 poses. Comparison with crystallographic coordinates showed RMSD value of 1.1260 Å for redocked structure and 0.7049 Å after classical refinement. Results obtained using the Autodock software (Morris et al., 2009). b) Superposition of 3α-Bis-4-fluorophenyl-methoxytropane and nortriptilyne in binding pocket of DAT. Crystallographic orientation of nortriptilyne in yellow. Representative conformation of 3α-Bis-4-fluorophenyl-methoxytropaneobtained through docking in gray. Important binding pocket residues are shown in stick to guide visualization.

ANEXO 5

Matéria publicada no site de notícias *EurekAlert!* sobre os achados referentes ao capítulo quatro desta tese. Este é um site de notícias global cujo objetivo é a divulgação de pesquisas relevantes na área da saúde, medicina, ciência e tecnologia.

- Link para visualização da matéria: http://www.eurekalert.org/pub_releases/2016-05/pcc-emm052816.php

PUBLIC RELEASE: 28-MAY-2016

Ever-changing moods may be toxic to the brain of bipolar patients

The blood of bipolar patients is toxic to brain cells and affects the connectivity ability of neurons, a new study shows

PUBLICASE COMUNICAÇÃO CIENTÍFICA

Bipolar disorder (BD) is a severe and complex mental illness with a strong genetic component that affects 2% of the world population. The disorder is characterized by episodes of mania and depression that may alternate throughout life and usually first occur in the early 20s.

Most recently, physicians have started to group patients as early or late-stage. Early-stage BD patients are classified as those who have had fewer episodes of either mania or depression whereas late-stage patients have had more episodes with more severe effects and are less likely to respond to treatment.

This classification between early- and late-stage BD patients has more to do with episode recurrence and severity than the length of time the patient has had the disease. BD diagnosis may be difficult to establish and may take up to 10 years from the first episode. There is no cure for BD but psychotherapy and prescription medication such as antipsychotics, mood stabilizers and benzodiazepines may alleviate symptoms.

The brain of bipolar patients shows changes such as reduction in volume and neuroprogression. The latter is a pathological version of an otherwise normal mechanism by which the brain re-writes its neuronal connections, a process that is associated to learning, memory and even recovery from brain damage. In bipolar patients, the process is associated with loss of neuron connections and clinical and neurocognitive deterioration.

A previous study has shown that the blood levels of several markers related to inflammation, oxidative stress and neurotrophins (proteins that promote neuron growth and survival) in BD patients are associated to recurrent mood episodes. For instance, the brain-derived neurotrophic factor (BDNF), a protein that promotes neuron growth and survival and helps establishing neuron connections, is lower in BD patients, as is the early-growth response 3 (EGR3), a protein associated to helping the brain cope with environmental changes such as stressful stimuli. Besides these alterations, another study has shown that abnormally low levels of chemokines (which are proteins that send signals to other cell components) have also been observed in the blood of BD patients. If these blood markers can be associated to the severity and frequency of mood episodes in BD patients, is it possible that they are also associated to changes observed in the brain of BD patients?

To answer this intriguing question, a group led by Fabio Kiamt at the Laboratory of Cellular Biochemistry at the Federal University of Rio Grande do Sul (UFRGS), and Flávio Kapczinski at the Laboratory of Molecular Psychiatry at Clinics Hospital of Porto Alegre (HCPA), in Brazil, exposed differentiated neurons to blood serum from either healthy normal individuals or bipolar patients. The group then observed that neurons exposed to serum from bipolar patients had a significant loss in the density of neurites, which is used to estimate the number of neuron connections, if compared to neurite density of neurons exposed to serum from healthy individuals. Interestingly, when serum from early-stage and late-stage BD patients was analyzed separately, no difference in neurite density was observed between neurons exposed to serum from early-stage patients and those exposed to healthy controls' serum. However, a significant difference remained in the neurite density between neurons exposed to serum from late-stage patients and from early-stage patients or healthy controls. The group also found that the number of neurons was not that different between samples, except for those exposed to serum from patients at very late stages of the disease.

"Our results indicate that the blood of BD patients is toxic to brain cells and affects the connectivity ability of neurons. Considering our previous knowledge on the association between mood episodes and blood toxicity, we believe that the more episodes a patient has, the more cellular components are produced that impair the brain's ability to deal with environmental changes, inflammation and stress," says Kiamt.

This is the first study to show the toxic effects of BD serum on human neuronal cells and to present an in vitro study model for a disease for which no animal model has been yet developed. Future studies should focus on finding drugs that can protect BD brain cells from the toxic effects of their own blood.

###

The first draft of the study entitled "Reduced Neurite Density in Neuronal Cell Cultures Exposed to Serum of Patients with Bipolar Disorder" is available at the link below at the website of the *International Journal of Neuropsychopharmacology* http://ijnp.oxfordjournals.org/content/ijnp/early/2016/05/13/ijnp.pyw051.full.pdf

GRANT: National Council for Scientific and Technological Development- CNPq/MS/SCTIE/DECIT - Research on Neurodegenerative Diseases (#466989/2014-8)

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Ever-changing moods may be toxic to the brain of bipolar patients
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JOURNAL
International Journal of Neuropsychopharmacology

FUNDER
National Council for Scientific and Technological Development - Research on Neurodegenerative Diseases

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ANEXO 6

Capítulo aceito para publicação no livro: *Encyclopedia of Signaling Molecules, 2nd edition*, da *Springer Editorial Platform*, editado por Sangdun Choi. Neste capítulo, o conhecimento atual sobre o gene *EGR3* e sua via foram revisados, com foco em células neuronais e na sua associação a patologias como o câncer e transtornos psiquiátricos, com ênfase no TB.

Title: *EGR3* (early growth response 3)

Authors: Bianca Pfaffenseller[1, 2], Bianca Wollenhaupt de Aguiar[1, 2] and Fábio Klamt[1]

[1]Laboratory of Cellular Biochemistry, Department of Biochemistry, Institute of Basic Health Science (ICBS), Federal University of Rio Grande do Sul (UFRGS), 90035-003 Porto Alegre (RS) Brazil (00025267@ufrgs.br);

[2]Laboratory of Molecular Psychiatry, Hospital de Clínicas de Porto Alegre (HCPA), 90035-903 Porto Alegre (RS) Brazil.

Synonyms

Zinc Finger Protein Pilot
PILOT

Historical Background

In 1991, the human *EGR3* gene was first described by Patwardhan and colleagues. The *EGR3* is an immediate early growth response gene first observed to be induced by mitogenic stimulation of rodent and human fibroblasts and monkey kidney epithelial cell line. The *EGR3* cDNA sequence infers a 387 amino acid protein and the *EGR3* gene has a single intron and the cytogenetic location is 8p21.3 (Patwardhan et al. 1991).

The *EGR3* is part of the early growth response (EGR) transcription factors family, which has five members: *EGR1* (also known as *ZIF268, NGFI-A, TIS8, KROX-24* or *ZENK*), *EGR2* (also known as *KROX-20*), *EGR3* (also known as *PILOT*), *EGR4* (also known as *NGFI-C* or *pAT133*), and the product of the Wilms' tumor gene, *WT-1* (Pérez-Cadahía et al. 2011). The EGR family is characterized as immediate early genes (IEG)

encoded transcription factors and has a highly conserved DNA-binding domain containing three zinc-finger motifs proteins (Figure 1A). The EGR family proteins share extensive homology throughout the zinc finger DNA-binding domain and recognize the same consensus DNA-binding motif, the 5'-GCGGGGGCG-3' DNA sequence, leading to transcription activation (Figure 1B) (Pérez-Cadahía et al. 2011; O'Donovan et al. 1999).

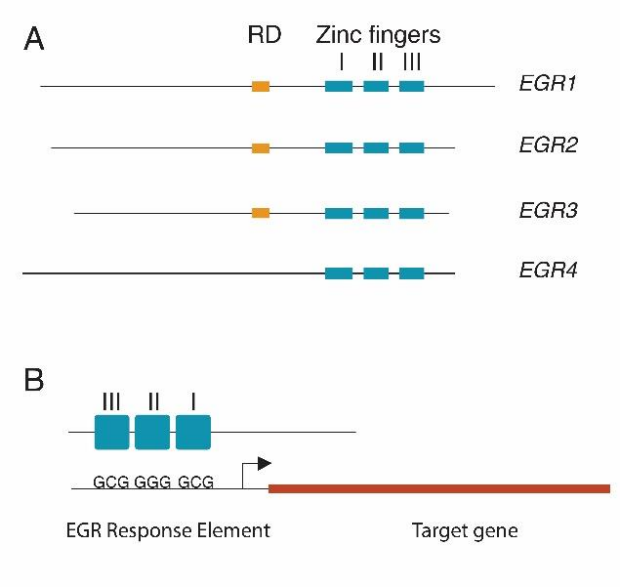

Figure 1. EGR family. (A) Representation of the EGR family aligned with their three zinc-finger motifs and the repression domain (RD). **(B)** Representation of an EGR-family member binding the EGR Response Element in a target gene. The zinc fingers, presented as blue squares, binds to a three-nucleotide site in a configuration where zinc-finger I binding to the 3'-most nucleotide triplet and zinc-finger III binding to the 5'-most nucleotide triplet. (Adapted from O'Donovan et al. 1999).

The expression of *EGR3* has been reported in various tissues, such as lymphocytes, muscle, endothelial cells and different brain regions. The *EGR3* plays important roles, as in cellular growth and in neuronal development in response to many cellular stimuli, including growth, stress, and inflammation (O'Donovan et al. 1999). In addition, studies have shown that *EGR3* is essential for normal hippocampal long-term

potentiation (LTP) and for hippocampal and amygdala dependent learning and memory (Li et al. 2007; Gallitano-Mendel et al. 2007).

Pathway of *EGR3*-Mediated Transcriptional Activation

As others IEG transcription factors, *EGR3* is rapidly and transiently induced by a large number of stimuli in the regulation of late response genes. *EGR3* is induced in response to growth factors or mitogens. In the brain, *EGR3* activation is triggered by neurotransmitter-receptor stimulation or depolarization (O'Donovan et al. 1999), indicating the relevance of this response also to mature neurons in the adult nervous system and not just in differentiating neurons.

At first, changes in the expression of EGR genes were considered as a general neuronal response to natural forms of stimulation involving normal synaptic activity. However, each IEG can be differently regulated via different stimuli in distinct brain regions. EGR genes are expressed at basal levels throughout the brain, including in the cortex, hippocampus and other limbic areas, and the basal ganglia. *EGR3* expression is rapidly induced at high levels in these regions in response to changes in the environment, including stressful stimuli across a range of intensities, such as novelty, handling, restraint, and pain as observed in animals (Gallitano et al. 2007). Studies have also been reported that agents that alter dopamine-dependent signaling induce the expression of EGR genes in the brain. Regarding *EGR3*, cocaine administration and haloperidol (a D2 antagonist) induces a rapid increase in its mRNA levels in the striatum, that is blocked by a selective D1 antagonist (Yamagata et al. 1994), suggesting the involvement of multiple neurotransmitter systems to mediate *EGR3* expression.

The neuronal expression of *EGR3* is regulated by synaptic activity and is coupled to MAPK-ERK signaling (Li et al. 2007; O'Donovan et al. 1999). Together with EGR1, EGR3 is the most abundant EGR proteins upregulated by synaptic activity in the brain. They may have some overlapping roles in regulating gene expression, but not completely redundant since they differ in expression patterns and phenotypes in mutant mice. In contrast to the rapid and transient rise in EGR1 protein levels, EGR3 protein is more stable and remains in neurons for longer periods after activity mediated activation (Li et al. 2007; O'Donovan et al. 1999). Sequential expression of these EGR members could represent a regulation mechanism of temporal expression pattern of specific target genes.

Regarding the signaling cascade that leads to *EGR3* expression, studies have reported that *EGR3* is activated downstream of numerous proteins, including neuregulin 1 (NRG1), calcineurin (CaN), N-methyl-D-aspartate (NMDA) receptors and neurotrophins such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) (Hippenmeyer et al. 2002; Yamada et al. 2007; Yamagata et al. 1994; Roberts et al. 2006; Eldredge et al. 2008), and its regulated expression is essential for the cell since EGR3 protein, as a transcription factor, could in turn activate downstream numerous targets (Figure 2) that integrate a network of constitutively expressed proteins, mostly involved in differentiation, growth, and response to extracellular signals. *EGR3* targets the promoter region of genes involved in neuroplasticity or stimuli response. So far, experimental studies show effects on NMDA receptor (Gallitano et al. 2007), type A GABA receptor (Roberts et al. 2006), and NGFR (*p75NTR*) expression (Gao et al. 2007), a receptor for neurotrophins that is involved in the regulation of axonal elongation. *EGR3* also regulates the activity regulated cytoskeletal associated gene (*Arc*) (Li et al. 2005) which modifies synapses in response to environmental stimuli, and possibly genes

involved in microglia deregulation associated with psychiatric disorders, such as the triggering receptor expressed on myeloid cells 1 (*TREM-1*) (Weigelt et al. 2011). Altogether, *EGR3* target genes trigger different downstream genes and pathways involved in processes such as synaptic plasticity, axon extension, regulation of neurotrophins and receptors expression. Thus, requirement of *EGR3* in processes of memory, learning, and synaptic plasticity, as will be discussed below, is likely to be mediated by these, and presumably other as-yet-unidentified, *EGR3* target genes.

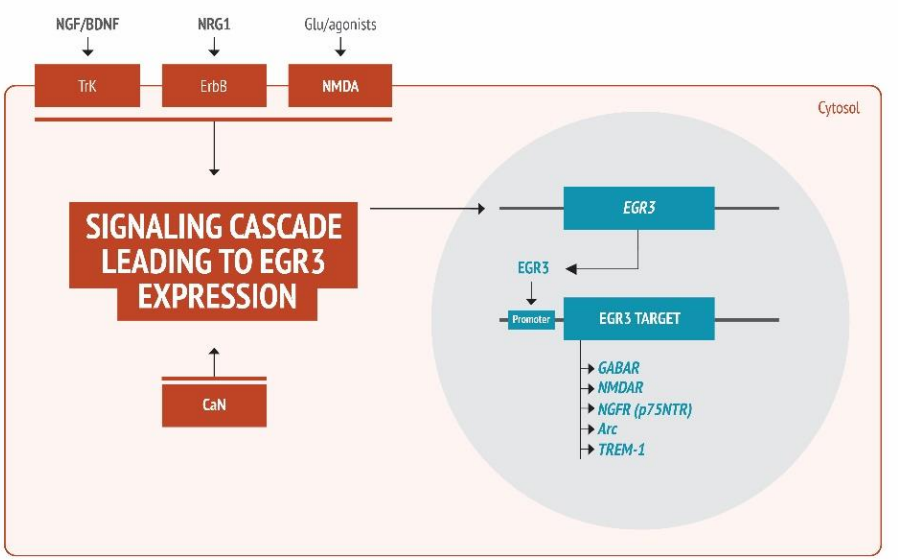

Figure 2. Representation of signaling cascade, focused on *EGR3* signaling in neurons involved in the nervous system transmission or neuromuscular junctions, leading to *EGR3* expression. *EGR3* is activated downstream of numerous proteins, such as neuregulin 1 (NRG1), calcineurin (CaN), N-methyl-D-aspartate (NMDA) receptors, brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). These proteins activate a signaling cascade that leads to *EGR3* expression. In turn, EGR3 protein could activate downstream numerous targets that integrate a network of constitutively expressed proteins. For instance, *EGR3* regulates NMDA receptor, type A GABA

receptor, and NGFR (*p75NTR*) receptor, the activity regulated cytoskeletal associated gene (*Arc*), and triggering receptor expressed on myeloid cells 1 (*TREM-1*), which are genes involved in neuroplasticity or stimuli response.

Once bound to the promoter of target genes, *EGR3* participates in regulating their expression by a process which molecular and cellular mechanisms are still poorly defined (Pérez-Cadahía et al. 2011). Several factors have been described to modulate the activity of EGR genes. One is the presence of activation–repression domains. All EGR-family members present the zinc-finger motifs that represent the DNA-binding domain, and they (except *EGR4*) also present a repressor domain (RD), the NAB-binding domain (NGFI-A binding) (Figure 1), where a pair of proteins (NAB1 and NAB2), produced in the brain as well as in other tissues, could bind to and suppress EGR activity. Thus, NAB may represent an endogenous negative-feedback mechanism that regulates EGR-mediated transcription. A second regulatory mechanism, studied in other EGR genes but likely applied also to *EGR3*, is the EGR posttranslational phosphorylation that increases the half-life of the protein and its DNA-binding activity. N-glucosylation in the second zinc finger and EGR crosstalk with AP-1 members has also been reported for EGR-family members as a way of regulating the DNA-binding activity (Pérez-Cadahía et al. 2011).

Physiological Functions of *EGR3*

Physiological functions of *EGR3* have been investigated in various organs using genetically modified animals. The protein encoded by the *EGR3* gene plays a role in a wide variety of processes including the transcriptional regulation of genes involved in controlling biological rhythm, muscle development, lymphocyte development,

endothelial cell growth and migration, neuronal development, and learning, memory and behavior (Figure 3).

Circadian rhythms

Studies evaluated the relationship between *EGR3* and circadian rhythms, using rodents maintained in constant darkness. They have searched for additional genes whose expression are induced in the suprachiasmatic nucleus by light exposure and have identified the gene encoding *EGR3* as a candidate transcription factor involved in this form of plasticity. The authors stated that *EGR3* probably participates in the transcriptional regulation of genes in response to retinal input in the suprachiasmatic nucleus of the hypothalamus, as had been proposed for FOS, a transcription-regulatory factor that is also rapidly produced in response to growth factors (Morris et al. 1998).

Muscle development

Muscle spindles are skeletal muscle sensory organs that provide axial and limb position information (proprioception) to the central nervous system. Spindles consist of encapsulated muscle fibers (intrafusal fibers) that are innervated by specialized motor and sensory axons. O'Donovan and colleagues (1998) found the absence of muscle spindles in *EGR3*-deficient mice, which displayed severe motor abnormalities (as sensory ataxia, scoliosis, resting tremor and ptosis). It is known that innervation of myotubes by proprioceptive Ia afferent fibers are responsible for triggering the differentiation of these fibers into muscle spindles during muscle development. The authors suggests that *EGR3* most probably has a key role in the differentiation process that occurs within the postsynaptic muscle cell, as the Ia afferents fibers appear to develop normally in *EGR3*-

deficient mice. These results indicated that type I myotubes are dependent upon *EGR3*-mediated transcription for proper spindle development. (O'Donovan et al. 1999).

Regulation of immune response

A study identified the *EGR3* as a key negative regulator of T cell activation. Overexpression of *EGR3* was associated with an increase in the E3 ubiquitin ligase Cbl-b and inhibition of T cell activation. Conversely, T cells from *EGR3*-deficient mice had lower expression of Cbl-b and were resistant to *in vivo* peptide-induced immunologic tolerance. Together, these data indicates that *EGR3* is involved in promoting a T cell receptor–induced negative regulatory genetic program (Safford et al. 2005).

Learning, memory and behavior

Considering that the expression of EGR family is extremely sensitive to environmental stimuli capable of inducing plasticity, it is expected that members of the EGR family are involved in learning, memory and behavior. As MAPK-ERK effector genes, they may regulate target neuronal gene expression required for long-term synaptic changes associated with these process (Li et al. 2007). In fact, numerous behavioral and electrophysiologic studies in animals have shown that the EGR family plays a role in memory acquisition and consolidation and hippocampal synaptic plasticity (Gallitano et al. 2007; Li et al. 2007). *EGR3*, in particular, is essential for the normal response to stress as well as in the neuroplasticity induced by this responsivity since *EGR3* regulates the expression of important plasticity-associated genes in a physiologically relevant manner (Gallitano et al. 2007), such as *Arc* gene involved in synaptic plasticity and memory formation.

EGR3-deficient (*EGR3*−/−) mice appear to have normal brains and basal synaptic transmission in CA3-CA1 hippocampal neurons where *EGR3* is highly expressed, however they have abnormal LTP in CA1 neurons, and present impairments in context of associative learning/memory and in short-term and long-term object recognition memory (Li et al. 2007). Other study with *EGR3*-deficient mice showed accentuated behavioral responses to the mild stress of handling and increased release of the stress hormone corticosterone. Moreover, these animals presented abnormal responses to novel environments and failure to habituate to social cues or acoustic stimuli (Gallitano-Mendel et al. 2007). Since stress and novelty stimulate hippocampal long-term depression (LTD), this form of synaptic plasticity in *EGR3*−/− mice was evaluated, showing that these animals failed to establish hippocampal LTD in response to low frequency stimulation and presented dysfunction of an ifenprodil-sensitive (NR1/NR2B) NMDA receptor subclass. This work demonstrated the requirement for *EGR3* in mediating the response to stress and novelty, and in the establishment of LTD (Gallitano-Mendel et al. 2007).

Regulation of Endothelial cell growth

EGR3 is upregulated by VEGF in endothelial cells, which indicates that *EGR3* has a critical downstream role in VEGF-mediated endothelial functions leading to angiogenesis and could be important in adult angiogenic processes involved in vascular repair and disease (Liu et al. 2008). Its role in tissue repair and fibrosis has been poorly studied.

Sympathetic neuron autonomous role

EGR3 is regulated by NGF signaling in sympathetic neurons during Sympathetic Nervous System development when they depend upon NGF for survival and target tissue

innervation. *EGR3*-deficient mice have severe sympathetic target tissue innervation abnormalities and profound physiological dysautonomia. *EGR3* modulates downstream target genes affecting the outgrowth and branching of sympathetic neuron dendrites and axons. The results indicate that *EGR3* is a novel NGF signaling effector that regulates sympathetic neuron gene expression required for normal target tissue innervation and function (Eldredge et al. 2008).

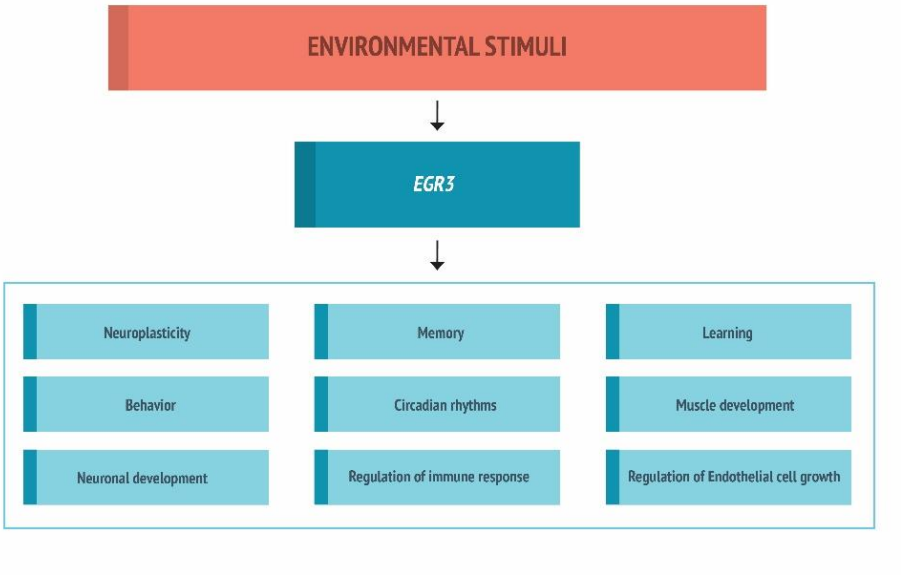

Figure 3. Physiological processes regulated by *EGR3* pathway. *EGR3* expression is induced in response to environmental stimuli, such as stress across a range of intensities. EGR3 protein play a role in a wide variety of processes, including the transcriptional regulation of genes involved in circadian rhythms, muscle development, regulation of immune response, regulation of endothelial cell growth, neuronal development, learning, memory and behavior.

EGR3 and pathologies

EGR3 in Psychiatry

EGR genes translate environmental events into long-term changes in neural gene expression. This has led to the hypothesis that dysfunction in EGRs may contribute for both the genetic and environmental influences on risk for psychiatric disorders. As mentioned before, mice lacking functional *EGR3* show behavioral and physiologic changes consistent with models of mental illness. These include a heightened response to stress (observed by elevated release of corticosterone and behavior alterations), hyperactivity, and difficulty to habituate to environmental stimuli and social cues (Gallitano et al. 2007). Furthermore, several proteins associated with risk for psychotic illness induce *EGR3,* including NRG1, CaN, NMDA receptors and BDNF (Gallitano et al. 2007; Hippenmeyer et al. 2002; Yamada et al. 2007; Roberts et al. 2006); the last has been proposed as a critical factor in the pathophysiology of bipolar disorder and schizophrenia.

In patients with bipolar disorder or schizophrenia, a study have found significantly increased expression of the TREM-1, a *EGR3* target expressed in activated monocytes and microglia and important in inflammation process (Weigelt et al. 2011). *EGR3* has been more closely studied in patients with schizophrenia; this gene has been significantly associated with this illness and has been considered a potential susceptibility candidate in schizophrenia (Yamada et al. 2007). Regarding a potential role for *EGR3* in bipolar disorder patients, a family-based association study identified a nominal association of *EGR3* with risk for child with bipolar disorder (Gallitano et al. 2012). And more recently, a study using an innovative approach to analyze transcriptional

regulation in bipolar disorder, identified the regulatory unit of *EGR3* robustly repressed in both of the two bipolar gene expression data sources examined from post-mortem prefrontal cortex (Pfaffenseller et al. 2016), indicating the *EGR3* as a potential key target in bipolar disorder. Altogether, these findings suggest that *EGR3,* and its targets, may be a fruitful pathway for future studies to identify mechanisms by which environment and genetic predisposition interact to influence psychiatric disorders.

EGR3 in Cancer

Several studies have shown association between *EGR3* gene and cancer. For instance, a study using a whole genome gene expression database evaluated that EGR3 mRNA is significantly over-expressed in prostate cancer compared to normal prostate tissue. Furthermore, EGR3 protein is significantly increased in patients with prostate cancer compared with normal patients. Analysis of EGR3 mRNA expression in relation to the relapse status reveals that EGR3 mRNA expression is increased in tumor cells of nonrelapsed samples compared to normal prostate cells, but is significantly lower in relapsed samples compared to non-relapse. The authors determined a list of genes correlated with this unique expression pattern; these EGR3-correlated genes were enriched with EGR binding sites in their promoters. The gene list contains inflammatory genes such as IL-6, IL-8, IL-1b and COX-2, which have extensive connections to prostate cancer (Pio et al. 2013).

Regarding gastric cancer, Liao and colleagues (2013) suggests that decreased *EGR3* expression might play a critical role in the differentiation, proliferation, metastasis and progression of these cancer cells and may be a potential diagnostic marker for gastric cancer. This study showed that *EGR3* expression was significantly lower in gastric cancer

tissues compared with matched non-tumors tissues and that patients with lower *EGR3* expression had a poorer prognosis compared with patients with higher *EGR3* expression (Liao et al. 2013). Taken together, these studies suggest the involvement of *EGR3* expression in cancer and its potential as a prognostic marker for this disease. More studies are required to verify the relationship between *EGR3* and other types of cancer and to evaluate its ability to become a marker that can assist in the prognosis of this condition.

Summary

In this chapter, the current knowledge about *EGR3* gene and its pathway were revised, with focus in neuronal cells since the major findings are found in these cells. The physiological functions of *EGR3* which have been investigated in various different tissues using genetically modified animals also were discussed. In this sense, the roles of the protein encoded by the *EGR3* gene in a wide variety of biological processes were explored, including the transcriptional regulation of genes involved in biological rhythms, muscle development, lymphocyte development, endothelial cell growth and migration, neuronal development, learning, memory and behavior. Furthermore, the association between *EGR3* gene and pathologies, such as psychiatric disorders and cancer, were discussed.

As a transcription factor of several genes and pathways that mediate critical biological processes, it is relevant to extend the studies about roles of *EGR3* in order to better understand the relationship between environment and the influence of numerous genes in physiological and pathological conditions. In addition, further studies are needed to evaluate *EGR3* targets, their role and the mechanisms of action of drugs associated to this pathway.

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ANEXO 7

Resultados complementares ao capítulo 3 desta tese. Nas tabelas a seguir estão descritos todos os processos biológicos, bem como seus respectivos genes, obtidos após a análise no *Gene Ontology* de cada fenótipo estudado: células AR-diferenciadas (tabela 3) e proliferativas (tabela 4).

Tabela 3. Representação completa dos processos biológicos e seus respectivos genes enriquecidos no fenótipo das células AR-diferenciadas.

Ont	Terms	Annotated	Significant	Expected	classic	Genes
BP	GO:0007399: Nervous system development	2027	157	87.46	5.90E-14	ABL1,ADM,AGTPBP1,AKT2,ALDH5A1,ALK,ANKRD1,APH1A,APLP1,ARHGAP26,ARID1A,ATP6AP2,ATP6V0D1,ATP8B1,BASP1,BCL2L11,BHLHB9,BMPR1B,BPTF,BTG2,CADM1,CAMK1,CCL2,CDH11,CDH2,CDK5R2,CDKN2C,CHRM3,CHRNA3,CLASP2,CLDN11,CLN5,CLU,CNP,CNR1,COL3A1,COX17,CRB1,CRIM1,CSPG5,CTNNA2,CTNND1,CYB5D2,CYP26A1,DCLK1,DCX,DLG2,DPYSL3,DRP2,ELL3,FARP1,FGF14,FN1,FOS,FOXC1,GAL,GAL3ST1,GDF6,GFRA1,GNG8,GRIP1,HES1,HEXB,HOXC8,HOXD1,HOXD10,HOXD3,HOXD9,HPCAL4,INHBA,ITGA1,JARID2,KALRN,KCNQ2,KCTD11,KIAA0319,KIAA1279,LIF,MAOB,MAP6,MAPK9,MAPT,MATN2,MEIS1,MPPED2,NAV1,NAV2,NBL1,NCAM2,NCAN,NCOA1,NDRG4,NFASC,NLGN1,NLGN3,NOTCH2,NPHP3,NRSN1,NRXN1,NTNG2,NTRK2,NUMB,OLFM3,PBX1,PBX3,PCDH9,PCDHB10,PCDHB14,PCDHB15,PCDHB3,PCDHB4,PDGFC,PHLDA1,PLK2,PLXNB1,PPARG,PRNP,PSD2,PSEN1,PTCH1,PTPRM,RARB,RBFOX2,RELN,RET,RND2,ROM1,RUNX1,SCN2A,SCN3B,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC8A3,SLC9A6,SLIT2,SMAD1,SMARCA2,SNAP25,SOX9,SPEN,SPTAN1,STAT3,STMN4,SYNGR3,TACC2,TIMP2,TPP1,TRIO,TULP3,TWSG1,VANGL2,VAV3,VCAN,WNT3,ZFP36L1
BP	GO:0048731: System development	3977	257	171.6	1.5e-13	ABL1,ACP2,ACTA2,ADM,AGTPBP1,AKT2,ALDH5A1,ALK,ANKRD1,ANKRD33,ANKRD6,ANXA2,ANXA3,APH1A,APLP1,APOLD1,AQP11,ARHGAP26,ARID1A,ARRDC3,ASS1,ATP6AP1,ATP6AP2,ATP6V0D1,ATP8B1,ATPIF1,ATXN1,BASP1,BCL2L11,BCOR,BHLHB9,BHLHE41,BMPR1B,BPTF,BTG2,BTK,CADM1,CALB1,CALCA,CAMK1,CCBE1,CCDC40,CCL2,CCND1,CD44,CDH11,CDH2,CDK5R2,CDKN1A,CDKN1B,CDKN2C,CHRM3,CHRNA3,CLASP2,CLDN11,CLN5,CLPTM1,CLU,CNP,CNR1,COL11A1,COL3A1,COX17,CRB1,CREB5,CRIM1,CSPG5,CTGF,CTNNA2,CTNND1,CTSH,CYB5D2,CYP1B1,CYP26A1,CYP26B1,CYR61,DCLK1,DCN,DCX,DDX5,DHRS3,DKK3,DLG2,DPYSL3,DRP2,DUSP6,EGLN1,ELL3,ENPP2,EPAS1,FAM101B,FARP1,FGF14,FLNB,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GAL3ST1,GATA4,GBA,GDF10,GDF6,GFRA1,GNG8,GPNMB,GRIP1,HBEGF,HCCS,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HOXC6,HOXC8,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,HPCAL4,HTR2B,IGF2,IGFBP7,INHBA,IRF6,ITGA1,ITGA7,JARID2,KALRN,KCNQ2,KCTD11,KIAA0319,KIAA1279,LIF,LUM,MAB21L1,MAOB,MAP6,MAPK9,MAPT,MATN2,MAX,MEIS1,MGP,MPPED2,NAV1,NAV2,NBL1,NCAM2,NCAN,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NLGN1,NLGN3,NOTCH2,NOTCH4,NPHP3,NPPB,NPR2,NRSN1,NRXN1,NTNG2,NTRK2,NUMB,OLFM3,PAF1,PBX1,PBX3,PCDH9,PCDHB10,PCDHB14,PCDHB15,PCDHB3,PCDHB4,PDGFC,PHLDA1,PKP2,PLAGL1,PLK2,PLN,PLXNB1,POLQ,PPARG,PRCP,PRNP,PSD2,PSEN1,PTCH1,PTGIS,PTPRM,RAB26,RAMP1,RARB,RBFOX2,RDH10,RELN,RET,RND2,ROM1,RUNX1,SCG2,SCN2A,SCN3B,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SGCB,SH2B3,SH3PXD2A,SIPA1L1,SLC12A6,SLC40A1,SLC8A3,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SOCS3,SOX9,SPARC,SPEN,SPRY1,SPTAN1,STAT3,STMN4,SYNGR3,TACC2,TFRC,TGM2,TIMP2,TNFRSF19,TNS3,TPP1,TRIM45,TRIO,TSHZ3,TULP3,TWSG1,TXK,VANGL2,VAV3,VCAN,VGF,WNT3,YAP1,ZFP36L1
BP	GO:0007275: Multicellular organismal development	4546	283	196.15	3.8e-13	ABL1,ACP2,ACTA2,ADM,AGTPBP1,AKT2,ALDH5A1,ALK,ANKRD1,ANKRD33,ANKRD6,ANXA2,ANXA3,APH1A,APLP1,APOLD1,AQP11,ARHGAP26,ARID1A,ARRDC3,ASS1,ATP6AP1,ATP6AP2,ATP6V0D1,ATP8B1,ATPIF1,ATXN1,BASP1,BCL2L11,BCOR,BHLHB9,BHLHE41,BMPR1B,BPTF,BTG2,BTK,CADM1,CALB1,CALCA,CAMK1,CCBE1,CCDC40,CCL2,CCND1,CD44,CDH11,CDH2,CDK5R2,CDKN1A,CDKN1B,CDKN2C,CHRM3,CHRNA3,CHURC1,CLASP2,CLDN11,CLN5,CLPTM1,CLU,CNP,CNR1,COL11A1,COL3A1,COX17,CRABP2,CRB1,CREB5,CREM,CRIM1,CSPG5,CTGF,CTNNA2,CTNND1,CTSH,CYB5D2,CYP1B1,CYP26A1,CYP26B1,CYR61,DACH1,DCLK1,DCN,DCX,DDX5,DHRS3,DKK2,DKK3,DLG2,DONSON,DPYSL3,DRP2,DUSP6,EBF1,EGLN1,ELL3,ENPP2,EPAS1,FAM101B,FARP1,FGF14,FLNB,FMN2,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GAL3ST1,GATA4,GBA,GDF10,GDF6,GFRA1,GNG8,GPNMB,GRIP1,HBEGF,HCCS,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HOXC6,HOXC8,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,HPCAL4,HTR2B,HUNK,IGF2,IGFBP7,INHBA,IRF6,ITGA1,ITGA7,ITGB5,JARID2,KALRN,KCNQ2,KCTD11,KIAA0319,KIAA1279,LAMA4,LBH,LIF,LUM,MAB21L1,MAOB,MAP6,MAPK9,MAPT,MATN2,MAX,MEIS1,MGP,MID1,MMP11,MPPED2,NAV1,NAV2,NBL1,NCAM2,NCAN,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NLGN1,NLGN3,NOTCH2,NOTCH4,NPHP3,NPPB,NPR2,NRSN1,NRXN1,NSD1,NTNG2,NTRK2,NUMB,OLFM3,PAF1,PBX1,PBX3,PCDH9,PCDHB10,PCDHB14,PCDHB15,PCDHB3,PCDHB4,PDGFC,PDGFD,PHLDA1,PIM1,PKP2,PLAGL1,PLK2,PLN,PLXNB1,POLQ,PPARG,PRCP,PRNP,PSD2,PSEN1,PTCH1,PTGIS,PTPRM,PTPRR,RAB26,RAI2,RAMP1,RARB,RBFOX2,RDH10,RELN,RET,RND2,ROM1,RUNX1,SCG2,SCN2A,SCN3B,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SFRP4,SGCB,SH2B3,SH3PXD2A,SIPA1L1,SLC12A6,SLC40A1,SLC8A3,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SOCS3,SOX9,SPARC,SPEN,SPRY1,SPTAN1,STAT3,STMN4,SYNGR3,TACC2,TAF7L,TANC2,TFRC,TGM2,TIMP1,TIMP2,TNFRSF19,TNS3,TPP1,TRIM45,TRIO,TSHZ3,TULP3,TWSG1,TXK,VANGL1,VANGL2,VAV3,VCAN,VGF,WNT3,YAP1,ZFP36L1,ZFR,ZNF521

BP	GO:0032502: Developmental process	5390	318	232.57	5.4e-12	ABCA1,ABL1,ACP2,ACTA2,ADM,AGTPBP1,AKT2,ALDH5A1,ALK,ANKRD1,ANKRD33,ANKRD6,ANXA2,ANXA3,APH1A,APLP1,APOLD1,AQP11,ARHGAP26,ARID1A,ARRDC3,ASAP1,ASS1,ATP6AP1,ATP6AP2,ATP6V0D1,ATP8B1,ATPIF1,ATXN1,BASP1,BCL2L11,BCOR,BHLHB9,BHLHE41,BMPR1B,BPTF,BTG2,BTK,C1GALT1C1,CACNA2D2,CADM1,CALB1,CALCA,CAMK1,CCBE1,CCDC40,CCL2,CCND1,CD44,CDC42EP3,CDH11,CDH2,CDK5R2,CDKL2,CDKN1A,CDKN1B,CDKN2C,CHRM3,CHRNA3,CHRNB1,CHURC1,CLASP2,CLDN11,CLN5,CLPTM1,CLU,CNP,CNR1,COCH,COL11A1,COL17A1,COL3A1,COX17,CRABP2,CRB1,CREB5,CREBL2,CREM,CRIM1,CSPG5,CTGF,CTNNA2,CTNND1,CTSH,CYB5D2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYR61,DACH1,DAPL1,DCLK1,DCN,DCX,DDX5,DHRS3,DKK2,DKK3,DLG2,DONSON,DPYSL3,DRP2,DUSP6,EBF1,EGLN1,ELL3,ENPP2,EPAS1,FAM101B,FARP1,FAT1,FGF14,FLNB,FMN2,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GAL3ST1,GATA4,GBA,GDF10,GDF15,GDF6,GFRA1,GNG8,GPNMB,GRIP1,HBEGF,HCCS,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HOXC6,HOXC8,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,HPCAL4,HTR2B,HUNK,IER3,IGF2,IGFBP7,INHBA,IRF6,ITGA1,ITGA7,ITGB5,JARID2,KALRN,KCNQ2,KCTD11,KIAA0319,KIAA1279,KRT18,LAMA4,LBH,LIF,LUM,MAB21L1,MAOB,MAP6,MAPK9,MAPT,MATN2,MAX,MEIS1,MEST,MGEA5,MGP,MID1,MMP11,MPPED2,MSN,NAV1,NAV2,NBL1,NCAM2,NCAN,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NLGN1,NLGN3,NOS1,NOTCH2,NOTCH4,NPHP3,NPPB,NPR2,NRSN1,NRXN1,NSD1,NTNG2,NTRK2,NUMB,OLFM3,PAF1,PAPPA,PBX1,PBX3,PCDH9,PCDHB10,PCDHB14,PCDHB15,PCDHB3,PCDHB4,PDGFC,PDGFD,PHLDA1,PIM1,PKP2,PLAGL1,PLK2,PLN,PLXNB1,POLQ,PPARG,PRCP,PRNP,PSD2,PSEN1,PSMB8,PTCH1,PTGIS,PTPRM,PTPRR,RAB26,RAB27A,RAB3IP,RAI2,RAMP1,RARB,RBFOX2,RDH10,RELN,RET,RGS2,RND2,ROM1,RSPH9,RUNX1,SCG2,SCN2A,SCN3B,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SERPING1,SFRP4,SGCB,SH2B3,SH3PXD2A,SIPA1L1,SLC12A6,SLC40A1,SLC8A3,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SOAT1,SOCS3,SOX9,SPARC,SPEN,SPRY1,SPTAN1,SQSTM1,STAT3,STMN4,STS,SYNGR3,SYP,TACC2,TAF7L,TANC2,TFRC,TGM2,TIMP1,TIMP2,TNFRSF19,TNS3,TPP1,TRIB2,TRIM45,TRIO,TRIOBP,TSHZ3,TTC30A,TTC30B,TULP3,TWSG1,TXK,VANGL1,VANGL2,VAV3,VCAN,VGF,WNT3,YAP1,ZFP36L1,ZFR,ZNF521
BP	GO:0009653: Anatomical structure morphogenesis	2462	173	106.23	1.2e-11	ABL1,ADM,AGTPBP1,ANKRD1,ANKRD6,ANXA2,ANXA3,APH1A,APLP1,APOLD1,ARID1A,ASAP1,ATP6AP2,ATP6V0D1,ATP8B1,ATPIF1,BASP1,BCL2L11,BCOR,BHLHB9,BHLHE41,BMPR1B,C1GALT1C1,CADM1,CALB1,CAMK1,CCBE1,CCDC40,CCL2,CD44,CDC42EP3,CDH11,CDH2,CDK5R2,CHRNA3,CLASP2,CLU,CNP,COCH,COL11A1,COL3A1,CRABP2,CRB1,CTGF,CTNNA2,CTSH,CYP1B1,CYP26B1,CYR61,DCLK1,DCN,DCX,DHRS3,DKK3,DPYSL3,DUSP6,EGLN1,ELL3,ENPP2,EPAS1,FAM101B,FARP1,FAT1,FN1,FOXC1,FOXO3,FRZB,GAL,GATA4,GBA,GDF15,GFRA1,HBEGF,HCCS,HES1,HEXB,HEY1,HIF1AN,HOXC8,HOXD10,HOXD3,HOXD8,HOXD9,HTR2B,IER3,IGF2,INHBA,ITGA1,ITGA7,ITGB5,KALRN,KCNQ2,KRT18,LIF,MAB21L1,MAP6,MAPK9,MAPT,MATN2,MEIS1,MGP,NBL1,NCAN,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NLGN3,NOS1,NOTCH2,NOTCH4,NPHP3,NPPB,NRXN1,NSD1,NTNG2,NTRK2,NUMB,OLFM3,PAF1,PBX1,PDGFC,PKP2,PLXNB1,PRCP,PRNP,PSEN1,PTCH1,PTGIS,PTPRM,RAB3IP,RAMP1,RARB,RBFOX2,RDH10,RELN,RET,RND2,ROM1,RSPH9,RUNX1,SCG2,SDCBP,SEMA3A,SEMA4F,SERPINE1,SH3PXD2A,SIPA1L1,SLC12A6,SLC40A1,SLC9A6,SLIT2,SMAD1,SOCS3,SOX9,SPARC,SPRY1,SPTAN1,STAT3,TGM2,TRIO,TRIOBP,TSHZ3,TTC30A,TTC30B,TULP3,TWSG1,VANGL2,VAV3,WNT3,YAP1,ZFP36L1
BP	GO:0048856: Anatomical structure development	4769	287	205.78	1.6e-11	ABL1,ACP2,ACTA2,ADM,AGTPBP1,AKT2,ALDH5A1,ALK,ANKRD1,ANKRD33,ANKRD6,ANXA2,ANXA3,APH1A,APLP1,APOLD1,AQP11,ARHGAP26,ARID1A,ARRDC3,ASAP1,ASS1,ATP6AP1,ATP6AP2,ATP6V0D1,ATP8B1,ATPIF1,ATXN1,BASP1,BCL2L11,BCOR,BHLHB9,BHLHE41,BMPR1B,BPTF,BTG2,BTK,C1GALT1C1,CACNA2D2,CADM1,CALB1,CALCA,CAMK1,CCBE1,CCDC40,CCL2,CCND1,CD44,CDC42EP3,CDH11,CDH2,CDK5R2,CDKN1A,CDKN1B,CDKN2C,CHRM3,CHRNA3,CHRNB1,CLASP2,CLDN11,CLN5,CLPTM1,CLU,CNP,CNR1,COCH,COL11A1,COL17A1,COL3A1,COX17,CRABP2,CRB1,CREB5,CRIM1,CSPG5,CTGF,CTNNA2,CTNND1,CTSH,CYB5D2,CYP1B1,CYP26A1,CYP26B1,CYR61,DCLK1,DCN,DCX,DDX5,DHRS3,DKK3,DLG2,DPYSL3,DRP2,DUSP6,EGLN1,ELL3,ENPP2,EPAS1,FAM101B,FARP1,FAT1,FGF14,FLNB,FMN2,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GAL3ST1,GATA4,GBA,GDF10,GDF15,GDF6,GFRA1,GNG8,GPNMB,GRIP1,HBEGF,HCCS,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HOXC6,HOXC8,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,HPCAL4,HTR2B,IER3,IGF2,IGFBP7,INHBA,IRF6,ITGA1,ITGA7,ITGB5,JARID2,KALRN,KCNQ2,KCTD11,KIAA0319,KIAA1279,KRT18,LAMA4,LIF,LUM,MAB21L1,MAOB,MAP6,MAPK9,MAPT,MATN2,MAX,MEIS1,MEST,MGP,MPPED2,MSN,NAV1,NAV2,NBL1,NCAM2,NCAN,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NLGN1,NLGN3,NOS1,NOTCH2,NOTCH4,NPHP3,NPPB,NPR2,NRSN1,NRXN1,NSD1,NTNG2,NTRK2,NUMB,OLFM3,PAF1,PBX1,PBX3,PCDH9,PCDHB10,PCDHB14,PCDHB15,PCDHB3,PCDHB4,PDGFC,PHLDA1,PKP2,PLAGL1,PLK2,PLN,PLXNB1,POLQ,PPARG,PRCP,PRNP,PSD2,PSEN1,PTCH1,PTGIS,PTPRM,PTPRR,RAB26,RAB27A,RAB3IP,RAI2,RAMP1,RARB,RBFOX2,RDH10,RELN,RET,RND2,ROM1,RSPH9,RUNX1,SCG2,SCN2A,SCN3B,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SFRP4,SGCB,SH2B3,SH3PXD2A,SIPA1L1,SLC12A6,SLC40A1,SLC8A3,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SOCS3,SOX9,SPARC,SPEN,SPRY1,SPTAN1,STAT3,STMN4,STS,SYNGR3,TACC2,TANC2,TFRC,TGM2,TIMP2,TNFRSF19,TNS3,TPP1,TRIM45,TRIO,TRIOBP,TSHZ3,TTC3

						0A,TTC30B,TULP3,TWSG1,TXK,VANGL2,VAV3,VCAN,VGF,WNT3,YAP1,ZFP36L1
BP	GO:0044767: Single-organism developmental process	5304	311	228.86	2.7e-11	ABCA1,ABL1,ACP2,ACTA2,ADM,AGTPBP1,AKT2,ALDH5A1,ALK,ANKRD1,ANKRD33,ANKRD6,ANXA2,ANXA3,APH1A,APLP1,APOLD1,AQP11,ARHGAP26,ARID1A,ARRDC3,ASAP1,ASS1,ATP6AP1,ATP6AP2,ATP6V0D1,ATP8B1,ATPIF1,ATXN1,BASP1,BCL2L11,BCOR,BHLHB9,BHLHE41,BMPR1B,BPTF,BTG2,BTK,C1GALT1C1,CACNA2D2,CADM1,CALB1,CALCA,CAMK1,CCBE1,CCDC40,CCL2,CCND1,CD44,CDC42EP3,CDH11,CDH2,CDK5R2,CDKN1A,CDKN1B,CDKN2C,CHRM3,CHRNA3,CHRNB1,CHURC1,CLASP2,CLDN11,CLN5,CLPTM1,CLU,CNP,CNR1,COCH,COL11A1,COL3A1,COX17,CRABP2,CRB1,CREB5,CREBL2,CREM,CRIM1,CSPG5,CTGF,CTNNA2,CTNND1,CTSH,CYB5D2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYR61,DACH1,DAPL1,DCLK1,DCN,DCX,DDX5,DHRS3,DKK2,DKK3,DLG2,DONSON,DPYSL3,DRP2,DUSP6,EBF1,EGLN1,ELL3,ENPP2,EPAS1,FAM101B,FARP1,FGF14,FLNB,FMN2,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GAL3ST1,GATA4,GBA,GDF10,GDF15,GDF6,GFRA1,GNG8,GPNMB,GRIP1,HBEGF,HCCS,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HOXC6,HOXC8,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,HPCAL4,HTR2B,HUNK,IGF2,IGFBP7,INHBA,IRF6,ITGA1,ITGA7,ITGB5,JARID2,KALRN,KCNQ2,KCTD11,KIAA0319,KIAA1279,LAMA4,LBH,LIF,LUM,MAB21L1,MAOB,MAP6,MAPK9,MAPT,MATN2,MAX,MEIS1,MGEA5,MGP,MID1,MMP11,MPPED2,MSN,NAV1,NAV2,NBL1,NCAM2,NCAN,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NLGN1,NLGN3,NOS1,NOTCH2,NOTCH4,NPHP3,NPPB,NPR2,NRSN1,NRXN1,NSD1,NTNG2,NTRK2,NUMB,OLFM3,PAF1,PAPPA,PBX1,PBX3,PCDH9,PCDHB10,PCDHB14,PCDHB15,PCDHB3,PCDHB4,PDGFC,PDGFD,PHLDA1,PIM1,PKP2,PLAGL1,PLK2,PLN,PLXNB1,POLQ,PPARG,PRCP,PRNP,PSD2,PSEN1,PSMB8,PTCH1,PTGIS,PTPRM,PTPRR,RAB26,RAB27A,RAB3IP,RAI2,RAMP1,RARB,RBFOX2,RDH10,RELN,RET,RGS2,RND2,ROM1,RSPH9,RUNX1,SCG2,SCN2A,SCN3B,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SERPING1,SFRP4,SGCB,SH2B3,SH3PXD2A,SIPA1L1,SLC12A6,SLC40A1,SLC8A3,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SOAT1,SOCS3,SOX9,SPARC,SPEN,SPRY1,SPTAN1,SQSTM1,STAT3,STMN4,SYNGR3,SYP,TACC2,TAF7L,TANC2,TFRC,TGM2,TIMP1,TIMP2,TNFRSF19,TNS3,TPP1,TRIB2,TRIM45,TRIO,TRIOBP,TSHZ3,TTC30A,TTC30B,TULP3,TWSG1,TXK,VANGL1,VANGL2,VAV3,VCAN,VGF,WNT3,YAP1,ZFP36L1,ZFR,ZNF521
BP	GO:0048518: Positive regulation of biological process	4956	290	213.85	3.3e-10	AAK1,ABCA1,ABI3BP,ABL1,ACOX1,ADM,AHRR,AHSA2,AIFM2,AKT2,ALK,ANKRD1,ANKRD6,ANXA2,ANXA3,APH1A,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARMCX3,ARRDC3,ASAP1,ASAP2,ASS1,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATPIF1,ATXN1,BASP1,BCL2L11,BHLHB9,BMPR1B,BPTF,BTG2,BTK,C18orf32,C1GALT1C1,C1RL,C7,CACNA2D2,CADM1,CALCA,CAMK1,CCBE1,CCL2,CCND1,CD44,CDC42EP3,CDH2,CDK5R2,CDKL2,CDKN1A,CDKN1B,CEBPD,CHMP2B,CHRM3,CHRNA3,CHURC1,CIRBP,CLU,CNR1,COCH,COL3A1,COLEC12,CREB5,CREBL2,CREM,CTGF,CTNNA2,CTSA,CTSH,CYB5D2,CYB5R1,CYFIP2,CYP1B1,CYP26B1,CYR61,DCN,DDX5,DKK2,DNAJB11,DNAJB6,DNAJC27,DNAJC3,DOCK9,DPYSL3,DUSP6,EBF1,ELL3,ELMO2,ELMOD1,EPAS1,EPM2AIP1,FABP3,FAM129A,FAM13A,FAM13B,FARP1,FBXO4,FGF14,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GATA4,GBA,GCH1,GDF10,GDF15,GDF6,GRIP1,GRK5,GUCA1A,HBEGF,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HLA-C,HLA-E,HOXD10,HOXD3,HOXD8,HOXD9,HTR2B,IER3,IFNAR1,IGF2,IL20RA,INHBA,IRF6,ITGA1,ITPR2,JARID2,KALRN,KCNMA1,KCTD11,LBH,LIF,LMCD1,LPXN,LUM,MAB21L1,MAOB,MAPK9,MAPT,MED13,MEIS1,MGEA5,MID1,MID1IP1,MSN,NANOS1,NBL1,NCOA1,NCOA3,NCOA7,NDRG4,NFAT5,NLGN1,NLGN3,NOS1,NOTCH2,NOTCH4,NPEPPS,NPPA,NPPB,NRXN1,NSD1,NSF,NTRK2,NUMB,OSCP1,PACSIN3,PAF1,PBX1,PDGFC,PDGFD,PDIA3,PFKFB2,PHLDA1,PIM1,PKP2,PLAGL1,PLAT,PLEKHA2,PLK2,PLXNB1,PPARG,PRNP,PROS1,PSD2,PSEN1,PSMB8,PTCH1,PTGIR,PTGIS,PTPRM,PTX3,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RARB,RASL10B,RBPMS,RELN,RET,RFTN1,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RIMS2,RND2,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SAMD4A,SCG2,SCN3B,SCPEP1,SDC4,SDCBP,SEMA3A,SERPINE1,SERPING1,SFRP4,SGIP1,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SKAP2,SLC40A1,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SOAT1,SOCS3,SOX9,SPARC,SPEN,SPRY1,SQSTM1,STAT3,SYNGR3,SYTL4,TAF11,TAOK3,TFRC,TGM2,TIMP1,TIMP2,TMED4,TNFRSF19,TNS3,TOM1L1,TPP1,TRAF3IP2,TRIB2,TRIO,TRIOBP,TSHZ3,TSPAN31,TWSG1,TXK,VANGL2,VAV3,WDFY3,WNT3,YAP1
BP	GO:0023051: Regulation of signaling	2891	189	124.74	5.1e-10	AAK1,ABCA1,ABL1,ADM,ALK,ANKRD1,ANKRD6,ANXA2,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARRDC3,ASAP1,ASAP2,ATP2B4,ATP6AP1,ATP6AP2,ATPIF1,ATXN1,BCL2A1,BCL2L11,BMPR1B,C18orf32,CACNA2D2,CACNG2,CALB1,CALCA,CCBE1,CCL2,CCND1,CD44,CDH2,CHRM3,CHRNA3,CLU,CNGA1,CNKSR2,CNR1,COL3A1,CSPG5,CTGF,CTNND1,CTSH,CYP1B1,CYP26A1,CYP26B1,CYR61,DDX5,DHRS3,DKK2,DKK3,DNAJC27,DOCK9,DUSP16,DUSP6,ELL3,ELMOD1,ENSA,FAM13A,FAM13B,FARP1,FOXO3,FRZB,GAL,GATA4,GBA,GDF10,GDF15,GDF6,GNG7,GPRASP1,GRK5,GUCA1A,HBEGF,HES1,HEXIM1,HEY1,HIF1AN,HTR2B,IER3,IFNAR1,IGF2,IGFBP6,IL20RA,INHBA,ITGA1,ITPR2,KALRN,KCNB1,KCTD11,LIF,LMCD1,LPXN,MAP4K4,MAPK9,MCC,MGEA5,MID1,NBL1,NCOA3,NDRG4,NFAT5,NLGN1,NLGN3,NOS1,NOTCH2,NPHP3,NRXN1,NSF,NTRK2,NUMB,OPTN,PDIA3,PFKFB2,PLAT,PLK2,PLXNB1,PPARG,PRCP,PRNP,PSD2,PSEN1,PSMB8,PTCH1,PTGIR,PTGIS,PTPRR,RAB3B,RAB3IP,RABIF,RAMP1,RASL10B,RBPMS,RELN,RET,RFFL,RGL2,RGS13,RGS16,RGS

						2,RGS7,RHBDF1,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SCG2,SCG5,SDCBP,SERPINE1,SESN1,SFRP4,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SKAP2,SLC9A6,SLIT2,SNAP25,SNCAIP,SOCS3,SOX9,SPRY1,SQSTM1,STAT3,SYP,SYT11,SYTL4,TAOK3,TGM2,TIMP1,TIMP2,TMED4,TNFRSF19,TRAF3IP2,TRIB2,TRIO,TULP3,TWSG1,TXK,VANGL2,VAV3,YAP1
BP	GO:0010646: Regulation of cell communication	2903	189	125.26	7.2e-10	AAK1,ABCA1,ABL1,ADM,ALK,ANKRD1,ANKRD6,ANXA2,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARRDC3,ASAP1,ASAP2,ATP2B4,ATP6AP1,ATP6AP2,ATPIF1,ATXN1,BCL2A1,BCL2L11,BMPR1B,C18orf32,CACNA2D2,CACNG2,CALB1,CALCA,CCBE1,CCL2,CCND1,CD44,CDH2,CHRM3,CHRNA3,CLU,CNGA1,CNKSR2,CNR1,COL3A1,CSPG5,CTGF,CTNND1,CTSH,CYP1B1,CYP26A1,CYP26B1,CYR61,DDX5,DHRS3,DKK2,DKK3,DNAJC27,DOCK9,DUSP16,DUSP6,ELL3,ELMOD1,ENSA,FAM13A,FAM13B,FARP1,FOXO3,FRZB,GAL,GATA4,GBA,GDF10,GDF15,GDF6,GNG7,GPRASP1,GRK5,GUCA1A,HBEGF,HES1,HEXIM1,HEY1,HIF1AN,HTR2B,IER3,IFNAR1,IGF2,IGFBP6,IL20RA,INHBA,ITGA1,ITPR2,KALRN,KCNB1,KCTD11,LIF,LMCD1,LPXN,MAP4K4,MAPK9,MCC,MGEA5,MID1,NBL1,NCOA3,NDRG4,NFAT5,NLGN1,NLGN3,NOS1,NOTCH2,NPHP3,NRXN1,NTRK2,NUMB,OPTN,PDIA3,PFKFB2,PLAT,PLK2,PLXNB1,PPARG,PRCP,PRNP,PSD2,PSEN1,PSMB8,PTCH1,PTGIR,PTGIS,PTPRR,RAB3B,RAB3IP,RABIF,RAMP1,RASL10B,RBPMS,RELN,RET,RFFL,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SCG2,SCG5,SDCBP,SERPINE1,SESN1,SFRP4,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SKAP2,SLC9A6,SLIT2,SNAP25,SNCAIP,SOCS3,SOX9,SPRY1,SQSTM1,STAT3,SYP,SYT11,SYTL4,TAOK3,TGM2,TIMP1,TIMP2,TMED4,TNFRSF19,TRAF3IP2,TRIB2,TRIO,TULP3,TWSG1,TXK,VANGL2,VAV3,WDFY3,YAP1
BP	GO:0022008: Neurogenesis	1385	108	59.76	7.8e-10	ABL1,ADM,AGTPBP1,AKT2,ALK,ANKRD1,APH1A,ATP8B1,BHLHB9,BMPR1B,BTG2,CAMK1,CCL2,CDH11,CDH2,CDK5R2,CDKN2C,CHRNA3,CLASP2,CLN5,CLU,CNP,CNR1,COL3A1,CRB1,CSPG5,CTNNA2,CYB5D2,DCLK1,DCX,DPYSL3,ELL3,FARP1,FN1,GDF6,GFRA1,GRIP1,HES1,HEXB,HOXC8,HOXD1,HOXD10,HOXD3,HOXD9,ITGA1,KALRN,KCNQ2,KCTD11,KIAA0319,LIF,MAP6,MAPK9,MAPT,MATN2,MEIS1,NAV1,NBL1,NCAM2,NCAN,NCOA1,NDRG4,NFASC,NLGN1,NLGN3,NRXN1,NTNG2,NTRK2,NUMB,OLFM3,PBX1,PBX3,PHLDA1,PLK2,PLXNB1,PPARG,PRNP,PSD2,PSEN1,PTCH1,PTPRM,RARB,RBFOX2,RELN,RET,RND2,ROM1,RUNX1,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SMAD1,SNAP25,SOX9,SPEN,SPTAN1,STAT3,STMN4,TACC2,TIMP2,TRIO,TULP3,VANGL2,VAV3,VCAN,WNT3
BP	GO:0044700: Single organism signaling	5983	334	258.16	1.5e-09	AAK1,ABCA1,ABL1,ADM,AHRR,AKT2,AKT3,ALDH5A1,ALK,AMOTL2,ANKRD1,ANKRD6,ANXA2,APH1A,APLP1,ARF3,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARRDC3,ASAP1,ASAP2,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATPIF1,ATXN1,BCL2A1,BCL2L11,BCO2,BMPR1B,BTBD11,BTK,BZRAP1,C18orf32,CACNA2D2,CACNG2,CALB1,CALCA,CAMK1,CCBE1,CCL2,CCND1,CD44,CDC42EP3,CDH2,CDKL2,CDKN1A,CDKN1B,CHRM3,CHRNA3,CHRNB1,CLU,CNGA1,CNKSR2,CNP,CNR1,COL3A1,COLEC12,CRABP2,CRB1,CREBL2,CREM,CRIM1,CSPG5,CTGF,CTNND1,CTSH,CYFIP2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYR61,DCBLD2,DCLK1,DCLK2,DCX,DDX5,DHRS3,DKK2,DKK3,DLG2,DNAJB11,DNAJC27,DNAJC3,DOCK9,DTNA,DUSP16,DUSP6,ECEL1,EFEMP2,EIF4E3,ELL3,ELMO2,ELMOD1,ENPP2,ENSA,EPAS1,EPB41L1,FAM13A,FAM13B,FARP1,FAT1,FGF14,FLNB,FLRT1,FMN2,FOS,FOXC1,FOXO3,FRZB,GABRP,GAL,GATA4,GBA,GDF10,GDF15,GDF6,GFRA1,GNG2,GNG7,GNG8,GPR19,GPR22,GPRASP1,GRIP1,GRK5,GUCA1A,HBEGF,HES1,HEXIM1,HEY1,HIF1AN,HLA-C,HLA-E,HOXD3,HPCAL1,HPCAL4,HTR2B,HUNK,IER3,IFNAR1,IGF2,IGFBP6,IL10RB,IL17RD,IL20RA,INADL,INHBA,IRF6,IRF9,ITGA1,ITGA7,ITGB5,ITPR2,KALRN,KCNB1,KCNMA1,KCNQ2,KCTD11,KRT18,LIF,LMCD1,LPXN,MAP4K4,MAPK9,MAPRE2,MCC,MED13,MGEA5,MID1,NBL1,NCOA1,NCOA3,NDRG4,NFASC,NFAT5,NLGN1,NLGN3,NMI,NOS1,NOTCH2,NOTCH4,NPHP3,NPPA,NPPB,NPR2,NPTX2,NRXN1,NSF,NTRK2,NUMB,OAS1,OPTN,PAF1,PCDHB10,PCDHB14,PCDHB3,PCDHB4,PCLO,PDGFC,PDGFD,PDIA3,PEX11B,PFKFB2,PIM1,PKP2,PLAT,PLCD4,PLK2,PLN,PLXNB1,PPARG,PRCP,PRNP,PSD2,PSEN1,PSMB8,PTCH1,PTGER2,PTGIR,PTGIS,PTPRM,PTPRR,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RARB,RASEF,RASL10B,RBFOX2,RBP1,RBPMS,RDH10,RELN,RET,RFFL,RFTN1,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RIC3,RIMS2,RIT1,RIT2,RLN1,RND2,RNF175,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SCG2,SCG5,SCN2A,SCN3A,SCN3B,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SESN1,SFRP4,SH2B3,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SKAP2,SLC22A17,SLC6A2,SLC9A6,SLIT2,SMAD1,SMOC1,SNAP25,SNCAIP,SOCS3,SORCS1,SOX9,SPARC,SPEN,SPRY1,SQSTM1,STAT3,SYN2,SYP,SYT11,SYT4,SYTL4,TAOK3,TEX2,TGM2,TIMP1,TIMP2,TMED4,TNFRSF19,TOM1L1,TOM1L2,TPP1,TRAF3IP2,TRIB2,TRIO,TULP3,TULP4,TWSG1,TXK,VANGL2,VAV3,VGF,WNT3,YAP1,ZCCHC12
BP	GO:0007154: Cell communication	6077	338	262.22	1.7e-09	AAK1,ABCA1,ABL1,ADM,AHRR,AKT2,AKT3,ALDH5A1,ALK,AMOTL2,ANKRD1,ANKRD6,ANXA2,APH1A,APLP1,ARF3,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARRDC3,ASAP1,ASAP2,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATPIF1,ATXN1,BCL2A1,BCL2L11,BCO2,BMPR1B,BTBD11,BTK,BZRAP1,C18orf32,CACNA2D2,CACNG2,CALB1,CALCA,CAMK1,CCBE1,CCL2,CCND1,CD44,CDC42EP3,CDH2,CDKL2,CDKN1A,CDKN1B,CHRM3,CHRNA3,CHRNB1,CLU,CNGA1,CNKSR2,CNP,CNR1,COL3A1,COLEC12,CRABP2,CRB1,CREBL2,CREM,CRIM1,CS

						PG5,CTGF,CTNND1,CTSH,CYFIP2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYR61,DCBLD2,DCLK1,DCLK2,DCX,DDX5,DHRS3,DKK2,DKK3,DLG2,DNAJB11,DNAJC27,DNAJC3,DOCK9,DTNA,DUSP16,DUSP6,ECEL1,EFEMP2,EIF4E3,ELL3,ELMO2,ELMOD1,ENPP2,ENSA,EPAS1,EPB41L1,FAM13A,FAM13B,FARP1,FAT1,FGF14,FLNB,FLRT1,FMN2,FOS,FOXC1,FOXO3,FRZB,GABARAPL1,GABRP,GAL,GATA4,GBA,GDF10,GDF15,GDF6,GFRA1,GNG2,GNG7,GNG8,GPR19,GPR22,GPRASP1,GRIP1,GRK5,GUCA1A,HBEGF,HES1,HEXIM1,HEY1,HIF1AN,HLA-C,HLA-E,HOXD3,HPCAL1,HPCAL4,HTR2B,HUNK,IER3,IFNAR1,IGF2,IGFBP6,IL10RB,IL17RD,IL20RA,INADL,INHBA,IRF6,IRF9,ITGA1,ITGA7,ITGB5,ITPR2,KALRN,KCNB1,KCNMA1,KCNQ2,KCTD11,KRT18,LIF,LMCD1,LPXN,MAP4K4,MAPK9,MAPRE2,MAX,MCC,MED13,MGEA5,MID1,NBL1,NCOA1,NCOA3,NDRG4,NFASC,NFAT5,NLGN1,NLGN3,NMI,NOS1,NOTCH2,NOTCH4,NPHP3,NPPA,NPPB,NPR2,NPTX2,NRXN1,NSF,NTRK2,NUMB,OAS1,OPTN,PAF1,PCDHB10,PCDHB14,PCDHB3,PCDHB4,PCLO,PDGFC,PDGFD,PDIA3,PEX11B,PFKFB2,PIM1,PKP2,PLAT,PLCD4,PLK2,PLN,PLXNB1,PPARG,PRCP,PRNP,PSD2,PSEN1,PSMB8,PTCH1,PTGER2,PTGIR,PTGIS,PTPRM,PTPRR,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RARB,RASEF,RASL10B,RBFOX2,RBP1,RBPMS,RDH10,RELN,RET,RFFL,RFTN1,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RIC3,RIMS2,RIT1,RIT2,RLN1,RND2,RNF175,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SCG2,SCG5,SCN2A,SCN3A,SCN3B,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SESN1,SFRP4,SH2B3,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SKAP2,SLC22A17,SLC6A2,SLC8A3,SLC9A6,SLIT2,SMAD1,SMOC1,SNAP25,SNCAIP,SOCS3,SORCS1,SOX9,SPARC,SPEN,SPRY1,SQSTM1,STAT3,SYN2,SYP,SYT11,SYT4,SYTL4,TAOK3,TEX2,TGM2,TIMP1,TIMP2,TMED4,TNFRSF19,TOM1L1,TOM1L2,TPP1,TRAF3IP2,TRIB2,TRIO,TULP3,TULP4,TWSG1,TXK,VANGL2,VAV3,VGF,WDFY3,WNT3,YAP1,ZCCHC12
BP	GO:0023052: Signaling	5989	334	258.42	1.7e-09	AAK1,ABCA1,ABL1,ADM,AHRR,AKT2,AKT3,ALDH5A1,ALK,AMOTL2,ANKRD1,ANKRD6,ANXA2,APH1A,APLP1,ARF3,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARRDC3,ASAP1,ASAP2,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATPIF1,ATXN1,BCL2A1,BCL2L11,BCO2,BMPR1B,BTBD11,BTK,BZRAP1,C18orf32,CACNA2D2,CACNG2,CALB1,CALCA,CAMK1,CCBE1,CCL2,CCND1,CD44,CDC42EP3,CDH2,CDKL2,CDKN1A,CDKN1B,CHRM3,CHRNA3,CHRNB1,CLU,CNGA1,CNKSR2,CNP,CNR1,COL3A1,COLEC12,CRABP2,CRB1,CREBL2,CREM,CRIM1,CSPG5,CTGF,CTNND1,CTSH,CYFIP2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYR61,DCBLD2,DCLK1,DCLK2,DCX,DDX5,DHRS3,DKK2,DKK3,DLG2,DNAJB11,DNAJC27,DNAJC3,DOCK9,DTNA,DUSP16,DUSP6,ECEL1,EFEMP2,EIF4E3,ELL3,ELMO2,ELMOD1,ENPP2,ENSA,EPAS1,EPB41L1,FAM13A,FAM13B,FARP1,FAT1,FGF14,FLNB,FLRT1,FMN2,FOS,FOXC1,FOXO3,FRZB,GABRP,GAL,GATA4,GBA,GDF10,GDF15,GDF6,GFRA1,GNG2,GNG7,GNG8,GPR19,GPR22,GPRASP1,GRIP1,GRK5,GUCA1A,HBEGF,HES1,HEXIM1,HEY1,HIF1AN,HLA-C,HLA-E,HOXD3,HPCAL1,HPCAL4,HTR2B,HUNK,IER3,IFNAR1,IGF2,IGFBP6,IL10RB,IL17RD,IL20RA,INADL,INHBA,IRF6,IRF9,ITGA1,ITGA7,ITGB5,ITPR2,KALRN,KCNB1,KCNMA1,KCNQ2,KCTD11,KRT18,LIF,LMCD1,LPXN,MAP4K4,MAPK9,MAPRE2,MCC,MED13,MGEA5,MID1,NBL1,NCOA1,NCOA3,NDRG4,NFASC,NFAT5,NLGN1,NLGN3,NMI,NOS1,NOTCH2,NOTCH4,NPHP3,NPPA,NPPB,NPR2,NPTX2,NRXN1,NSF,NTRK2,NUMB,OAS1,OPTN,PAF1,PCDHB10,PCDHB14,PCDHB3,PCDHB4,PCLO,PDGFC,PDGFD,PDIA3,PEX11B,PFKFB2,PIM1,PKP2,PLAT,PLCD4,PLK2,PLN,PLXNB1,PPARG,PRCP,PRNP,PSD2,PSEN1,PSMB8,PTCH1,PTGER2,PTGIR,PTGIS,PTPRM,PTPRR,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RARB,RASEF,RASL10B,RBFOX2,RBP1,RBPMS,RDH10,RELN,RET,RFFL,RFTN1,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RIC3,RIMS2,RIT1,RIT2,RLN1,RND2,RNF175,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SCG2,SCG5,SCN2A,SCN3A,SCN3B,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SESN1,SFRP4,SH2B3,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SKAP2,SLC22A17,SLC6A2,SLC9A6,SLIT2,SMAD1,SMOC1,SNAP25,SNCAIP,SOCS3,SORCS1,SOX9,SPARC,SPEN,SPRY1,SQSTM1,STAT3,SYN2,SYP,SYT11,SYT4,SYTL4,TAOK3,TEX2,TGM2,TIMP1,TIMP2,TMED4,TNFRSF19,TOM1L1,TOM1L2,TPP1,TRAF3IP2,TRIB2,TRIO,TULP3,TULP4,TWSG1,TXK,VANGL2,VAV3,VGF,WNT3,YAP1,ZCCHC12
BP	GO:0030182: Neuron differentiation	1202	95	51.86	4.9e-09	ABL1,ADM,AGTPBP1,ALK,ANKRD1,APH1A,ATP8B1,BHLHB9,BMPR1B,BTG2,CAMK1,CDH11,CHRNA3,CLASP2,CLN5,CNP,CNR1,COL3A1,CRB1,CSPG5,CTNNA2,CYB5D2,DCLK1,DCX,DPYSL3,FARP1,FN1,GDF6,GFRA1,GRIP1,HES1,HOXC8,HOXD1,HOXD10,HOXD3,HOXD9,ITGA1,KALRN,KCNQ2,KCTD11,KIAA0319,LIF,MAP6,MAPK9,MAPT,MATN2,MEIS1,NBL1,NCAM2,NCAN,NCOA1,NDRG4,NFASC,NLGN1,NLGN3,NRXN1,NTNG2,NTRK2,NUMB,OLFM3,PBX1,PBX3,PHLDA1,PLK2,PLXNB1,PRNP,PSD2,PSEN1,PTCH1,PTPRM,RARB,RBFOX2,RELN,RET,RND2,ROM1,RUNX1,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SMAD1,SNAP25,SOX9,SPTAN1,STAT3,STMN4,TIMP2,TRIO,TULP3,VANGL2,VAV3,WNT3
BP	GO:0048699: Generation of neurons	1309	100	56.48	1.1e-08	ABL1,ADM,AGTPBP1,ALK,ANKRD1,APH1A,ATP8B1,BHLHB9,BMPR1B,BTG2,CAMK1,CDH11,CDK5R2,CHRNA3,CLASP2,CLN5,CNP,CNR1,COL3A1,CRB1,CSPG5,CTNNA2,CYB5D2,DCLK1,DCX,DPYSL3,ELL3,FARP1,FN1,GDF6,GFRA1,GRIP1,HES1,HOXC8,HOXD1,HOXD10,HOXD3,HOXD9,ITGA1,KALRN,KCNQ2,KCTD11,KIAA0319,LIF,MAP6,MAPK9,MAPT,MATN2,MEIS1,NAV1,NBL1,NCAM2,NCAN,NCOA1,NDRG4,NFASC,NLGN1,NLGN3,NRXN1,NTNG2,NTRK2,NUMB,OLF

						M3,PBX1,PBX3,PHLDA1,PLK2,PLXNB1,PPARG,PRNP,PSD2,PSEN1,PTCH1,PTPRM,RARB,RBFOX2,RELN,RET,RND2,ROM1,RUNX1,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SMAD1,SNAP25,SOX9,SPEN,SPTAN1,STAT3,STMN4,TIMP2,TRIO,TULP3,VANGL2,VAV3,WNT3
BP	GO:0009966: Regulation of signal transduction	2595	167	111.97	2.4e-08	AAK1,ABCA1,ABL1,ADM,ALK,ANKRD1,ANKRD6,ANXA2,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARRDC3,ASAP1,ASAP2,ATP2B4,ATP6AP1,ATP6AP2,ATPIF1,ATXN1,BCL2A1,BCL2L11,BMPR1B,C18orf32,CACNG2,CALCA,CCBE1,CCND1,CD44,CDH2,CLU,CNGA1,CNKSR2,COL3A1,CTGF,CTNND1,CTSH,CYP1B1,CYP26A1,CYP26B1,CYR61,DDX5,DHRS3,DKK2,DKK3,DNAJC27,DOCK9,DUSP16,DUSP6,ELL3,ELMOD1,FAM13A,FAM13B,FARP1,FOXO3,FRZB,GATA4,GBA,GDF10,GDF15,GDF6,GNG7,GPRASP1,GRK5,GUCA1A,HBEGF,HES1,HEXIM1,HEY1,HIF1AN,HTR2B,IER3,IFNAR1,IGF2,IGFBP6,IL20RA,INHBA,ITGA1,KALRN,KCTD11,LIF,LMCD1,LPXN,MAP4K4,MAPK9,MCC,MID1,NBL1,NCOA3,NDRG4,NFAT5,NLGN1,NLGN3,NOS1,NOTCH2,NPHP3,NRXN1,NTRK2,NUMB,OPTN,PDIA3,PLK2,PLXNB1,PPARG,PRCP,PRNP,PSD2,PSEN1,PSMB8,PTCH1,PTGIR,PTGIS,PTPRR,RAB3IP,RABIF,RAMP1,RBPMS,RELN,RET,RFFL,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SCG2,SDCBP,SERPINE1,SESN1,SFRP4,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SKAP2,SLC9A6,SLIT2,SOCS3,SOX9,SPRY1,SQSTM1,STAT3,SYP,TAOK3,TGM2,TIMP1,TIMP2,TMED4,TNFRSF19,TRAF3IP2,TRIB2,TRIO,TULP3,TWSG1,TXK,VANGL2,VAV3,YAP1
BP	GO:0065008: Regulation of biological quality	3220	198	138.94	2.7e-08	AAK1,ABCA1,ABL1,ACOX1,ACTA2,ADM,ALDH5A1,ANO3,ANXA2,AQP11,ARRDC3,ATP10D,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,ATXN1,B4GALNT1,BCL2L11,BCO2,BHLHB9,BRPF3,BTK,BZRAP1,C1GALT1C1,C7,CACNA2D2,CACNG2,CALB1,CALCA,CAMK1,CCL2,CCND1,CD44,CDC42EP3,CHMP2B,CHRM3,CHRNA3,CHRNB1,CIRBP,CLASP2,CLN5,CLU,CNGA1,CNP,CNR1,COCH,COL3A1,CRABP2,CREBL2,CRTAP,CSRP1,CTGF,CTNNA2,CTSH,CYP1B1,CYP26A1,CYP26B1,DHRS3,DKK3,DNAJC16,DOCK9,EFEMP2,EGLN1,ENSA,EPAS1,FABP3,FBXO4,FLNB,FN1,FOXC1,FOXO3,GAL,GATA4,GBA,GCH1,GNG2,HEXB,HTR2B,IER3,IGF2,IL20RA,INHBA,ITGA1,ITGA7,ITPR2,KCNB1,KCNMA1,LBH,LIF,MAPT,MEST,MGEA5,NAV2,NBL1,NCAN,NCOA1,NLGN1,NLGN3,NOS1,NPC2,NPHP3,NPPA,NPPB,NPR2,NRXN1,NTRK2,OAS1,OS9,PCLO,PDIA3,PEX11B,PFKFB2,PKP2,PLAT,PLK2,PLN,PLXNB1,POPDC3,PPARG,PRCP,PRNP,PROS1,PSEN1,PTCH1,PTGIR,PTPRM,PTX3,PYGL,RAB27A,RAB3B,RASL10B,RBFOX2,RDH10,RELN,RET,RGS2,RIC3,RIMS2,RND2,RUNX1,SCG5,SCN2A,SCN3A,SCN3B,SCPEP1,SEMA3A,SEMA4F,SERPINE1,SERPING1,SFRP4,SGIP1,SH2B3,SH3BGRL3,SIPA1L1,SLC22A17,SLC31A2,SLC40A1,SLC4A8,SLC8A3,SLC9A6,SLIT2,SMAD1,SNAP25,SNCAIP,SOAT1,SOX9,SPARC,SPTAN1,STAT3,SYN2,SYP,SYT11,SYT4,SYTL4,TAF11,TAP1,TEP1,TFRC,TGM2,TIMP1,TMX4,TPP1,TRIOBP,TSPAN8,TXNDC15,VAV3,VGF,VPS13D,WNT3,ZFP36L1
BP	GO:0072358: Cardiovascular system development	868	73	37.45	3.0e-08	ACTA2,ADM,ANKRD1,ANXA2,ANXA3,APOLD1,ARID1A,ATPIF1,BASP1,BCOR,CALCA,CCBE1,CCDC40,CCL2,CDH2,COL11A1,COL3A1,COX17,CTGF,CTSH,CYP1B1,CYR61,DHRS3,DUSP6,EGLN1,ENPP2,EPAS1,FN1,FOXC1,GATA4,HES1,HEXIM1,HEY1,HIF1AN,HTR2B,ITGA7,LIF,MEIS1,NDRG4,NEBL,NOTCH2,NOTCH4,NPHP3,NPPB,NRXN1,NTRK2,PKP2,PLN,PPARG,PRCP,PSEN1,PTCH1,PTGIS,PTPRM,RAMP1,RARB,ROM1,RUNX1,SCG2,SERPINE1,SGCB,SLC12A6,SLIT2,SMAD1,SMARCA2,SOCS3,SOX9,SPARC,VANGL2,VAV3,VCAN,YAP1,ZFP36L1
BP	GO:0072359: Circulatory system development	868	73	37.45	3.0e-08	ACTA2,ADM,ANKRD1,ANXA2,ANXA3,APOLD1,ARID1A,ATPIF1,BASP1,BCOR,CALCA,CCBE1,CCDC40,CCL2,CDH2,COL11A1,COL3A1,COX17,CTGF,CTSH,CYP1B1,CYR61,DHRS3,DUSP6,EGLN1,ENPP2,EPAS1,FN1,FOXC1,GATA4,HES1,HEXIM1,HEY1,HIF1AN,HTR2B,ITGA7,LIF,MEIS1,NDRG4,NEBL,NOTCH2,NOTCH4,NPHP3,NPPB,NRXN1,NTRK2,PKP2,PLN,PPARG,PRCP,PSEN1,PTCH1,PTGIS,PTPRM,RAMP1,RARB,ROM1,RUNX1,SCG2,SERPINE1,SGCB,SLC12A6,SLIT2,SMAD1,SMARCA2,SOCS3,SOX9,SPARC,VANGL2,VAV3,VCAN,YAP1,ZFP36L1
BP	GO:0044707: Single-multicellular organism process	6400	346	276.15	3.1e-08	ABCA1,ABL1,ACP2,ACTA2,ADM,AGTPBP1,AKT2,ALDH5A1,ALK,ANKRD1,ANKRD33,ANKRD6,ANXA2,ANXA3,APH1A,APLP1,APOLD1,AQP11,ARHGAP26,ARID1A,ARRDC3,ASS1,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP8B1,ATPIF1,ATXN1,BASP1,BCL2L11,BCOR,BHLHB9,BHLHE40,BHLHE41,BMPR1B,BPTF,BRPF3,BTG2,BTK,C1GALT1C1,CACNA2D2,CACNG2,CADM1,CALB1,CALCA,CAMK1,CCBE1,CCDC40,CCL2,CCND1,CD44,CDH11,CDH2,CDK5R2,CDKN1A,CDKN1B,CDKN2C,CELF2,CHMP2B,CHRM3,CHRNA3,CHRNB1,CHURC1,CLASP2,CLDN11,CLN5,CLPTM1,CLU,CNGA1,CNP,CNR1,COCH,COL11A1,COL17A1,COL23A1,COL3A1,COX11,COX17,CRABP2,CRB1,CREB5,CREM,CRIM1,CSPG5,CSRP1,CTGF,CTNNA2,CTNND1,CTSH,CYB5D2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYP4V2,CYR61,DACH1,DCLK1,DCN,DCX,DDX5,DHRS3,DKK2,DKK3,DLG2,DOCK9,DONSON,DPYSL3,DRP2,DTNA,DUSP6,EBF1,ECEL1,EFEMP2,EGLN1,ELL3,ENPP2,EPAS1,FAM101B,FARP1,FGF14,FLNB,FMN2,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GAL3ST1,GATA4,GBA,GCH1,GDF10,GDF6,GFRA1,GNG2,GNG7,GNG8,GPNMB,GRIP1,GUCA1A,HBEGF,HCCS,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HLA-E,HOXC6,HOXC8,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,HPCAL4,HTR2B,HUNK,IER3,IFNAR1,IGF2,IGFBP7,IL20RA,INHBA,IRF6,IRF9,ITGA1,ITGA7,ITGB5,ITPR2,JAKMIP1,JARID2,KALRN,KCNMA1,KCNQ2,KCTD11,KIAA0319,KIAA1279,LAMA4,LBH,LIF,LMCD1,LUM,MAB21L1,MAOB,MAP6,MAPK9,MAPT,MATN2,MAX,MCC,MEIS1,MGEA5,MGP,MID1,

						MMP11,MPPED2,NANOS1,NAV1,NAV2,NBL1,NCAM2,NCAN,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NFAT5,NLGN1,NLGN3,NOS1,NOTCH2,NOTCH4,NPHP3,NPPA,NPPB,NPR2,NRSN1,NRXN1,NSD1,NTNG2,NTRK2,NUMB,OLFM3,PAF1,PBX1,PBX3,PCDH9,PCDHB10,PCDHB14,PCDHB15,PCDHB3,PCDHB4,PDGFC,PDGFD,PHLDA1,PIM1,PKP2,PLAGL1,PLAT,PLK2,PLN,PLXNB1,POLQ,PPARG,PRCP,PRNP,PROS1,PSD2,PSEN1,PTCH1,PTGIR,PTGIS,PTPRM,PTPRR,RAB26,RAB27A,RAI2,RAMP1,RARB,RASL10B,RBFOX2,RDH10,RELN,RET,RFTN1,RGS16,RGS2,RND2,ROM1,RUNX1,SCG2,SCN2A,SCN3A,SCN3B,SCPEP1,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SERPING1,SFRP4,SGCB,SGIP1,SH2B3,SH3BGRL3,SH3PXD2A,SIPA1L1,SLC12A6,SLC26A2,SLC40A1,SLC6A2,SLC8A3,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SOAT1,SOCS3,SOX9,SPARC,SPEN,SPRY1,SPTAN1,SSPN,STAT3,STMN4,SYNGR3,TACC2,TAF7L,TANC2,TFRC,TGM2,TIMP1,TIMP2,TIMP3,TNFRSF19,TNS3,TPP1,TRIB2,TRIM45,TRIO,TSHZ3,TSPAN8,TULP3,TWSG1,TXK,VANGL1,VANGL2,VAV3,VCAN,VGF,WNT3,YAP1,ZFHX2,ZFP36L1,ZFR,ZNF521
BP	GO:0051239: Regulation of multicellular organismal process	2243	148	96.78	4.2e-08	ABL1,ADM,ANKRD1,ANKRD6,ANXA2,ANXA3,APOLD1,ARRDC3,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,BASP1,BCL2L11,BCOR,BHLHB9,BMPR1B,BTK,CACNA2D2,CADM1,CALCA,CAMK1,CCBE1,CCL2,CCND1,CDKN1B,CELF2,CHRM3,CHRNA3,CLPTM1,CLU,CNR1,COL3A1,CTGF,CTSH,CYB5D2,CYP1B1,CYP26B1,CYR61,DDX5,DHRS3,DPYSL3,DUSP6,EGLN1,ELL3,ENPP2,EPAS1,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GATA4,GBA,GDF6,HBEGF,HES1,HEY1,HIF1AN,HLA-E,HOXD3,HTR2B,IFNAR1,IL20RA,INHBA,KCTD11,KIAA0319,LAMA4,LBH,LIF,LMCD1,MAPK9,MAPT,MCC,MEIS1,MGEA5,MGP,NBL1,NCOA1,NCOA3,NDRG4,NLGN1,NLGN3,NOS1,NOTCH4,NPHP3,NPPA,NPPB,NPR2,NRXN1,NTRK2,NUMB,PAF1,PBX1,PBX3,PKP2,PLAT,PLK2,PLN,PLXNB1,PPARG,PRCP,PRNP,PROS1,PSEN1,PTCH1,PTGIS,PTPRM,PTPRR,RARB,RBFOX2,RELN,RET,RGS2,RND2,RUNX1,SCN3B,SCPEP1,SEMA3A,SEMA4F,SERPINE1,SERPING1,SFRP4,SGIP1,SH3BGRL3,SIPA1L1,SLIT2,SMAD1,SMOC1,SNAP25,SOX9,SPARC,SPEN,SPRY1,STAT3,TFRC,TIMP1,TIMP2,TRIB2,TSHZ3,TSPAN8,TULP3,TWSG1,TXK,VANGL2,WNT3,YAP1
BP	GO:0048468: Cell development	1920	131	82.85	4.5e-08	ABL1,ACTA2,ADM,AKT2,ALK,ANKRD1,ANXA2,APH1A,ATP6AP1,ATP8B1,BASP1,BCL2L11,BHLHB9,BMPR1B,BTG2,BTK,C1GALT1C1,CACNA2D2,CAMK1,CDH11,CDH2,CDKN1A,CHRNA3,CHRNB1,CLASP2,CLN5,CLU,CNP,CNR1,COL11A1,COL3A1,CRB1,CSPG5,CTNNA2,CYB5D2,CYP26A1,CYR61,DCLK1,DCX,DPYSL3,ELL3,EPAS1,FAM101B,FARP1,FMN2,FN1,FOXC1,FOXO3,FRZB,GAL,GATA4,GDF10,GDF15,GDF6,GFRA1,GRIP1,HES1,HEXB,HEY1,HOXD10,HOXD3,HOXD9,HTR2B,INHBA,IRF6,ITGA1,KALRN,KCNQ2,KCTD11,KIAA0319,LIF,MAP6,MAPK9,MAPT,MATN2,MEIS1,MSN,NBL1,NCAM2,NCAN,NCOA1,NDRG4,NEBL,NFASC,NLGN1,NLGN3,NOTCH2,NOTCH4,NPR2,NRXN1,NTNG2,NTRK2,NUMB,OLFM3,PAF1,PBX1,PBX3,PLK2,PLXNB1,PPARG,PRNP,PSEN1,PTPRM,RARB,RBFOX2,RDH10,RELN,RET,RND2,RUNX1,SDCBP,SEMA3A,SEMA4F,SGCB,SIPA1L1,SLC9A6,SLIT2,SMAD1,SNAP25,SOX9,SPEN,SPTAN1,STAT3,STMN4,TIMP2,TRIO,TRIOBP,VANGL2,VAV3,WNT3,YAP1
BP	GO:0045597: Positive regulation of cell differentiation	725	63	31.28	8.9e-08	ABL1,ADM,ANKRD1,ATP6AP1,BHLHB9,BMPR1B,BTK,CALCA,CAMK1,CDH2,CNR1,CREBL2,CTGF,CTNNA2,CYB5D2,CYP26B1,CYR61,DPYSL3,ELL3,FN1,FOS,FOXC1,FOXO3,FRZB,GATA4,GDF15,GDF6,HES1,HEY1,HIF1AN,HOXD3,INHBA,KCTD11,LIF,MAPK9,MAPT,NBL1,NCOA1,NCOA3,NDRG4,NLGN1,NTRK2,NUMB,PLXNB1,PPARG,PSEN1,RARB,RELN,RET,RND2,RUNX1,SEMA3A,SFRP4,SLIT2,SMAD1,SOCS3,SOX9,SPEN,TIMP2,TRIOBP,TSHZ3,WNT3,YAP1
BP	GO:0048583: Regulation of response to stimulus	3356	202	144.81	1.0e-07	AAK1,ABCA1,ABL1,ADM,AKT2,ALK,ANKRD1,ANKRD6,ANXA2,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARRDC3,ASAP1,ASAP2,ATP2B4,ATP6AP1,ATP6AP2,ATPIF1,ATXN1,BCL2A1,BCL2L11,BMPR1B,BTK,C18orf32,C1RL,C7,CACNG2,CADM1,CALCA,CCBE1,CCL2,CCND1,CD44,CDH2,CDKN1A,CDKN1B,CLU,CNGA1,CNKSR2,CNR1,COCH,COL3A1,COLEC12,CTGF,CTNNA2,CTNND1,CTSH,CYFIP2,CYP1B1,CYP26A1,CYP26B1,CYR61,DDX5,DHRS3,DKK2,DKK3,DNAJC27,DNAJC3,DOCK9,DUSP16,DUSP6,ELL3,ELMO2,ELMOD1,FAM13A,FAM13B,FARP1,FOS,FOXO3,FRZB,GATA4,GBA,GDF10,GDF15,GDF6,GNG7,GPRASP1,GRK5,GUCA1A,HBEGF,HES1,HEXIM1,HEY1,HIF1AN,HLA-C,HLA-E,HTR2B,ICAM2,IER3,IFNAR1,IGF2,IGFBP6,IL20RA,INHBA,ITGA1,ITPR2,KALRN,KCTD11,LBH,LIF,LMCD1,LPXN,MAP4K4,MAPK9,MCC,MGEA5,MID1,MMP28,NBL1,NCOA1,NCOA3,NDRG4,NFAT5,NLGN1,NLGN3,NOS1,NOTCH2,NPHP3,NRXN1,NTRK2,NUMB,OPTN,PARP9,PDIA3,PLAT,PLK2,PLXNB1,POLQ,PPARG,PRCP,PRNP,PROS1,PSD2,PSEN1,PSMB8,PTCH1,PTGIR,PTGIS,PTPRR,RAB3IP,RABIF,RAMP1,RBPMS,RELN,RET,RFFL,RFTN1,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SCG2,SDCBP,SEMA3A,SERPINE1,SERPING1,SESN1,SFRP4,SGIP1,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SKAP2,SLC9A6,SLIT2,SOCS3,SOX9,SPRY1,SQSTM1,STAT3,SYP,TAOK3,TGM2,TIMP1,TIMP2,TMED4,TNFRSF19,TRAF3IP2,TRIB2,TRIO,TSPAN8,TULP3,TWSG1,TXK,VANGL2,VAV3,WDFY3,WNT3,YAP1
BP	GO:0032501: Multicellular organismal process	6651	354	286.98	1.2e-07	ABCA1,ABL1,ACOX1,ACP2,ACTA2,ADAM29,ADM,AGTPBP1,AKT2,ALDH5A1,ALK,ANKRD1,ANKRD33,ANKRD6,ANXA2,ANXA3,APH1A,APLP1,APOLD1,AQP11,ARHGAP26,ARID1A,ARRDC3,ASS1,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP8B1,ATPIF1,ATXN1,B4GALNT1,BASP1,BCL2L11,BCOR,BHLHB9,BHLHE40,BHLHE41,BMPR1B,BPTF,BRPF3,BTG2,BTK,C1GALT1C1,CACNA2D2,CACNG2,CADM1,CALB1,CALCA,CAMK1,CCBE1,CCDC40,CCL2,CCNA1,CCND1,CD44,CDH11,CDH2,CDK5R2,CDKN1A,CDKN1B,CDKN

						2C,CELF2,CHMP2B,CHRM3,CHRNA3,CHRNB1,CHURC1,CLASP2,CLDN11,CLN5,CLPTM1,CLU,CNGA1,CNP,CNR1,COCH,COL11A1,COL17A1,COL23A1,COL3A1,COX11,COX17,CRABP2,CRB1,CREB5,CREM,CRIM1,CRTAP,CSPG5,CSRP1,CTGF,CTNNA2,CTNND1,CTSH,CYB5D2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYP4V2,CYR61,DACH1,DCLK1,DCN,DCX,DDX5,DHRS3,DKK2,DKK3,DLG2,DOCK9,DONSON,DPYSL3,DRP2,DTNA,DUSP6,EBF1,ECEL1,EFEMP2,EGLN1,ELL3,ENPP2,EPAS1,FAM101B,FARP1,FGF14,FLNB,FMN2,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GAL3ST1,GATA4,GBA,GCH1,GDF10,GDF6,GFRA1,GNG2,GNG7,GNG8,GPNMB,GRIP1,GUCA1A,HBEGF,HCCS,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HLA-E,HOXC6,HOXC8,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,HPCAL4,HTR2B,HUNK,IER3,IFNAR1,IGF2,IGFBP7,IL20RA,INHBA,IRF6,IRF9,ITGA1,ITGA7,ITGB5,ITPR2,JAKMIP1,JARID2,KALRN,KCNMA1,KCNQ2,KCTD11,KIAA0319,KIAA1279,LAMA4,LBH,LIF,LMCD1,LUM,MAB21L1,MAOB,MAP6,MAPK9,MAPT,MATN2,MAX,MCC,MEIS1,MGEA5,MGP,MID1,MMP11,MPPED2,NANOS1,NAV1,NAV2,NBL1,NCAM2,NCAN,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NFAT5,NLGN1,NLGN3,NOS1,NOTCH2,NOTCH4,NPHP3,NPPA,NPPB,NPR2,NRSN1,NRXN1,NSD1,NTNG2,NTRK2,NUMB,OLFM3,PAF1,PAPPA,PBX1,PBX3,PCDH9,PCDHB10,PCDHB14,PCDHB15,PCDHB3,PCDHB4,PDGFC,PDGFD,PHLDA1,PIM1,PKP2,PLAGL1,PLAT,PLK2,PLN,PLXNB1,POLQ,PPARG,PRCP,PRNP,PROS1,PSD2,PSEN1,PTCH1,PTGIR,PTGIS,PTPRM,PTPRR,RAB26,RAB27A,RAI2,RAMP1,RARB,RASL10B,RBFOX2,RDH10,RELN,RET,RFTN1,RGS16,RGS2,RLN1,RND2,ROM1,RUNX1,SCG2,SCN2A,SCN3A,SCN3B,SCPEP1,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SERPING1,SFRP4,SGCB,SGIP1,SH2B3,SH3BGRL3,SH3PXD2A,SIPA1L1,SLC12A6,SLC26A2,SLC40A1,SLC6A2,SLC8A3,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SOAT1,SOCS3,SOX9,SPARC,SPEN,SPRY1,SPTAN1,SSPN,STAT3,STMN4,STS,SYNGR3,TACC2,TAF7L,TANC2,TFRC,TGM2,TIMP1,TIMP2,TIMP3,TNFRSF19,TNS3,TPP1,TRIB2,TRIM45,TRIO,TSHZ3,TSPAN8,TULP3,TWSG1,TXK,VANGL1,VANGL2,VAV3,VCAN,VGF,WNT3,YAP1,ZFHX2,ZFP36L1,ZFR,ZNF521
BP	GO:0009887: Organ morphogenesis	902	73	38.92	1.4e-07	ABL1,ADM,AGTPBP1,ANKRD1,ANKRD6,APLP1,ARID1A,BASP1,BCL2L11,BCOR,BHLHE41,BMPR1B,CALB1,CCDC40,CCL2,CD44,COL11A1,COL3A1,CRB1,CTGF,CTNNA2,CTSH,CYP26B1,CYR61,DCN,DHRS3,EGLN1,FOXC1,FRZB,GATA4,GBA,HCCS,HES1,HEY1,HOXC8,HOXD10,HOXD3,HOXD8,HOXD9,HTR2B,IGF2,INHBA,LIF,MEIS1,MGP,NCOA3,NDRG4,NOTCH2,NPHP3,NTRK2,NUMB,OLFM3,PBX1,PDGFC,PKP2,PSEN1,PTCH1,PTPRM,RARB,RDH10,ROM1,SEMA3A,SLC40A1,SLIT2,SOX9,SPRY1,STAT3,TGM2,TSHZ3,TULP3,TWSG1,VANGL2,YAP1
BP	GO:0048666: Neuron development	965	76	41.64	2.3e-07	ABL1,ADM,ALK,ANKRD1,APH1A,ATP8B1,BHLHB9,BMPR1B,BTG2,CAMK1,CDH11,CHRNA3,CLASP2,CLN5,CNP,CNR1,COL3A1,CRB1,CSPG5,CTNNA2,DCLK1,DCX,DPYSL3,FARP1,FN1,GFRA1,GRIP1,HES1,HOXD10,HOXD9,ITGA1,KALRN,KCNQ2,KIAA0319,LIF,MAP6,MAPK9,MAPT,MATN2,NBL1,NCAM2,NCAN,NDRG4,NFASC,NLGN1,NLGN3,NRXN1,NTNG2,NTRK2,NUMB,OLFM3,PBX3,PLK2,PLXNB1,PRNP,PSEN1,PTPRM,RBFOX2,RELN,RET,RND2,RUNX1,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SMAD1,SNAP25,SPTAN1,STMN4,TRIO,VANGL2,VAV3,WNT3
BP	GO:0001944: Vasculature development	569	51	24.55	6.3e-07	ACTA2,ADM,ANXA2,ANXA3,APOLD1,ARID1A,ATPIF1,CALCA,CCBE1,CCL2,CDH2,COL3A1,CTGF,CTSH,CYP1B1,CYR61,EGLN1,ENPP2,EPAS1,FN1,FOXC1,GATA4,HES1,HEY1,HIF1AN,ITGA7,LIF,MEIS1,NOTCH2,NOTCH4,NPPB,NRXN1,NTRK2,PRCP,PSEN1,PTGIS,PTPRM,RAMP1,ROM1,RUNX1,SCG2,SERPINE1,SGCB,SLC12A6,SLIT2,SMARCA2,SOCS3,SPARC,VAV3,YAP1,ZFP36L1
BP	GO:0051094: Positive regulation of developmental process	993	76	42.85	7.1e-07	ABL1,ADM,ANKRD1,ANXA3,ATP6AP1,BASP1,BHLHB9,BMPR1B,BTK,CACNA2D2,CALCA,CAMK1,CCBE1,CCND1,CDH2,CNR1,CREBL2,CTGF,CTNNA2,CTSH,CYB5D2,CYP1B1,CYP26B1,CYR61,DPYSL3,ELL3,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GATA4,GDF15,GDF6,HES1,HEY1,HIF1AN,HOXD3,INHBA,KCTD11,LIF,MAPK9,MAPT,NBL1,NCOA1,NCOA3,NDRG4,NLGN1,NLGN3,NRXN1,NTRK2,NUMB,PLXNB1,PPARG,PSEN1,PTGIS,RARB,RELN,RET,RND2,RUNX1,SEMA3A,SERPINE1,SFRP4,SLIT2,SMAD1,SOCS3,SOX9,SPEN,SPRY1,TIMP2,TRIOBP,TSHZ3,WNT3,YAP1
BP	GO:0007165: Signal transduction	5503	298	237.45	7.4e-07	AAK1,ABCA1,ABL1,ADM,AHRR,AKT2,AKT3,ALK,AMOTL2,ANKRD1,ANKRD6,ANXA2,APH1A,APLP1,ARF3,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARRDC3,ASAP1,ASAP2,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATPIF1,ATXN1,BCL2A1,BCL2L11,BCO2,BMPR1B,BTBD11,BTK,C18orf32,CACNG2,CALCA,CAMK1,CCBE1,CCL2,CCND1,CD44,CDC42EP3,CDH2,CDKL2,CDKN1A,CDKN1B,CHRM3,CHRNA3,CHRNB1,CLU,CNGA1,CNKSR2,CNR1,COL3A1,COLEC12,CRABP2,CREBL2,CREM,CRIM1,CTGF,CTNND1,CTSH,CYFIP2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYR61,DCBLD2,DCLK1,DCLK2,DCX,DDX5,DHRS3,DKK2,DKK3,DNAJB11,DNAJC27,DNAJC3,DOCK9,DTNA,DUSP16,DUSP6,ECEL1,EFEMP2,EIF4E3,ELL3,ELMO2,ELMOD1,ENPP2,EPAS1,FAM13A,FAM13B,FARP1,FGF14,FLNB,FLRT1,FMN2,FOS,FOXC1,FOXO3,FRZB,GABRP,GAL,GATA4,GBA,GDF10,GDF15,GDF6,GFRA1,GNG2,GNG7,GNG8,GPR19,GPR22,GPRASP1,GRIP1,GRK5,GUCA1A,HBEGF,HES1,HEXIM1,HEY1,HIF1AN,HLA-C,HLA-E,HOXD3,HPCAL1,HPCAL4,HTR2B,HUNK,IER3,IFNAR1,IGF2,IGFBP6,IL10RB,IL17RD,IL20RA,INADL,INHBA,IRF6,IRF9,ITGA1,ITGA7,ITGB5,ITPR2,KALRN,KCTD11,KRT18,LIF,LMCD1,LPXN,MAP4K4,MAPK9,MAPRE2,MCC,MED13,MID1,NBL1,NCOA1,NCOA3,NDRG4,NFAT5,NLGN1,NLGN3,NMI,NOS1,NOTCH2,NOTCH4,NPHP3,NPPA,NPPB,NPR2,NRXN1,

						NTRK2,NUMB,OAS1,OPTN,PAF1,PCLO,PDGFC,PDGFD,PDIA3,PEX11B,PIM1,PLAT,PLCD4,PLK2,PLN,PLXNB1,PPARG,PRCP,PRNP,PSD2,PSEN1,PSMB8,PTCH1,PTGER2,PTGIR,PTGIS,PTPRM,PTPRR,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RARB,RASEF,RASL10B,RBFOX2,RBP1,RBPMS,RDH10,RELN,RET,RFFL,RFTN1,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RIMS2,RIT1,RIT2,RLN1,RND2,RNF175,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SCG2,SCG5,SCN2A,SDC4,SDCBP,SEMA3A,SERPINE1,SESN1,SFRP4,SH2B3,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SKAP2,SLC22A17,SLC9A6,SLIT2,SMAD1,SMOC1,SOCS3,SORCS1,SOX9,SPARC,SPEN,SPRY1,SQSTM1,STAT3,SYP,TAOK3,TEX2,TGM2,TIMP1,TIMP2,TMED4,TNFRSF19,TOM1L1,TOM1L2,TPP1,TRAF3IP2,TRIB2,TRIO,TULP3,TULP4,TWSG1,TXK,VANGL2,VAV3,WNT3,YAP1,ZCCHC12
BP	GO:2000026: Regulation of multicellular organismal development	1417	99	61.14	9.4e-07	ABL1,ADM,ANKRD1,ANKRD6,ANXA3,APOLD1,ATP6AP1,BASP1,BCOR,BHLHB9,BMPR1B,BTK,CALCA,CAMK1,CCBE1,CCL2,CCND1,CDKN1B,CHRNA3,CLPTM1,CNR1,COL3A1,CTGF,CTSH,CYB5D2,CYP1B1,CYP26B1,CYR61,DDX5,DPYSL3,DUSP6,EGLN1,ELL3,ENPP2,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GATA4,GDF6,HES1,HEY1,HIF1AN,HOXD3,INHBA,KCTD11,KIAA0319,LAMA4,LIF,MAPT,MEIS1,MGP,NBL1,NCOA1,NCOA3,NDRG4,NLGN1,NLGN3,NOTCH4,NPHP3,NPPB,NRXN1,NTRK2,NUMB,PAF1,PBX1,PLK2,PLXNB1,PPARG,PSEN1,PTGIS,PTPRM,RARB,RBFOX2,RELN,RET,RND2,RUNX1,SEMA3A,SEMA4F,SERPINE1,SFRP4,SIPA1L1,SLIT2,SMAD1,SNAP25,SOX9,SPARC,SPEN,SPRY1,STAT3,TIMP1,TIMP2,TULP3,VANGL2,WNT3,YAP1
BP	GO:0050769: Positive regulation of neurogenesis	303	33	13.07	1.0e-06	ANKRD1,BHLHB9,CAMK1,CNR1,CYB5D2,DPYSL3,ELL3,FN1,GDF6,HES1,HOXD3,KCTD11,LIF,MAPT,NBL1,NCOA1,NDRG4,NLGN1,NTRK2,NUMB,PLXNB1,PPARG,PSEN1,RARB,RELN,RET,RND2,SEMA3A,SLIT2,SMAD1,SPEN,TIMP2,WNT3
BP	GO:0051240: Positive regulation of multicellular organismal process	1236	89	53.33	1.0e-06	ABL1,ADM,ANKRD1,ANXA3,ATP6AP1,ATP6AP2,BASP1,BHLHB9,BMPR1B,BTK,CACNA2D2,CADM1,CALCA,CAMK1,CCBE1,CCL2,CCND1,CHRM3,CLU,CNR1,CTGF,CTSH,CYB5D2,CYP1B1,CYP26B1,CYR61,DPYSL3,ELL3,FN1,FOS,FOXC1,FOXO3,GAL,GATA4,GDF6,HBEGF,HES1,HEY1,HIF1AN,HLA-E,HOXD3,HTR2B,IFNAR1,INHBA,KCTD11,LIF,MAPK9,MAPT,NBL1,NCOA1,NCOA3,NDRG4,NLGN1,NLGN3,NOS1,NPPA,NPPB,NRXN1,NTRK2,NUMB,PLAT,PLXNB1,PPARG,PSEN1,PTGIS,PTPRM,RARB,RELN,RET,RGS2,RND2,RUNX1,SCN3B,SCPEP1,SEMA3A,SERPINE1,SFRP4,SGIP1,SLIT2,SMAD1,SOX9,SPARC,SPEN,SPRY1,TFRC,TIMP2,TXK,WNT3,YAP1
BP	GO:0007167: Enzyme linked receptor protein signaling pathway	1092	81	47.12	1.0e-06	ABL1,AKT2,ALK,APH1A,ARHGEF3,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATXN1,BCL2L11,BMPR1B,BTBD11,BTK,CCBE1,CCL2,CDKN1A,CDKN1B,CHRNA3,COL3A1,CRIM1,CTGF,CTNND1,CYFIP2,CYR61,DUSP6,ELMO2,FOS,FOXC1,FOXO3,GATA4,GDF10,GDF15,GDF6,GFRA1,GNG7,HBEGF,HES1,IGF2,IGFBP6,INHBA,ITGA1,ITGB5,ITPR2,KALRN,LIF,NBL1,NDRG4,NOTCH2,NPPA,NPPB,NPR2,NTRK2,PDGFC,PDGFD,PLAT,PSEN1,PTGIR,PTPRR,RBPMS,RET,RHBDF1,RIT1,RIT2,SDCBP,SERPINE1,SIPA1L1,SLC9A6,SMAD1,SOCS3,SOX9,SPRY1,SQSTM1,STAT3,TRIO,TWSG1,TXK,VAV3,ZCCHC12
BP	GO:0009893: Positive regulation of metabolic process	3181	188	137.26	1.2e-06	ABCA1,ABL1,ADM,AHRR,AHSA2,AKT2,ALK,ANKRD1,ANKRD6,ANXA2,APH1A,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARMCX3,ARRDC3,ASAP1,ASAP2,ASS1,ATP1B1,ATP2B4,ATP6AP1,ATP6V0D1,ATPIF1,ATXN1,BCL2L11,BPTF,BTG2,C1GALT1C1,CALCA,CAMK1,CCBE1,CCL2,CCND1,CD44,CDH2,CDK5R2,CDKN1A,CDKN1B,CEBPD,CHRNA3,CHURC1,CIRBP,CLU,CREB5,CREBL2,CREM,CTGF,CTSA,CTSH,CYFIP2,CYP26B1,CYR61,DCN,DDX5,DNAJB11,DNAJB6,DNAJC27,DNAJC3,DOCK9,EBF1,ELL3,ELMOD1,EPAS1,EPM2AIP1,FABP3,FAM129A,FAM13A,FAM13B,FARP1,FBXO4,FN1,FOS,FOXC1,FOXO3,GAL,GATA4,GBA,GCH1,GDF10,GDF15,GDF6,GRIP1,GUCA1A,HES1,HEXB,HEY1,HOXD10,HOXD3,HOXD8,HOXD9,HTR2B,IER3,IGF2,INHBA,IRF6,ITGA1,ITPR2,JARID2,KALRN,LBH,LIF,LUM,MAOB,MAPK9,MED13,MEIS1,MGEA5,MID1,MID1IP1,MSN,NANOS1,NCOA1,NCOA3,NCOA7,NDRG4,NFAT5,NOS1,NOTCH4,NSD1,NSF,NTRK2,PACSIN3,PAF1,PBX1,PDGFC,PFKFB2,PIM1,PLAGL1,PLK2,PLXNB1,PPARG,PSD2,PSEN1,PSMB8,PTGIR,PTX3,RAB27A,RAB3IP,RABIF,RAMP1,RARB,RBPMS,RELN,RET,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RIMS2,RUNX1,SAMD4A,SDC4,SDCBP,SERPINE1,SFRP4,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SLC40A1,SMAD1,SMARCA2,SOAT1,SOX9,SPEN,SQSTM1,STAT3,TAF11,TAOK3,TIMP2,TOM1L1,TPP1,TRIB2,TRIO,TXK,VANGL2,VAV3,WDFY3,WNT3,YAP1
BP	GO:0016358: Dendrite development	159	22	6.86	1.3e-06	BHLHB9,CAMK1,CHRNA3,CTNNA2,DCLK1,DCX,FARP1,GRIP1,KIAA0319,MAP6,MATN2,NLGN1,NLGN3,NTRK2,PLK2,PSEN1,RBFOX2,RELN,SEMA3A,SIPA1L1,SLC9A6,SMAD1
BP	GO:0051962: Positive regulation of nervous system development	336	35	14.5	1.4e-06	ANKRD1,BHLHB9,CAMK1,CNR1,CYB5D2,DPYSL3,ELL3,FN1,GDF6,HES1,HOXD3,KCTD11,LIF,MAPT,NBL1,NCOA1,NDRG4,NLGN1,NLGN3,NRXN1,NTRK2,NUMB,PLXNB1,PPARG,PSEN1,RARB,RELN,RET,RND2,SEMA3A,SLIT2,SMAD1,SPEN,TIMP2,WNT3
BP	GO:0030154: Cell differentiation	3476	202	149.99	1.4e-06	ABCA1,ABL1,ACTA2,ADM,AGTPBP1,AKT2,ALK,ANKRD1,ANKRD33,ANXA2,APH1A,APOLD1,ATP6AP1,ATP8B1,ATPIF1,BASP1,BCL2L11,BHLHB9,BHLHE41,BMPR1B,BTG2,BTK,C1GALT1C1,CACNA2D2,CADM1,CALCA,CAMK1,CCL2,CCND1,CDH11,CDH2,CDK5R2,CDKN1A,CDKN2C,CHRNA3,CHRNB1,CLASP2,CLN5,CLPTM1,CLU,CNP,CNR1,COL11A1,COL3A1,CRB1,CREB5,CREBL2,CREM,CSPG5,CTGF,CTNNA2,CYB5D2,CYP24A1,CYP26A1,CYP26B1,CYR61,DAPL1,DCLK1,DCX,DDX5,DPYSL3,DUSP6,ELL3,EPAS1,FAM101B,FARP1,FLNB,FMN2,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GAT

						A4,GDF10,GDF15,GDF6,GFRA1,GPNMB,GRIP1,HES1,HEXB,HEY1,HIF1AN,HOXC8,HOXD1,HOXD10,HOXD3,HOXD9,HTR2B,IGF2,INHBA,IRF6,ITGA1,ITGA7,ITGB5,JARID2,KALRN,KCNQ2,KCTD11,KIAA0319,KIAA1279,LIF,MAP6,MAPK9,MAPT,MATN2,MEIS1,MGP,MMP11,MSN,NAV1,NBL1,NCAM2,NCAN,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NLGN1,NLGN3,NOS1,NOTCH2,NOTCH4,NPHP3,NPR2,NRXN1,NTNG2,NTRK2,NUMB,OLFM3,PAF1,PAPPA,PBX1,PBX3,PHLDA1,PKP2,PLAGL1,PLK2,PLXNB1,PPARG,PRNP,PSD2,PSEN1,PSMB8,PTCH1,PTPRM,RAB27A,RARB,RBFOX2,RDH10,RELN,RET,RGS2,RND2,ROM1,RUNX1,SDCBP,SEMA3A,SEMA4F,SFRP4,SGCB,SH2B3,SH3PXD2A,SIPA1L1,SLC8A3,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SOAT1,SOCS3,SOX9,SPEN,SPRY1,SPTAN1,SQSTM1,STAT3,STMN4,TACC2,TAF7L,TFRC,TIMP2,TPP1,TRIB2,TRIO,TRIOBP,TSHZ3,TULP3,TWSG1,TXK,VANGL2,VAV3,VCAN,WNT3,YAP1,ZFP36L1,ZNF521
BP	GO:0044699: Single-organism process	13148	614	567.32	1.5e-06	AAK1,ABCA1,ABCB1,ABCB4,ABI3BP,ABL1,ACOX1,ACP2,ACTA2,ADAM29,ADM,AGPAT4,AGTPBP1,AHNAK,AHRR,AIFM2,AKT2,AKT3,ALDH5A1,ALK,AMACR,AMOTL2,ANKRD1,ANKRD33,ANKRD6,ANO3,ANXA2,ANXA3,APH1A,APLP1,APOLD1,AQP11,ARF3,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARRDC3,ARSD,ASAP1,ASAP2,ASS1,ATP10D,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,ATXN1,B3GALNT1,B3GNT7,B3GNT9,B4GALNT1,B4GALT6,BASP1,BCL2A1,BCL2L11,BCO2,BCOR,BHLHB9,BHLHE40,BHLHE41,BLCAP,BMPR1B,BPTF,BRPF3,BTBD11,BTG2,BTK,BZRAP1,C18orf32,C1GALT1C1,C1RL,C7,C8orf4,CACNA2D2,CACNG2,CADM1,CALB1,CALCA,CAMK1,CCBE1,CCDC40,CCL2,CCNA1,CCND1,CCNDBP1,CD44,CDC42EP3,CDH11,CDH2,CDK19,CDK5R2,CDKL2,CDKN1A,CDKN1B,CDKN2C,CELF2,CHMP2B,CHRFAM7A,CHRM3,CHRNA3,CHRNB1,CHURC1,CLASP2,CLDN11,CLN5,CLPTM1,CLU,CNGA1,CNKSR2,CNP,CNR1,COCH,COL11A1,COL17A1,COL23A1,COL3A1,COLEC12,COX11,COX17,CPA4,CRABP2,CRB1,CREB5,CREBL2,CREM,CRIM1,CRTAP,CSPG5,CSRP1,CTGF,CTNNA2,CTNND1,CTSA,CTSH,CYB561,CYB5D2,CYB5R1,CYFIP2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYP4V2,CYR61,DACH1,DAPL1,DCBLD2,DCLK1,DCLK2,DCN,DCX,DDX5,DHRS3,DKK2,DKK3,DLG2,DNAJB11,DNAJB6,DNAJC16,DNAJC27,DNAJC3,DOCK9,DOLK,DONSON,DPT,DPYSL3,DRAM1,DRP2,DTNA,DTX3L,DUSP16,DUSP6,EBF1,ECEL1,EFEMP2,EGLN1,EIF4E3,ELFN1,ELL3,ELMO2,ELMOD1,ENPP2,ENPP6,ENSA,EPAS1,EPB41L1,EPM2AIP1,ERI1,EXOC6B,EXOC7,FABP3,FAM101B,FAM13A,FAM13B,FAR2,FARP1,FAT1,FBXO2,FBXO4,FBXO6,FGF14,FLNB,FLRT1,FMN2,FN1,FOS,FOXC1,FOXO3,FRMD4A,FRZB,FUCA1,FUCA2,GABARAPL1,GABRP,GAL,GAL3ST1,GAL3ST3,GALNT14,GALNT2,GALNT6,GATA4,GBA,GCH1,GDF10,GDF15,GDF6,GFRA1,GNG2,GNG7,GNG8,GNS,GPNMB,GPR19,GPR22,GPRASP1,GPX3,GRIP1,GRK5,GUCA1A,H1F0,HBEGF,HCCS,HES1,HEXB,HEXIM1,HEY1,HGSNAT,HIF1AN,HLA-C,HLA-E,HOXC6,HOXC8,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,HPCAL1,HPCAL4,HS3ST2,HSDL1,HTR2B,HUNK,ICAM2,IDS,IER3,IFNAR1,IGF2,IGFBP6,IGFBP7,IL10RB,IL17RD,IL20RA,INADL,INHBA,IRF6,IRF9,ITGA1,ITGA7,ITGB5,ITPR2,JAKMIP1,JARID2,KALRN,KCNB1,KCNMA1,KCNQ2,KCTD11,KDM5C,KDSR,KIAA0319,KIAA1279,KRCC1,KRT18,LAMA4,LBH,LIF,LMAN2L,LMCD1,LOXL4,LPCAT3,LPXN,LUM,MAB21L1,MAN2B2,MAOB,MAP4K4,MAP6,MAPK9,MAPRE2,MAPT,MATN2,MAX,MCC,MED13,MEIS1,MFSD1,MGEA5,MGP,MID1,MID1IP1,MMP11,MMP28,MPPED2,MSN,MSRB3,MTRF1L,NANOS1,NAV1,NAV2,NBEA,NBL1,NCAM2,NCAN,NCEH1,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NFAT5,NIPAL2,NLGN1,NLGN3,NMI,NOS1,NOTCH2,NOTCH4,NPC2,NPEPPS,NPHP3,NPPA,NPPB,NPR2,NPTX2,NRSN1,NRXN1,NSD1,NSF,NTNG2,NTRK2,NUMB,OAS1,OLFM3,OPTN,ORAI3,OS9,OSBPL10,OSCP1,P4HA2,PACSIN3,PAF1,PAPPA,PARP9,PBX1,PBX3,PCDH9,PCDHB10,PCDHB14,PCDHB15,PCDHB3,PCDHB4,PCLO,PDGFC,PDGFD,PDIA3,PDZRN3,PEAR1,PEX11B,PFKFB2,PHLDA1,PHYH,PIGZ,PIM1,PIPOX,PKP2,PLAGL1,PLAT,PLCD4,PLK2,PLN,PLXNB1,POLQ,PPAPDC1B,PPARG,PPP1R3B,PPP1R3D,PRCP,PRNP,PROS1,PRPSAP1,PRSS12,PSD2,PSEN1,PSMB8,PTCH1,PTGER2,PTGIR,PTGIS,PTPRH,PTPRM,PTPRR,PTX3,PXDNL,PYGL,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAET1L,RAI2,RAMP1,RARB,RARRES1,RASEF,RASL10B,RBFOX2,RBP1,RBPMS,RDH10,RELN,RET,REV3L,RFFL,RFTN1,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RHCE,RIC3,RIMS2,RIT1,RIT2,RLN1,RND2,RNF175,ROM1,RPRM,RRAGB,RRAGC,RRAGD,RSPH9,RUNX1,RUSC1,SCD,SCD5,SCG2,SCG5,SCN2A,SCN3A,SCN3B,SCPEP1,SDC4,SDCBP,SEMA3A,SEMA4F,SEPHS2,SERPINE1,SERPING1,SESN1,SFRP4,SGCB,SGIP1,SH2B3,SH3BGRL3,SH3BP4,SH3PXD2A,SIPA1L1,SIPA1L2,SKAP2,SLC12A6,SLC18A1,SLC22A17,SLC26A11,SLC26A2,SLC2A10,SLC31A2,SLC35A2,SLC35D2,SLC35D3,SLC36A1,SLC40A1,SLC44A5,SLC4A8,SLC6A2,SLC8A3,SLC9A6,SLCO3A1,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SNCAIP,SOAT1,SOCS3,SORBS2,SORCS1,SOX9,SPAG1,SPARC,SPEN,SPRY1,SPTAN1,SQSTM1,SSPN,STAG3,STARD4,STAT3,STMN4,STOM,STS,SULT1C4,SYN2,SYNGR3,SYP,SYT11,SYT4,SYTL4,TACC2,TAF7L,TANC2,TAOK3,TAP1,TEP1,TES,TEX2,TEX261,TFRC,TGM2,THSD4,TIMP1,TIMP2,TIMP3,TM7SF2,TMED4,TMEM38A,TMX4,TNFRSF19,TNS3,TOM1L1,TOM1L2,TPP1,TRAF3IP2,TRIB2,TRIM45,TRIO,TRIOBP,TSHZ3,TSPAN31,TSPAN8,TTC30A,TTC30B,TULP3,TULP4,TWSG1,TXK,TXNDC15,UNC80,UPB1,VANGL1,VANGL2,VAV3,VCAN,VGF,VPS13D,VPS53,WDFY3,WNT3,WTAP,XYLT1,YAP1,ZCCHC12,ZFHX2,ZFP36L1,ZFR,ZNF521

BP	GO:0051179: Localization	5338	288	230.33	2.0e-06	AAK1,ABCA1,ABCB1,ABCB4,ABL1,ADM,AHNAK,AKT2,ALDH5A1,ANKRD1,ANO3,ANXA2,ANXA3,APLP1,APOLD1,APPBP2,AQP11,ARF3,ARHGAP27,ARID1A,ARMCX3,ATP10D,ATP1B1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,ATXN1,B4GALNT1,BCL2L11,BRPF3,BTK,BZRAP1,CACNA2D2,CACNG2,CADM1,CALCA,CAMK1,CCBE1,CCDC40,CCL2,CCND1,CD44,CDH2,CDK5R2,CDKL2,CDKN1A,CDKN1B,CHMP2B,CHRFAM7A,CHRM3,CHRNA3,CHRNB1,CLASP2,CLU,CNGA1,CNP,CNR1,COL3A1,COLEC12,COX11,COX17,CRABP2,CREBL2,CSPG5,CTGF,CTNNA2,CTSA,CTSH,CYB561,CYB5R1,CYFIP2,CYP1B1,CYR61,DACH1,DCLK1,DCX,DLG2,DNAJC27,DPYSL3,DUSP16,ELMO2,ELMOD1,ENPP2,ENSA,EXOC6B,EXOC7,FABP3,FAT1,FGF14,FLNB,FMN2,FN1,FNBP1,FOXC1,GABRP,GAL,GATA4,GPRASP1,GRIP1,HBEGF,HES1,HEXB,HGSNAT,HLA-E,HTR2B,IER3,IFNAR1,IGF2,INHBA,ITGA1,ITGA7,ITPR2,JAKMIP1,KALRN,KCNB1,KCNMA1,KCNQ2,KIAA0319,KIAA1279,KRT18,LAMA4,LIF,LMAN2L,LOXL4,LRP10,MAOB,MAP6,MAPK9,MAPT,MATN2,MCC,MEST,MFSD1,MGEA5,MID1,MMP28,MSN,NANOS1,NAV1,NBEA,NBL1,NCOA1,NDRG4,NFASC,NIPAL2,NLGN1,NLGN3,NOS1,NOTCH2,NPC2,NPEPPS,NPPA,NPPB,NRXN1,NSF,NTRK2,NUMB,OPTN,ORAI3,OS9,OSBPL10,OSCP1,PACSIN3,PAF1,PARP9,PCLO,PDIA3,PEAR1,PFKFB2,PKP2,PLAT,PLCD4,PLN,PLXNB1,PPARG,PRCP,PRNP,PROS1,PRSS12,PSEN1,PTCH1,PTPRM,PTPRR,PTX3,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RARB,RASEF,RASL10B,RBFOX2,RBP1,RBPMS,RELN,RET,RFFL,RFTN1,RHBDF1,RHCE,RIMS2,RRAGB,RRAGC,RRAGD,RUNX1,SCG2,SCG5,SCN2A,SCN3A,SCN3B,SDC4,SDCBP,SEMA3A,SERPINE1,SERPING1,SFRP4,SGIP1,SH3BGRL3,SH3BP4,SLC12A6,SLC18A1,SLC22A17,SLC26A11,SLC26A2,SLC2A10,SLC31A2,SLC35A2,SLC35D2,SLC35D3,SLC36A1,SLC40A1,SLC44A5,SLC4A8,SLC6A2,SLC8A3,SLC9A6,SLCO3A1,SLIT2,SNAP25,SNCAIP,SNX24,SOAT1,SORBS2,SOX9,SPARC,SPRY1,SQSTM1,STARD4,STAT3,STAU2,STOM,SYN2,SYNGR3,SYP,SYT11,SYT4,SYTL4,TACC2,TAP1,TEX261,TFRC,TGM2,TIMP1,TMED4,TMEM38A,TNS3,TOM1L1,TOM1L2,TRAF3IP2,TTC30A,TTC30B,UNC80,VANGL2,VAV3,VCAN,VGF,VPS13D,VPS53,WDFY3,WNT3
BP	GO:0045595: Regulation of cell differentiation	1390	96	59.98	2.3e-06	ABCA1,ABL1,ADM,ANKRD1,APOLD1,ATP6AP1,BHLHB9,BHLHE41,BMPR1B,BTK,CALCA,CAMK1,CCND1,CDH2,CHRNA3,CLPTM1,CNR1,COL3A1,CREBL2,CTGF,CTNNA2,CYB5D2,CYP26B1,CYR61,DDX5,DPYSL3,DUSP6,ELL3,EPAS1,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GATA4,GDF15,GDF6,HES1,HEY1,HIF1AN,HOXD3,INHBA,KCTD11,KIAA0319,LIF,MAPK9,MAPT,MEIS1,MMP11,NBL1,NCOA1,NCOA3,NDRG4,NLGN1,NLGN3,NOTCH2,NOTCH4,NPHP3,NPR2,NTRK2,NUMB,PAF1,PBX1,PKP2,PLK2,PLXNB1,PPARG,PSEN1,PTCH1,RARB,RBFOX2,RELN,RET,RND2,RUNX1,SEMA3A,SEMA4F,SFRP4,SIPA1L1,SLIT2,SMAD1,SMOC1,SNAP25,SOCS3,SOX9,SPEN,STAT3,TIMP2,TRIB2,TRIOBP,TSHZ3,TWSG1,VANGL2,WNT3,YAP1
BP	GO:0048869: Cellular developmental process	3696	211	159.48	2.6e-06	ABCA1,ABL1,ACTA2,ADM,AGTPBP1,AKT2,ALK,ANKRD1,ANKRD33,ANXA2,APH1A,APOLD1,ASAP1,ATP6AP1,ATP6V0D1,ATP8B1,ATPIF1,BASP1,BCL2L11,BHLHB9,BHLHE41,BMPR1B,BTG2,BTK,C1GALT1C1,CACNA2D2,CADM1,CALCA,CAMK1,CCL2,CCND1,CDC42EP3,CDH11,CDH2,CDK5R2,CDKN1A,CDKN2C,CHRNA3,CHRNB1,CLASP2,CLN5,CLPTM1,CLU,CNP,CNR1,COCH,COL11A1,COL3A1,CRB1,CREB5,CREBL2,CREM,CSPG5,CTGF,CTNNA2,CYB5D2,CYP24A1,CYP26A1,CYP26B1,CYR61,DAPL1,DCLK1,DCX,DDX5,DPYSL3,DUSP6,ELL3,EPAS1,FAM101B,FARP1,FLNB,FMN2,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GATA4,GDF10,GDF15,GDF6,GFRA1,GPNMB,GRIP1,HES1,HEXB,HEY1,HIF1AN,HOXC8,HOXD1,HOXD10,HOXD3,HOXD9,HTR2B,IGF2,INHBA,IRF6,ITGA1,ITGA7,ITGB5,JARID2,KALRN,KCNQ2,KCTD11,KIAA0319,KIAA1279,LIF,MAP6,MAPK9,MAPT,MATN2,MEIS1,MGP,MMP11,MSN,NAV1,NBL1,NCAM2,NCAN,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NLGN1,NLGN3,NOS1,NOTCH2,NOTCH4,NPHP3,NPR2,NRXN1,NTNG2,NTRK2,NUMB,OLFM3,PAF1,PAPPA,PBX1,PBX3,PHLDA1,PKP2,PLAGL1,PLK2,PLXNB1,PPARG,PRNP,PSD2,PSEN1,PSMB8,PTCH1,PTPRM,RAB27A,RAB3IP,RARB,RBFOX2,RDH10,RELN,RET,RGS2,RND2,ROM1,RSPH9,RUNX1,SDCBP,SEMA3A,SEMA4F,SFRP4,SGCB,SH2B3,SH3PXD2A,SIPA1L1,SLC8A3,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SOAT1,SOCS3,SOX9,SPARC,SPEN,SPRY1,SPTAN1,SQSTM1,STAT3,STMN4,TACC2,TAF7L,TFRC,TIMP2,TPP1,TRIB2,TRIO,TRIOBP,TSHZ3,TTC30A,TTC30B,TULP3,TWSG1,TXK,VANGL2,VAV3,VCAN,WNT3,YAP1,ZFP36L1,ZNF521
BP	GO:0001101: Response to acid chemical	275	30	11.87	3.0e-06	ABCA1,ASS1,ATP2B4,ATP6V0E1,CCL2,CDKN1B,COL3A1,CTGF,CTSH,CYP26A1,CYP26B1,FABP3,GATA4,GNG2,IGFBP7,MEST,NCOA1,PDGFC,PDGFD,PPARG,PTCH1,PTGER2,RET,RRAGB,RRAGC,RRAGD,SH3BP4,SOX9,SPARC,WNT3
BP	GO:0032940: Secretion by cell	875	67	37.76	3.3e-06	ABCA1,ABL1,ADM,ALDH5A1,ANKRD1,ANXA3,ATP6AP1,BRPF3,BTK,BZRAP1,CACNA2D2,CADM1,CDK5R2,CHRM3,CHRNA3,CLU,CNR1,CTGF,ENSA,EXOC6B,EXOC7,FN1,GAL,HLA-E,HTR2B,IFNAR1,IGF2,INHBA,ITPR2,KCNB1,LIF,MAOB,MGEA5,NLGN1,NOTCH2,NRXN1,NSF,NTRK2,PCLO,PFKFB2,PLCD4,PROS1,PRSS12,PSEN1,RAB26,RAB27A,RAB3B,RASL10B,RHBDF1,RIMS2,RUNX1,SCG2,SCG5,SDC4,SDCBP,SERPINE1,SERPING1,SNAP25,SNCAIP,SPARC,SYN2,SYT11,SYT4,SYTL4,TIMP1,TRAF3IP2,VGF
BP	GO:0048522: Positive regulation of cellular process	4180	233	180.36	3.6e-06	AAK1,ABCA1,ABI3BP,ABL1,ADM,AHRR,AIFM2,AKT2,ALK,ANKRD1,ANKRD6,ANXA2,ANXA3,APH1A,ARHGEF3,ARID1A,ARMCX3,ARRDC3,ASS1,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATPIF1,ATXN1,BCL2L11,BHLHB9,BMPR1B,BPTF,BTG2,BTK,C18orf32,CADM1,CALCA,CAMK1,CCBE1,CCL2,CCND1,CD44,CDC42EP3,CDH2,CDK5R2,CDKL2,

						CDKN1A,CDKN1B,CEBPD,CHMP2B,CHRNA3,CHURC1,CIRBP,CLU,CNR1,COL3A1,CREB5,CREBL2,CREM,CTGF,CTNNA2,CTSH,CYB5D2,CYB5R1,CYFIP2,CYP1B1,CYP26B1,CYR61,DCN,DDX5,DKK2,DNAJB11,DNAJC27,DNAJC3,DPYSL3,DUSP6,EBF1,ELL3,ELMOD1,EPAS1,EPM2AIP1,FABP3,FAM129A,FBXO4,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GATA4,GBA,GDF10,GDF15,GDF6,GRIP1,GRK5,GUCA1A,HBEGF,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HLA-E,HOXD10,HOXD3,HOXD8,HOXD9,HTR2B,IFNAR1,IGF2,IL20RA,INHBA,IRF6,ITGA1,JARID2,KALRN,KCNMA1,KCTD11,LBH,LIF,LMCD1,LUM,MAB21L1,MAOB,MAPK9,MAPT,MED13,MEIS1,MGEA5,MID1,MID1IP1,NANOS1,NBL1,NCOA1,NCOA3,NCOA7,NDRG4,NFAT5,NLGN1,NLGN3,NOS1,NOTCH2,NOTCH4,NPEPPS,NPPA,NRXN1,NSD1,NSF,NTRK2,NUMB,OSCP1,PACSIN3,PAF1,PBX1,PDGFC,PDGFD,PDIA3,PFKFB2,PHLDA1,PIM1,PLAGL1,PLEKHA2,PLK2,PLXNB1,PPARG,PSEN1,PSMB8,PTGIR,PTGIS,PTX3,RAB27A,RAB3B,RAMP1,RARB,RASL10B,RBPMS,RELN,RET,RFWD2,RGS2,RND2,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SAMD4A,SCG2,SDC4,SDCBP,SEMA3A,SERPINE1,SFRP4,SGIP1,SH3BP4,SKAP2,SLC40A1,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SOAT1,SOCS3,SOX9,SPARC,SPEN,SQSTM1,STAT3,SYTL4,TAF11,TAOK3,TGM2,TIMP1,TIMP2,TMED4,TNFRSF19,TNS3,TOM1L1,TPP1,TRAF3IP2,TRIB2,TRIO,TRIOBP,TSHZ3,TSPAN31,TWSG1,TXK,VANGL2,VAV3,WDFY3,WNT3,YAP1
BP	GO:0030198: Extracellular matrix organization	382	37	16.48	3.9e-06	ABI3BP,ABL1,ANXA2,APLP1,CD44,COL11A1,COL17A1,COL23A1,COL3A1,CRTAP,CTGF,CYP1B1,CYR61,DCN,DPT,EFEMP2,FN1,FOXC1,ICAM2,ITGA1,ITGA7,ITGB5,LAMA4,LUM,MMP11,NCAN,NRXN1,PSEN1,SDC4,SERPINE1,SMOC1,SOX9,SPARC,THSD4,TIMP1,TIMP2,VCAN
BP	GO:0043062: Extracellular structure organization	383	37	16.53	4.1e-06	ABI3BP,ABL1,ANXA2,APLP1,CD44,COL11A1,COL17A1,COL23A1,COL3A1,CRTAP,CTGF,CYP1B1,CYR61,DCN,DPT,EFEMP2,FN1,FOXC1,ICAM2,ITGA1,ITGA7,ITGB5,LAMA4,LUM,MMP11,NCAN,NRXN1,PSEN1,SDC4,SERPINE1,SMOC1,SOX9,SPARC,THSD4,TIMP1,TIMP2,VCAN
BP	GO:0010033: Response to organic substance	2465	150	106.36	4.5e-06	ABCA1,ABL1,ADM,AKT2,ANKRD1,APH1A,APLP1,ARHGEF3,ASS1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,BCL2L11,BTG2,BTK,CALB1,CALCA,CALCOCO2,CCBE1,CCL2,CCND1,CD44,CDKN1A,CDKN1B,CHRNA3,CHRNB1,CLU,CNP,CNR1,COL3A1,COLEC12,CREM,CTGF,CTSH,CYP1B1,CYP24A1,CYP26A1,CYP26B1,DCN,DNAJB11,DNAJC3,DPYSL3,DUSP6,EIF4E3,ENSA,EPM2AIP1,FABP3,FBXO6,FLNB,FOS,FOXC1,FOXO3,GAL,GATA4,GBA,GCH1,GDF10,GDF15,GNG2,GNG7,GNG8,GPR22,GPX3,HBEGF,HEY1,HLA-C,HLA-E,IFNAR1,IGF2,IGFBP7,IL10RB,IL17RD,IL20RA,INHBA,IRF6,IRF9,ITGB5,ITPR2,KALRN,KCNMA1,KRT18,LUM,MAOB,MAPK9,MAX,MEST,MGEA5,MID1,NCOA1,NCOA3,NOS1,NPPA,NPR2,NRXN1,NTRK2,OAS1,PAF1,PARP9,PDGFC,PDGFD,PFKFB2,PIM1,PLAT,PLN,PPARG,PRCP,PSMB8,PTCH1,PTGER2,PTGIR,PTGIS,RARB,RET,RFFL,RFTN1,RIT1,RIT2,RNF175,RRAGB,RRAGC,RRAGD,RUNX1,SERPINE1,SFRP4,SH3BP4,SLC8A3,SLC9A6,SLIT2,SMAD1,SOCS3,SOX9,SPARC,SPRY1,SQSTM1,STAT3,SYP,TIMP1,TIMP2,TIMP3,TNFRSF19,TPP1,TRIO,TXK,VAV3,VGF,WNT3
BP	GO:0016049:Cell growth	416	39	17.95	4.7e-06	ABL1,ATP6V0E1,ATP6V0E2,CADM1,CDKN1A,CDKN1B,CDKN2C,CRIM1,CTGF,CYR61,DCBLD2,DCLK1,DCX,DDX5,FN1,FRZB,GAL,GATA4,HBEGF,IGFBP6,IGFBP7,INHBA,MAPT,NDRG4,NLGN3,NOTCH2,NPPA,NPPB,PPARG,RND2,RRAGC,SEMA3A,SEMA4F,SH3BP4,SLC9A6,SLIT2,SMARCA2,SOX9,WNT3
BP	GO:0010720: Positive regulation of cell development	387	37	16.7	5.2e-06	ANKRD1,ATP6AP1,BHLHB9,CAMK1,CNR1,CYB5D2,DPYSL3,ELL3,FN1,GDF6,HES1,HOXD3,KCTD11,LIF,MAPK9,MAPT,NBL1,NCOA1,NDRG4,NLGN1,NTRK2,NUMB,PLXNB1,PPARG,PSEN1,RARB,RELN,RET,RND2,SEMA3A,SLIT2,SMAD1,SPEN,TIMP2,TRIOBP,WNT3,YAP1
BP	GO:0007417: Central nervous system development	838	64	36.16	6.1e-06	ABL1,AGTPBP1,ALDH5A1,APLP1,ARID1A,ATP6V0D1,BASP1,BCL2L11,BPTF,BTG2,CADM1,CDH11,CDK5R2,CDKN2C,CLN5,CLU,CNP,COL3A1,COX17,CTNNA2,CTNND1,CYP26A1,DCLK1,DCX,DRP2,FOXC1,HES1,HOXD10,HPCAL4,JARID2,LIF,MAOB,MAPK9,NAV2,NCAN,NCOA1,NLGN3,NRXN1,NTRK2,NUMB,PBX3,PCDH9,PDGFC,PHLDA1,PPARG,PSEN1,PTCH1,RARB,RBFOX2,RELN,RUNX1,SEMA3A,SLC8A3,SLIT2,SMAD1,SOX9,STAT3,SYNGR3,TACC2,TIMP2,TPP1,TULP3,TWSG1,VCAN
BP	GO:0031175: Neuron projection development	839	64	36.2	6.3e-06	ABL1,ADM,ANKRD1,APH1A,BHLHB9,BMPR1B,BTG2,CAMK1,CDH11,CHRNA3,CLASP2,CNP,CNR1,COL3A1,CSPG5,CTNNA2,DCLK1,DCX,DPYSL3,FARP1,FN1,GFRA1,GRIP1,ITGA1,KALRN,KCNQ2,KIAA0319,MAP6,MAPK9,MAPT,MATN2,NBL1,NCAM2,NCAN,NDRG4,NFASC,NLGN1,NLGN3,NRXN1,NTNG2,NTRK2,NUMB,PLK2,PLXNB1,PRNP,PSEN1,PTPRM,RBFOX2,RELN,RET,RND2,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SMAD1,SNAP25,SPTAN1,STMN4,TRIO,VAV3,WNT3
BP	GO:0050793: Regulation of developmental process	1973	124	85.13	8.2e-06	ABCA1,ABL1,ADM,ANKRD1,ANKRD6,ANXA3,APOLD1,AP6AP1,BASP1,BCL2L11,BCOR,BHLHB9,BHLHE41,BMPR1B,BTK,CACNA2D2,CALCA,CAMK1,CCBE1,CCL2,CCND1,CDC42EP3,CDH2,CDKN1B,CHRNA3,CLPTM1,CNR1,COCH,COL3A1,CREBL2,CTGF,CTNNA2,CTSH,CYB5D2,CYP1B1,CYP26B1,CYR61,DDX5,DPYSL3,DUSP6,EGLN1,ELL3,ENPP2,EPAS1,FN1,FOS,FOXC1,FOXO3,FRZB,GAL,GATA4,GDF15,GDF6,HES1,HEXB,HEY1,HIF1AN,HOXD3,INHBA,ITGA7,KCTD11,KIAA0319,LAMA4,LIF,MAPK9,MAPT,MEIS1,MGP,MMP11,NBL1,NCOA1,NCOA3,NDRG4,NLGN1,NLGN3,NOTCH2,NOTCH4,NPHP3,NPPB,NPR2,NRXN1,NTRK2,NUMB,PAF1,PBX1,PKP2,PLK2,PLXNB1,PPARG,PSEN1,PTCH1,PTGIS,PTPRM,RARB,RBFOX2,RELN,RET,RND2,RUNX1,SEMA3A,SEMA4F,SERPINE1,SFRP4,SIPA1L1,SLIT2,SMAD1,SMOC1,SNAP25,SOCS3,SOX9,SPARC,SPEN,SPRY1,STAT3,TIMP1,TIMP2

						,TRIB2,TRIOBP,TSHZ3,TULP3,TWSG1,VANGL2,WNT3,YAP1
BP	GO:0035556: Intracellular signal transduction	2524	151	108.91	1.1e-05	ABCA1,ABL1,ADM,ALK,AMOTL2,ANKRD1,ANKRD6,ARF3,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,BCL2A1,BCL2L11,BTK,C18orf32,CCL2,CD44,CDC42EP3,CDH2,CDKN1A,CDKN1B,CLU,COL3A1,CTGF,CTSH,CYP1B1,CYR61,DCLK1,DCLK2,DCX,DDX5,DNAJC27,DOCK9,DUSP16,DUSP6,ELL3,ELMOD1,FAM13A,FAM13B,FARP1,FGF14,FLRT1,FMN2,FOS,FOXO3,GAL,GBA,GDF10,GDF15,GDF6,GRIP1,HBEGF,HES1,HEXIM1,HTR2B,HUNK,IER3,IFNAR1,IGF2,IL20RA,INADL,INHBA,ITGA1,ITPR2,KALRN,LIF,LMCD1,MAP4K4,MAPK9,MID1,NDRG4,NFAT5,NLGN1,NMI,NOS1,NOTCH2,NPR2,NTRK2,OPTN,PCLO,PLCD4,PLK2,PLN,PLXNB1,PRNP,PSD2,PSEN1,PSMB8,PTGIR,PTPRR,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RASEF,RASL10B,RELN,RET,RFFL,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RIMS2,RIT1,RIT2,RND2,RRAGB,RRAGC,RRAGD,SCG2,SCN2A,SDCBP,SESN1,SH2B3,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SLIT2,SMAD1,SOCS3,SOX9,SPRY1,SQSTM1,STAT3,TAOK3,TGM2,TIMP2,TMED4,TNFRSF19,TRAF3IP2,TRIB2,TRIO,TULP4,VANGL2,VAV3,YAP1
BP	GO:0046903: Secretion	998	72	43.06	1.1e-05	ABCA1,ABL1,ADM,ALDH5A1,ANKRD1,ANXA2,ANXA3,ATP6AP1,BRPF3,BTK,BZRAP1,CACNA2D2,CADM1,CCND1,CDK5R2,CHRM3,CHRNA3,CLU,CNR1,CTGF,ENSA,EXOC6B,EXOC7,FN1,GAL,HLA-E,HTR2B,IFNAR1,IGF2,INHBA,ITPR2,KCNB1,LIF,MAOB,MAPK9,MGEA5,NCOA1,NLGN1,NOTCH2,NPPB,NRXN1,NSF,NTRK2,PCLO,PFKFB2,PLCD4,PROS1,PRSS12,PSEN1,RAB26,RAB27A,RAB3B,RASL10B,RHBDF1,RIMS2,RUNX1,SCG2,SCG5,SDC4,SDCBP,SERPINE1,SERPING1,SNAP25,SNCAIP,SPARC,SYN2,SYT11,SYT4,SYTL4,TIMP1,TRAF3IP2,VGF
BP	GO:0045666: Positive regulation of neuron differentiation	236	26	10.18	1.1e-05	ANKRD1,BHLHB9,CAMK1,CNR1,CYB5D2,DPYSL3,FN1,GDF6,HOXD3,KCTD11,MAPT,NBL1,NCOA1,NDRG4,NLGN1,NTRK2,PLXNB1,PSEN1,RARB,RELN,RET,RND2,SLIT2,SMAD1,TIMP2,WNT3
BP	GO:0008285: Negative regulation of cell proliferation	613	50	26.45	1.2e-05	ADM,ATPIF1,BMPR1B,BTG2,CDKN1A,CDKN1B,CDKN2C,CYP1B1,DACH1,DPT,FABP3,FBXO2,FRZB,GAL,GPNMB,HES1,IGFBP6,IGFBP7,INHBA,IRF6,ITGA1,JARID2,KCTD11,LIF,MCC,NDRG4,NOTCH2,PKP2,PLXNB1,PPARG,PRNP,PTCH1,PTGIR,PTPRM,RARB,RARRES1,SCG2,SESN1,SFRP4,SH3BP4,SKAP2,SLIT2,SMAD1,SMARCA2,SOX9,SPARC,SPRY1,STAT3,TES,TIMP2
BP	GO:0050808: Synapse organization	168	21	7.25	1.2e-05	BHLHB9,CACNA2D2,CACNG2,CADM1,CAMK1,CTNNA2,ELFN1,FARP1,NCAN,NFASC,NLGN1,NLGN3,NRXN1,NTRK2,PCDHB10,PCDHB14,PCDHB3,PCDHB4,PDZRN3,RELN,SLC9A6
BP	GO:0065007: Biological regulation	10810	518	466.44	1.2e-05	AAK1,ABCA1,ABI3BP,ABL1,ACOX1,ACTA2,ADM,AHNAK,AHRR,AHSA2,AIFM2,AKT2,AKT3,ALDH5A1,ALK,AMOTL2,ANKRD1,ANKRD33,ANKRD6,ANO3,ANXA2,ANXA2P2,ANXA3,APH1A,APLP1,APOLD1,AQP11,ARF3,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARMCX3,ARRDC3,ASAP1,ASAP2,ASS1,ATP10D,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,ATXN1,B4GALNT1,BACH2,BASP1,BCL2A1,BCL2L11,BCO2,BCOR,BHLHB9,BHLHE40,BHLHE41,BMPR1B,BPTF,BRPF3,BTBD11,BTG2,BTK,BZRAP1,C18orf32,C1GALT1C1,C1RL,C7,CACNA2D2,CACNG2,CADM1,CALB1,CALCA,CAMK1,CAMK2N1,CCBE1,CCDC40,CCL2,CCNA1,CCND1,CCNDBP1,CD44,CDC42EP3,CDH2,CDK19,CDK5R2,CDKL2,CDKN1A,CDKN1B,CDKN2C,CEBPD,CELF2,CELF6,CHMP2B,CHRM3,CHRNA3,CHRNB1,CHURC1,CIRBP,CLASP2,CLN5,CLPTM1,CLU,CNGA1,CNKSR2,CNP,CNR1,COCH,COL3A1,COLEC12,COX11,CRABP2,CREB5,CREBL2,CREM,CRIM1,CRTAP,CSPG5,CSRP1,CTGF,CTNNA2,CTNND1,CTSA,CTSH,CYB5D2,CYB5R1,CYFIP2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYR61,DACH1,DCBLD2,DCLK1,DCLK2,DCN,DCX,DDX5,DHRS3,DKK2,DKK3,DLG2,DNAJB11,DNAJB6,DNAJC16,DNAJC27,DNAJC3,DOCK9,DPT,DPYSL3,DRAM1,DTNA,DUSP16,DUSP6,EBF1,ECEL1,EFEMP2,EGLN1,EIF4E3,ELFN1,ELL3,ELMO2,ELMOD1,ENPP2,ENSA,EPAS1,EPM2AIP1,ERI1,FABP3,FAM111A,FAM129A,FAM13A,FAM13B,FARP1,FBXO2,FBXO4,FGF14,FLNB,FLRT1,FMN2,FN1,FOS,FOXC1,FOXO3,FRZB,FUCA2,GABRP,GAL,GATA4,GBA,GCH1,GDF10,GDF15,GDF6,GFRA1,GNG2,GNG7,GNG8,GPNMB,GPR19,GPR22,GPRASP1,GRIP1,GRK5,GTF2IRD2,GUCA1A,HBEGF,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HIVEP2,HLA-C,HLA-E,HOXC6,HOXC8,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,HPCAL1,HPCAL4,HTR2B,HUNK,ICAM2,IER3,IFNAR1,IGF2,IGFBP6,IGFBP7,IGSF11,IL10RB,IL17RD,IL20RA,INADL,INHBA,IRF6,IRF9,ITGA1,ITGA7,ITGB5,ITPR2,JARID2,KALRN,KCNB1,KCNMA1,KCNQ2,KCTD11,KDM5C,KIAA0319,KRCC1,KRT18,LAMA4,LARP6,LBH,LIF,LMCD1,LPCAT3,LPXN,LUM,MAB21L1,MAOB,MAP4K4,MAPK9,MAPRE2,MAPT,MAX,MCC,MED13,MEIS1,MEST,MGEA5,MGP,MID1,MID1IP1,MMP11,MMP28,MSN,NANOS1,NAV2,NBL1,NCAN,NCOA1,NCOA3,NCOA7,NDRG4,NFAT5,NFKBIZ,NLGN1,NLGN3,NMI,NOS1,NOTCH2,NOTCH4,NPC2,NPEPPS,NPHP3,NPPA,NPPB,NPR2,NRXN1,NSD1,NSF,NTRK2,NUMB,OAS1,OPTN,OS9,OSCP1,PACSIN3,PAF1,PARP14,PARP9,PBX1,PBX3,PCLO,PDGFC,PDGFD,PDIA3,PEX11B,PFKFB2,PHLDA1,PI15,PIM1,PKP2,PLAGL1,PLAT,PLCD4,PLEKHA2,PLK2,PLN,PLXNB1,POLQ,POPDC3,PPARG,PPP1R3B,PPP1R3D,PRCP,PRNP,PROS1,PRPSAP1,PSD2,PSEN1,PSMB8,PTCH1,PTGER2,PTGIR,PTGIS,PTPRM,PTPRR,PTX3,PYGL,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RARB,RARRES1,RASEF,RASL10B,RBFOX2,RBP1,RBPMS,RDH10,RELN,RET,RFFL,RFTN1,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RIC3,RIMS2,RIT1,RIT2,RLN1,RND2,RNF175,ROM1,RPRM,RRAGB,RRAGC,R

						RAGD,RUNX1,RUNX1T1,RUSC1,SAMD4A,SAP30L,SCG2,SCG5,SCN2A,SCN3A,SCN3B,SCPEP1,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SERPING1,SESN1,SFRP4,SGIP1,SH2B3,SH3BGRL3,SH3BP4,SIAE,SIPA1L1,SIPA1L2,SKAP2,SLC22A17,SLC31A2,SLC40A1,SLC4A8,SLC8A3,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SNCAIP,SOAT1,SOCS3,SORCS1,SOX9,SPARC,SPEN,SPRY1,SPTAN1,SQSTM1,SSBP2,STAT3,STMN4,STOM,SYN2,SYNGR3,SYP,SYT11,SYT4,SYTL4,TACC2,TAF11,TAF7L,TAOK3,TAP1,TAPBPL,TCEAL2,TCEAL3,TCEAL6,TCEAL7,TEP1,TES,TEX2,TFRC,TGM2,TIMP1,TIMP2,TIMP3,TMED4,TMX4,TNFRSF19,TNS3,TOM1L1,TOM1L2,TOX2,TPP1,TRAF3IP2,TRIB2,TRIO,TRIOBP,TSHZ3,TSPAN31,TSPAN8,TULP3,TULP4,TWSG1,TXK,TXNDC15,USP31,VANGL2,VAV3,VGF,VPS13D,WDFY3,WNT3,WTAP,YAP1,ZCCHC12,ZFHX2,ZFHX4,ZFP3,ZFP36L1,ZFYVE1,ZNF280B,ZNF425,ZNF521,ZNF562,ZNF599,ZNF641,ZNF789,ZSCAN18
BP	GO:0001568: Blood vessel development	549	46	23.69	1.3e-05	ACTA2,ADM,ANXA2,ANXA3,APOLD1,ARID1A,ATPIF1,CCBE1,CCL2,CDH2,COL3A1,CTGF,CTSH,CYP1B1,CYR61,EGLN1,ENPP2,EPAS1,FN1,FOXC1,GATA4,HES1,HEY1,HIF1AN,ITGA7,MEIS1,NOTCH2,NOTCH4,NPPB,NRXN1,NTRK2,PRCP,PSEN1,PTGIS,PTPRM,RAMP1,RUNX1,SCG2,SERPINE1,SLC12A6,SLIT2,SOCS3,SPARC,VAV3,YAP1,ZFP36L1
BP	GO:0001501: Skeletal system development	484	42	20.88	1.4e-05	ACP2,ANXA2,ATP6AP1,BMPR1B,CADM1,CD44,CDH11,COL11A1,COL3A1,CTGF,CYP26B1,CYR61,DHRS3,FOXC1,FRZB,GDF10,HEXB,HOXC6,HOXC8,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,IGF2,LUM,MEIS1,MGP,NCAN,NPR2,PBX1,PLXNB1,PSEN1,RARB,RDH10,RUNX1,SMAD1,SOX9,SPARC,TRIM45,TULP3,VCAN
BP	GO:0051960: Regulation of nervous system development	600	49	25.89	1.4e-05	ANKRD1,BHLHB9,CAMK1,CHRNA3,CNR1,COL3A1,CYB5D2,DPYSL3,ELL3,FN1,GDF6,HES1,HOXD3,KCTD11,KIAA0319,LIF,MAPT,MEIS1,NBL1,NCOA1,NDRG4,NLGN1,NLGN3,NPHP3,NRXN1,NTRK2,NUMB,PBX1,PLK2,PLXNB1,PPARG,PSEN1,RARB,RELN,RET,RND2,SEMA3A,SEMA4F,SIPA1L1,SLIT2,SMAD1,SNAP25,SOX9,SPEN,STAT3,TIMP2,TULP3,VANGL2,WNT3
BP	GO:0050767: Regulation of neurogenesis	536	45	23.13	1.6e-05	ANKRD1,BHLHB9,CAMK1,CHRNA3,CNR1,COL3A1,CYB5D2,DPYSL3,ELL3,FN1,GDF6,HES1,HOXD3,KCTD11,KIAA0319,LIF,MAPT,MEIS1,NBL1,NCOA1,NDRG4,NLGN1,NLGN3,NTRK2,NUMB,PBX1,PLK2,PLXNB1,PPARG,PSEN1,RARB,RELN,RET,RND2,SEMA3A,SEMA4F,SIPA1L1,SLIT2,SMAD1,SNAP25,SOX9,SPEN,STAT3,TIMP2,WNT3
BP	GO:0007267: Cell-cell signaling	1211	83	52.25	1.6e-05	ADM,ALDH5A1,ATXN1,BTK,BZRAP1,CACNA2D2,CACNG2,CALB1,CALCA,CCL2,CHRM3,CHRNA3,CHRNB1,CNP,CNR1,CRB1,CSPG5,CTGF,CYR61,DLG2,DTNA,ENSA,EPB41L1,FAT1,FGF14,GAL,GATA4,GDF15,GNG2,GNG7,GNG8,GRIP1,HES1,INHBA,ITPR2,KCNB1,KCNMA1,KCNQ2,LIF,MGEA5,NLGN1,NLGN3,NOS1,NPTX2,NRXN1,NSF,NTRK2,PCDHB10,PCDHB14,PCDHB3,PCDHB4,PCLO,PFKFB2,PKP2,PLAT,PLK2,PSEN1,PTGIR,RAB27A,RAB3B,RASL10B,RELN,RIC3,RIMS2,RIT2,RUNX1,SCG5,SCN3B,SDCBP,SEMA4F,SIPA1L1,SLC6A2,SNAP25,SNCAIP,SOX9,SPRY1,SYN2,SYP,SYT11,SYT4,SYTL4,VGF,WNT3
BP	GO:0050789: Regulation of biological process	10322	497	445.38	1.8e-05	AAK1,ABCA1,ABI3BP,ABL1,ACOX1,ADM,AHNAK,AHRR,AHSA2,AIFM2,AKT2,AKT3,ALK,AMOTL2,ANKRD1,ANKRD33,ANKRD6,ANXA2,ANXA2P2,ANXA3,APH1A,APLP1,APOLD1,ARF3,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARMCX3,ARRDC3,ASAP1,ASAP2,ASS1,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,ATXN1,BACH2,BASP1,BCL2A1,BCL2L11,BCO2,BCOR,BHLHB9,BHLHE40,BHLHE41,BMPR1B,BPTF,BTBD11,BTG2,BTK,C18orf32,C1GALT1C1,C1RL,C7,CACNA2D2,CACNG2,CADM1,CALB1,CALCA,CAMK1,CAMK2N1,CCBE1,CCDC40,CCL2,CCNA1,CCND1,CCNDBP1,CD44,CDC42EP3,CDH2,CDK19,CDK5R2,CDKL2,CDKN1A,CDKN1B,CDKN2C,CEBPD,CELF2,CELF6,CHMP2B,CHRM3,CHRNA3,CHRNB1,CHURC1,CIRBP,CLASP2,CLPTM1,CLU,CNGA1,CNKSR2,CNR1,COCH,COL3A1,COLEC12,COX11,CRABP2,CREB5,CREBL2,CREM,CRIM1,CRTAP,CSPG5,CTGF,CTNNA2,CTNND1,CTSA,CTSH,CYB5D2,CYB5R1,CYFIP2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYR61,DACH1,DCBLD2,DCLK1,DCLK2,DCN,DCX,DDX5,DHRS3,DKK2,DKK3,DLG2,DNAJB11,DNAJB6,DNAJC16,DNAJC27,DNAJC3,DOCK9,DPT,DPYSL3,DRAM1,DTNA,DUSP16,DUSP6,EBF1,ECEL1,EFEMP2,EGLN1,EIF4E3,ELFN1,ELL3,ELMO2,ELMOD1,ENPP2,ENSA,EPAS1,EPM2AIP1,ERI1,FABP3,FAM111A,FAM129A,FAM13A,FAM13B,FARP1,FBXO2,FBXO4,FGF14,FLNB,FLRT1,FMN2,FN1,FOS,FOXC1,FOXO3,FRZB,FUCA2,GABRP,GAL,GATA4,GBA,GCH1,GDF10,GDF15,GDF6,GFRA1,GNG2,GNG7,GNG8,GPNMB,GPR19,GPR22,GPRASP1,GRIP1,GRK5,GTF2IRD2,GUCA1A,HBEGF,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HIVEP2,HLA-C,HLA-E,HOXC6,HOXC8,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,HPCAL1,HPCAL4,HTR2B,HUNK,ICAM2,IER3,IFNAR1,IGF2,IGFBP6,IGFBP7,IGSF11,IL10RB,IL17RD,IL20RA,INADL,INHBA,IRF6,IRF9,ITGA1,ITGA7,ITGB5,ITPR2,JARID2,KALRN,KCNB1,KCNMA1,KCNQ2,KCTD11,KDM5C,KIAA0319,KRCC1,KRT18,LAMA4,LARP6,LBH,LIF,LMCD1,LPCAT3,LPXN,LUM,MAB21L1,MAOB,MAP4K4,MAPK9,MAPRE2,MAPT,MAX,MCC,MED13,MEIS1,MEST,MGEA5,MGP,MID1,MID1IP1,MMP11,MMP28,MSN,NANOS1,NBL1,NCAN,NCOA1,NCOA3,NCOA7,NDRG4,NFAT5,NFKBIZ,NLGN1,NLGN3,NMI,NOS1,NOTCH2,NOTCH4,NPC2,NPEPPS,NPHP3,NPPA,NPPB,NPR2,NRXN1,NSD1,NSF,NTRK2,NUMB,OAS1,OPTN,OS9,OSCP1,PACSIN3,PAF1,PARP14,PARP9,PBX1,PBX3,PCLO,PDGFC,PDGFD,PDIA3,PEX11B,PFKFB2,PHLDA1,PI15,PIM1,PKP2,PLAGL1,PLAT,PLCD4,PLEKHA2,PLK2,PLN,PLXNB1,POLQ,PPARG,PPP1R3B,PPP1R3D,PRCP,PRNP,PROS1,PRPSAP1,PSD2,PSEN1,PSMB8,PTCH1,PTGER2,PTGIR,PTGIS,PTPRM,PTPR

						R,PTX3,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RARB,RARRES1,RASEF,RASL10B,RBFOX2,RBP1,RBPMS,RDH10,RELN,RET,RFFL,RFTN1,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RIMS2,RIT1,RIT2,RLN1,RND2,RNF175,ROM1,RPRM,RRAGB,RRAGC,RRAGD,RUNX1,RUNX1T1,RUSC1,SAMD4A,SAP30L,SCG2,SCG5,SCN2A,SCN3A,SCN3B,SCPEP1,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SERPING1,SESN1,SFRP4,SGIP1,SH2B3,SH3BGRL3,SH3BP4,SIAE,SIPA1L1,SIPA1L2,SKAP2,SLC22A17,SLC31A2,SLC40A1,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SNCAIP,SOAT1,SOCS3,SORCS1,SOX9,SPARC,SPEN,SPRY1,SPTAN1,SQSTM1,SSBP2,STAT3,STMN4,STOM,SYNGR3,SYP,SYT11,SYT4,SYTL4,TACC2,TAF11,TAF7L,TAOK3,TAP1,TAPBPL,TCEAL2,TCEAL3,TCEAL6,TCEAL7,TES,TEX2,TFRC,TGM2,TIMP1,TIMP2,TIMP3,TMED4,TMX4,TNFRSF19,TNS3,TOM1L1,TOM1L2,TOX2,TPP1,TRAF3IP2,TRIB2,TRIO,TRIOBP,TSHZ3,TSPAN31,TSPAN8,TULP3,TULP4,TWSG1,TXK,TXNDC15,USP31,VANGL2,VAV3,WDFY3,WNT3,WTAP,YAP1,ZCCHC12,ZFHX2,ZFHX4,ZFP3,ZFP36L1,ZFYVE1,ZNF280B,ZNF425,ZNF521,ZNF562,ZNF599,ZNF641,ZNF789,ZSCAN18
BP	GO:0048646: Anatomical structure formation involved in morphogenesis	1031	73	44.49	1.9e-05	ADM,AGTPBP1,ANKRD1,ANXA2,ANXA3,APOLD1,ARID1A,ATP6V0D1,ATP8B1,ATPIF1,BCL2L11,CALB1,CAMK1,CCBE1,CCL2,CDK5R2,COL11A1,CTGF,CTSH,CYP1B1,CYR61,DUSP6,EGLN1,ENPP2,EPAS1,FN1,FOXC1,GATA4,GDF15,HES1,HEY1,INHBA,ITGA7,ITGB5,MEIS1,NEBL,NFASC,NOS1,NOTCH4,NPHP3,NPPB,NRXN1,PAF1,PRCP,PSEN1,PTCH1,PTGIS,PTPRM,RAB3IP,RAMP1,RDH10,RELN,RET,RSPH9,RUNX1,SCG2,SERPINE1,SH3PXD2A,SLC12A6,SLC40A1,SLIT2,SMAD1,SOX9,SPARC,SPRY1,TGM2,TTC30A,TTC30B,TULP3,TWSG1,VANGL2,VAV3,WNT3
BP	GO:0001822: Kidney development	258	27	11.13	2.0e-05	ACTA2,APH1A,AQP11,ASS1,BASP1,BCL2L11,CALB1,CD44,CTSH,DCN,FOXC1,HES1,LIF,NPHP3,PBX1,PTCH1,RARB,RDH10,RET,SDC4,SLIT2,SMAD1,SOX9,SPRY1,TSHZ3,VANGL2,YAP1
BP	GO:0045664: Regulation of neuron differentiation	427	38	18.42	2.0e-05	ANKRD1,BHLHB9,CAMK1,CHRNA3,CNR1,CYB5D2,DPYSL3,FN1,GDF6,HES1,HOXD3,KCTD11,KIAA0319,MAPT,MEIS1,NBL1,NCOA1,NDRG4,NLGN1,NLGN3,NTRK2,PBX1,PLK2,PLXNB1,PSEN1,RARB,RELN,RET,RND2,SEMA3A,SEMA4F,SIPA1L1,SLIT2,SMAD1,SNAP25,SOX9,TIMP2,WNT3
BP	GO:0048729: Tissue morphogenesis	593	48	25.59	2.1e-05	ABL1,ADM,ANKRD1,ANKRD6,ARID1A,CALB1,CCDC40,CD44,COL11A1,COL3A1,CTSH,CYR61,EGLN1,FOXC1,FRZB,GATA4,HBEGF,HES1,HEY1,INHBA,LIF,NCOA3,NDRG4,NOTCH2,NOTCH4,NPHP3,NUMB,PBX1,PKP2,PSEN1,PTCH1,PTPRM,RDH10,RET,ROM1,RUNX1,SEMA3A,SLIT2,SMAD1,SOCS3,SOX9,SPRY1,TGM2,TULP3,TWSG1,VANGL2,WNT3,YAP1
BP	GO:0007268: Synaptic transmission	715	55	30.85	2.3e-05	ALDH5A1,ATXN1,BZRAP1,CACNA2D2,CACNG2,CALB1,CCL2,CHRM3,CHRNA3,CHRNB1,CNP,CNR1,CSPG5,DLG2,DTNA,EPB41L1,FGF14,GNG2,GNG7,GNG8,GRIP1,KCNB1,KCNMA1,KCNQ2,NLGN1,NLGN3,NOS1,NPTX2,NRXN1,NSF,NTRK2,PCDHB10,PCDHB14,PCDHB3,PCDHB4,PCLO,PLAT,PLK2,PSEN1,RAB27A,RAB3B,RELN,RIC3,RIMS2,RIT2,SDCBP,SIPA1L1,SLC6A2,SNAP25,SNCAIP,SYN2,SYP,SYT11,SYT4,SYTL4
BP	GO:0060284: Regulation of cell development	681	53	29.38	2.4e-05	ANKRD1,ATP6AP1,BHLHB9,CAMK1,CHRNA3,CNR1,COL3A1,CYB5D2,DPYSL3,ELL3,FN1,FOXC1,FRZB,GAL,GDF6,HES1,HOXD3,KCTD11,KIAA0319,LIF,MAPK9,MAPT,MEIS1,NBL1,NCOA1,NDRG4,NLGN1,NLGN3,NPR2,NTRK2,NUMB,PBX1,PLK2,PLXNB1,PPARG,PSEN1,RARB,RELN,RET,RND2,SEMA3A,SEMA4F,SIPA1L1,SLIT2,SMAD1,SNAP25,SOX9,SPEN,STAT3,TIMP2,TRIOBP,WNT3,YAP1
BP	GO:0006022: Aminoglycan metabolic process	176	21	7.59	2.4e-05	B3GNT7,B4GALT6,CD44,CSPG5,DCN,FOXC1,FUCA1,GAL3ST3,GNS,HEXB,HGSNAT,HS3ST2,IDS,LUM,NCAN,PIM1,SDC4,SLC26A2,SLC35D2,VCAN,XYLT1
BP	GO:0001657: Ureteric bud development	100	15	4.31	2.4e-05	BASP1,CALB1,CD44,FOXC1,HES1,PBX1,PTCH1,RARB,RET,SDC4,SLIT2,SMAD1,SOX9,SPRY1,TSHZ3
BP	GO:0040007: Growth	876	64	37.8	2.4e-05	ABL1,ADM,ATP6V0E1,ATP6V0E2,BASP1,BCL2L11,BMPR1B,CACNA2D2,CADM1,CDKN1A,CDKN1B,CDKN2C,CRIM1,CSPG5,CTGF,CYR61,DCBLD2,DCLK1,DCX,DDX5,DUSP6,FN1,FOXC1,FOXO3,FRZB,GAL,GATA4,GDF10,GDF6,HBEGF,IGFBP6,IGFBP7,IGSF11,INHBA,KCTD11,MAPT,NCOA3,NDRG4,NLGN3,NOTCH2,NPPA,NPPB,PPARG,PTCH1,RARB,RDH10,RFTN1,RND2,RRAGC,SEMA3A,SEMA4F,SH3BP4,SLC9A6,SLIT2,SMAD1,SMARCA2,SOCS3,SOX9,SPRY1,STAT3,VANGL2,WNT3,YAP1,ZFP36L1
BP	GO:0009888: Tissue development	1708	108	73.7	2.7e-05	ABL1,ACTA2,ADM,AKT2,ANKRD1,ANKRD33,ANKRD6,APOLD1,AQP11,ARID1A,ARRDC3,ATP6AP2,BASP1,BCOR,BMPR1B,BPTF,BTG2,BTK,CALB1,CCDC40,CCND1,CD44,CDKN1A,COL11A1,COL17A1,COL3A1,CRABP2,CREB5,CTGF,CTSH,CYP1B1,CYP26A1,CYP26B1,CYR61,DCN,DDX5,DUSP6,EGLN1,ELL3,FAM101B,FLNB,FN1,FOS,FOXC1,FRZB,GAL,GATA4,GPNMB,HBEGF,HES1,HEY1,HOXD10,HOXD3,HOXD9,HTR2B,INHBA,IRF6,ITGA7,ITGB5,LIF,LUM,MAX,MEST,MGP,MSN,NCOA3,NDRG4,NEBL,NOTCH2,NOTCH4,NPHP3,NUMB,PAF1,PBX1,PKP2,PLAGL1,PLN,PPARG,PSEN1,PTCH1,PTPRM,RAB27A,RARB,RDH10,RET,ROM1,RUNX1,SDC4,SEMA3A,SFRP4,SGCB,SLC40A1,SLIT2,SMAD1,SOCS3,SOX9,SPRY1,STS,TGM2,TNFRSF19,TPP1,TSHZ3,TULP3,TWSG1,VANGL2,WNT3,YAP1,ZFP36L1
BP	GO:0072163: Mesonephric epithelium development	101	15	4.36	2.7e-05	BASP1,CALB1,CD44,FOXC1,HES1,PBX1,PTCH1,RARB,RET,SDC4,SLIT2,SMAD1,SOX9,SPRY1,TSHZ3
BP	GO:0072164:	101	15	4.36	2.7e-05	BASP1,CALB1,CD44,FOXC1,HES1,PBX1,PTCH1,RARB,RET,SDC4,SLIT2,SMAD1,SOX9,SPRY1,TSHZ3

	Mesonephric tubule development					
BP	GO:0048514: Blood vessel morphogenesis	482	41	20.8	2.8e-05	ADM,ANXA2,ANXA3,APOLD1,ATPIF1,CCBE1,CCL2,CDH2,COL3A1,CTGF,CTSH,CYP1B1,CYR61,EGLN1,ENPP2,EPAS1,FN1,FOXC1,GATA4,HES1,HEY1,HIF1AN,ITGA7,MEIS1,NOTCH4,NPPB,NRXN1,NTRK2,PRCP,PTGIS,PTPRM,RAMP1,RUNX1,SCG2,SERPINE1,SLC12A6,SLIT2,SPARC,VAV3,YAP1,ZFP36L1
BP	GO:0071310: Cellular response to organic substance	1906	118	82.24	2.8e-05	ABCA1,ABL1,AKT2,ANKRD1,APH1A,APLP1,ARHGEF3,ASS1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,BCL2L11,CALB1,CALCA,CCBE1,CCL2,CCND1,CD44,CDKN1A,CDKN1B,COL3A1,COLEC12,CTGF,CTSH,CYP1B1,CYP24A1,CYP26A1,CYP26B1,DNAJB11,DNAJC3,DPYSL3,DUSP6,EIF4E3,FLNB,FOS,FOXC1,FOXO3,GATA4,GBA,GDF10,GDF15,GNG2,GNG7,GNG8,GPR22,HBEGF,HEY1,HLA-C,HLA-E,IFNAR1,IGF2,IGFBP7,IL10RB,IL17RD,IL20RA,INHBA,IRF6,IRF9,ITGB5,ITPR2,KALRN,KRT18,MAPK9,MAX,MID1,NCOA1,NCOA3,NOS1,NPR2,NRXN1,NTRK2,OAS1,PAF1,PDGFC,PDGFD,PIM1,PLAT,PPARG,PRCP,PSMB8,PTCH1,PTGER2,PTGIS,RARB,RET,RFFL,RIT1,RIT2,RNF175,RRAGB,RRAGC,RRAGD,RUNX1,SERPINE1,SH3BP4,SLC8A3,SLC9A6,SLIT2,SMAD1,SOCS3,SOX9,SPARC,SPRY1,SQSTM1,STAT3,SYP,TIMP2,TIMP3,TNFRSF19,TPP1,TRIO,TXK,VAV3,WNT3
BP	GO:0048585: Negative regulation of response to stimulus	1242	83	53.59	4.0e-05	ABL1,ADM,ANKRD6,ANXA2,ARRDC3,ATP2B4,ATXN1,BCL2A1,CALCA,CCL2,CCND1,CD44,CDH2,CLU,COL3A1,CTNNA2,CTNND1,CYP26A1,CYP26B1,DHRS3,DKK2,DKK3,DNAJC3,DUSP16,DUSP6,ELL3,FOXO3,FRZB,GBA,GPRASP1,GRK5,HEY1,HIF1AN,HLA-E,HTR2B,IER3,ITGA1,KCTD11,LIF,LPXN,MCC,MGEA5,MMP28,NBL1,NDRG4,NOS1,NPHP3,NRXN1,NUMB,OPTN,PLAT,POLQ,PPARG,PRNP,PROS1,PSEN1,PSMB8,PTCH1,PTGIR,PTGIS,PTPRR,RFFL,RGS13,RGS16,RGS2,RGS7,SCG2,SEMA3A,SERPINE1,SERPING1,SFRP4,SH3BP4,SLIT2,SOCS3,SOX9,SPRY1,TAOK3,TIMP2,TSPAN8,TULP3,TWSG1,WNT3,YAP1
BP	GO:0061061: Muscle structure development	540	44	23.3	4.0e-05	ABL1,ADM,ANKRD1,ANKRD33,ASS1,BASP1,BHLHE41,BTG2,CACNA2D2,CAMK1,CDH2,CHRNB1,COL11A1,COL3A1,CTNNA2,CYP26B1,DCN,DDX5,EGLN1,EPAS1,FLNB,FOS,FOXC1,GATA4,GDF15,HBEGF,HES1,HEY1,HIF1AN,HOXD10,HOXD9,IGF2,ITGA7,LIF,NEBL,NOS1,PKP2,PLAGL1,RARB,SGCB,SMARCA2,SOX9,TSHZ3,VANGL2
BP	GO:0072073: Kidney epithelium development	142	18	6.13	4.0e-05	AQP11,BASP1,CALB1,CD44,FOXC1,HES1,LIF,PBX1,PTCH1,RARB,RET,SDC4,SLIT2,SMAD1,SOX9,SPRY1,TSHZ3,YAP1
BP	GO:0032879: Regulation of localization	2102	127	90.7	4.1e-05	AAK1,ABCA1,ABL1,AHNAK,AKT2,ANKRD1,ANXA2,ANXA3,ATP1B1,ATP2B4,ATP6AP1,ATPIF1,BCL2L11,CACNA2D2,CACNG2,CADM1,CALCA,CAMK1,CCBE1,CCDC40,CCL2,CDK5R2,CDKL2,CDKN1A,CDKN1B,CHRM3,CHRNA3,CNR1,COL3A1,CREBL2,CTSH,CYB5R1,CYP1B1,CYR61,DACH1,DNAJC27,DPYSL3,ELMOD1,ENPP2,ENSA,FGF14,GAL,GATA4,HBEGF,HES1,HLA-E,HTR2B,IER3,IFNAR1,INHBA,ITPR2,KCNB1,KCNMA1,KCNQ2,LAMA4,LIF,MAOB,MAPK9,MAPT,MCC,MEST,MGEA5,MMP28,MSN,NBL1,NDRG4,NLGN1,NLGN3,NOS1,NPEPPS,NPPA,NPPB,NRXN1,NSF,NTRK2,NUMB,OS9,OSCP1,PACSIN3,PCLO,PDIA3,PFKFB2,PKP2,PLN,PPARG,PRCP,PRNP,PTCH1,PTPRM,PTPRR,PTX3,RAB26,RAB27A,RAB3B,RASL10B,RBPMS,RELN,RET,RFFL,RHBDF1,RIMS2,RUNX1,SCG5,SCN2A,SCN3A,SCN3B,SDC4,SDCBP,SEMA3A,SERPINE1,SFRP4,SGIP1,SH3BGRL3,SLC31A2,SLIT2,SNAP25,SNCAIP,SOX9,SPARC,STAT3,STOM,SYNGR3,SYT11,SYT4,SYTL4,TIMP1,WNT3
BP	GO:0030203: Glycosaminoglycan metabolic process	169	20	7.29	4.2e-05	B3GNT7,B4GALT6,CD44,CSPG5,DCN,FOXC1,FUCA1,GNS,HEXB,HGSNAT,HS3ST2,IDS,LUM,NCAN,PIM1,SDC4,SLC26A2,SLC35D2,VCAN,XYLT1
BP	GO:0001823: Mesonephros development	105	15	4.53	4.3e-05	BASP1,CALB1,CD44,FOXC1,HES1,PBX1,PTCH1,RARB,RET,SDC4,SLIT2,SMAD1,SOX9,SPRY1,TSHZ3
BP	GO:0048523: Negative regulation of cellular process	3881	212	167.46	5.0e-05	ABCA1,ABL1,ADM,AHRR,AKT2,ANKRD1,ANKRD33,ANKRD6,ANXA2,APLP1,ARID1A,ASS1,ATP2B4,ATP8B1,ATPIF1,ATXN1,BACH2,BASP1,BCL2A1,BCOR,BHLHB9,BHLHE40,BHLHE41,BMPR1B,BPTF,BTG2,CALCA,CAMK2N1,CCL2,CCND1,CD44,CDH2,CDKN1A,CDKN1B,CDKN2C,CIRBP,CLASP2,CLU,CNR1,COL3A1,COX11,CREM,CRIM1,CRTAP,CTGF,CTNND1,CTSH,CYP1B1,CYP26A1,CYP26B1,CYR61,DACH1,DCBLD2,DDX5,DHRS3,DKK2,DKK3,DLG2,DNAJB6,DNAJC3,DPT,DPYSL3,DUSP16,DUSP6,EGLN1,ELFN1,ELL3,EPAS1,FABP3,FAM111A,FAM129A,FARP1,FBXO2,FMN2,FOXC1,FOXO3,FRZB,GAL,GATA4,GBA,GPNMB,GPRASP1,GRK5,HBEGF,HES1,HEXIM1,HEY1,HIF1AN,HOXC6,HOXC8,HOXD8,HOXD9,HTR2B,IER3,IGFBP6,IGFBP7,INHBA,IRF6,ITGA1,JARID2,KCTD11,KDM5C,KIAA0319,KRT18,LIF,LMCD1,LPXN,MAOB,MAP4K4,MCC,MEIS1,MGEA5,MID1,MID1IP1,MMP11,MMP28,NANOS1,NBL1,NDRG4,NOS1,NOTCH2,NOTCH4,NPHP3,NPPA,NPPB,NPR2,NRXN1,NSD1,NTRK2,NUMB,OAS1,OPTN,PACSIN3,PAF1,PBX1,PI15,PIM1,PKP2,PLAGL1,PLAT,PLK2,PLN,PLXNB1,POLQ,PPARG,PRNP,PROS1,PRPSAP1,PSEN1,PSMB8,PTCH1,PTGIR,PTGIS,PTPRM,PTPRR,PTX3,RARB,RARRES1,RBFOX2,RFFL,RFWD2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RPRM,RUNX1,RUNX1T1,SAMD4A,SCG2,SEMA3A,SEMA4F,SERPINE1,SERPING1,SESN1,SFRP4,SH3BP4,SKAP2,SLC40A1,SLIT2,SMAD1,SMARCA2,SOCS3,SOX9,SPARC,SPEN,SPRY1,SPTAN1,SQSTM1,STAT3,SYT11,SYT4,SYTL4,TAOK3,TCEAL7,TES,TIMP1,TIMP2,TIMP3,TOM1L1,TOM1L2,TRIB2,TRIOBP,TSHZ3,TULP3,TWSG1,VANGL2,WNT3,YAP1,ZFYVE1,ZNF425

BP	GO:0072001: Renal system development	273	27	11.78	5.4e-05	ACTA2,APH1A,AQP11,ASS1,BASP1,BCL2L11,CALB1,CD44,CTSH,DCN,FOXC1,HES1,LIF,NPHP3,PBX1,PTCH1,RARB,RDH10,RET,SDC4,SLIT2,SMAD1,SOX9,SPRY1,TSHZ3,VANGL2,YAP1
BP	GO:0008277: Regulation of G-protein coupled receptor protein signaling pathway	146	18	6.3	5.8e-05	ADM,ARRDC3,ATP2B4,CALCA,CNGA1,GNG7,GPRASP1,GRK5,GUCA1A,HTR2B,NOS1,RAMP1,RGS13,RGS16,RGS2,RGS7,SYP,TULP3
BP	GO:0065009: Regulation of molecular function	2549	148	109.99	6.2e-05	ABL1,AHNAK,AHSA2,ALK,ANKRD33,ANXA2,ANXA2P2,ANXA3,APH1A,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARRDC3,ASAP1,ASAP2,ATP1B1,ATP2B4,ATP6V0D1,ATPIF1,BCL2L11,BHLHE40,BTK,C1GALT1C1,CACNG2,CALCA,CAMK1,CAMK2N1,CCL2,CCNA1,CCND1,CD44,CDK5R2,CDKN1A,CDKN1B,CDKN2C,CHRNA3,CLU,CNR1,COX11,CRIM1,CTGF,CTSA,CTSH,CYFIP2,CYP1B1,CYR61,DLG2,DNAJB11,DNAJB6,DNAJC3,DOCK9,DUSP16,DUSP6,EGLN1,ELFN1,ELMOD1,ENSA,EPM2AIP1,FAM13A,FAM13B,FARP1,FN1,FOS,GAL,GBA,GCH1,GNG7,GUCA1A,HES1,HEXIM1,HEY1,HTR2B,IGF2,ITGA1,ITPR2,KALRN,MAPK9,MID1IP1,NCOA3,NLGN1,NLGN3,NOS1,NPPA,NRXN1,NTRK2,OAS1,PBX1,PDGFC,PFKFB2,PI15,PIM1,PLK2,PLN,PLXNB1,PPARG,PPP1R3B,PRNP,PROS1,PRPSAP1,PSD2,PSEN1,PSMB8,PTCH1,PTGIR,PTGIS,PTX3,RAB3IP,RABIF,RELN,RET,RFFL,RGL2,RGS13,RGS16,RGS2,RGS7,SCG5,SCN3B,SDC4,SERPINE1,SERPING1,SFRP4,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SLIT2,SOCS3,SPRY1,STOM,SYNGR3,TAOK3,TCEAL7,TIMP1,TIMP2,TIMP3,TOM1L1,TPP1,TRIB2,TRIO,TXK,VANGL2,VAV3,ZFYVE1
BP	GO:0016477: Cell migration	1093	74	47.16	7.1e-05	ABL1,AKT2,ANXA3,ATP1B1,CALCA,CCBE1,CCL2,CD44,CDH2,CDK5R2,COL3A1,CTGF,CTNNA2,CTSH,CYP1B1,CYR61,DACH1,DCLK1,DCX,DPYSL3,ELMO2,ENPP2,FAT1,FN1,FOXC1,HBEGF,HES1,HEXB,HTR2B,ITGA1,ITGA7,KIAA0319,LAMA4,MAPT,MATN2,MCC,MMP28,MSN,NANOS1,NAV1,NBL1,NDRG4,NTRK2,NUMB,PARP9,PKP2,PLAT,PLXNB1,PRCP,PROS1,PSEN1,PTPRM,PTPRR,RBFOX2,RELN,RET,RFFL,RHBDF1,SCG2,SDC4,SDCBP,SEMA3A,SERPINE1,SH3BGRL3,SLIT2,SORBS2,SOX9,SPARC,STAT3,TIMP1,TNS3,VANGL2,VAV3,VCAN
BP	GO:0048519: Negative regulation of biological process	4226	227	182.35	7.2e-05	ABCA1,ABL1,ADM,AHRR,AKT2,ANKRD1,ANKRD33,ANKRD6,ANXA2,ANXA2P2,ANXA3,APLP1,ARID1A,ARRDC3,ASS1,ATP2B4,ATP8B1,ATPIF1,ATXN1,BACH2,BASP1,BCL2A1,BCOR,BHLHB9,BHLHE40,BHLHE41,BMPR1B,BPTF,BTG2,CALCA,CAMK2N1,CCL2,CCND1,CD44,CDH2,CDKN1A,CDKN1B,CDKN2C,CIRBP,CLASP2,CLU,CNR1,COL3A1,COX11,CREM,CRIM1,CRTAP,CTGF,CTNNA2,CTNND1,CTSH,CYP1B1,CYP26A1,CYP26B1,CYR61,DACH1,DCBLD2,DDX5,DHRS3,DKK2,DKK3,DLG2,DNAJB6,DNAJC3,DPT,DPYSL3,DUSP16,DUSP6,EGLN1,ELFN1,ELL3,ENSA,EPAS1,ERI1,FABP3,FAM111A,FAM129A,FARP1,FBXO2,FMN2,FOXC1,FOXO3,FRZB,GAL,GATA4,GBA,GPNMB,GPRASP1,GRK5,HBEGF,HES1,HEXIM1,HEY1,HIF1AN,HLA-E,HOXC6,HOXC8,HOXD8,HOXD9,HTR2B,IER3,IGFBP6,IGFBP7,INHBA,IRF6,ITGA1,JARID2,KCTD11,KDM5C,KIAA0319,KRT18,LIF,LMCD1,LPXN,MAOB,MAP4K4,MAPT,MAX,MCC,MEIS1,MGEA5,MID1,MID1IP1,MMP11,MMP28,NANOS1,NBL1,NDRG4,NOS1,NOTCH2,NOTCH4,NPHP3,NPPA,NPPB,NPR2,NRXN1,NSD1,NTRK2,NUMB,OAS1,OPTN,OS9,PACSIN3,PAF1,PBX1,PDIA3,PI15,PIM1,PKP2,PLAGL1,PLAT,PLK2,PLN,PLXNB1,POLQ,PPARG,PRNP,PROS1,PRPSAP1,PSEN1,PSMB8,PTCH1,PTGIR,PTGIS,PTPRM,PTPRR,PTX3,RARB,RARRES1,RBFOX2,RFFL,RFWD2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RPRM,RUNX1,RUNX1T1,SAMD4A,SAP30L,SCG2,SCG5,SEMA3A,SEMA4F,SERPINE1,SERPING1,SESN1,SFRP4,SH3BP4,SKAP2,SLC40A1,SLIT2,SMAD1,SMARCA2,SOCS3,SOX9,SPARC,SPEN,SPRY1,SPTAN1,SQSTM1,STAT3,SYT11,SYT4,SYTL4,TAOK3,TAPBPL,TCEAL7,TES,TIMP1,TIMP2,TIMP3,TOM1L1,TOM1L2,TRIB2,TRIOBP,TSHZ3,TSPAN8,TULP3,TWSG1,VANGL2,WNT3,YAP1,ZFYVE1,ZNF425
BP	GO:0048667: Cell morphogenesis involved in neuron differentiation	640	49	27.62	7.2e-05	ABL1,APH1A,BHLHB9,BMPR1B,CDH11,CHRNA3,CLASP2,CNP,COL3A1,CTNNA2,DCLK1,DCX,DPYSL3,FARP1,FN1,GFRA1,HES1,ITGA1,KALRN,KCNQ2,MAP6,MAPT,MATN2,NCAN,NFASC,NLGN3,NRXN1,NTNG2,NTRK2,NUMB,PLXNB1,PRNP,PSEN1,PTPRM,RBFOX2,RELN,RET,RND2,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SMAD1,SPTAN1,TRIO,VAV3,WNT3
BP	GO:1901700: Response to oxygen-containing compound	1303	85	56.22	7.5e-05	ABCA1,ABL1,ADM,AKT2,ANKRD1,APLP1,ASS1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,BTG2,BTK,CCL2,CCND1,CDKN1A,CDKN1B,CNP,CNR1,COL3A1,COLEC12,CREM,CTGF,CTSH,CYP1B1,CYP24A1,CYP26A1,CYP26B1,DCN,EGLN1,ENSA,EPM2AIP1,FABP3,FOS,GAL,GATA4,GBA,GCH1,GNG2,GNG7,GNG8,GPR22,GPX3,IGF2,IGFBP7,INHBA,ITPR2,KCNMA1,MAOB,MAPK9,MAX,MEST,NCOA1,NPPA,NRXN1,PAF1,PDGFC,PDGFD,PFKFB2,PIM1,PLAT,PLN,PPARG,PTCH1,PTGER2,PTGIR,RET,RRAGB,RRAGC,RRAGD,SERPINE1,SESN1,SH3BP4,SLC8A3,SLIT2,SOCS3,SOX9,SPARC,STAT3,TIMP1,VGF,WNT3
BP	GO:0048513: Organ development	2881	163	124.31	9.3e-05	ABL1,ACTA2,ADM,AGTPBP1,AKT2,ANKRD1,ANKRD33,ANKRD6,ANXA2,APH1A,APLP1,AQP11,ARID1A,ARRDC3,ASS1,ATP6AP1,ATP6V0D1,ATP8B1,ATPIF1,ATXN1,BASP1,BCL2L11,BCOR,BHLHE41,BMPR1B,BPTF,BTG2,BTK,CADM1,CALB1,CALCA,CCDC40,CCL2,CCND1,CD44,CDK5R2,CDKN1A,CDKN1B,CLN5,CLPTM1,CNP,COL11A1,COL3A1,COX17,CRB1,CREB5,CTGF,CTNNA2,CTNND1,CTSH,CYP1B1,CYP26A1,CYP26B1,CYR61,DCLK1,DCN,DCX,DDX5,DHRS3,D

						KK3,DUSP6,EGLN1,ELL3,EPAS1,FAM101B,FLNB,FOS,FOXC1,FOXO3,FRZB,GAL,GATA4,GBA,GPNMB,HBEGF,HCCS,HES1,HEXIM1,HEY1,HOXC8,HOXD10,HOXD3,HOXD8,HOXD9,HTR2B,IGF2,IGFBP7,INHBA,IRF6,ITGA7,JARID2,LIF,LUM,MAB21L1,MAOB,MAX,MEIS1,MGP,NCOA1,NCOA3,NDRG4,NEBL,NOTCH2,NOTCH4,NPHP3,NPR2,NRXN1,NTRK2,NUMB,OLFM3,PAF1,PBX1,PBX3,PCDH9,PDGFC,PHLDA1,PKP2,PLAGL1,PLN,PLXNB1,PPARG,PSEN1,PTCH1,PTPRM,RARB,RBFOX2,RDH10,RELN,RET,ROM1,RUNX1,SDC4,SEMA3A,SGCB,SH2B3,SH3PXD2A,SLC40A1,SLC8A3,SLIT2,SMAD1,SMOC1,SOCS3,SOX9,SPARC,SPRY1,STAT3,SYNGR3,TACC2,TFRC,TGM2,TNFRSF19,TNS3,TRIM45,TSHZ3,TULP3,TWSG1,TXK,VANGL2,VCAN,VGF,WNT3,YAP1,ZFP36L1
BP	GO:0008015: Blood circulation	409	35	17.65	9.4e-05	ACTA2,ADM,ATP1B1,ATP2B4,ATP6AP2,CALCA,CELF2,CHRM3,CNR1,CTGF,EPAS1,FOXC1,GATA4,GCH1,HBEGF,HTR2B,IER3,ITGA1,NAV2,NOS1,NPPA,NPPB,NPR2,PKP2,PLN,PPARG,PRCP,PTPRM,RASL10B,RGS2,SCN3B,SCPEP1,SEMA3A,SERPING1,SLIT2
BP	GO:0007389: Pattern specification process	443	37	19.11	9.9e-05	ATP6AP2,BASP1,BCOR,BMPR1B,BPTF,BTG2,CCDC40,CYP26A1,CYP26B1,DUSP6,FOXC1,GATA4,HES1,HEY1,HOXC6,HOXC8,HOXD10,HOXD3,HOXD8,HOXD9,MID1,NBL1,NDRG4,NOTCH2,NOTCH4,NPHP3,PBX1,PBX3,PSEN1,PTCH1,RELN,SEMA3A,SMAD1,SPRY1,TULP3,VANGL2,WNT3
BP	GO:0007507: Heart development	443	37	19.11	9.9e-05	ADM,ANKRD1,ARID1A,BASP1,BCOR,CCDC40,COL11A1,COL3A1,COX17,CYR61,DHRS3,DUSP6,EGLN1,FOXC1,GATA4,HES1,HEXIM1,HEY1,HTR2B,NDRG4,NEBL,NOTCH2,NPHP3,PKP2,PLN,PPARG,PSEN1,PTCH1,RARB,SGCB,SMAD1,SOX9,SPARC,VANGL2,VCAN,YAP1,ZFP36L1
BP	GO:0071229: Cellular response to acid chemical	152	18	6.56	9.9e-05	ABCA1,ASS1,CCL2,COL3A1,CYP26A1,CYP26B1,GNG2,PDGFC,PDGFD,PPARG,PTGER2,RET,RRAGB,RRAGC,RRAGD,SH3BP4,SOX9,WNT3
BP	GO:0003013: Circulatory system process	411	35	17.73	0.00010	ACTA2,ADM,ATP1B1,ATP2B4,ATP6AP2,CALCA,CELF2,CHRM3,CNR1,CTGF,EPAS1,FOXC1,GATA4,GCH1,HBEGF,HTR2B,IER3,ITGA1,NAV2,NOS1,NPPA,NPPB,NPR2,PKP2,PLN,PPARG,PRCP,PTPRM,RASL10B,RGS2,SCN3B,SCPEP1,SEMA3A,SERPING1,SLIT2
BP	GO:0060560: Developmental growth involved in morphogenesis	167	19	7.21	0.00011	ABL1,CADM1,DCLK1,DCX,FN1,GAL,MAPT,NLGN3,RARB,RDH10,RND2,SEMA3A,SEMA4F,SLC9A6,SLIT2,SOX9,SPRY1,VANGL2,WNT3
BP	GO:0048812: Neuron projection morphogenesis	652	49	28.13	0.00011	ABL1,APH1A,BHLHB9,BMPR1B,CDH11,CHRNA3,CLASP2,CNP,COL3A1,CTNNA2,DCLK1,DCX,DPYSL3,FARP1,FN1,GFRA1,ITGA1,KALRN,KCNQ2,MAP6,MAPT,MATN2,NBL1,NCAN,NFASC,NLGN3,NRXN1,NTNG2,NTRK2,NUMB,PLXNB1,PRNP,PSEN1,PTPRM,RBFOX2,RELN,RET,RND2,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SMAD1,SPTAN1,TRIO,VAV3,WNT3
BP	GO:0007169: Transmembrane receptor protein tyrosine kinase signaling pathway	796	57	34.35	0.00012	ABL1,AKT2,ALK,APH1A,ARHGEF3,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATXN1,BCL2L11,BTK,CCBE1,CCL2,CDKN1A,CDKN1B,CHRNA3,CRIM1,CTGF,CTNND1,CYFIP2,DUSP6,ELMO2,FOXC1,FOXO3,GFRA1,HBEGF,IGF2,IGFBP6,ITGA1,ITPR2,KALRN,NDRG4,NTRK2,PDGFC,PDGFD,PLAT,PSEN1,PTGIR,PTPRR,RET,RHBDF1,RIT1,RIT2,SDCBP,SIPA1L1,SLC9A6,SOCS3,SOX9,SPRY1,SQSTM1,STAT3,TRIO,TXK,VAV3
BP	GO:0022603: Regulation of anatomical structure morphogenesis	796	57	34.35	0.00012	ABL1,ADM,ANKRD6,ANXA3,BASP1,BCOR,BHLHB9,CAMK1,CCBE1,CCL2,CDC42EP3,CHRNA3,COCH,CTSH,CYP1B1,DUSP6,EGLN1,ELL3,ENPP2,FN1,FOXC1,GAL,GATA4,GDF15,HES1,HEXB,HEY1,HIF1AN,ITGA7,LIF,MAPK9,MAPT,NLGN3,NPHP3,NPPB,NTRK2,NUMB,PLXNB1,PSEN1,PTGIS,PTPRM,RELN,RET,RND2,RUNX1,SEMA3A,SEMA4F,SERPINE1,SIPA1L1,SLIT2,SMAD1,SOX9,SPARC,SPRY1,TRIOBP,VANGL2,WNT3
BP	GO:1902531: Regulation of intracellular signal transduction	1633	101	70.46	0.00012	ABCA1,ABL1,ALK,ANKRD1,ANKRD6,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,ATP2B4,ATP6AP1,ATP6AP2,BCL2A1,BCL2L11,C18orf32,CD44,CDH2,CLU,COL3A1,CTGF,CYP1B1,CYR61,DDX5,DNAJC27,DOCK9,DUSP16,DUSP6,ELL3,ELMOD1,FAM13A,FAM13B,FARP1,GBA,GDF10,GDF15,GDF6,HBEGF,HES1,HEXIM1,HTR2B,IGF2,IL20RA,INHBA,ITGA1,KALRN,LIF,LMCD1,MAP4K4,MAPK9,MID1,NDRG4,NFAT5,NLGN1,NOTCH2,NTRK2,OPTN,PLK2,PLXNB1,PRNP,PSD2,PSEN1,PTGIR,PTPRR,RAB3IP,RABIF,RELN,RFFL,RGL2,RGS13,RGS16,RGS2,RGS7,RRAGB,RRAGC,RRAGD,SDCBP,SESN1,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SLIT2,SOCS3,SOX9,SPRY1,SQSTM1,TAOK3,TGM2,TIMP2,TMED4,TNFRSF19,TRAF3IP2,TRIB2,TRIO,VANGL2,VAV3
BP	GO:0044765: Single-organism transport	3640	198	157.06	0.00013	ABCA1,ABCB1,ABCB4,ABL1,ADM,AHNAK,AKT2,ALDH5A1,ANKRD1,ANO3,ANXA2,ANXA3,APOLD1,AQP11,ATP10D,ATP1B1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,BCL2L11,BRPF3,BTK,BZRAP1,CACNA2D2,CACNG2,CADM1,CALCA,CAMK1,CCL2,CCND1,CDK5R2,CDKL2,CDKN1A,CDKN1B,CHMP2B,CHRFAM7A,CHRM3,CHRNA3,CHRNB1,CLU,CNGA1,CNP,CNR1,COLEC12,COX11,COX17,CRABP2,CREBL2,CTGF,CYB561,CYB5R1,CYFIP2,DCLK1,DNAJC27,DUSP16,ELMO2,ELMOD1,ENSA,EXOC6B,EXOC7,FABP3,FGF14,FN1,GABRP,GAL,GPRASP1,HES1,HGSNAT,HLA-E,HTR2B,IER3,IFNAR1,IGF2,INHBA,ITPR2,KCNB1,KCNMA1,KCNQ2,KIAA1279,KRT18,LIF,LMAN2L,MAOB,MAPK9,MAPT,MFSD1,MGEA5,NBEA,NCOA1,NIPAL2,NLGN1,NLGN3,NOS1,NOTCH2,NPC2,NPEPPS,NPPA,NPPB,NRXN1,NSF,NTRK2,OPTN,ORAI3,OS9,OSBPL10,OSCP1,PACSIN3,PCLO,PDIA3,PEAR1,PFKFB2,PKP2,PLAT,PLCD4,PLN,PPARG,PRNP,PROS1,PRSS12,PSEN1,PTCH1,PTX3,RAB26,RAB27A,RAB3B,RAB3IP,RAMP1,RARB,RASL10B,RBPMS,RELN,RFTN1,RHBDF1,RHCE,RIMS2,RUNX1,SCG2,SCG5,SCN2A,SCN3A,SCN3B,SDC4,SDCBP,SERPINE1,SERPING1,SFRP4,SLC12A6,SLC1

						8A1,SLC22A17,SLC26A11,SLC26A2,SLC2A10,SLC31A2,SLC35A2,SLC35D2,SLC35D3,SLC36A1,SLC40A1,SLC44A5,SLC4A8,SLC6A2,SLC8A3,SLC9A6,SLCO3A1,SNAP25,SNCAIP,SOAT1,SPARC,SQSTM1,STARD4,STAT3,STOM,SYN2,SYP,SYT11,SYT4,SYTL4,TAP1,TEX261,TFRC,TGM2,TIMP1,TMEM38A,TRAF3IP2,TTC30A,TTC30B,UNC80,VAV3,VGF,VPS13D,VPS53,WDFY3
BP	GO:0000904: Cell morphogenesis involved in differentiation	836	59	36.07	0.00013	ABL1,APH1A,BASP1,BHLHB9,BMPR1B,C1GALT1C1,CDH11,CHRNA3,CLASP2,CNP,COL3A1,CTNNA2,DCLK1,DCX,DPYSL3,ELL3,FAM101B,FARP1,FN1,GFRA1,HES1,HEY1,ITGA1,KALRN,KCNQ2,LIF,MAP6,MAPK9,MAPT,MATN2,NCAN,NFASC,NLGN3,NOTCH4,NRXN1,NTNG2,NTRK2,NUMB,PLXNB1,PRNP,PSEN1,PTPRM,RBFOX2,RELN,RET,RND2,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SMAD1,SOX9,SPTAN1,TRIO,TRIOBP,VAV3,WNT3
BP	GO:0050896: Response to stimulus	7912	389	341.39	0.00014	AAK1,ABCA1,ABCB1,ABCB4,ABL1,ABTB2,ACTA2,ADM,AHRR,AKT2,AKT3,ALK,AMOTL2,ANKRD1,ANKRD6,ANXA2,ANXA3,APH1A,APLP1,APOLD1,ARF3,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARPP21,ARRDC3,ASAP1,ASAP2,ASS1,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,ATXN1,BCL2A1,BCL2L11,BCO2,BHLHE40,BMPR1B,BRPF3,BTBD11,BTG2,BTK,C18orf32,C1GALT1C1,C1RL,C7,CACNG2,CADM1,CALB1,CALCA,CALCOCO2,CAMK1,CCBE1,CCL2,CCND1,CD44,CDC42EP3,CDH2,CDKL2,CDKN1A,CDKN1B,CHRM3,CHRNA3,CHRNB1,CIRBP,CLASP2,CLU,CMTM6,CNGA1,CNKSR2,CNP,CNR1,COCH,COL11A1,COL3A1,COLEC12,CRABP2,CREBL2,CREM,CRIM1,CSPG5,CSRP1,CTGF,CTNNA2,CTNND1,CTSH,CYFIP2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYP4V2,CYR61,DCBLD2,DCLK1,DCLK2,DCN,DCX,DDX5,DHRS3,DKK2,DKK3,DNAJB11,DNAJC27,DNAJC3,DOCK9,DPYSL3,DTNA,DTX3L,DUSP16,DUSP6,ECEL1,EFEMP2,EGLN1,EIF4E3,ELL3,ELMO2,ELMOD1,ENPP2,ENSA,EPAS1,EPM2AIP1,FABP3,FAM111A,FAM129A,FAM13A,FAM13B,FARP1,FBXO6,FGF14,FLNB,FLRT1,FMN2,FN1,FOS,FOXC1,FOXO3,FRZB,FUCA2,GABARAPL1,GABRP,GAL,GATA4,GBA,GCH1,GDF10,GDF15,GDF6,GFRA1,GNG2,GNG7,GNG8,GPR19,GPR22,GPRASP1,GPX3,GRIP1,GRK5,GUCA1A,HBEGF,HES1,HEXIM1,HEY1,HIF1AN,HIST1H2BK,HLA-C,HLA-E,HOXD3,HPCAL1,HPCAL4,HTR2B,HUNK,ICAM2,IER3,IFNAR1,IGF2,IGFBP6,IGFBP7,IL10RB,IL17RD,IL20RA,INADL,INHBA,IRF6,IRF9,ITGA1,ITGA7,ITGB5,ITPR2,KALRN,KCNMA1,KCNQ2,KCTD11,KRT18,LBH,LIF,LMCD1,LPXN,LUM,MAOB,MAP4K4,MAPK9,MAPRE2,MATN2,MAX,MCC,MED13,MEST,MGEA5,MID1,MMP28,MSRB3,NBL1,NCAN,NCOA1,NCOA3,NDRG4,NFASC,NFAT5,NFKBIZ,NLGN1,NLGN3,NMI,NOS1,NOTCH2,NOTCH4,NPC2,NPEPPS,NPHP3,NPPA,NPPB,NPR2,NRXN1,NTRK2,NUMB,OAS1,OPTN,OS9,PAF1,PARP9,PCLO,PDGFC,PDGFD,PDIA3,PEX11B,PFKFB2,PIM1,PLAT,PLCD4,PLK2,PLN,PLXNB1,POLQ,PPARG,PRCP,PRNP,PROS1,PSD2,PSEN1,PSMB8,PTCH1,PTGER2,PTGIR,PTGIS,PTPRM,PTPRR,PTX3,PXDNL,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAET1L,RAMP1,RARB,RASEF,RASL10B,RBFOX2,RBP1,RBPMS,RDH10,RELN,RET,REV3L,RFFL,RFTN1,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RIMS2,RIT1,RIT2,RLN1,RND2,RNF175,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SCG2,SCG5,SCN2A,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SERPING1,SESN1,SFRP4,SGIP1,SH2B3,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SKAP2,SLC12A6,SLC18A1,SLC22A17,SLC26A2,SLC40A1,SLC6A2,SLC8A3,SLC9A6,SLIT2,SMAD1,SMOC1,SOCS3,SORCS1,SOX9,SPARC,SPEN,SPRY1,SPTAN1,SQSTM1,STAT3,SULT1C4,SYP,TAOK3,TAP1,TEX2,TFRC,TGM2,TIMP1,TIMP2,TIMP3,TMED4,TMX4,TNFRSF19,TOM1L1,TOM1L2,TPP1,TPST1,TRAF3IP2,TRIB2,TRIO,TSPAN8,TULP3,TULP4,TWSG1,TXK,VANGL2,VAV3,VGF,WDFY3,WNT3,XYLT1,YAP1,ZCCHC12
BP	GO:1901136: Carbohydrate derivative catabolic process	172	19	7.42	0.00016	CD44,CSPG5,DCN,EGLN1,FBXO2,FBXO6,FUCA1,FUCA2,GBA,GNS,HEXB,HGSNAT,IDS,LUM,MGEA5,NCAN,SDC4,UPB1,VCAN
BP	GO:0006810: Transport	4303	228	185.67	0.00017	AAK1,ABCA1,ABCB1,ABCB4,ABL1,ADM,AHNAK,AKT2,ALDH5A1,ANKRD1,ANO3,ANXA2,ANXA3,APLP1,APOLD1,APPBP2,AQP11,ARF3,ARHGAP27,ARID1A,ATP10D,ATP1B1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,ATXN1,BCL2L11,BRPF3,BTK,BZRAP1,CACNA2D2,CACNG2,CADM1,CALCA,CAMK1,CCL2,CCND1,CDK5R2,CDKL2,CDKN1A,CDKN1B,CHMP2B,CHRFAM7A,CHRM3,CHRNA3,CHRNB1,CLU,CNGA1,CNP,CNR1,COL3A1,COLEC12,COX11,COX17,CRABP2,CREBL2,CSPG5,CTGF,CTSA,CYB561,CYB5R1,CYFIP2,DCLK1,DNAJC27,DUSP16,ELMO2,ELMOD1,ENPP2,ENSA,EXOC6B,EXOC7,FABP3,FGF14,FMN2,FN1,FNBP1,GABRP,GAL,GPRASP1,HES1,HGSNAT,HLA-E,HTR2B,IER3,IFNAR1,IGF2,INHBA,ITPR2,JAKMIP1,KALRN,KCNB1,KCNMA1,KCNQ2,KIAA1279,KRT18,LIF,LMAN2L,LOXL4,LRP10,MAOB,MAP6,MAPK9,MAPT,MFSD1,MGEA5,NBEA,NCOA1,NIPAL2,NLGN1,NLGN3,NOS1,NOTCH2,NPC2,NPEPPS,NPPA,NPPB,NRXN1,NSF,NTRK2,OPTN,ORAI3,OS9,OSBPL10,OSCP1,PACSIN3,PCLO,PDIA3,PEAR1,PFKFB2,PKP2,PLAT,PLCD4,PLN,PPARG,PRNP,PROS1,PRSS12,PSEN1,PTCH1,PTX3,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RARB,RASEF,RASL10B,RBP1,RBPMS,RELN,RFFL,RFTN1,RHBDF1,RHCE,RIMS2,RUNX1,SCG2,SCG5,SCN2A,SCN3A,SCN3B,SDC4,SDCBP,SERPINE1,SERPING1,SFRP4,SGIP1,SH3BP4,SLC12A6,SLC18A1,SLC22A17,SLC26A11,SLC26A2,SLC2A10,SLC31A2,SLC35A2,SLC35D2,SLC35D3,SLC36A1,SLC40A1,SLC44A5,SLC4A8,SLC6A2,SLC8A3,SLC9A6,SLCO3A1,SNAP25,SNCAIP,SNX24,SOAT1,SPARC,SQSTM1,ST

						ARD4,STAT3,STAU2,STOM,SYN2,SYNGR3,SYP,SYT11,SYT4,SYTL4,TAP1,TEX261,TFRC,TGM2,TIMP1,TMED4,TMEM38A,TOM1L1,TOM1L2,TRAF3IP2,TTC30A,TTC30B,UNC80,VAV3,VGF,VPS13D,VPS53,WDFY3
BP	GO:1901654: Response to ketone	118	15	5.09	0.00017	ASS1,CCL2,CCND1,CDKN1A,FOS,GBA,GNG2,IGFBP7,MAOB,NCOA1,PLAT,PLN,PPARG,PTGER2,SLIT2
BP	GO:0000902: Cell morphogenesis	1181	77	50.96	0.00017	ABL1,APH1A,ASAP1,ATP6V0D1,BASP1,BHLHB9,BMPR1B,C1GALT1C1,CADM1,CCL2,CDC42EP3,CDH11,CHRNA3,CLASP2,CLU,CNP,COCH,COL3A1,CTNNA2,DCLK1,DCX,DPYSL3,ELL3,FAM101B,FARP1,FN1,GFRA1,HES1,HEXB,HEY1,ITGA1,ITGA7,KALRN,KCNQ2,LIF,MAP6,MAPK9,MAPT,MATN2,NBL1,NCAN,NFASC,NLGN3,NOTCH4,NPHP3,NRXN1,NTNG2,NTRK2,NUMB,PLXNB1,PRNP,PSEN1,PTPRM,RAB3IP,RBFOX2,RELN,RET,RND2,RSPH9,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SMAD1,SOX9,SPARC,SPTAN1,TRIO,TRIOBP,TTC30A,TTC30B,VANGL2,VAV3,WNT3,YAP1
BP	GO:0051716: Cellular response to stimulus	6572	330	283.57	0.00017	AAK1,ABCA1,ABL1,ABTB2,ADM,AHRR,AKT2,AKT3,ALK,AMOTL2,ANKRD1,ANKRD6,ANXA2,APH1A,APLP1,ARF3,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARPP21,ARRDC3,ASAP1,ASAP2,ASS1,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATPIF1,ATXN1,BCL2A1,BCL2L11,BCO2,BMPR1B,BTBD11,BTG2,BTK,C18orf32,CACNG2,CALB1,CALCA,CAMK1,CCBE1,CCL2,CCND1,CD44,CDC42EP3,CDH2,CDKL2,CDKN1A,CDKN1B,CHRM3,CHRNA3,CHRNB1,CLU,CNGA1,CNKSR2,CNR1,COL3A1,COLEC12,CRABP2,CREBL2,CREM,CRIM1,CSPG5,CTGF,CTNND1,CTSH,CYFIP2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYR61,DCBLD2,DCLK1,DCLK2,DCX,DDX5,DHRS3,DKK2,DKK3,DNAJB11,DNAJC27,DNAJC3,DOCK9,DPYSL3,DTNA,DTX3L,DUSP16,DUSP6,ECEL1,EFEMP2,EGLN1,EIF4E3,ELL3,ELMO2,ELMOD1,ENPP2,EPAS1,FAM129A,FAM13A,FAM13B,FARP1,FBXO6,FGF14,FLNB,FLRT1,FMN2,FOS,FOXC1,FOXO3,FRZB,GABARAPL1,GABRP,GAL,GATA4,GBA,GDF10,GDF15,GDF6,GFRA1,GNG2,GNG7,GNG8,GPR19,GPR22,GPRASP1,GRIP1,GRK5,GUCA1A,HBEGF,HES1,HEXIM1,HEY1,HIF1AN,HLA-C,HLA-E,HOXD3,HPCAL1,HPCAL4,HTR2B,HUNK,IER3,IFNAR1,IGF2,IGFBP6,IGFBP7,IL10RB,IL17RD,IL20RA,INADL,INHBA,IRF6,IRF9,ITGA1,ITGA7,ITGB5,ITPR2,KALRN,KCTD11,KRT18,LIF,LMCD1,LPXN,MAOB,MAP4K4,MAPK9,MAPRE2,MATN2,MAX,MCC,MED13,MID1,MMP28,NBL1,NCOA1,NCOA3,NDRG4,NFAT5,NLGN1,NLGN3,NMI,NOS1,NOTCH2,NOTCH4,NPEPPS,NPHP3,NPPA,NPPB,NPR2,NRXN1,NTRK2,NUMB,OAS1,OPTN,OS9,PAF1,PARP9,PCLO,PDGFC,PDGFD,PDIA3,PEX11B,PIM1,PLAT,PLCD4,PLK2,PLN,PLXNB1,POLQ,PPARG,PRCP,PRNP,PSD2,PSEN1,PSMB8,PTCH1,PTGER2,PTGIR,PTGIS,PTPRM,PTPRR,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RARB,RASEF,RASL10B,RBFOX2,RBP1,RBPMS,RDH10,RELN,RET,REV3L,RFFL,RFTN1,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RIMS2,RIT1,RIT2,RLN1,RND2,RNF175,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SCG2,SCG5,SCN2A,SDC4,SDCBP,SEMA3A,SERPINE1,SESN1,SFRP4,SH2B3,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SKAP2,SLC12A6,SLC22A17,SLC26A2,SLC40A1,SLC8A3,SLC9A6,SLIT2,SMAD1,SMOC1,SOCS3,SORCS1,SOX9,SPARC,SPEN,SPRY1,SQSTM1,STAT3,SULT1C4,SYP,TAOK3,TEX2,TFRC,TGM2,TIMP1,TIMP2,TIMP3,TMED4,TMX4,TNFRSF19,TOM1L1,TOM1L2,TPP1,TRAF3IP2,TRIB2,TRIO,TULP3,TULP4,TWSG1,TXK,VANGL2,VAV3,WDFY3,WNT3,XYLT1,YAP1,ZCCHC12
BP	GO:0061564: Axon development	593	45	25.59	0.00017	ABL1,APH1A,BMPR1B,CDH11,CLASP2,CNP,CNR1,COL3A1,CSPG5,CTNNA2,DCLK1,DCX,DPYSL3,FN1,GFRA1,ITGA1,KALRN,KCNQ2,MAPT,MATN2,NCAM2,NCAN,NFASC,NLGN3,NRXN1,NTNG2,NTRK2,NUMB,PLXNB1,PRNP,PSEN1,PTPRM,RELN,RET,RND2,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SPTAN1,TRIO,VAV3,WNT3
BP	GO:0007264: Small GTPase mediated signal transduction	808	57	34.86	0.00017	ABCA1,ARF3,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,CDC42EP3,CDKN1A,COL3A1,DNAJC27,DOCK9,ELMOD1,FAM13A,FAM13B,FARP1,HTR2B,KALRN,NOTCH2,NTRK2,PLK2,PLXNB1,PSD2,PTGIR,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RASEF,RASL10B,RELN,RGL2,RGS13,RGS16,RGS2,RGS7,RIT1,RIT2,RND2,RRAGC,SDCBP,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SLIT2,SPRY1,SQSTM1,TIMP2,TRIO,VANGL2,VAV3
BP	GO:0010976: Positive regulation of neuron projection development	159	18	6.86	0.00018	ANKRD1,BHLHB9,CAMK1,CNR1,DPYSL3,FN1,MAPT,NDRG4,NLGN1,NTRK2,PLXNB1,PSEN1,RELN,RET,RND2,SLIT2,SMAD1,WNT3
BP	GO:0048588: Developmental cell growth	119	15	5.13	0.00018	ABL1,DCLK1,DCX,FN1,GAL,GATA4,MAPT,NLGN3,RND2,SEMA3A,SEMA4F,SLC9A6,SLIT2,SOX9,WNT3
BP	GO:0031325: Positive regulation of cellular metabolic process	2547	145	109.9	0.00019	ABCA1,ABL1,ADM,AHRR,AKT2,ALK,ANKRD1,ANKRD6,ANXA2,ARID1A,ARMCX3,ARRDC3,ASS1,ATP2B4,ATP6AP1,ATP6V0D1,ATPIF1,ATXN1,BCL2L11,BPTF,BTG2,CALCA,CAMK1,CCL2,CCND1,CD44,CDH2,CDK5R2,CDKN1A,CDKN1B,CEBPD,CHRNA3,CHURC1,CIRBP,CLU,CREB5,CREBL2,CREM,CTGF,CTSH,CYFIP2,CYR61,DCN,DDX5,DNAJB11,DNAJC27,DNAJC3,EBF1,ELL3,EPAS1,EPM2AIP1,FABP3,FAM129A,FBXO4,FN1,FOS,FOXC1,FOXO3,GAL,GATA4,GBA,GDF10,GDF15,GDF6,GRIP1,GUCA1A,HES1,HEXB,HEY1,HOXD10,HOXD8,HOXD9,HTR2B,IGF2,INHBA,IRF6,ITGA1,JARID2,LBH,LIF,LUM,MAOB,MAPK9,MED13,MEIS1,MGEA5,MID1,MID1IP1,NANOS1,NCOA1,NCOA3,NCOA7,NDRG4,NFAT5,NOS1,NOTCH4,NSD1,NSF,NTRK2,PACSIN3,PAF1,PBX1,PDGFC,PFKFB2,PIM1,PLAGL1,PLK2,PPARG,PSEN1,PSMB8,PT

						GIR,PTX3,RAB27A,RAMP1,RARB,RBPMS,RELN,RET,RFWD2,RUNX1,SAMD4A,SDC4,SDCBP,SERPINE1,SFRP4,SH3BP4,SLC40A1,SMAD1,SMARCA2,SOAT1,SOX9,SPEN,SQSTM1,STAT3,TAF11,TAOK3,TIMP2,TOM1L1,TPP1,TRIB2,TXK,VANGL2,VAV3,WDFY3,YAP1
BP	GO:0010243: Response to organonitrogen compound	758	54	32.71	0.00020	ABL1,ADM,AKT2,APLP1,ASS1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,BTG2,CCL2,CCND1,CDKN1A,CDKN1B,CHRNA3,CHRNB1,CNR1,COL3A1,CREM,CTGF,EPM2AIP1,FABP3,FOS,GAL,GNG2,GNG7,GNG8,GPR22,IGF2,ITPR2,MAPK9,MAX,NPPA,PDGFC,PDGFD,PLAT,PLN,PPARG,RRAGB,RRAGC,RRAGD,SH3BP4,SLC8A3,SLIT2,SMAD1,SOCS3,SOX9,SPARC,STAT3,TIMP1,VGF
BP	GO:0070887: Cellular response to chemical stimulus	2365	136	102.05	0.00021	ABCA1,ABL1,ABTB2,AKT2,ANKRD1,APH1A,APLP1,ARHGEF3,ASS1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,BCL2L11,BTK,CALB1,CALCA,CCBE1,CCL2,CCND1,CD44,CDKN1A,CDKN1B,COL3A1,COLEC12,CTGF,CTSH,CYP1B1,CYP24A1,CYP26A1,CYP26B1,DNAJB11,DNAJC3,DPYSL3,DUSP6,EGLN1,EIF4E3,ELMO2,EPAS1,FLNB,FMN2,FOS,FOXC1,FOXO3,GATA4,GBA,GDF10,GDF15,GNG2,GNG7,GNG8,GPR22,HBEGF,HEY1,HIF1AN,HLA-C,HLA-E,IFNAR1,IGF2,IGFBP7,IL10RB,IL17RD,IL20RA,INHBA,IRF6,IRF9,ITGA1,ITGB5,ITPR2,KALRN,KRT18,MAOB,MAPK9,MAX,MID1,MMP28,NBL1,NCOA1,NCOA3,NOS1,NPEPPS,NPR2,NRXN1,NTRK2,OAS1,PAF1,PDGFC,PDGFD,PIM1,PLAT,PPARG,PRCP,PRNP,PSMB8,PTCH1,PTGER2,PTGIS,RARB,RET,RFFL,RIT1,RIT2,RNF175,RRAGB,RRAGC,RRAGD,RUNX1,SCG2,SERPINE1,SH3BP4,SLC26A2,SLC40A1,SLC8A3,SLC9A6,SLIT2,SMAD1,SOCS3,SOX9,SPARC,SPRY1,SQSTM1,STAT3,SULT1C4,SYP,TFRC,TIMP2,TIMP3,TNFRSF19,TPP1,TRIO,TXK,VAV3,WNT3
BP	GO:0001655: Urogenital system development	312	28	13.46	0.00021	ACTA2,APH1A,AQP11,ASS1,BASP1,BCL2L11,CALB1,CD44,CDKN1B,CTSH,DCN,FOXC1,HES1,LIF,NPHP3,PBX1,PTCH1,RARB,RDH10,RET,SDC4,SLIT2,SMAD1,SOX9,SPRY1,TSHZ3,VANGL2,YAP1
BP	GO:0010647: Positive regulation of cell communication	1388	87	59.89	0.00024	AAK1,ABL1,ALK,ANKRD1,ANKRD6,ARRDC3,ATP6AP1,ATP6AP2,ATPIF1,BCL2L11,BMPR1B,C18orf32,CCBE1,CCL2,CD44,CDH2,CLU,COL3A1,CTGF,CTSH,CYP1B1,CYR61,DDX5,DKK2,DNAJC27,GAL,GATA4,GDF10,GDF15,GDF6,HBEGF,HES1,HEXIM1,HTR2B,IGF2,IL20RA,INHBA,ITGA1,LIF,LMCD1,MAPK9,MGEA5,MID1,NDRG4,NLGN1,NLGN3,NOS1,NOTCH2,NRXN1,NTRK2,PDIA3,PFKFB2,PLK2,PLXNB1,PSEN1,PSMB8,PTGIR,PTGIS,RAB3B,RASL10B,RBPMS,RELN,RET,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SDCBP,SFRP4,SKAP2,SNAP25,SOX9,SQSTM1,STAT3,TAOK3,TGM2,TIMP2,TMED4,TNFRSF19,TRAF3IP2,TWSG1,TXK,VANGL2,VAV3,WDFY3,YAP1
BP	GO:0072593: Reactive oxygen species metabolic process	222	22	9.58	0.00025	ASS1,ATP2B4,ATPIF1,BCO2,CDKN1A,CLU,CTGF,CYP1B1,CYR61,FOXO3,GCH1,GPX3,IER3,MAOB,MAPK9,NOS1,PRCP,PTGIS,PTX3,PXDNL,RAB27A,SH3PXD2A
BP	GO:0050794: Regulation of cellular process	9916	472	427.86	0.00026	AAK1,ABCA1,ABI3BP,ABL1,ADM,AHNAK,AHRR,AIFM2,AKT2,AKT3,ALK,AMOTL2,ANKRD1,ANKRD33,ANKRD6,ANXA2,ANXA3,APH1A,APLP1,APOLD1,ARF3,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARMCX3,ARRDC3,ASAP1,ASAP2,ASS1,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,ATXN1,BACH2,BASP1,BCL2A1,BCL2L11,BCO2,BCOR,BHLHB9,BHLHE40,BHLHE41,BMPR1B,BPTF,BTBD11,BTG2,BTK,C18orf32,CACNA2D2,CACNG2,CADM1,CALB1,CALCA,CAMK1,CAMK2N1,CCBE1,CCDC40,CCL2,CCNA1,CCND1,CCNDBP1,CD44,CDC42EP3,CDH2,CDK19,CDK5R2,CDKL2,CDKN1A,CDKN1B,CDKN2C,CEBPD,CELF6,CHMP2B,CHRM3,CHRNA3,CHRNB1,CHURC1,CIRBP,CLASP2,CLPTM1,CLU,CNGA1,CNKSR2,CNR1,COCH,COL3A1,COLEC12,COX11,CRABP2,CREB5,CREBL2,CREM,CRIM1,CRTAP,CSPG5,CTGF,CTNNA2,CTNND1,CTSH,CYB5D2,CYB5R1,CYFIP2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYR61,DACH1,DCBLD2,DCLK1,DCLK2,DCN,DCX,DDX5,DHRS3,DKK2,DKK3,DLG2,DNAJB11,DNAJB6,DNAJC16,DNAJC27,DNAJC3,DOCK9,DPT,DPYSL3,DRAM1,DTNA,DUSP16,DUSP6,EBF1,ECEL1,EFEMP2,EGLN1,EIF4E3,ELFN1,ELL3,ELMO2,ELMOD1,ENPP2,ENSA,EPAS1,EPM2AIP1,FABP3,FAM111A,FAM129A,FAM13A,FAM13B,FARP1,FBXO2,FBXO4,FGF14,FLNB,FLRT1,FMN2,FN1,FOS,FOXC1,FOXO3,FRZB,GABRP,GAL,GATA4,GBA,GDF10,GDF15,GDF6,GFRA1,GNG2,GNG7,GNG8,GPNMB,GPR19,GPR22,GPRASP1,GRIP1,GRK5,GTF2IRD2,GUCA1A,HBEGF,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HIVEP2,HLA-C,HLA-E,HOXC6,HOXC8,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,HPCAL1,HPCAL4,HTR2B,HUNK,IER3,IFNAR1,IGF2,IGFBP6,IGFBP7,IL10RB,IL17RD,IL20RA,INADL,INHBA,IRF6,IRF9,ITGA1,ITGA7,ITGB5,ITPR2,JARID2,KALRN,KCNB1,KCNMA1,KCNQ2,KCTD11,KDM5C,KIAA0319,KRCC1,KRT18,LAMA4,LARP6,LBH,LIF,LMCD1,LPXN,LUM,MAB21L1,MAOB,MAP4K4,MAPK9,MAPRE2,MAPT,MAX,MCC,MED13,MEIS1,MGEA5,MID1,MID1IP1,MMP11,MMP28,MSN,NANOS1,NBL1,NCAN,NCOA1,NCOA3,NCOA7,NDRG4,NFAT5,NFKBIZ,NLGN1,NLGN3,NMI,NOS1,NOTCH2,NOTCH4,NPC2,NPEPPS,NPHP3,NPPA,NPPB,NPR2,NRXN1,NSD1,NSF,NTRK2,NUMB,OAS1,OPTN,OSCP1,PACSIN3,PAF1,PARP14,PBX1,PBX3,PCLO,PDGFC,PDGFD,PDIA3,PEX11B,PFKFB2,PHLDA1,PI15,PIM1,PKP2,PLAGL1,PLAT,PLCD4,PLEKHA2,PLK2,PLN,PLXNB1,POLQ,PPARG,PPP1R3B,PPP1R3D,PRCP,PRNP,PROS1,PRPSAP1,PSD2,PSEN1,PSMB8,PTCH1,PTGER2,PTGIR,PTGIS,PTPRM,PTPRR,PTX3,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RARB,RARRES1,RASEF,RASL10B,RBFOX2,RBP1,

						RBPMS,RDH10,RELN,RET,RFFL,RFTN1,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RIMS2,RIT1,RIT2,RLN1,RND2,RNF175,RPRM,RRAGB,RRAGC,RRAGD,RUNX1,RUNX1T1,RUSC1,SAMD4A,SAP30L,SCG2,SCG5,SCN2A,SCN3A,SCN3B,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SERPING1,SESN1,SFRP4,SGIP1,SH2B3,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SKAP2,SLC22A17,SLC31A2,SLC40A1,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SNCAIP,SOAT1,SOCS3,SORCS1,SOX9,SPARC,SPEN,SPRY1,SPTAN1,SQSTM1,SSBP2,STAT3,STMN4,STOM,SYP,SYT11,SYT4,SYTL4,TACC2,TAF11,TAF7L,TAOK3,TAP1,TCEAL2,TCEAL3,TCEAL6,TCEAL7,TES,TEX2,TGM2,TIMP1,TIMP2,TIMP3,TMED4,TMX4,TNFRSF19,TNS3,TOM1L1,TOM1L2,TOX2,TPP1,TRAF3IP2,TRIB2,TRIO,TRIOBP,TSHZ3,TSPAN31,TULP3,TULP4,TWSG1,TXK,TXNDC15,USP31,VANGL2,VAV3,WDFY3,WNT3,WTAP,YAP1,ZCCHC12,ZFHX2,ZFHX4,ZFP3,ZFP36L1,ZFYVE1,ZNF280B,ZNF425,ZNF521,ZNF562,ZNF599,ZNF641,ZNF789,ZSCAN18
BP	GO:0042493: Response to drug	398	33	17.17	0.00026	ABCA1,ABCB1,ABCB4,ANKRD1,ASS1,ATP8B1,CCL2,CCND1,CDKN1A,CDKN1B,DUSP6,FABP3,FOS,GAL,GATA4,HTR2B,IGF2,INHBA,MAOB,MAPK9,NCOA1,NOS1,PPARG,PTCH1,PTPRM,RET,SLC18A1,SLC6A2,SMAD1,STAT3,TFRC,TIMP2,VAV3
BP	GO:0032526: Response to retinoic acid	110	14	4.75	0.00027	ABCA1,CCL2,CTSH,CYP26A1,CYP26B1,GATA4,IGFBP7,MEST,NCOA1,PPARG,PTCH1,RET,SOX9,WNT3
BP	GO:0050790: Regulation of catalytic activity	2114	123	91.22	0.00028	ABL1,AHSA2,ALK,ANXA2,ANXA2P2,ANXA3,APH1A,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARRDC3,ASAP1,ASAP2,ATP1B1,ATP2B4,ATP6V0D1,ATPIF1,BCL2L11,C1GALT1C1,CALCA,CAMK1,CAMK2N1,CCL2,CCNA1,CCND1,CD44,CDK5R2,CDKN1A,CDKN1B,CDKN2C,CHRNA3,CLU,CNR1,COX11,CRIM1,CTGF,CTSA,CTSH,CYFIP2,CYR61,DLG2,DNAJB11,DNAJB6,DNAJC3,DOCK9,DUSP16,DUSP6,EGLN1,ELFN1,ELMOD1,ENSA,EPM2AIP1,FAM13A,FAM13B,FARP1,FN1,GBA,GCH1,GNG7,GUCA1A,HEXIM1,HTR2B,IGF2,ITGA1,ITPR2,KALRN,MAPK9,MID1IP1,NOS1,NTRK2,OAS1,PDGFC,PFKFB2,PI15,PIM1,PLN,PLXNB1,PPARG,PPP1R3B,PROS1,PRPSAP1,PSD2,PSEN1,PSMB8,PTGIR,PTX3,RAB3IP,RABIF,RELN,RET,RFFL,RGL2,RGS13,RGS16,RGS2,RGS7,SCG5,SDC4,SERPINE1,SERPING1,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SLIT2,SOCS3,SPRY1,TAOK3,TIMP1,TIMP2,TIMP3,TOM1L1,TPP1,TRIB2,TRIO,TXK,VANGL2,VAV3,ZFYVE1
BP	GO:0006887: Exocytosis	367	31	15.84	0.00029	ANXA3,ATP6AP1,BRPF3,BTK,CDK5R2,CLU,EXOC6B,EXOC7,FN1,IGF2,NLGN1,NSF,PCLO,PLCD4,PROS1,PRSS12,PSEN1,RAB26,RAB27A,RAB3B,RIMS2,SDC4,SDCBP,SERPINE1,SERPING1,SNAP25,SPARC,SYT11,SYT4,SYTL4,TIMP1
BP	GO:1902578: Single-organism localization	3826	204	165.09	0.00032	ABCA1,ABCB1,ABCB4,ABL1,ADM,AHNAK,AKT2,ALDH5A1,ANKRD1,ANO3,ANXA2,ANXA3,APOLD1,AQP11,ATP10D,ATP1B1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,BCL2L11,BRPF3,BTK,BZRAP1,CACNA2D2,CACNG2,CADM1,CALCA,CAMK1,CCL2,CCND1,CDK5R2,CDKL2,CDKN1A,CDKN1B,CHMP2B,CHRFAM7A,CHRM3,CHRNA3,CHRNB1,CLASP2,CLU,CNGA1,CNP,CNR1,COLEC12,COX11,COX17,CRABP2,CREBL2,CTGF,CYB561,CYB5R1,CYFIP2,DCLK1,DLG2,DNAJC27,DUSP16,ELMO2,ELMOD1,ENSA,EXOC6B,EXOC7,FABP3,FGF14,FLNB,FMN2,FN1,GABRP,GAL,GPRASP1,HES1,HGSNAT,HLA-E,HTR2B,IER3,IFNAR1,IGF2,INHBA,ITPR2,KCNB1,KCNMA1,KCNQ2,KIAA1279,KRT18,LIF,LMAN2L,MAOB,MAPK9,MAPT,MFSD1,MGEA5,NBEA,NCOA1,NIPAL2,NLGN1,NLGN3,NOS1,NOTCH2,NPC2,NPEPPS,NPPA,NPPB,NRXN1,NSF,NTRK2,NUMB,OPTN,ORAI3,OS9,OSBPL10,OSCP1,PACSIN3,PCLO,PDIA3,PEAR1,PFKFB2,PKP2,PLAT,PLCD4,PLN,PPARG,PRNP,PROS1,PRSS12,PSEN1,PTCH1,PTX3,RAB26,RAB27A,RAB3B,RAB3IP,RAMP1,RARB,RASL10B,RBPMS,RELN,RFTN1,RHBDF1,RHCE,RIMS2,RUNX1,SCG2,SCG5,SCN2A,SCN3A,SCN3B,SDC4,SDCBP,SERPINE1,SERPING1,SFRP4,SLC12A6,SLC18A1,SLC22A17,SLC26A11,SLC26A2,SLC2A10,SLC31A2,SLC35A2,SLC35D2,SLC35D3,SLC36A1,SLC40A1,SLC44A5,SLC4A8,SLC6A2,SLC8A3,SLC9A6,SLCO3A1,SNAP25,SNCAIP,SOAT1,SPARC,SPRY1,SQSTM1,STARD4,STAT3,STOM,SYN2,SYP,SYT11,SYT4,SYTL4,TAP1,TEX261,TFRC,TGM2,TIMP1,TMEM38A,TRAF3IP2,TTC30A,TTC30B,UNC80,VAV3,VGF,VPS13D,VPS53,WDFY3
BP	GO:0023056: Positive regulation of signaling	1380	86	59.55	0.00032	AAK1,ABL1,ALK,ANKRD1,ANKRD6,ARRDC3,ATP6AP1,ATP6AP2,ATPIF1,BCL2L11,BMPR1B,C18orf32,CCBE1,CCL2,CD44,CDH2,CLU,COL3A1,CTGF,CTSH,CYP1B1,CYR61,DDX5,DKK2,DNAJC27,GAL,GATA4,GDF10,GDF15,GDF6,HBEGF,HES1,HEXIM1,HTR2B,IGF2,IL20RA,INHBA,ITGA1,LIF,LMCD1,MAPK9,MGEA5,MID1,NDRG4,NLGN1,NLGN3,NOS1,NOTCH2,NRXN1,NSF,NTRK2,PDIA3,PFKFB2,PLK2,PLXNB1,PSEN1,PSMB8,PTGIR,PTGIS,RAB3B,RASL10B,RBPMS,RELN,RET,RRAGB,RRAGC,RRAGD,RUNX1,RUSC1,SDCBP,SFRP4,SKAP2,SNAP25,SOX9,STAT3,TAOK3,TGM2,TIMP2,TMED4,TNFRSF19,TRAF3IP2,TWSG1,TXK,VANGL2,VAV3,YAP1
BP	GO:0048598: Embryonic morphogenesis	574	43	24.77	0.00032	ADM,ARID1A,BCL2L11,CCDC40,COL11A1,CRABP2,CYP26B1,CYR61,DUSP6,FN1,FOXC1,FRZB,GATA4,HES1,HOXD10,HOXD3,HOXD9,HTR2B,INHBA,ITGA7,ITGB5,NCOA1,NCOA3,NDRG4,NOTCH2,NPHP3,NSD1,PAF1,PBX1,PSEN1,PTCH1,RARB,RDH10,RET,SMAD1,SOCS3,SOX9,TULP3,TWSG1,VANGL2,WNT3,YAP1,ZFP36L1
BP	GO:0043068: Positive regulation of programmed cell death	557	42	24.03	0.00032	ABL1,ADM,AIFM2,ANKRD1,APH1A,ARHGEF3,ATPIF1,BCL2L11,BMPR1B,CDKN1A,CDKN1B,CLU,CNR1,CTGF,CTSH,CYP1B1,CYR61,DUSP6,FOXO3,FRZB,GAL,IL20RA,INHBA,ITGA1,KALRN,KCNMA1,MAPK9,NCOA1,NOTCH2,PDIA3,PHLDA1,PPARG,PSEN1,PTGIS,RARB,RET,SFRP4,SLIT2,SQSTM1,TGM2,TRIO,VAV3

BP	GO:0009952: Anterior/posterior pattern specification	211	21	9.1	0.00032	ATP6AP2,BASP1,BPTF,BTG2,CYP26A1,FOXC1,GATA4,HES1,HEY1,HOXC6,HOXC8,HOXD10,HOXD3,HOXD8,HOXD9,PBX1,PBX3,PSEN1,TULP3,VANGL2,WNT3
BP	GO:0019220: Regulation of phosphate metabolic process	1460	90	63	0.00033	ABCA1,ABL1,ADM,AKT2,ALK,ANKRD6,ANXA2,APLP1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATPIF1,ATXN1,CALCA,CAMK1,CAMK2N1,CCL2,CCNA1,CCND1,CD44,CDH2,CDK5R2,CDKN1A,CDKN1B,CDKN2C,CHRNA3,CLU,COX11,CREBL2,CTGF,CYR61,DLG2,DNAJB11,DNAJC27,DNAJC3,DUSP16,DUSP6,EGLN1,ELFN1,FABP3,FAM129A,FARP1,GBA,GDF10,GDF15,GDF6,GNG7,GUCA1A,HES1,HEXIM1,HTR2B,IGF2,INHBA,ITGA1,LIF,MAP4K4,MAPK9,MID1,NDRG4,NOS1,NTRK2,PDGFC,PDGFD,PFKFB2,PIM1,PRNP,PRPSAP1,PSEN1,PTGIR,PTPRR,RAMP1,RBPMS,RELN,RGS2,SDC4,SDCBP,SLIT2,SOCS3,SOX9,SPRY1,SQSTM1,TAOK3,TIMP2,TOM1L1,TPP1,TRIB2,VANGL2,VAV3,ZFYVE1
BP	GO:0009790: Embryo development	978	65	42.2	0.00033	ADM,ARID1A,ATP6AP2,BASP1,BCL2L11,BPTF,CCDC40,COL11A1,CRABP2,CYP26B1,CYR61,DDX5,DUSP6,EGLN1,EPAS1,FN1,FOXC1,FRZB,GATA4,HES1,HEY1,HOXC6,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,HTR2B,INHBA,ITGA7,ITGB5,LAMA4,LIF,NCOA1,NCOA3,NDRG4,NOTCH2,NOTCH4,NPHP3,NSD1,PAF1,PBX1,PDGFC,PSEN1,PTCH1,PTPRR,RAI2,RARB,RDH10,RET,RUNX1,SEMA3A,SH2B3,SLIT2,SMAD1,SOCS3,SOX9,TANC2,TSHZ3,TULP3,TWSG1,VANGL2,WNT3,YAP1,ZFP36L1
BP	GO:0035295: Tube development	593	44	25.59	0.00033	ADM,AQP11,ARID1A,ASS1,ATP6AP2,ATXN1,BASP1,BCL2L11,CALB1,CCDC40,CD44,CDKN1A,COL3A1,CTGF,CTSH,EPAS1,FOXC1,GATA4,HES1,LIF,NCOA3,NDRG4,NOTCH4,NPHP3,NUMB,PBX1,PSEN1,PTCH1,RARB,RDH10,RET,SDC4,SLIT2,SMAD1,SOX9,SPARC,SPRY1,TGM2,TNS3,TSHZ3,TULP3,VANGL2,YAP1,ZFP36L1
BP	GO:0048568: Embryonic organ development	421	34	18.17	0.00035	ADM,ARID1A,BPTF,CCDC40,COL11A1,CYR61,EGLN1,EPAS1,FOXC1,FRZB,GATA4,HES1,HEY1,HOXD10,HOXD3,HOXD9,LIF,NCOA1,NCOA3,NDRG4,NPHP3,PBX1,PSEN1,PTCH1,RARB,RDH10,RUNX1,SH2B3,SOCS3,SOX9,TULP3,VANGL2,YAP1,ZFP36L1
BP	GO:0048858: Cell projection morphogenesis	831	57	35.86	0.00036	ABL1,APH1A,ASAP1,ATP6V0D1,BHLHB9,BMPR1B,CDH11,CHRNA3,CLASP2,CNP,COL3A1,CTNNA2,DCLK1,DCX,DPYSL3,FARP1,FN1,GFRA1,ITGA1,KALRN,KCNQ2,MAP6,MAPT,MATN2,NBL1,NCAN,NFASC,NLGN3,NPHP3,NRXN1,NTNG2,NTRK2,NUMB,PLXNB1,PRNP,PSEN1,PTPRM,RAB3IP,RBFOX2,RELN,RET,RND2,RSPH9,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SMAD1,SPTAN1,TRIO,TTC30A,TTC30B,VANGL2,VAV3,WNT3
BP	GO:0001525: Angiogenesis	405	33	17.48	0.00036	ADM,ANXA2,ANXA3,APOLD1,ATPIF1,CCBE1,CCL2,CTGF,CTSH,CYP1B1,CYR61,EGLN1,ENPP2,EPAS1,FN1,FOXC1,GATA4,HEY1,MEIS1,NOTCH4,NPPB,NRXN1,PRCP,PTGIS,PTPRM,RAMP1,RUNX1,SCG2,SERPINE1,SLC12A6,SLIT2,SPARC,VAV3
BP	GO:0016043: Cellular component organization	5550	282	239.48	0.00037	AAK1,ABCA1,ABI3BP,ABL1,ACOX1,ACP2,ADM,AGTPBP1,AHNAK,AIFM2,AKT2,AKT3,ALDH5A1,ANKRD1,ANO3,ANXA2,APH1A,APLP1,AQP11,ARHGAP26,ARID1A,ASAP1,ATP10D,ATP1B1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,BASP1,BCL2L11,BCOR,BHLHB9,BLCAP,BMPR1B,BPTF,BRPF3,BTG2,C1GALT1C1,CACNA2D2,CACNG2,CADM1,CAMK1,CCDC40,CCL2,CCNA1,CCND1,CD44,CDC42EP3,CDH11,CDH2,CDKL2,CDKN1A,CDKN1B,CDKN2C,CHMP2B,CHRNA3,CHRNB1,CIRBP,CLASP2,CLN5,CLU,CNP,CNR1,COCH,COL11A1,COL17A1,COL23A1,COL3A1,COLEC12,COX11,CPA4,CRB1,CRIM1,CRTAP,CSPG5,CTGF,CTNNA2,CTNND1,CYB5R1,CYP1B1,CYP26B1,CYR61,DACH1,DCBLD2,DCLK1,DCN,DCX,DLG2,DNAJB6,DPT,DPYSL3,DTX3L,EFEMP2,ELFN1,ELL3,ELMOD1,ENSA,EPAS1,EPB41L1,EXOC7,FAM101B,FAM13B,FARP1,FAT1,FBXO4,FLNB,FMN2,FN1,FOXC1,FRZB,GABARAPL1,GAL,GCH1,GDF15,GFRA1,GPX3,GRIP1,H1F0,HBEGF,HES1,HEXB,HEY1,HGSNAT,HIST1H2BD,HIST1H2BK,ICAM2,IER3,IGF2,IGFBP6,IGFBP7,INADL,INHBA,ITGA1,ITGA7,ITGB5,JARID2,KALRN,KCNB1,KCNQ2,KCTD11,KDM5C,KIAA0319,KRCC1,KRT18,LAMA4,LIF,LMCD1,LPXN,LUM,MAP6,MAPK9,MAPRE2,MAPT,MATN2,MAX,MGEA5,MID1,MID1IP1,MMP11,MTRF1L,NAP1L3,NAP1L5,NAV1,NBL1,NCAM2,NCAN,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NLGN1,NLGN3,NOS1,NOTCH4,NPEPPS,NPHP3,NPLOC4,NPPA,NPPB,NRXN1,NSD1,NSF,NTNG2,NTRK2,NUMB,OAS1,OPTN,OSCP1,PACSIN3,PAF1,PCDHB10,PCDHB14,PCDHB3,PCDHB4,PCLO,PDGFC,PDZRN3,PEX11B,PKP2,PLK2,PLN,PLXNB1,POLQ,PPARG,PRNP,PSEN1,PTCH1,PTPRM,PTX3,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RBFOX2,RELN,RET,RFTN1,RGS2,RIC3,RND2,RSPH9,SAP30L,SCN3B,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SFRP4,SGIP1,SH3BGRL3,SH3BP4,SIPA1L1,SKAP2,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SNCAIP,SOAT1,SORBS2,SOX9,SPAG1,SPARC,SPRY1,SPTAN1,SQSTM1,STAG3,STMN4,STOM,SYP,SYT11,SYT4,SYTL4,TACC2,TAF7L,TEP1,TGM2,THSD4,TIMP1,TIMP2,TOM1L1,TOM1L2,TOX2,TPP1,TRIO,TRIOBP,TTC30A,TTC30B,VANGL2,VAV3,VCAN,WNT3,YAP1
BP	GO:1901135: Carbohydrate derivative metabolic process	1134	73	48.93	0.00037	ABCA1,ADM,ALDH5A1,APLP1,ARSD,ATP6V1A,ATPIF1,B3GALNT1,B3GNT7,B3GNT9,B4GALNT1,B4GALT6,BMPR1B,C1GALT1C1,CALCA,CD44,COL11A1,CREM,CSPG5,CTSA,DCN,DOLK,EGLN1,FBXO2,FBXO6,FOXC1,FUCA1,FUCA2,GAL3ST1,GAL3ST3,GALNT14,GALNT2,GALNT6,GBA,GNG7,GNS,GUCA1A,HBEGF,HEXB,HGSNAT,HS3ST2,HTR2B,IDS,LPCAT3,LUM,MGEA5,NCAN,NOS1,NPPA,NPPB,NPR2,NSF,NTRK2,PDIA3,PFKFB2,PHLDA1,PIGZ,PIM1,PSEN1,PTGIR,PTX3,PYGL,RAMP1,SDC4,SLC26A2,SLC35D2,SOAT1,STS,SULT1C4,TIMP2,UPB1,VCAN,XYLT1

BP	GO:0003007: Heart morphogenesis	213	21	9.19	0.00037	ANKRD1,CCDC40,COL11A1,CYR61,DHRS3,EGLN1,FOXC1,GATA4,HES1,HEY1,HTR2B,NDRG4,NOTCH2,NPHP3,PKP2,PSEN1,PTCH1,RARB,SOX9,VANGL2,YAP1
BP	GO:1903510: Mucopolysaccharide metabolic process	127	15	5.48	0.00038	B3GNT7,B4GALT6,CD44,CSPG5,DCN,GNS,HEXB,IDS,LUM,NCAN,PIM1,SDC4,SLC35D2,VCAN,XYLT1
BP	GO:0010975: Regulation of neuron projection development	292	26	12.6	0.00040	ANKRD1,BHLHB9,CAMK1,CHRNA3,CNR1,DPYSL3,FN1,KIAA0319,MAPT,NDRG4,NLGN1,NLGN3,NTRK2,PLK2,PLXNB1,PSEN1,RELN,RET,RND2,SEMA3A,SEMA4F,SIPA1L1,SLIT2,SMAD1,SNAP25,WNT3
BP	GO:0051234: Establishment of localization	4407	230	190.16	0.00040	AAK1,ABCA1,ABCB1,ABCB4,ABL1,ADM,AHNAK,AKT2,ALDH5A1,ANKRD1,ANO3,ANXA2,ANXA3,APLP1,APOLD1,APPBP2,AQP11,ARF3,ARHGAP27,ARID1A,ATP10D,ATP1B1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,ATXN1,BCL2L11,BRPF3,BTK,BZRAP1,CACNA2D2,CACNG2,CADM1,CALCA,CAMK1,CCL2,CCND1,CDK5R2,CDKL2,CDKN1A,CDKN1B,CHMP2B,CHRFAM7A,CHRM3,CHRNA3,CHRNB1,CLU,CNGA1,CNP,CNR1,COL3A1,COLEC12,COX11,COX17,CRABP2,CREBL2,CSPG5,CTGF,CTSA,CYB561,CYB5R1,CYFIP2,DCLK1,DNAJC27,DUSP16,ELMO2,ELMOD1,ENPP2,ENSA,EXOC6B,EXOC7,FABP3,FGF14,FMN2,FN1,FNBP1,GABRP,GAL,GPRASP1,HES1,HGSNAT,HLA-E,HTR2B,IER3,IFNAR1,IGF2,INHBA,ITPR2,JAKMIP1,KALRN,KCNB1,KCNMA1,KCNQ2,KIAA1279,KRT18,LIF,LMAN2L,LOXL4,LRP10,MAOB,MAP6,MAPK9,MAPT,MCC,MFSD1,MGEA5,NBEA,NCOA1,NIPAL2,NLGN1,NLGN3,NOS1,NOTCH2,NPC2,NPEPPS,NPPA,NPPB,NRXN1,NSF,NTRK2,OPTN,ORAI3,OS9,OSBPL10,OSCP1,PACSIN3,PCLO,PDIA3,PEAR1,PFKFB2,PKP2,PLAT,PLCD4,PLN,PPARG,PRNP,PROS1,PRSS12,PSEN1,PTCH1,PTX3,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RARB,RASEF,RASL10B,RBP1,RBPMS,RELN,RFFL,RFTN1,RHBDF1,RHCE,RIMS2,RUNX1,SCG2,SCG5,SCN2A,SCN3A,SCN3B,SDC4,SDCBP,SERPINE1,SERPING1,SFRP4,SGIP1,SH3BP4,SLC12A6,SLC18A1,SLC22A17,SLC26A11,SLC26A2,SLC2A10,SLC31A2,SLC35A2,SLC35D2,SLC35D3,SLC36A1,SLC40A1,SLC44A5,SLC4A8,SLC6A2,SLC8A3,SLC9A6,SLCO3A1,SNAP25,SNCAIP,SNX24,SOAT1,SPARC,SPRY1,SQSTM1,STARD4,STAT3,STAU2,STOM,SYN2,SYNGR3,SYP,SYT11,SYT4,SYTL4,TAP1,TEX261,TFRC,TGM2,TIMP1,TMED4,TMEM38A,TOM1L1,TOM1L2,TRAF3IP2,TTC30A,TTC30B,UNC80,VAV3,VGF,VPS13D,VPS53,WDFY3
BP	GO:0009605: Response to external stimulus	2093	121	90.31	0.00040	ABCA1,ABL1,ACTA2,ADM,ANKRD1,ANXA2,ANXA3,APH1A,ASS1,BCL2L11,BCO2,BHLHE40,BMPR1B,BTG2,BTK,C7,CALCA,CCL2,CCND1,CDKN1A,CLASP2,CLU,CMTM6,CNGA1,CNP,CNR1,COCH,COL11A1,COL3A1,CTNNA2,CYP24A1,CYR61,DCLK1,DCN,DCX,DHRS3,DNAJC3,DPYSL3,ELMO2,ENPP2,ENSA,FAM111A,FOS,FUCA2,GABARAPL1,GATA4,GBA,GCH1,GFRA1,GUCA1A,HIST1H2BK,HLA-E,IER3,IFNAR1,IGF2,IL10RB,IRF9,ITGA1,KALRN,KCNQ2,LBH,MAOB,MAPK9,MATN2,MAX,MMP28,NBL1,NCAN,NCOA1,NFASC,NOTCH2,NPC2,NPPA,NRXN1,NTRK2,NUMB,OAS1,OPTN,PAF1,PIM1,PLAT,PLXNB1,PPARG,PRNP,PROS1,PSEN1,PTCH1,PTGER2,PTGIR,PTGIS,PTPRM,PTX3,RBP1,RDH10,RELN,RRAGB,RRAGC,RRAGD,SCG2,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SERPING1,SGIP1,SLIT2,SOCS3,SOX9,SPARC,SPTAN1,SQSTM1,TGM2,TRAF3IP2,TRIO,TSPAN8,TULP4,VAV3,VGF,WDFY3,WNT3
BP	GO:0051174: Regulation of phosphorus metabolic process	1473	90	63.56	0.00044	ABCA1,ABL1,ADM,AKT2,ALK,ANKRD6,ANXA2,APLP1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATPIF1,ATXN1,CALCA,CAMK1,CAMK2N1,CCL2,CCNA1,CCND1,CD44,CDH2,CDK5R2,CDKN1A,CDKN1B,CDKN2C,CHRNA3,CLU,COX11,CREBL2,CTGF,CYR61,DLG2,DNAJB11,DNAJC27,DNAJC3,DUSP16,DUSP6,EGLN1,ELFN1,FABP3,FAM129A,FARP1,GBA,GDF10,GDF15,GDF6,GNG7,GUCA1A,HES1,HEXIM1,HTR2B,IGF2,INHBA,ITGA1,LIF,MAP4K4,MAPK9,MID1,NDRG4,NOS1,NTRK2,PDGFC,PDGFD,PFKFB2,PIM1,PRNP,PRPSAP1,PSEN1,PTGIR,PTPRR,RAMP1,RBPMS,RELN,RGS2,SDC4,SDCBP,SLIT2,SOCS3,SOX9,SPRY1,SQSTM1,TAOK3,TIMP2,TOM1L1,TPP1,TRIB2,VANGL2,VAV3,ZFYVE1
BP	GO:0001890: Placenta development	143	16	6.17	0.00045	ADM,ARID1A,BPTF,CYR61,DCN,EGLN1,EPAS1,HES1,HEY1,LIF,NCOA1,NCOA3,NOTCH2,PPARG,SOCS3,ZFP36L1
BP	GO:0007265: Ras protein signal transduction	712	50	30.72	0.00048	ABCA1,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,CDC42EP3,CDKN1A,COL3A1,DNAJC27,DOCK9,ELMOD1,FAM13A,FAM13B,FARP1,HTR2B,KALRN,NOTCH2,NTRK2,PLK2,PLXNB1,PSD2,PTGIR,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RASEF,RGL2,RGS13,RGS16,RGS2,RGS7,RIT1,SDCBP,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SPRY1,SQSTM1,TIMP2,TRIO,VANGL2,VAV3
BP	GO:0044763: Single-organism cellular process	11917	552	514.2	0.00050	AAK1,ABCA1,ABCB1,ABCB4,ABI3BP,ABL1,ACOX1,ACTA2,ADM,AGPAT4,AGTPBP1,AHNAK,AHRR,AIFM2,AKT2,AKT3,ALDH5A1,ALK,AMACR,AMOTL2,ANKRD1,ANKRD33,ANKRD6,ANO3,ANXA2,ANXA3,APH1A,APLP1,APOLD1,AQP11,ARF3,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARRDC3,ARSD,ASAP1,ASAP2,ASS1,ATP10D,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,ATXN1,B3GALNT1,B3GNT7,B3GNT9,B4GALNT1,B4GALT6,BASP1,BCL2A1,BCL2L11,BCO2,BCOR,BHLHB9,BHLHE41,BLCAP,BMPR1B,BRPF3,BTBD11,BTG2,BTK,BZRAP1,C18orf32,C1GALT1C1,C7,C8orf4,CACNA2D2,CACNG2,CADM1,CALB1,CALCA,CAMK1,CCBE1,CCDC40,CCL2,CCNA1,CCND1,CCNDBP1,CD44,CDC42EP3,CDH11,CDH2,CDK19,CDK5R2,CDKL2,CDKN1A,CDKN1B,CDKN2C,CHMP2B,CHRFAM7A,CHRM3,CHRNA3,CHRNB1,CLASP2,CLDN11,CLN5,CLPTM1,CLU,CNGA1,CNKSR2,CNP,CNR1,CO

						CH,COL11A1,COL17A1,COL23A1,COL3A1,COLEC12,COX11,CPA4,CRABP2,CRB1,CREB5,CREBL2,CREM,CRIM1,CRTAP,CSPG5,CSRP1,CTGF,CTNNA2,CTNND1,CTSA,CTSH,CYB561,CYB5D2,CYFIP2,CYP1B1,CYP24A1,CYP26A1,CYP26B1,CYP4V2,CYR61,DACH1,DAPL1,DCBLD2,DCLK1,DCLK2,DCN,DCX,DDX5,DHRS3,DKK2,DKK3,DLG2,DNAJB11,DNAJB6,DNAJC16,DNAJC27,DNAJC3,DOCK9,DOLK,DPT,DPYSL3,DRAM1,DTNA,DTX3L,DUSP16,DUSP6,ECEL1,EFEMP2,EGLN1,EIF4E3,ELFN1,ELL3,ELMO2,ELMOD1,ENPP2,ENPP6,ENSA,EPAS1,EPB41L1,EPM2AIP1,ERI1,EXOC6B,EXOC7,FABP3,FAM101B,FAM13A,FAM13B,FAR2,FARP1,FAT1,FBXO4,FBXO6,FGF14,FLNB,FLRT1,FMN2,FN1,FOS,FOXC1,FOXO3,FRMD4A,FRZB,GABARAPL1,GABRP,GAL,GAL3ST1,GALNT14,GALNT2,GALNT6,GATA4,GBA,GCH1,GDF10,GDF15,GDF6,GFRA1,GNG2,GNG7,GNG8,GNS,GPNMB,GPR19,GPR22,GPRASP1,GPX3,GRIP1,GRK5,GUCA1A,H1F0,HBEGF,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HLA-C,HLA-E,HOXC8,HOXD1,HOXD10,HOXD3,HOXD9,HPCAL1,HPCAL4,HTR2B,HUNK,ICAM2,IDS,IER3,IFNAR1,IGF2,IGFBP6,IGFBP7,IL10RB,IL17RD,IL20RA,INADL,INHBA,IRF6,IRF9,ITGA1,ITGA7,ITGB5,ITPR2,JARID2,KALRN,KCNB1,KCNMA1,KCNQ2,KCTD11,KDM5C,KDSR,KIAA0319,KIAA1279,KRCC1,KRT18,LAMA4,LIF,LMCD1,LPCAT3,LPXN,LUM,MAOB,MAP4K4,MAP6,MAPK9,MAPRE2,MAPT,MATN2,MAX,MCC,MED13,MEIS1,MFSD1,MGEA5,MGP,MID1,MID1IP1,MMP11,MMP28,MSN,MTRF1L,NANOS1,NAV1,NBL1,NCAM2,NCAN,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NFAT5,NLGN1,NLGN3,NMI,NOS1,NOTCH2,NOTCH4,NPC2,NPHP3,NPPA,NPPB,NPR2,NPTX2,NRXN1,NSD1,NSF,NTNG2,NTRK2,NUMB,OAS1,OLFM3,OPTN,OS9,P4HA2,PACSIN3,PAF1,PAPPA,PARP9,PBX1,PBX3,PCDHB10,PCDHB14,PCDHB3,PCDHB4,PCLO,PDGFC,PDGFD,PDIA3,PDZRN3,PEAR1,PEX11B,PFKFB2,PHLDA1,PHYH,PIGZ,PIM1,PIPOX,PKP2,PLAGL1,PLAT,PLCD4,PLK2,PLN,PLXNB1,POLQ,PPAPDC1B,PPARG,PPP1R3B,PPP1R3D,PRCP,PRNP,PROS1,PRPSAP1,PRSS12,PSD2,PSEN1,PSMB8,PTCH1,PTGER2,PTGIR,PTGIS,PTPRH,PTPRM,PTPRR,PXDNL,PYGL,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RARB,RASEF,RASL10B,RBFOX2,RBP1,RBPMS,RDH10,RELN,RET,REV3L,RFFL,RFTN1,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RHCE,RIC3,RIMS2,RIT1,RIT2,RLN1,RND2,RNF175,ROM1,RPRM,RRAGB,RRAGC,RRAGD,RSPH9,RUNX1,RUSC1,SCD,SCD5,SCG2,SCG5,SCN2A,SCN3A,SCN3B,SCPEP1,SDC4,SDCBP,SEMA3A,SEMA4F,SEPHS2,SERPINE1,SERPING1,SESN1,SFRP4,SGCB,SGIP1,SH2B3,SH3BGRL3,SH3BP4,SH3PXD2A,SIPA1L1,SIPA1L2,SKAP2,SLC12A6,SLC18A1,SLC22A17,SLC26A11,SLC26A2,SLC2A10,SLC31A2,SLC35A2,SLC35D2,SLC36A1,SLC40A1,SLC44A5,SLC4A8,SLC6A2,SLC8A3,SLC9A6,SLCO3A1,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SNCAIP,SOAT1,SOCS3,SORBS2,SORCS1,SOX9,SPARC,SPEN,SPRY1,SPTAN1,SQSTM1,STAG3,STAT3,STMN4,STOM,STS,SULT1C4,SYN2,SYP,SYT11,SYT4,SYTL4,TACC2,TAF7L,TAOK3,TAP1,TEP1,TEX2,TFRC,TGM2,THSD4,TIMP1,TIMP2,TMED4,TMEM38A,TMX4,TNFRSF19,TNS3,TOM1L1,TOM1L2,TPP1,TRAF3IP2,TRIB2,TRIO,TRIOBP,TSHZ3,TTC30A,TTC30B,TULP3,TULP4,TWSG1,TXK,TXNDC15,UNC80,UPB1,VANGL2,VAV3,VCAN,VGF,VPS13D,WDFY3,WNT3,WTAP,XYLT1,YAP1,ZCCHC12,ZFP36L1,ZNF521
BP	GO:0032989: Cellular component morphogenesis	1264	79	54.54	0.00051	ABL1,ANKRD1,APH1A,ASAP1,ATP6V0D1,BASP1,BHLHB9,BMPR1B,C1GALT1C1,CADM1,CCL2,CDC42EP3,CDH11,CHRNA3,CLASP2,CLU,CNP,COCH,COL3A1,CTNNA2,DCLK1,DCX,DPYSL3,ELL3,FAM101B,FARP1,FN1,GFRA1,HES1,HEXB,HEY1,ITGA1,ITGA7,KALRN,KCNQ2,LIF,MAP6,MAPK9,MAPT,MATN2,NBL1,NCAN,NEBL,NFASC,NLGN3,NOTCH4,NPHP3,NRXN1,NTNG2,NTRK2,NUMB,PLXNB1,PRNP,PSEN1,PTPRM,RAB3IP,RBFOX2,RELN,RET,RND2,RSPH9,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SMAD1,SOX9,SPARC,SPTAN1,TRIO,TRIOBP,TTC30A,TTC30B,VANGL2,VAV3,WNT3,YAP1
BP	GO:0043065: Positive regulation of apoptotic process	552	41	23.82	0.00051	ABL1,ADM,AIFM2,ANKRD1,APH1A,ARHGEF3,ATPIF1,BCL2L11,BMPR1B,CDKN1B,CLU,CNR1,CTGF,CTSH,CYP1B1,CYR61,DUSP6,FOXO3,FRZB,GAL,IL20RA,INHBA,ITGA1,KALRN,KCNMA1,MAPK9,NCOA1,NOTCH2,PDIA3,PHLDA1,PPARG,PSEN1,PTGIS,RARB,RET,SFRP4,SLIT2,SQSTM1,TGM2,TRIO,VAV3
BP	GO:0007409: Axonogenesis	570	42	24.59	0.00052	ABL1,APH1A,BMPR1B,CDH11,CLASP2,CNP,COL3A1,CTNNA2,DCLK1,DCX,DPYSL3,FN1,GFRA1,ITGA1,KALRN,KCNQ2,MAPT,MATN2,NCAN,NFASC,NLGN3,NRXN1,NTNG2,NTRK2,NUMB,PLXNB1,PRNP,PSEN1,PTPRM,RELN,RET,RND2,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SPTAN1,TRIO,VAV3,WNT3
BP	GO:0003002: Regionalization	347	29	14.97	0.00054	ATP6AP2,BASP1,BMPR1B,BPTF,BTG2,CYP26A1,CYP26B1,DUSP6,FOXC1,GATA4,HES1,HEY1,HOXC6,HOXC8,HOXD10,HOXD3,HOXD8,HOXD9,NBL1,PBX1,PBX3,PSEN1,PTCH1,RELN,SEMA3A,SPRY1,TULP3,VANGL2,WNT3
BP	GO:1903530: Regulation of secretion by cell	557	41	24.03	0.00062	ABL1,ANKRD1,ATP6AP1,CACNA2D2,CADM1,CDK5R2,CHRM3,CHRNA3,CNR1,ENSA,GAL,HLA-E,HTR2B,IFNAR1,INHBA,ITPR2,KCNB1,LIF,MAOB,MGEA5,NLGN1,NRXN1,NSF,NTRK2,PCLO,PFKFB2,RAB26,RAB27A,RAB3B,RASL10B,RHBDF1,RIMS2,RUNX1,SCG5,SDC4,SDCBP,SNAP25,SNCAIP,SYT11,SYT4,SYTL4
BP	GO:0034341: Response to interferon-gamma	133	15	5.74	0.00062	ASS1,CALCOCO2,CCL2,CD44,GCH1,HLA-C,HLA-E,IRF6,IRF9,MID1,OAS1,PARP9,PPARG,SOCS3,TXK
BP	GO:0032990: Cell part morphogenesis	850	57	36.68	0.00062	ABL1,APH1A,ASAP1,ATP6V0D1,BHLHB9,BMPR1B,CDH11,CHRNA3,CLASP2,CNP,COL3A1,CTNNA2,DCLK1,DCX,DPYSL3,FARP1,FN1,GFRA1,ITGA1,KALRN,KCNQ2,MAP6,MAPT,MATN2,NBL1,NCAN,NFASC,NLGN3,NPHP3,NRXN1,NTNG2,NTRK2,NUMB,PLXNB1,PRNP,PSEN1,PTPRM,RAB3IP,RBFOX2,RELN,RET,RND2,RSPH9,SDCBP,SEMA3A,SEMA4F,

						SIPA1L1,SLC9A6,SLIT2,SMAD1,SPTAN1,TRIO,TTC30A,TTC30B,VANGL2,VAV3,WNT3
BP	GO:0015672: Monovalent inorganic cation transport	540	40	23.3	0.00063	ATP1B1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,BTK,CDKN1B,CHRNA3,CNGA1,CNR1,COX11,FGF14,GAL,KCNB1,KCNMA1,KCNQ2,MAOB,NOS1,NPPA,NSF,PKP2,PRNP,PSEN1,RAB3B,RHCE,SCN2A,SCN3A,SCN3B,SLC12A6,SLC2A10,SLC35A2,SLC36A1,SLC4A8,SLC8A3,SLC9A6,STOM,TMEM38A
BP	GO:1901698: Response to nitrogen compound	832	56	35.9	0.00063	ABL1,ADM,AKT2,APLP1,ASS1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,BTG2,CCL2,CCND1,CDKN1A,CDKN1B,CHRNA3,CHRNB1,CNR1,COL3A1,CREM,CTGF,EGLN1,EPM2AIP1,FABP3,FOS,GAL,GNG2,GNG7,GNG8,GPR22,IGF2,ITPR2,MAPK9,MAX,NPPA,PDGFC,PDGFD,PLAT,PLN,PPARG,RFTN1,RRAGB,RRAGC,RRAGD,SH3BP4,SLC8A3,SLIT2,SMAD1,SOCS3,SOX9,SPARC,STAT3,TIMP1,VGF
BP	GO:0048870: Cell motility	1176	74	50.74	0.00064	ABL1,AKT2,ANXA3,ATP1B1,CALCA,CCBE1,CCL2,CD44,CDH2,CDK5R2,COL3A1,CTGF,CTNNA2,CTSH,CYP1B1,CYR61,DACH1,DCLK1,DCX,DPYSL3,ELMO2,ENPP2,FAT1,FN1,FOXC1,HBEGF,HES1,HEXB,HTR2B,ITGA1,ITGA7,KIAA0319,LAMA4,MAPT,MATN2,MCC,MMP28,MSN,NANOS1,NAV1,NBL1,NDRG4,NTRK2,NUMB,PARP9,PKP2,PLAT,PLXNB1,PRCP,PROS1,PSEN1,PTPRM,PTPRR,RBFOX2,RELN,RET,RFFL,RHBDF1,SCG2,SDC4,SDCBP,SEMA3A,SERPINE1,SH3BGRL3,SLIT2,SORBS2,SOX9,SPARC,STAT3,TIMP1,TNS3,VANGL2,VAV3,VCAN
BP	GO:0051674: Localization of cell	1176	74	50.74	0.00064	ABL1,AKT2,ANXA3,ATP1B1,CALCA,CCBE1,CCL2,CD44,CDH2,CDK5R2,COL3A1,CTGF,CTNNA2,CTSH,CYP1B1,CYR61,DACH1,DCLK1,DCX,DPYSL3,ELMO2,ENPP2,FAT1,FN1,FOXC1,HBEGF,HES1,HEXB,HTR2B,ITGA1,ITGA7,KIAA0319,LAMA4,MAPT,MATN2,MCC,MMP28,MSN,NANOS1,NAV1,NBL1,NDRG4,NTRK2,NUMB,PARP9,PKP2,PLAT,PLXNB1,PRCP,PROS1,PSEN1,PTPRM,PTPRR,RBFOX2,RELN,RET,RFFL,RHBDF1,SCG2,SDC4,SDCBP,SEMA3A,SERPINE1,SH3BGRL3,SLIT2,SORBS2,SOX9,SPARC,STAT3,TIMP1,TNS3,VANGL2,VAV3,VCAN
BP	GO:0009968: Negative regulation of signal transduction	1005	65	43.36	0.00068	ABL1,ADM,ANKRD6,ATP2B4,ATXN1,BCL2A1,CALCA,CCND1,CD44,CDH2,CLU,CTNND1,CYP26A1,CYP26B1,DHRS3,DKK2,DKK3,DUSP16,DUSP6,ELL3,FOXO3,FRZB,GBA,GPRASP1,GRK5,HEY1,HIF1AN,HTR2B,IER3,ITGA1,KCTD11,LIF,LPXN,MCC,NBL1,NDRG4,NOS1,NPHP3,NUMB,OPTN,PPARG,PRNP,PSEN1,PSMB8,PTCH1,PTGIR,PTPRR,RFFL,RGS13,RGS16,RGS2,RGS7,SCG2,SERPINE1,SFRP4,SH3BP4,SLIT2,SOCS3,SOX9,SPRY1,TAOK3,TIMP2,TULP3,TWSG1,YAP1
BP	GO:0023061: Signal release	420	33	18.12	0.00068	ADM,ALDH5A1,BTK,BZRAP1,CACNA2D2,CHRM3,CHRNA3,CNR1,ENSA,GAL,INHBA,ITPR2,KCNB1,LIF,MGEA5,NLGN1,NRXN1,NTRK2,PCLO,PFKFB2,PSEN1,RAB3B,RASL10B,RIMS2,RUNX1,SCG5,SNAP25,SNCAIP,SYN2,SYT11,SYT4,SYTL4,VGF
BP	GO:0009719: Response to endogenous stimulus	1396	85	60.24	0.00071	ABCA1,ABL1,ADM,AKT2,ANKRD1,APLP1,ASS1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,BTG2,CALCA,CCL2,CCND1,CD44,CDKN1A,CDKN1B,CHRNA3,CHRNB1,CNR1,COL3A1,CREM,CTGF,CTSH,DUSP6,EPM2AIP1,FABP3,FOS,FOXO3,GAL,GATA4,GBA,GDF10,GDF15,GNG2,GNG7,GNG8,GPR22,HBEGF,HEY1,IGF2,IGFBP7,INHBA,ITGB5,ITPR2,MAOB,MAPK9,MAX,MGEA5,NCOA1,NCOA3,NPPA,NTRK2,PDGFC,PDGFD,PLAT,PLN,PPARG,PRCP,PTCH1,PTGER2,RARB,RRAGB,RRAGC,RRAGD,RUNX1,SERPINE1,SFRP4,SH3BP4,SLC8A3,SLIT2,SMAD1,SOCS3,SOX9,SPARC,SPRY1,STAT3,TIMP1,TIMP2,TIMP3,VGF
BP	GO:0010942: Positive regulation of cell death	579	42	24.98	0.00071	ABL1,ADM,AIFM2,ANKRD1,APH1A,ARHGEF3,ATPIF1,BCL2L11,BMPR1B,CDKN1A,CDKN1B,CLU,CNR1,CTGF,CTSH,CYP1B1,CYR61,DUSP6,FOXO3,FRZB,GAL,IL20RA,INHBA,ITGA1,KALRN,KCNMA1,MAPK9,NCOA1,NOTCH2,PDIA3,PHLDA1,PPARG,PSEN1,PTGIS,RARB,RET,SFRP4,SLIT2,SQSTM1,TGM2,TRIO,VAV3
BP	GO:0009100:Glycoprotein metabolic process	421	33	18.17	0.00071	B3GALNT1,B3GNT7,B3GNT9,B4GALNT1,B4GALT6,BMPR1B,C1GALT1C1,COL11A1,CSPG5,CTSA,DCN,DOLK,FBXO2,FBXO6,GAL3ST1,GAL3ST3,GALNT14,GALNT2,GALNT6,HBEGF,HEXB,IDS,MGEA5,NCAN,PDIA3,PHLDA1,PSEN1,PTX3,RAMP1,SDC4,SOAT1,VCAN,XYLT1
BP	GO:0006836: Neurotransmitter transport	194	19	8.37	0.00075	ALDH5A1,BZRAP1,CHRNA3,NLGN1,NOS1,NRXN1,NTRK2,PCLO,PSEN1,RAB3B,RIMS2,SLC18A1,SLC6A2,SNAP25,SNCAIP,SYN2,SYT11,SYT4,SYTL4
BP	GO:0043085: Positive regulation of catalytic activity	1379	84	59.5	0.00075	ABL1,AHSA2,ALK,APH1A,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARRDC3,ASAP1,ASAP2,ATP1B1,ATP2B4,ATP6V0D1,BCL2L11,C1GALT1C1,CALCA,CAMK1,CCL2,CCND1,CDK5R2,CDKN1A,CDKN1B,CHRNA3,CLU,CTGF,CTSA,CTSH,CYFIP2,CYR61,DNAJB11,DNAJB6,DNAJC3,DOCK9,ELMOD1,EPM2AIP1,FAM13A,FAM13B,FARP1,FN1,GCH1,GUCA1A,HTR2B,IGF2,ITGA1,ITPR2,KALRN,MAPK9,MID1IP1,NOS1,NTRK2,PDGFC,PFKFB2,PIM1,PLXNB1,PPARG,PSD2,PSEN1,PSMB8,PTGIR,RAB3IP,RABIF,RELN,RET,RGL2,RGS13,RGS16,RGS2,RGS7,SDC4,SH3BGRL3,SIPA1L1,SIPA1L2,TAOK3,TIMP2,TOM1L1,TPP1,TRIO,TXK,VANGL2,VAV3
BP	GO:0030030: Cell projection organization	1184	74	51.09	0.00078	ABL1,ADM,ANKRD1,APH1A,ASAP1,ATP6V0D1,ATP8B1,BHLHB9,BMPR1B,BTG2,CAMK1,CDC42EP3,CDH11,CHRNA3,CLASP2,CNP,CNR1,COL3A1,CSPG5,CTNNA2,DCLK1,DCX,DPYSL3,FARP1,FN1,GFRA1,GRIP1,ITGA1,KALRN,KCNQ2,KIAA0319,MAP6,MAPK9,MAPT,MATN2,NBL1,NCAM2,NCAN,NDRG4,NFASC,NLGN1,NLGN3,NPHP3,NRXN1,NTNG2,NTRK2,NUMB,PLK2,PLXNB1,PRNP,PSEN1,PTPRM,RAB3IP,RBFOX2,RELN,RET,RND2,RSPH9,SDCBP,SEMA3A,SEMA4F,SIPA1L1,SLC9A6,SLIT2,SMAD1,SNAP25,SPTAN1,STMN4,TRIO,TTC30A,TTC30B,VANGL2,VAV3,WNT3
BP	GO:0048589: Developmental growth	407	32	17.56	0.00081	ABL1,ADM,BASP1,BCL2L11,BMPR1B,CACNA2D2,CADM1,DCLK1,DCX,DUSP6,FN1,FOXC1,FOXO3,GAL,GATA4,MAPT,NCOA3,NLGN3,PTCH1,RARB,RDH10,RND2,SEMA3A,SE

						MA4F,SLC9A6,SLIT2,SOX9,SPRY1,STAT3,VANGL2,WNT3,YAP1
BP	GO:0007269: Neurotransmitter secretion	151	16	6.52	0.00082	ALDH5A1,BZRAP1,CHRNA3,NLGN1,NRXN1,NTRK2,PCLO,PSEN1,RAB3B,RIMS2,SNAP25,SNCAIP,SYN2,SYT11,SYT4,SYTL4
BP	GO:0051336: Regulation of hydrolase activity	1188	74	51.26	0.00085	ABL1,AHSA2,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,ATP1B1,ATP6V0D1,ATPIF1,BCL2L11,CCL2,CD44,CDKN1B,CRIM1,CTGF,CTSH,CYFIP2,CYR61,DLG2,DNAJB11,DNAJB6,DNAJC3,DOCK9,EGLN1,ELFN1,ELMOD1,FAM13A,FAM13B,FARP1,FN1,HTR2B,ITGA1,ITPR2,KALRN,MAPK9,NOS1,NTRK2,OAS1,PI15,PLN,PLXNB1,PPARG,PROS1,PSD2,PTGIR,PTX3,RAB3IP,RABIF,RET,RFFL,RGL2,RGS13,RGS16,RGS2,RGS7,SERPINE1,SERPING1,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,TIMP1,TIMP2,TIMP3,TPP1,TRIO,TXK,VAV3,ZFYVE1
BP	GO:0060541: Respiratory system development	212	20	9.15	0.00088	ASS1,ATXN1,BASP1,CCDC40,CTGF,CTSH,EPAS1,GATA4,HES1,LIF,NPHP3,NUMB,RDH10,SOX9,SPARC,SPRY1,TNS3,TSHZ3,TULP3,VANGL2
BP	GO:0030308: Negative regulation of cell growth	152	16	6.56	0.00089	CDKN1A,CDKN1B,CDKN2C,DCBLD2,FRZB,GAL,INHBA,NPPA,NPPB,PPARG,SEMA3A,SEMA4F,SH3BP4,SLIT2,SMARCA2,WNT3
BP	GO:0051056: Regulation of small GTPase mediated signal transduction	569	41	24.55	0.00093	ABCA1,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,COL3A1,DOCK9,ELMOD1,FAM13A,FAM13B,FARP1,HTR2B,KALRN,NOTCH2,NTRK2,PLXNB1,PSD2,PTGIR,RAB3IP,RABIF,RELN,RGL2,RGS13,RGS16,RGS2,RGS7,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SLIT2,SPRY1,SQSTM1,TIMP2,TRIO,VAV3
BP	GO:0048584: Positive regulation of response to stimulus	1771	103	76.42	0.00094	AAK1,ABL1,AKT2,ALK,ANKRD1,ANKRD6,ARRDC3,ATP6AP1,ATP6AP2,ATPIF1,BCL2L11,BMPR1B,BTK,C18orf32,C1RL,C7,CADM1,CCBE1,CCL2,CD44,CDH2,CLU,CNR1,COCH,COL3A1,COLEC12,CTGF,CTSH,CYFIP2,CYP1B1,CYR61,DDX5,DKK2,DNAJC27,DUSP6,ELMO2,FOS,GATA4,GDF10,GDF15,GDF6,HBEGF,HES1,HEXIM1,HLA-C,HLA-E,HTR2B,IGF2,IL20RA,INHBA,ITGA1,ITPR2,LIF,LMCD1,LPXN,MAPK9,MID1,NDRG4,NLGN1,NLGN3,NOS1,NOTCH2,NTRK2,PDIA3,PLK2,PLXNB1,PRNP,PROS1,PSEN1,PSMB8,PTGIR,PTGIS,RBPMS,RELN,RET,RFTN1,RRAGB,RRAGC,RRAGD,RUSC1,SCG2,SDCBP,SERPINE1,SERPING1,SFRP4,SGIP1,SKAP2,SLIT2,SOX9,SQSTM1,STAT3,TAOK3,TGM2,TIMP2,TMED4,TNFRSF19,TRAF3IP2,TWSG1,TXK,VANGL2,VAV3,WDFY3,YAP1
BP	GO:0033993: Response to lipid	717	49	30.94	0.00099	ABCA1,ABL1,ADM,ANKRD1,ASS1,CCL2,CCND1,CDKN1A,CDKN1B,CNP,CNR1,CTGF,CTSH,CYP24A1,CYP26A1,CYP26B1,DCN,FABP3,FOS,GAL,GATA4,GBA,GCH1,GNG2,HEY1,IGF2,IGFBP7,INHBA,MAOB,MAPK9,MEST,MGEA5,NCOA1,PAF1,PIM1,PLAT,PLN,PPARG,PTCH1,PTGER2,PTGIR,RARB,RET,SERPINE1,SLIT2,SOX9,SPARC,STAT3,WNT3
BP	GO:0010562: Positive regulation of phosphorus metabolic process	963	62	41.55	0.00102	ABCA1,ABL1,ADM,AKT2,ALK,ANKRD6,ANXA2,ATP2B4,ATP6AP1,ATP6V0D1,CALCA,CAMK1,CCL2,CCND1,CD44,CDH2,CDK5R2,CDKN1A,CHRNA3,CLU,CREBL2,CTGF,CYR61,DNAJB11,DNAJC27,DNAJC3,FABP3,FAM129A,GBA,GDF10,GDF15,GDF6,GUCA1A,HES1,HTR2B,IGF2,INHBA,ITGA1,LIF,MAPK9,MID1,NDRG4,NOS1,NTRK2,PDGFC,PFKFB2,PIM1,PSEN1,PTGIR,RAMP1,RBPMS,RELN,SDC4,SDCBP,SOX9,SQSTM1,TAOK3,TIMP2,TOM1L1,TPP1,VANGL2,VAV3
BP	GO:0045937: Positive regulation of phosphate metabolic process	963	62	41.55	0.00102	ABCA1,ABL1,ADM,AKT2,ALK,ANKRD6,ANXA2,ATP2B4,ATP6AP1,ATP6V0D1,CALCA,CAMK1,CCL2,CCND1,CD44,CDH2,CDK5R2,CDKN1A,CHRNA3,CLU,CREBL2,CTGF,CYR61,DNAJB11,DNAJC27,DNAJC3,FABP3,FAM129A,GBA,GDF10,GDF15,GDF6,GUCA1A,HES1,HTR2B,IGF2,INHBA,ITGA1,LIF,MAPK9,MID1,NDRG4,NOS1,NTRK2,PDGFC,PFKFB2,PIM1,PSEN1,PTGIR,RAMP1,RBPMS,RELN,SDC4,SDCBP,SOX9,SQSTM1,TAOK3,TIMP2,TOM1L1,TPP1,VANGL2,VAV3
BP	GO:0051046: Regulation of secretion	608	43	26.23	0.00103	ABL1,ANKRD1,ATP6AP1,CACNA2D2,CADM1,CDK5R2,CHRM3,CHRNA3,CNR1,ENSA,GAL,HLA-E,HTR2B,IFNAR1,INHBA,ITPR2,KCNB1,LIF,MAOB,MAPK9,MGEA5,NLGN1,NPPB,NRXN1,NSF,NTRK2,PCLO,PFKFB2,RAB26,RAB27A,RAB3B,RASL10B,RHBDF1,RIMS2,RUNX1,SCG5,SDC4,SDCBP,SNAP25,SNCAIP,SYT11,SYT4,SYTL4
BP	GO:0060537: Muscle tissue development	328	27	14.15	0.00103	ANKRD1,ANKRD33,BTG2,COL11A1,COL3A1,CYP26B1,DCN,DDX5,EGLN1,FLNB,FOS,FOXC1,GATA4,HEY1,HOXD10,HOXD9,ITGA7,NDRG4,NEBL,PKP2,PLAGL1,PLN,RARB,SGCB,SMAD1,SOX9,TSHZ3
BP	GO:0023057: Negative regulation of signaling	1099	69	47.42	0.00104	ABL1,ADM,ANKRD6,ATP2B4,ATXN1,BCL2A1,CALCA,CCND1,CD44,CDH2,CLU,CTNND1,CYP26A1,CYP26B1,DHRS3,DKK2,DKK3,DUSP16,DUSP6,ELL3,FOXO3,FRZB,GBA,GPRASP1,GRK5,HEY1,HIF1AN,HTR2B,IER3,INHBA,ITGA1,KCTD11,LIF,LPXN,MCC,NBL1,NDRG4,NOS1,NPHP3,NUMB,OPTN,PLK2,PPARG,PRNP,PSEN1,PSMB8,PTCH1,PTGIR,PTPRR,RFFL,RGS13,RGS16,RGS2,RGS7,SCG2,SERPINE1,SFRP4,SH3BP4,SLIT2,SOCS3,SOX9,SPRY1,SYT11,SYTL4,TAOK3,TIMP2,TULP3,TWSG1,YAP1
BP	GO:0003205: Cardiac chamber development	126	14	5.44	0.00108	ARID1A,COL11A1,CYR61,DHRS3,EGLN1,FOXC1,GATA4,HES1,HEY1,NOTCH2,NPHP3,PKP2,RARB,VANGL2
BP	GO:0031329: Regulation of cellular catabolic process	628	44	27.1	0.00109	ABL1,AKT2,ANXA2,ATP1B1,ATP2B4,ATPIF1,BTG2,CLU,CNR1,CSPG5,DCN,DRAM1,EGLN1,FAM13B,GATA4,GBA,HTR2B,IER3,KRCC1,LMCD1,MAPT,NANOS1,PACSIN3,PLK2,PPP1R3B,PPP1R3D,PSEN1,PSMB8,RFWD2,RHBDF1,RRAGB,RRAGC,RRAGD,SFRP4,SH3BP4,SQSTM1,STAT3,STOM,TIMP1,TIMP2,TIMP3,TRIB2,USP31,WDFY3
BP	GO:0048608: Reproductive structure development	415	32	17.91	0.00112	ADM,ARID1A,BASP1,BCL2L11,BMPR1B,BPTF,CCND1,CD44,CDKN1B,CYR61,DCN,EGLN1,EPAS1,FOXC1,FOXO3,GATA4,HES1,HEY1,INHBA,LIF,NCOA1,NCOA3,NOTCH2,PPARG,RDH10,RUNX1,SEMA3A,SLIT2,SOCS3,SOX9,VGF,ZFP36L1

BP	GO:0048732: Gland development	398	31	17.17	0.00113	ABL1,AKT2,ASS1,BCL2L11,CADM1,CCDC40,CCND1,CD44,CDKN1B,DKK3,FOXC1,FRZB,HES1,HOXD3,HOXD9,IRF6,JARID2,NCOA1,NCOA3,NOTCH4,NPHP3,PBX1,PSEN1,PTCH1,RUNX1,SEMA3A,SLIT2,SOX9,TGM2,TWSG1,WNT3
BP	GO:0042063: Gliogenesis	201	19	8.67	0.00114	ABL1,AKT2,CCL2,CDH2,CDK5R2,CDKN2C,CLU,CNP,HES1,HEXB,LIF,MATN2,NLGN3,NTRK2,PPARG,RELN,SOX9,STAT3,VCAN
BP	GO:0051271: Negative regulation of cellular component movement	201	19	8.67	0.00114	CCL2,CDKN1B,COL3A1,CYP1B1,DACH1,DPYSL3,MCC,MMP28,NBL1,NDRG4,PKP2,PTPRM,PTPRR,SEMA3A,SERPINE1,SLIT2,STAT3,TIMP1,WNT3
BP	GO:0071840: Cellular component organization or biogenesis	5665	283	244.44	0.00115	AAK1,ABCA1,ABI3BP,ABL1,ACOX1,ACP2,ADM,AGTPBP1,AHNAK,AIFM2,AKT2,AKT3,ALDH5A1,ANKRD1,ANO3,ANXA2,APH1A,APLP1,AQP11,ARHGAP26,ARID1A,ASAP1,ATP10D,ATP1B1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,ATPIF1,BASP1,BCL2L11,BCOR,BHLHB9,BLCAP,BMPR1B,BPTF,BRPF3,BTG2,C1GALT1C1,CACNA2D2,CACNG2,CADM1,CAMK1,CCDC40,CCL2,CCNA1,CCND1,CD44,CDC42EP3,CDH11,CDH2,CDKL2,CDKN1A,CDKN1B,CDKN2C,CHMP2B,CHRNA3,CHRNB1,CIRBP,CLASP2,CLN5,CLU,CNP,CNR1,COCH,COL11A1,COL17A1,COL23A1,COL3A1,COLEC12,COX11,CPA4,CRB1,CRIM1,CRTAP,CSPG5,CTGF,CTNNA2,CTNND1,CYB5R1,CYP1B1,CYP26B1,CYR61,DACH1,DCBLD2,DCLK1,DCN,DCX,DLG2,DNAJB6,DPT,DPYSL3,DTX3L,EFEMP2,ELFN1,ELL3,ELMOD1,ENSA,EPAS1,EPB41L1,ERI1,EXOC7,FAM101B,FAM13B,FARP1,FAT1,FBXO4,FLNB,FMN2,FN1,FOXC1,FRZB,GABARAPL1,GAL,GCH1,GDF15,GFRA1,GPX3,GRIP1,H1F0,HBEGF,HES1,HEXB,HEY1,HGSNAT,HIST1H2BD,HIST1H2BK,ICAM2,IER3,IGF2,IGFBP6,IGFBP7,INADL,INHBA,ITGA1,ITGA7,ITGB5,JARID2,KALRN,KCNB1,KCNQ2,KCTD11,KDM5C,KIAA0319,KRCC1,KRT18,LAMA4,LIF,LMCD1,LPXN,LUM,MAP6,MAPK9,MAPRE2,MAPT,MATN2,MAX,MGEA5,MID1,MID1IP1,MMP11,MTRF1L,NAP1L3,NAP1L5,NAV1,NBL1,NCAM2,NCAN,NCOA1,NCOA3,NDRG4,NEBL,NFASC,NLGN1,NLGN3,NOS1,NOTCH4,NPEPPS,NPHP3,NPLOC4,NPPA,NPPB,NRXN1,NSD1,NSF,NTNG2,NTRK2,NUMB,OAS1,OPTN,OSCP1,PACSIN3,PAF1,PCDHB10,PCDHB14,PCDHB3,PCDHB4,PCLO,PDGFC,PDZRN3,PEX11B,PKP2,PLK2,PLN,PLXNB1,POLQ,PPARG,PRNP,PSEN1,PTCH1,PTPRM,PTX3,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RAMP1,RBFOX2,RELN,RET,RFTN1,RGS2,RIC3,RND2,RSPH9,SAP30L,SCN3B,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SFRP4,SGIP1,SH3BGRL3,SH3BP4,SIPA1L1,SKAP2,SLC9A6,SLIT2,SMAD1,SMARCA2,SMOC1,SNAP25,SNCAIP,SOAT1,SORBS2,SOX9,SPAG1,SPARC,SPRY1,SPTAN1,SQSTM1,STAG3,STMN4,STOM,SYP,SYT11,SYT4,SYTL4,TACC2,TAF7L,TEP1,TGM2,THSD4,TIMP1,TIMP2,TOM1L1,TOM1L2,TOX2,TPP1,TRIO,TRIOBP,TTC30A,TTC30B,VANGL2,VAV3,VCAN,WNT3,YAP1
BP	GO:0097305: Response to alcohol	281	24	12.12	0.00117	ABCA1,ASS1,CCL2,CCND1,CDKN1A,CDKN1B,CNR1,CTGF,CYP24A1,FOS,GBA,IGF2,IGFBP7,INHBA,ITPR2,MAOB,NCOA1,PIM1,PLAT,PLN,PTCH1,SLIT2,SPARC,STAT3
BP	GO:0010648: Negative regulation of cell communication	1106	69	47.72	0.00123	ABL1,ADM,ANKRD6,ATP2B4,ATXN1,BCL2A1,CALCA,CCND1,CD44,CDH2,CLU,CTNND1,CYP26A1,CYP26B1,DHRS3,DKK2,DKK3,DUSP16,DUSP6,ELL3,FOXO3,FRZB,GBA,GPRASP1,GRK5,HEY1,HIF1AN,HTR2B,IER3,INHBA,ITGA1,KCTD11,LIF,LPXN,MCC,NBL1,NDRG4,NOS1,NPHP3,NUMB,OPTN,PLK2,PPARG,PRNP,PSEN1,PSMB8,PTCH1,PTGIR,PTPRR,RFFL,RGS13,RGS16,RGS2,RGS7,SCG2,SERPINE1,SFRP4,SH3BP4,SLIT2,SOCS3,SOX9,SPRY1,SYT11,SYTL4,TAOK3,TIMP2,TULP3,TWSG1,YAP1
BP	GO:0030323: Respiratory tube development	187	18	8.07	0.00124	ATXN1,CCDC40,CTGF,CTSH,EPAS1,GATA4,HES1,LIF,NPHP3,NUMB,RDH10,SOX9,SPARC,SPRY1,TNS3,TSHZ3,TULP3,VANGL2
BP	GO:0019222: Regulation of metabolic process	6417	316	276.89	0.00124	AAK1,ABCA1,ABL1,ADM,AHNAK,AHRR,AHSA2,AKT2,ALK,ANKRD1,ANKRD33,ANKRD6,ANXA2,ANXA2P2,ANXA3,APH1A,APLP1,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ARID1A,ARMCX3,ARRDC3,ASAP1,ASAP2,ASS1,ATP1B1,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATP8B1,ATPIF1,ATXN1,BACH2,BASP1,BCL2L11,BCO2,BCOR,BHLHE40,BHLHE41,BMPR1B,BPTF,BTG2,BTK,C1GALT1C1,C7,CALCA,CAMK1,CAMK2N1,CCBE1,CCL2,CCNA1,CCND1,CD44,CDH2,CDK5R2,CDKN1A,CDKN1B,CDKN2C,CEBPD,CELF6,CHRNA3,CHURC1,CIRBP,CLU,CNR1,COX11,CRABP2,CREB5,CREBL2,CREM,CRIM1,CRTAP,CSPG5,CTGF,CTNND1,CTSA,CTSH,CYFIP2,CYP1B1,CYP26B1,CYR61,DACH1,DCN,DDX5,DKK3,DLG2,DNAJB11,DNAJB6,DNAJC27,DNAJC3,DOCK9,DRAM1,DUSP16,DUSP6,EBF1,EGLN1,EIF4E3,ELFN1,ELL3,ELMOD1,ENSA,EPAS1,EPM2AIP1,ERI1,FABP3,FAM129A,FAM13A,FAM13B,FARP1,FBXO2,FBXO4,FMN2,FN1,FOS,FOXC1,FOXO3,GAL,GATA4,GBA,GCH1,GDF10,GDF15,GDF6,GNG7,GRIP1,GTF2IRD2,GUCA1A,HBEGF,HES1,HEXB,HEXIM1,HEY1,HIF1AN,HIVEP2,HOXC6,HOXC8,HOXD1,HOXD10,HOXD3,HOXD8,HOXD9,HTR2B,IER3,IGF2,IGFBP7,INHBA,IRF6,IRF9,ITGA1,ITPR2,JARID2,KALRN,KDM5C,KRCC1,LARP6,LBH,LIF,LMCD1,LPXN,LUM,MAOB,MAP4K4,MAPK9,MAPT,MAX,MED13,MEIS1,MGEA5,MID1,MID1IP1,MSN,NANOS1,NBL1,NCOA1,NCOA3,NCOA7,NDRG4,NFAT5,NFKBIZ,NMI,NOS1,NOTCH2,NOTCH4,NPC2,NSD1,NSF,NTRK2,OAS1,OPTN,PACSIN3,PAF1,PARP14,PBX1,PBX3,PDGFC,PDGFD,PFKFB2,PI15,PIM1,PLAGL1,PLAT,PLK2,PLN,PLXNB1,POLQ,PPARG,PPP1R3B,PPP1R3D,PRCP,PRNP,PROS1,PRPSAP1,PSD2,PSEN1,PSMB8,PTCH1,PTGIR,PTGIS,PTPRR,PTX3,RAB27A,RAB3IP,RABIF,RAMP1,RARB,RBFOX2,RBPMS,RELN,RET,RFFL,RFWD2,RGL2,RGS13,RGS16,RGS2,RGS7,RHBDF1,RIMS2,ROM1,RRAGB,RRAGC,RRAGD,RUNX1,RUNX1T1,SAMD4A,SAP30L,SCG5,SDC4,SDCBP,SERPINE1,SERPING1,SFRP4,SH3BGRL3,S

						H3BP4,SIPA1L1,SIPA1L2,SLC40A1,SLIT2,SMAD1,SMARCA2,SOAT1,SOCS3,SOX9,SPEN,SPRY1,SQSTM1,SSBP2,STAT3,STOM,TAF11,TAF7L,TAOK3,TCEAL2,TCEAL3,TCEAL6,TCEAL7,TIMP1,TIMP2,TIMP3,TOM1L1,TOX2,TPP1,TRIB2,TRIO,TSHZ3,TULP3,TULP4,TWSG1,TXK,USP31,VANGL2,VAV3,WDFY3,WNT3,WTAP,YAP1,ZCCHC12,ZFHX2,ZFHX4,ZFP3,ZFP36L1,ZFYVE1,ZNF280B,ZNF425,ZNF521,ZNF562,ZNF599,ZNF641,ZNF789,ZSCAN18
BP	GO:0008016: Regulation of heart contraction	157	16	6.77	0.00125	ADM,ATP1B1,ATP2B4,CALCA,CELF2,CTGF,EPAS1,GATA4,HBEGF,NOS1,NPPA,PKP2,PLN,RGS2,SCN3B,SEMA3A
BP	GO:0051049: Regulation of transport	1584	93	68.35	0.00126	AAK1,ABCA1,ABL1,AHNAK,AKT2,ANKRD1,ANXA2,ATP1B1,ATP2B4,ATP6AP1,ATPIF1,BCL2L11,CACNA2D2,CACNG2,CADM1,CALCA,CAMK1,CCL2,CDK5R2,CDKL2,CDKN1A,CHRM3,CHRNA3,CNR1,CREBL2,CYB5R1,DNAJC27,ELMOD1,ENSA,FGF14,GAL,HES1,HLA-E,HTR2B,IER3,IFNAR1,INHBA,ITPR2,KCNB1,KCNMA1,KCNQ2,LIF,MAOB,MAPK9,MAPT,MGEA5,NLGN1,NLGN3,NOS1,NPEPPS,NPPA,NPPB,NRXN1,NSF,NTRK2,OS9,OSCP1,PACSIN3,PCLO,PDIA3,PFKFB2,PKP2,PLN,PPARG,PRNP,PTCH1,PTX3,RAB26,RAB27A,RAB3B,RASL10B,RBPMS,RELN,RHBDF1,RIMS2,RUNX1,SCG5,SCN2A,SCN3A,SCN3B,SDC4,SDCBP,SERPINE1,SFRP4,SGIP1,SLC31A2,SNAP25,SNCAIP,STOM,SYNGR3,SYT11,SYT4,SYTL4
BP	GO:0046578: Regulation of Ras protein signal transduction	543	39	23.43	0.00131	ABCA1,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,COL3A1,DOCK9,ELMOD1,FAM13A,FAM13B,FARP1,HTR2B,KALRN,NOTCH2,NTRK2,PLXNB1,PSD2,PTGIR,RAB3IP,RABIF,RGL2,RGS13,RGS16,RGS2,RGS7,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,SPRY1,SQSTM1,TIMP2,TRIO,VAV3
BP	GO:0061458: Reproductive system development	419	32	18.08	0.00131	ADM,ARID1A,BASP1,BCL2L11,BMPR1B,BPTF,CCND1,CD44,CDKN1B,CYR61,DCN,EGLN1,EPAS1,FOXC1,FOXO3,GATA4,HES1,HEY1,INHBA,LIF,NCOA1,NCOA3,NOTCH2,PPARG,RDH10,RUNX1,SEMA3A,SLIT2,SOCS3,SOX9,VGF,ZFP36L1
BP	GO:0040011: Locomotion	1567	92	67.61	0.00134	ABL1,AKT2,ANXA3,APH1A,ARRDC3,ATP1B1,BMPR1B,CALCA,CCBE1,CCL2,CD44,CDH2,CDK5R2,CLASP2,CMTM6,COL3A1,CTGF,CTNNA2,CTSH,CYP1B1,CYR61,DACH1,DCLK1,DCX,DPYSL3,ELMO2,ENPP2,FAT1,FN1,FOXC1,FUCA2,GFRA1,HBEGF,HES1,HEXB,HTR2B,ITGA1,ITGA7,KALRN,KCNQ2,KIAA0319,LAMA4,MAPT,MATN2,MCC,MMP28,MSN,NANOS1,NAV1,NBL1,NCAN,NDRG4,NFASC,NRXN1,NTRK2,NUMB,PARP9,PKP2,PLAT,PLXNB1,PRCP,PRNP,PROS1,PSEN1,PTPRM,PTPRR,PTX3,RBFOX2,RELN,RET,RFFL,RHBDF1,SCG2,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SH3BGRL3,SLIT2,SORBS2,SOX9,SPARC,SPTAN1,STAT3,TIMP1,TNS3,TRIO,VANGL2,VAV3,VCAN,WNT3
BP	GO:0048878: Chemical homeostasis	919	59	39.65	0.00143	ABCA1,ABL1,ACOX1,ADM,AQP11,ATP1B1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,C7,CALB1,CALCA,CCL2,CLN5,CNR1,CTSH,CYP26B1,EGLN1,EPAS1,FABP3,FOXO3,GATA4,GBA,HEXB,HTR2B,KCNMA1,MGEA5,NOS1,NPC2,NPPB,NRXN1,OAS1,PKP2,PLN,PPARG,PRCP,PRNP,PSEN1,PTCH1,PYGL,RIC3,SCN3B,SFRP4,SLC22A17,SLC31A2,SLC40A1,SLC4A8,SLC8A3,SLC9A6,SOAT1,STAT3,TAP1,TFRC,TGM2,VGF
BP	GO:1903522: Regulation of blood circulation	221	20	9.54	0.00147	ADM,ATP1B1,ATP2B4,CALCA,CELF2,CHRM3,CTGF,EPAS1,GATA4,HBEGF,NOS1,NPPA,NPPB,PKP2,PLN,PTPRM,RGS2,SCN3B,SCPEP1,SEMA3A
BP	GO:0040013: Negative regulation of locomotion	223	20	9.62	0.00163	ARRDC3,CCL2,COL3A1,CYP1B1,DACH1,DPYSL3,MCC,MMP28,NBL1,NDRG4,PKP2,PTPRM,PTPRR,PTX3,SEMA3A,SERPINE1,SLIT2,STAT3,TIMP1,WNT3
BP	GO:0060429: Epithelium development	1061	66	45.78	0.00168	ABL1,ACTA2,ADM,AKT2,ANKRD6,APOLD1,AQP11,ARID1A,ATP6AP2,BASP1,CALB1,CCDC40,CCND1,CD44,CDKN1A,COL17A1,CRABP2,CTGF,CTSH,CYP26B1,CYR61,FOXC1,FRZB,GAL,GATA4,HBEGF,HES1,HEY1,INHBA,IRF6,LIF,MSN,NCOA3,NDRG4,NOTCH2,NOTCH4,NPHP3,NUMB,PBX1,PPARG,PSEN1,PTCH1,RAB27A,RARB,RDH10,RET,RUNX1,SDC4,SEMA3A,SFRP4,SLC40A1,SLIT2,SMAD1,SOCS3,SOX9,SPRY1,STS,TGM2,TNFRSF19,TPP1,TSHZ3,TULP3,VANGL2,WNT3,YAP1,ZFP36L1
BP	GO:0009967: Positive regulation of signal transduction	1258	76	54.28	0.00169	AAK1,ABL1,ALK,ANKRD1,ANKRD6,ARRDC3,ATP6AP1,ATP6AP2,ATPIF1,BCL2L11,BMPR1B,C18orf32,CCBE1,CD44,CDH2,CLU,COL3A1,CTGF,CTSH,CYP1B1,CYR61,DDX5,DKK2,DNAJC27,GATA4,GDF10,GDF15,GDF6,HBEGF,HES1,HEXIM1,HTR2B,IGF2,IL20RA,INHBA,ITGA1,LIF,LMCD1,MAPK9,MID1,NDRG4,NLGN1,NLGN3,NOS1,NOTCH2,NTRK2,PDIA3,PLK2,PLXNB1,PSEN1,PSMB8,PTGIR,PTGIS,RBPMS,RELN,RET,RRAGB,RRAGC,RRAGD,RUSC1,SDCBP,SFRP4,SKAP2,SOX9,STAT3,TAOK3,TGM2,TIMP2,TMED4,TNFRSF19,TRAF3IP2,TWSG1,TXK,VANGL2,VAV3,YAP1
BP	GO:0051050: Positive regulation of transport	794	52	34.26	0.00178	ABCA1,ABL1,AKT2,ANKRD1,ANXA2,ATP1B1,ATP6AP1,ATPIF1,BCL2L11,CADM1,CAMK1,CCL2,CDK5R2,CDKL2,CREBL2,CYB5R1,ELMOD1,FGF14,GAL,HES1,HLA-E,HTR2B,IFNAR1,INHBA,MAPK9,MGEA5,NLGN1,NLGN3,NOS1,NPEPPS,NPPA,NPPB,OSCP1,PFKFB2,PKP2,PPARG,PTCH1,PTX3,RAB27A,RAB3B,RASL10B,RBPMS,RELN,RUNX1,SCN3B,SDC4,SDCBP,SERPINE1,SFRP4,SGIP1,SYNGR3,SYTL4
BP	GO:0009894: Regulation of catabolic process	719	48	31.02	0.00180	ABL1,AKT2,ANXA2,ATP1B1,ATP2B4,ATPIF1,BTG2,CDKN1B,CLU,CNR1,CSPG5,DCN,DRAM1,EGLN1,FAM13B,FMN2,GATA4,GBA,HTR2B,IER3,KRCC1,LMCD1,MAPT,NANOS1,NSF,PACSIN3,PLK2,PPP1R3B,PPP1R3D,PSEN1,PSMB8,RFWD2,RHBDF1,RRAGB,RRAGC,RRAGD,SFRP4,SH3BP4,SOX9,SQSTM1,STAT3,STOM,TIMP1,TIMP2,TIMP3,TRIB2,USP31,WDFY3
BP	GO:0044093:	1623	94	70.03	0.00181	ABL1,AHSA2,ALK,ANXA2,ANXA3,APH1A,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,AR

	Positive regulation of molecular function					HGEF37,ARRDC3,ASAP1,ASAP2,ATP1B1,ATP2B4,ATP6V0D1,BCL2L11,BTK,C1GALT1C1,CALCA,CAMK1,CCL2,CCND1,CDK5R2,CDKN1A,CDKN1B,CHRNA3,CLU,CTGF,CTSA,CTSH,CYFIP2,CYR61,DNAJB11,DNAJB6,DNAJC3,DOCK9,ELMOD1,EPM2AIP1,FAM13A,FAM13B,FARP1,FN1,GAL,GCH1,GUCA1A,HES1,HTR2B,IGF2,ITGA1,ITPR2,KALRN,MAPK9,MID1IP1,NCOA3,NLGN3,NOS1,NPPA,NTRK2,PDGFC,PFKFB2,PIM1,PLK2,PLXNB1,PPARG,PSD2,PSEN1,PSMB8,PTGIR,RAB3IP,RABIF,RELN,RET,RGL2,RGS13,RGS16,RGS2,RGS7,SDC4,SH3BGRL3,SIPA1L1,SIPA1L2,SYNGR3,TAOK3,TIMP2,TOM1L1,TPP1,TRIO,TXK,VANGL2,VAV3
BP	GO:0001503: Ossification	358	28	15.45	0.00181	ATP6AP1,BCOR,BMPR1B,CALCA,CDH11,COL11A1,CTGF,CYP24A1,CYR61,DDX5,DHRS3,FOXC1,GPNMB,HEY1,IGF2,MGP,NPR2,PBX1,PLXNB1,PTCH1,SLC26A2,SMAD1,SMOC1,SOX9,SPARC,TWSG1,VCAN,WNT3
BP	GO:0050880: Regulation of blood vessel size	133	14	5.74	0.00182	ACTA2,ADM,CALCA,CHRM3,FOXC1,GCH1,HTR2B,ITGA1,NOS1,NPPA,NPPB,PTPRM,RGS2,SCPEP1
BP	GO:0044092: Negative regulation of molecular function	969	61	41.81	0.00190	ABL1,ANKRD33,ANXA2,ANXA2P2,ANXA3,ATP2B4,ATPIF1,BHLHE40,CAMK1,CAMK2N1,CD44,CDKN1A,CDKN1B,CDKN2C,CNR1,COX11,CRIM1,CYP1B1,DLG2,DNAJB6,DNAJC3,DUSP16,DUSP6,EGLN1,ELFN1,ENSA,FARP1,GBA,HEXIM1,HEY1,NOS1,PBX1,PI15,PIM1,PLN,PPARG,PRNP,PROS1,PRPSAP1,PSEN1,PSMB8,PTCH1,PTGIS,PTX3,RFFL,RGS2,SCG5,SERPINE1,SERPING1,SFRP4,SH3BP4,SLIT2,SOCS3,SPRY1,TAOK3,TCEAL7,TIMP1,TIMP2,TIMP3,TRIB2,ZFYVE1
BP	GO:0051641: Cellular localization	2729	147	117.75	0.00190	ABCA1,ABL1,ADM,AKT2,ALDH5A1,ANKRD1,ANXA2,ANXA3,APPBP2,ARMCX3,ATP10D,ATP1B1,ATP2B4,ATP6AP1,ATPIF1,ATXN1,BCL2L11,BRPF3,BTK,BZRAP1,CACNA2D2,CADM1,CALCA,CAMK1,CDK5R2,CDKL2,CDKN1A,CHMP2B,CHRM3,CHRNA3,CLASP2,CLU,CNP,CNR1,CSPG5,CTGF,CTSA,CYB5R1,DCLK1,DLG2,DNAJC27,DUSP16,ELMOD1,ENSA,EXOC6B,EXOC7,FLNB,FMN2,FN1,GAL,GPRASP1,HES1,HGSNAT,HLA-E,HTR2B,IER3,IFNAR1,IGF2,INHBA,ITPR2,KCNB1,KIAA1279,KRT18,LIF,LMAN2L,MAOB,MAP6,MAPK9,MAPT,MGEA5,MID1,NBEA,NFASC,NLGN1,NOS1,NOTCH2,NPC2,NPEPPS,NRXN1,NSF,NTRK2,NUMB,OPTN,OS9,OSCP1,PAF1,PCLO,PDIA3,PFKFB2,PKP2,PLCD4,PLN,PROS1,PRSS12,PSEN1,PTCH1,RAB26,RAB27A,RAB3B,RAB3IP,RAMP1,RASEF,RASL10B,RBPMS,RELN,RFFL,RFTN1,RHBDF1,RIMS2,RRAGB,RRAGC,RRAGD,RUNX1,SCG2,SCG5,SCN3B,SDC4,SDCBP,SERPINE1,SERPING1,SH3BP4,SLC22A17,SLC8A3,SNAP25,SNCAIP,SPARC,SPRY1,SQSTM1,STAT3,SYN2,SYP,SYT11,SYT4,SYTL4,TACC2,TAP1,TEX261,TIMP1,TOM1L1,TOM1L2,TRAF3IP2,TTC30A,TTC30B,VGF,VPS13D,VPS53,WDFY3
BP	GO:0035150: Regulation of tube size	134	14	5.78	0.00195	ACTA2,ADM,CALCA,CHRM3,FOXC1,GCH1,HTR2B,ITGA1,NOS1,NPPA,NPPB,PTPRM,RGS2,SCPEP1
BP	GO:0051899: Membrane depolarization	134	14	5.78	0.00195	ABL1,ATPIF1,ATXN1,CACNG2,CHRNA3,MGEA5,NLGN1,NLGN3,NRXN1,RELN,RIMS2,SCN2A,SCN3A,SCN3B
BP	GO:0003206: Cardiac chamber morphogenesis	106	12	4.57	0.00204	COL11A1,CYR61,DHRS3,EGLN1,FOXC1,GATA4,HES1,HEY1,NOTCH2,PKP2,RARB,VANGL2
BP	GO:0007610: Behavior	649	44	28	0.00206	ARRDC3,ATXN1,BHLHB9,BTG2,CALB1,CALCA,CCL2,CHRNA3,CHRNB1,CNP,CNR1,DACH1,FGF14,FOS,GAL,GNG7,HEXB,HOXD10,HOXD9,HTR2B,IGF2,MAPT,MMP28,NAV2,NBL1,NCOA1,NLGN1,NLGN3,NRXN1,NTRK2,PBX3,PLK2,PRNP,PSEN1,RELN,RUNX1,SCG2,SEMA3A,SERPINE1,SGIP1,SLIT2,STAT3,WNT3,ZFHX2
BP	GO:0006928: Movement of cell or subcellular component	1712	98	73.87	0.00207	ABL1,AKT2,ANXA3,APH1A,ATP1B1,BMPR1B,CALCA,CCBE1,CCDC40,CCL2,CD44,CDH2,CDK5R2,CDKN1B,CLASP2,COL3A1,CTGF,CTNNA2,CTSH,CYP1B1,CYR61,DACH1,DCLK1,DCX,DPYSL3,ELMO2,ENPP2,FAT1,FMN2,FN1,FOXC1,GATA4,GFRA1,HBEGF,HES1,HEXB,HTR2B,ITGA1,ITGA7,KALRN,KCNQ2,KIAA0319,LAMA4,MAPT,MATN2,MCC,MMP28,MSN,NANOS1,NAV1,NBL1,NCAN,NDRG4,NFASC,NPHP3,NRXN1,NTRK2,NUMB,PARP9,PKP2,PLAT,PLN,PLXNB1,PRCP,PRNP,PROS1,PSEN1,PTPRM,PTPRR,RBFOX2,RELN,RET,RFFL,RHBDF1,RSPH9,SCG2,SCN3B,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SH3BGRL3,SLIT2,SORBS2,SOX9,SPARC,SPTAN1,STAT3,TIMP1,TNS3,TRIO,TTC30A,TTC30B,VANGL2,VAV3,VCAN,WNT3
BP	GO:0002009: Morphogenesis of an epithelium	467	34	20.15	0.00209	ABL1,ADM,ANKRD6,ARID1A,CCDC40,CD44,CTSH,CYR61,FRZB,GATA4,HBEGF,HES1,LIF,NCOA3,NDRG4,NOTCH2,NOTCH4,NPHP3,NUMB,PBX1,PSEN1,PTCH1,RDH10,RET,RUNX1,SEMA3A,SLIT2,SOCS3,SOX9,SPRY1,TGM2,TULP3,VANGL2,YAP1
BP	GO:0035107: Appendage morphogenesis	150	15	6.47	0.00212	BCL2L11,BMPR1B,CRABP2,CYP26B1,HOXD10,HOXD9,NOTCH2,PBX1,PSEN1,PTCH1,RARB,RDH10,SOX9,TULP3,WNT3
BP	GO:0035108: Limb morphogenesis	150	15	6.47	0.00212	BCL2L11,BMPR1B,CRABP2,CYP26B1,HOXD10,HOXD9,NOTCH2,PBX1,PSEN1,PTCH1,RARB,RDH10,SOX9,TULP3,WNT3
BP	GO:0042325: Regulation of phosphorylation	1250	75	53.94	0.00217	ABL1,AKT2,ALK,ANKRD6,ANXA2,ATP2B4,ATP6AP1,ATP6AP2,ATP6V0D1,ATXN1,CALCA,CAMK1,CAMK2N1,CCL2,CCNA1,CCND1,CD44,CDH2,CDK5R2,CDKN1A,CDKN1B,CDKN2C,CHRNA3,CLU,COX11,CREBL2,CTGF,CYR61,DNAJB11,DNAJC27,DNAJC3,DUSP16,DUSP6,FAM129A,GBA,GDF10,GDF15,GDF6,HES1,HEXIM1,HTR2B,IGF2,INHBA,ITGA1,LIF,MAP4K4,MAPK9,MID1,NDRG4,NTRK2,PDGFC,PDGFD,PFKFB2,PIM1,PRNP,PRPSAP1,PSEN1,PTPRR,RBPMS,RELN,RGS2,SDC4,SDCBP,SLIT2,SOCS3,SOX9,SPRY1,SQSTM1,TAOK3,TIMP2,TOM1L1,TPP1,TRIB2,VANGL2,VAV3

BP	GO:0030336: Negative regulation of cell migration	181	17	7.81	0.00218	CCL2,COL3A1,CYP1B1,DACH1,DPYSL3,MCC,MMP28,NBL1,NDRG4,PKP2,PTPRM,PTPRR,SEMA3A,SERPINE1,SLIT2,STAT3,TIMP1
BP	GO:0022414: Reproductive process	1172	71	50.57	0.00223	ACOX1,ADAM29,ADM,ARID1A,B4GALNT1,BASP1,BCL2L11,BMPR1B,BPTF,CADM1,CALCA,CCL2,CCNA1,CCND1,CD44,CDKL2,CDKN1B,CLDN11,CNR1,CREM,CRTAP,CTSH,CYP26B1,CYR61,DACH1,DCN,EGLN1,ELL3,EPAS1,FMN2,FOS,FOXC1,FOXO3,GAL3ST1,GATA4,HES1,HEXB,HEY1,HOXD10,HOXD9,IGF2,IGFBP7,INHBA,LIF,NCOA1,NCOA3,NOTCH2,NPPA,NPR2,PAPPA,PBX1,PLAT,PLCD4,PPARG,RDH10,RGS2,RLN1,RUNX1,SEMA3A,SLIT2,SMAD1,SOCS3,SOX9,SPAG1,STAT3,STS,TAF7L,TIMP1,VGF,WNT3,ZFP36L1
BP	GO:0052652: Cyclic purine nucleotide metabolic process	151	15	6.52	0.00226	ABCA1,ADM,APLP1,CALCA,GNG7,GUCA1A,HTR2B,NOS1,NPPA,NPPB,NPR2,NTRK2,PTGIR,RAMP1,TIMP2
BP	GO:0051128: Regulation of cellular component organization	1985	111	85.65	0.00227	AAK1,ABL1,AKT2,ANKRD1,ANXA2,ATP1B1,ATP8B1,ATPIF1,BCL2L11,BCOR,BHLHB9,CAMK1,CCL2,CDC42EP3,CDKL2,CDKN1A,CDKN1B,CDKN2C,CHMP2B,CHRNA3,CLASP2,CLU,CNR1,COCH,CRIM1,CSPG5,CTGF,CTNNA2,CYB5R1,CYR61,DCBLD2,DNAJB6,DPYSL3,ELL3,ELMOD1,FAM13B,FN1,FRZB,GAL,GDF15,HBEGF,HES1,HEXB,IER3,IGF2,IGFBP6,IGFBP7,INHBA,ITGA7,JARID2,KIAA0319,KRCC1,LIF,LMCD1,MAPK9,MAPT,MGEA5,MID1,MID1IP1,NCAN,NDRG4,NLGN1,NLGN3,NOS1,NPEPPS,NPPA,NPPB,NRXN1,NTRK2,NUMB,OSCP1,PACSIN3,PAF1,PKP2,PLK2,PLXNB1,PPARG,PSEN1,PTX3,RAB27A,RELN,RET,RGS2,RND2,SDC4,SDCBP,SEMA3A,SEMA4F,SERPINE1,SFRP4,SGIP1,SH3BGRL3,SH3BP4,SIPA1L1,SLIT2,SMAD1,SMARCA2,SNAP25,SNCAIP,SOX9,SPARC,SPTAN1,SQSTM1,STMN4,STOM,SYT4,TOM1L1,TOM1L2,TRIOBP,VANGL2,WNT3
BP	GO:0032486: Rap protein signal transduction	488	35	21.06	0.00232	ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,DOCK9,ELMOD1,FAM13A,FAM13B,FARP1,HTR2B,KALRN,NTRK2,PLK2,PLXNB1,PSD2,PTGIR,RAB3IP,RABIF,RGL2,RGS13,RGS16,RGS2,RGS7,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,TIMP2,TRIO,VAV3
BP	GO:0051649: Establishment of localization in cell	2384	130	102.87	0.00235	ABCA1,ABL1,ADM,AKT2,ALDH5A1,ANKRD1,ANXA2,ANXA3,APPBP2,ATP10D,ATP1B1,ATP2B4,ATP6AP1,ATPIF1,ATXN1,BCL2L11,BRPF3,BTK,BZRAP1,CACNA2D2,CADM1,CALCA,CAMK1,CDK5R2,CDKL2,CDKN1A,CHMP2B,CHRM3,CHRNA3,CLU,CNP,CNR1,CSPG5,CTGF,CTSA,CYB5R1,DCLK1,DNAJC27,DUSP16,ELMOD1,ENSA,EXOC6B,EXOC7,FMN2,FN1,GAL,GPRASP1,HES1,HGSNAT,HLA-E,HTR2B,IER3,IFNAR1,IGF2,INHBA,ITPR2,KCNB1,KIAA1279,KRT18,LIF,LMAN2L,MAOB,MAPK9,MAPT,MGEA5,NBEA,NLGN1,NOS1,NOTCH2,NPC2,NPEPPS,NRXN1,NSF,NTRK2,OPTN,OS9,OSCP1,PCLO,PDIA3,PFKFB2,PLCD4,PLN,PROS1,PRSS12,PSEN1,PTCH1,RAB26,RAB27A,RAB3B,RAB3IP,RAMP1,RASEF,RASL10B,RBPMS,RFFL,RFTN1,RHBDF1,RIMS2,RUNX1,SCG2,SCG5,SDC4,SDCBP,SERPINE1,SERPING1,SLC22A17,SLC8A3,SNAP25,SNCAIP,SPARC,SPRY1,SQSTM1,STAT3,SYN2,SYP,SYT11,SYT4,SYTL4,TAP1,TEX261,TIMP1,TOM1L1,TOM1L2,TRAF3IP2,TTC30A,TTC30B,VGF,VPS13D,VPS53,WDFY3
BP	GO:0019932: Second-messenger-mediated signaling	198	18	8.54	0.00235	ADM,ATP1B1,ATP2B4,BTK,GAL,HTR2B,ITPR2,LMCD1,NFAT5,NOS1,NTRK2,PCLO,PLN,PRNP,PTGIR,RGS2,RIMS2,SOX9
BP	GO:0031346: Positive regulation of cell projection organization	214	19	9.23	0.00237	ANKRD1,BHLHB9,CAMK1,CDC42EP3,CNR1,DPYSL3,FN1,MAPT,NDRG4,NLGN1,NTRK2,PLXNB1,PSEN1,RELN,RET,RND2,SLIT2,SMAD1,WNT3
BP	GO:0044057: Regulation of system process	400	30	17.26	0.00240	ADM,ATP1B1,ATP2B4,CALCA,CELF2,CHRM3,CHRNA3,CTGF,EPAS1,GAL,GATA4,HBEGF,INHBA,LMCD1,MGEA5,NLGN1,NLGN3,NOS1,NPPA,NPPB,PBX3,PKP2,PLN,PTPRM,RGS2,RUNX1,SCN3B,SCPEP1,SEMA3A,TSHZ3
BP	GO:0003018: Vascular process in circulatory system	152	15	6.56	0.00241	ACTA2,ADM,CALCA,CHRM3,FOXC1,GCH1,HTR2B,ITGA1,NOS1,NPPA,NPPB,PTPRM,RGS2,SCPEP1,SLIT2
BP	GO:0009190: Cyclic nucleotide biosynthetic process	152	15	6.56	0.00241	ABCA1,ADM,APLP1,CALCA,GNG7,GUCA1A,HTR2B,NOS1,NPPA,NPPB,NPR2,NTRK2,PTGIR,RAMP1,TIMP2
BP	GO:0030324: Lung development	183	17	7.9	0.00245	ATXN1,CCDC40,CTGF,CTSH,EPAS1,GATA4,HES1,LIF,NPHP3,NUMB,RDH10,SOX9,SPARC,SPRY1,TNS3,TSHZ3,VANGL2
BP	GO:0006812: Cation transport	980	61	42.29	0.00246	ABL1,AHNAK,ATP10D,ATP1B1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,BTK,CACNA2D2,CACNG2,CALCA,CCL2,CDKN1B,CHRNA3,CHRNB1,CNGA1,CNR1,COX11,COX17,CTGF,FGF14,GAL,HTR2B,ITPR2,KCNB1,KCNMA1,KCNQ2,MAOB,MGEA5,NIPAL2,NOS1,NPPA,NSF,ORAI3,PACSIN3,PKP2,PLN,PRNP,PSEN1,RAB3B,RAMP1,RHCE,SCN2A,SCN3A,SCN3B,SLC12A6,SLC2A10,SLC31A2,SLC35A2,SLC36A1,SLC40A1,SLC4A8,SLC8A3,SLC9A6,STOM,TFRC,TMEM38A
BP	GO:0050804: Regulation of synaptic transmission	248	21	10.7	0.00256	CACNA2D2,CALB1,CCL2,CHRNA3,CNR1,CSPG5,NLGN1,NLGN3,NOS1,NRXN1,NTRK2,PLAT,PLK2,PSEN1,RAB3B,RELN,SIPA1L1,SNAP25,SNCAIP,SYP,SYT11
BP	GO:0000165: MAPK cascade	657	44	28.35	0.00259	ABL1,ALK,ANKRD6,ATP6AP1,ATP6AP2,CCL2,CD44,CDH2,CTGF,CTSH,CYR61,DNAJC27,DUSP16,DUSP6,FGF14,FOS,GBA,GDF10,GDF15,GDF6,HTR2B,IGF2,INHBA,ITGA1,LIF,MAP4K4,MAPK9,MID1,NDRG4,NTRK2,PSEN1,PTPRR,RET,R

						GS2,SCG2,SDCBP,SMAD1,SOX9,SPRY1,TAOK3,TIMP2,TNFRSF19,TRIB2,VANGL2
BP	GO:0012501: Programmed cell death	1787	101	77.11	0.00263	ABL1,ADM,AIFM2,AKT2,ALK,ANKRD1,APH1A,APLP1,ARHGEF3,ATPIF1,BCL2A1,BCL2L11,BHLHB9,BLCAP,BMPR1B,BTG2,BTK,C8orf4,CADM1,CCL2,CD44,CDKN1A,CDKN1B,CLU,CNR1,CTGF,CTSH,CYFIP2,CYP1B1,CYP26B1,CYR61,DAPL1,DDX5,DNAJB6,DNAJC3,DRAM1,DUSP6,ELL3,ELMO2,FMN2,FOXC1,FOXO3,FRZB,GAL,GDF10,GDF15,GDF6,GRK5,H1F0,HTR2B,IER3,IL20RA,INHBA,ITGA1,KALRN,KCNMA1,KRT18,MAP4K4,MAPK9,MAPT,MAX,NCOA1,NOTCH2,NTRK2,PDIA3,PHLDA1,PIM1,PLAGL1,PLK2,PPARG,PRNP,PSEN1,PSMB8,PTGIS,PTPRH,PYGL,RARB,RET,RFFL,RRAGC,SCG2,SCN2A,SEMA3A,SERPINE1,SFRP4,SLC40A1,SLIT2,SMAD1,SOCS3,SOX9,SPTAN1,SQSTM1,STAT3,TGM2,TIMP1,TNFRSF19,TRAF3IP2,TRIO,VAV3,YAP1,ZFP36L1
BP	GO:0042391: Regulation of membrane potential	316	25	13.64	0.00267	ABL1,ATP1B1,ATPIF1,ATXN1,BCO2,CACNG2,CHRNA3,CHRNB1,CNGA1,CNR1,KCNMA1,MGEA5,NLGN1,NLGN3,NPPA,NRXN1,PKP2,PLN,POPDC3,PSEN1,RELN,RIMS2,SCN2A,SCN3A,SCN3B
BP	GO:0048736: Appendage development	169	16	7.29	0.00268	BCL2L11,BMPR1B,CRABP2,CYP26B1,HOXD10,HOXD9,NOTCH2,PBX1,PSEN1,PTCH1,RARB,RDH10,SMOC1,SOX9,TULP3,WNT3
BP	GO:0060173: Limb development	169	16	7.29	0.00268	BCL2L11,BMPR1B,CRABP2,CYP26B1,HOXD10,HOXD9,NOTCH2,PBX1,PSEN1,PTCH1,RARB,RDH10,SMOC1,SOX9,TULP3,WNT3
BP	GO:0042327: Positive regulation of phosphorylation	850	54	36.68	0.00281	ABL1,AKT2,ALK,ANKRD6,ANXA2,ATP2B4,ATP6AP1,ATP6V0D1,CALCA,CAMK1,CCL2,CCND1,CD44,CDH2,CDK5R2,CDKN1A,CHRNA3,CLU,CREBL2,CTGF,CYR61,DNAJB11,DNAJC27,DNAJC3,FAM129A,GDF10,GDF15,GDF6,HES1,HTR2B,IGF2,INHBA,ITGA1,LIF,MAPK9,MID1,NDRG4,NTRK2,PDGFC,PFKFB2,PIM1,PSEN1,RBPMS,RELN,SDC4,SDCBP,SOX9,SQSTM1,TAOK3,TIMP2,TOM1L1,TPP1,VANGL2,VAV3
BP	GO:0010817: Regulation of hormone levels	458	33	19.76	0.00284	ADM,ATP6AP2,BCO2,BTK,CACNA2D2,CHRM3,CNR1,CRABP2,CYP1B1,CYP26A1,CYP26B1,DHRS3,DKK3,ENSA,GAL,IGF2,INHBA,ITPR2,KCNB1,LIF,MGEA5,NRXN1,PCLO,PFKFB2,RASL10B,RDH10,RIMS2,RUNX1,SCG5,SCPEP1,SNAP25,SYTL4,VGF
BP	GO:0051093: Negative regulation of developmental process	812	52	35.04	0.00284	ABCA1,ABL1,BCOR,BHLHE41,CALCA,CCL2,CCND1,CDH2,CDKN1B,COL3A1,DPYSL3,EPAS1,FOXC1,FOXO3,FRZB,GAL,HES1,INHBA,KCTD11,KIAA0319,LIF,MEIS1,MMP11,NOTCH2,NOTCH4,NPHP3,NPPB,NPR2,PAF1,PBX1,PKP2,PLK2,PPARG,PSEN1,PTCH1,PTPRM,RARB,RUNX1,SEMA3A,SEMA4F,SERPINE1,SLIT2,SOX9,SPARC,STAT3,TIMP1,TRIB2,TULP3,TWSG1,VANGL2,WNT3,YAP1
BP	GO:0007155: Cell adhesion	1365	80	58.9	0.00292	ABI3BP,ABL1,AJAP1,APLP1,ASS1,ATP1B1,BCL2L11,CADM1,CALCA,CCL2,CD44,CDH11,CDH2,CLDN11,CLPTM1,CLSTN2,CNTNAP5,COL17A1,COL3A1,CSRP1,CTGF,CTNNA2,CTNND1,CYFIP2,CYP1B1,CYR61,DPT,FAT1,FLRT1,FN1,GPNMB,HES1,HLA-E,HOXD3,ICAM2,IFNAR1,IGF2,IGFBP7,IGSF11,ITGA1,ITGA7,ITGB5,LAMA4,LPXN,MSN,NCAM2,NCAN,NFASC,NLGN1,NLGN3,NRXN1,PCDH9,PCDHB10,PCDHB14,PCDHB15,PCDHB3,PCDHB4,PKP2,PLEKHA2,PLXNB1,PRNP,PSEN1,PTPRM,RAB27A,RELN,RET,ROM1,SDC4,SERPINE1,SLIT2,SMOC1,SORBS2,SOX9,SSPN,TGM2,TRIOBP,TXK,VAV3,VCAN,ZFP36L1
BP	GO:0006811: Ion transport	1446	84	62.39	0.00293	ABCA1,ABL1,AHNAK,AKT2,ANO3,ATP10D,ATP1B1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,ATP8B1,BTK,BZRAP1,CACNA2D2,CACNG2,CALCA,CCL2,CDKN1B,CHRFAM7A,CHRNA3,CHRNB1,CNGA1,CNR1,COX11,COX17,CTGF,FABP3,FGF14,GABRP,GAL,HTR2B,ITPR2,KCNB1,KCNMA1,KCNQ2,MAOB,MAPK9,MGEA5,NIPAL2,NLGN1,NLGN3,NOS1,NPC2,NPPA,NRXN1,NSF,NTRK2,ORAI3,PACSIN3,PKP2,PLN,PPARG,PRNP,PSEN1,RAB3B,RAMP1,RELN,RHCE,SCN2A,SCN3A,SCN3B,SFRP4,SLC12A6,SLC22A17,SLC26A11,SLC26A2,SLC2A10,SLC31A2,SLC35A2,SLC36A1,SLC40A1,SLC4A8,SLC8A3,SLC9A6,SLCO3A1,SNAP25,STOM,TFRC,TMEM38A,UNC80
BP	GO:0032482: Rab protein signal transduction	550	38	23.73	0.00294	ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,DNAJC27,DOCK9,ELMOD1,FAM13A,FAM13B,FARP1,HTR2B,KALRN,NTRK2,PLXNB1,PSD2,PTGIR,RAB26,RAB27A,RAB3B,RAB3IP,RABIF,RASEF,RGL2,RGS13,RGS16,RGS2,RGS7,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,TRIO,VAV3
BP	GO:0051130: Positive regulation of cellular component organization	873	55	37.67	0.00308	AKT2,ANKRD1,ANXA2,ATPIF1,BCL2L11,BHLHB9,CAMK1,CCL2,CDC42EP3,CDKL2,CDKN1B,CLU,CNR1,CTGF,CYB5R1,DPYSL3,ELMOD1,FN1,GDF15,HES1,IGF2,JARID2,LIF,MAPK9,MAPT,MGEA5,NDRG4,NLGN1,NLGN3,NOS1,NPEPPS,NRXN1,NTRK2,OSCP1,PAF1,PLXNB1,PPARG,PSEN1,PTX3,RAB27A,RELN,RET,RGS2,RND2,SDC4,SDCBP,SERPINE1,SFRP4,SGIP1,SLIT2,SMAD1,SOX9,SQSTM1,TRIOBP,WNT3
BP	GO:0016192: Vesicle-mediated transport	1268	75	54.71	0.00313	AAK1,ABCA1,ABL1,ADM,AKT2,ANXA2,ANXA3,APLP1,ARF3,ARHGAP27,ATP6AP1,BRPF3,BTK,CALCA,CCL2,CDK5R2,CHMP2B,CLU,COL3A1,COLEC12,CYFIP2,ELMO2,ELMOD1,ENPP2,EXOC6B,EXOC7,FMN2,FN1,FNBP1,HTR2B,IGF2,ITPR2,KALRN,KRT18,LMAN2L,LOXL4,LRP10,NLGN1,NLGN3,NSF,OPTN,PACSIN3,PCLO,PEAR1,PLCD4,PPARG,PROS1,PRSS12,PSEN1,PTX3,RAB26,RAB27A,RAB3B,RAB3IP,RAMP1,RIMS2,SDC4,SDCBP,SERPINE1,SERPING1,SFRP4,SGIP1,SH3BP4,SNAP25,SPARC,SYP,SYT11,SYT4,SYTL4,TEX261,TFRC,TGM2,TIMP1,VAV3,VPS53
BP	GO:2000146: Negative regulation of cell motility	188	17	8.11	0.00324	CCL2,COL3A1,CYP1B1,DACH1,DPYSL3,MCC,MMP28,NBL1,NDRG4,PKP2,PTPRM,PTPRR,SEMA3A,SERPINE1,SLIT2,STAT3,TIMP1
BP	GO:0051345: Positive regulation of hydrolase activity	818	52	35.3	0.00330	AHSA2,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,ATP1B1,ATP6V0D1,BCL2L11,CCL2,CDKN1B,CTGF,CTSH,CYFIP2,CYR61,DNAJB11,DNAJB6,DNAJC3,DOCK9,ELMOD1,FAM13A,FA

						M13B,FARP1,FN1,HTR2B,ITGA1,ITPR2,KALRN,MAPK9,PLXNB1,PPARG,PSD2,PTGIR,RAB3IP,RABIF,RET,RGL2,RGS13,RGS16,RGS2,RGS7,SH3BGRL3,SIPA1L1,SIPA1L2,TPP1,TRIO,TXK,VAV3
BP	GO:0031960: Response to corticosteroid	142	14	6.13	0.00334	ADM,ASS1,CCL2,CCND1,CDKN1A,CTGF,FOS,GBA,HEY1,IGFBP7,MAOB,PLAT,SLIT2,SPARC
BP	GO:0022610: Biological adhesion	1372	80	59.2	0.00334	ABI3BP,ABL1,AJAP1,APLP1,ASS1,ATP1B1,BCL2L11,CADM1,CALCA,CCL2,CD44,CDH11,CDH2,CLDN11,CLPTM1,CLSTN2,CNTNAP5,COL17A1,COL3A1,CSRP1,CTGF,CTNNA2,CTNND1,CYFIP2,CYP1B1,CYR61,DPT,FAT1,FLRT1,FN1,GPNMB,HES1,HLA-E,HOXD3,ICAM2,IFNAR1,IGF2,IGFBP7,IGSF11,ITGA1,ITGA7,ITGB5,LAMA4,LPXN,MSN,NCAM2,NCAN,NFASC,NLGN1,NLGN3,NRXN1,PCDH9,PCDHB10,PCDHB14,PCDHB15,PCDHB3,PCDHB4,PKP2,PLEKHA2,PLXNB1,PRNP,PSEN1,PTPRM,RAB27A,RELN,RET,ROM1,SDC4,SERPINE1,SLIT2,SMOC1,SORBS2,SOX9,SSPN,TGM2,TRIOBP,TXK,VAV3,VCAN,ZFP36L1
BP	GO:0014070: Response to organic cyclic compound	724	47	31.24	0.00344	ABCA1,ABL1,ADM,ANKRD1,APLP1,ASS1,ATP2B4,BTG2,CCL2,CCND1,CDKN1A,CDKN1B,CHRNA3,CHRNB1,CNR1,CREM,CTGF,CYP1B1,CYP24A1,DUSP6,FOS,GAL,GATA4,GBA,GNG2,HEY1,IGF2,IGFBP7,INHBA,ITPR2,LUM,MAOB,MGEA5,NCOA1,PIM1,PLAT,PLN,PPARG,PTCH1,RARB,RFTN1,SLC8A3,SLIT2,SMAD1,SPARC,STAT3,VGF
BP	GO:0007266: Rho protein signal transduction	537	37	23.17	0.00347	ABCA1,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,CDC42EP3,COL3A1,DOCK9,ELMOD1,FAM13A,FAM13B,FARP1,HTR2B,KALRN,NTRK2,PLXNB1,PSD2,PTGIR,RAB3IP,RABIF,RGL2,RGS13,RGS16,RGS2,RGS7,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,TRIO,VANGL2,VAV3
BP	GO:0071346: Cellular response to interferon-gamma	113	12	4.88	0.00349	ASS1,CCL2,CD44,HLA-C,HLA-E,IRF6,IRF9,MID1,OAS1,PPARG,SOCS3,TXK
BP	GO:0010506:Regulation of autophagy	238	20	10.27	0.00349	ABL1,ATP1B1,ATPIF1,CSPG5,DCN,DRAM1,FAM13B,GATA4,HTR2B,KRCC1,LMCD1,MAPT,RRAGB,RRAGC,RRAGD,SFRP4,SH3BP4,SQSTM1,STOM,WDFY3
BP	GO:0008217: Regulation of blood pressure	158	15	6.82	0.00349	ACTA2,ATP6AP2,CALCA,CNR1,GCH1,IER3,NAV2,NOS1,NPPA,NPPB,NPR2,PPARG,PRCP,RASL10B,SCPEP1
BP	GO:0030001: Metal ion transport	763	49	32.92	0.00352	ABL1,AHNAK,ATP1B1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,CACNA2D2,CACNG2,CALCA,CCL2,CDKN1B,CNGA1,COX17,CTGF,FGF14,GAL,HTR2B,ITPR2,KCNB1,KCNMA1,KCNQ2,MGEA5,NIPAL2,NOS1,NPPA,NSF,ORAI3,PACSIN3,PKP2,PLN,PRNP,PSEN1,RAMP1,SCN2A,SCN3A,SCN3B,SLC12A6,SLC31A2,SLC40A1,SLC4A8,SLC8A3,SLC9A6,STOM,TFRC,TMEM38A
BP	GO:0031344: Regulation of cell projection organization	393	29	16.96	0.00355	ANKRD1,ATP8B1,BHLHB9,CAMK1,CDC42EP3,CHRNA3,CNR1,DPYSL3,FN1,KIAA0319,MAPT,NDRG4,NLGN1,NLGN3,NRXN1,NTRK2,PLK2,PLXNB1,PSEN1,RELN,RET,RND2,SEMA3A,SEMA4F,SIPA1L1,SLIT2,SMAD1,SNAP25,WNT3
BP	GO:0032487: Regulation of Rap protein signal transduction	483	34	20.84	0.00357	ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,DOCK9,ELMOD1,FAM13A,FAM13B,FARP1,HTR2B,KALRN,NTRK2,PLXNB1,PSD2,PTGIR,RAB3IP,RABIF,RGL2,RGS13,RGS16,RGS2,RGS7,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,TIMP2,TRIO,VAV3
BP	GO:0001505: Regulation of neurotransmitter levels	190	17	8.2	0.00362	ALDH5A1,BZRAP1,CHRNA3,NLGN1,NOS1,NRXN1,NTRK2,PCLO,PSEN1,RAB3B,RIMS2,SNAP25,SNCAIP,SYN2,SYT11,SYT4,SYTL4
BP	GO:0023014: Signal transduction by phosphorylation	689	45	29.73	0.00373	ABL1,ALK,ANKRD6,ATP6AP1,ATP6AP2,BMPR1B,CCL2,CD44,CDH2,CTGF,CTSH,CYR61,DNAJC27,DUSP16,DUSP6,FGF14,FOS,GBA,GDF10,GDF15,GDF6,HTR2B,IGF2,INHBA,ITGA1,LIF,MAP4K4,MAPK9,MID1,NDRG4,NTRK2,PSEN1,PTPRR,RET,RGS2,SCG2,SDCBP,SMAD1,SOX9,SPRY1,TAOK3,TIMP2,TNFRSF19,TRIB2,VANGL2
BP	GO:0001704: Formation of primary germ layer	114	12	4.92	0.00375	COL11A1,DUSP6,FN1,FOXC1,GATA4,INHBA,ITGA7,ITGB5,PAF1,SMAD1,TWSG1,WNT3
BP	GO:0032488: Cdc42 protein signal transduction	485	34	20.93	0.00381	ABCA1,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,DOCK9,ELMOD1,FAM13A,FAM13B,FARP1,HTR2B,KALRN,NTRK2,PLXNB1,PSD2,PTGIR,RAB3IP,RABIF,RGL2,RGS13,RGS16,RGS2,RGS7,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,TRIO,VAV3
BP	GO:0032489: Regulation of Cdc42 protein signal transduction	485	34	20.93	0.00381	ABCA1,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,DOCK9,ELMOD1,FAM13A,FAM13B,FARP1,HTR2B,KALRN,NTRK2,PLXNB1,PSD2,PTGIR,RAB3IP,RABIF,RGL2,RGS13,RGS16,RGS2,RGS7,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,TRIO,VAV3
BP	GO:2000377: Regulation of reactive oxygen species metabolic process	129	13	5.57	0.00381	ASS1,ATP2B4,BCO2,CDKN1A,CLU,CYP1B1,FOXO3,IER3,MAPK9,PRCP,PTGIS,PTX3,RAB27A
BP	GO:0009187: Cyclic nucleotide metabolic process	191	17	8.24	0.00382	ABCA1,ADM,APLP1,CALCA,CNP,EGLN1,GNG7,GUCA1A,HTR2B,NOS1,NPPA,NPPB,NPR2,NTRK2,PTGIR,RAMP1,TIMP2
BP	GO:1901565: Organonitrogen compound catabolic process	325	25	14.02	0.00385	ALDH5A1,ATP2B4,CD44,CSPG5,CTSH,DCN,DPYSL3,EGLN1,ENPP2,FUCA1,GBA,GNS,HEXB,HGSNAT,IDS,LUM,MAOB,NCAN,NOS1,PIPOX,SDC4,TPP1,UPB1,VCAN,XPNPEP1

BP	GO:0006915: Apoptotic process	1769	99	76.33	0.00389	ABL1,ADM,AIFM2,AKT2,ALK,ANKRD1,APH1A,APLP1,ARHGEF3,ATPIF1,BCL2A1,BCL2L11,BHLHB9,BLCAP,BMPR1B,BTG2,BTK,C8orf4,CADM1,CCL2,CD44,CDKN1A,CDKN1B,CLU,CNR1,CTGF,CTSH,CYFIP2,CYP1B1,CYR61,DAPL1,DDX5,DNAJB6,DNAJC3,DRAM1,DUSP6,ELL3,ELMO2,FMN2,FOXC1,FOXO3,FRZB,GAL,GDF10,GDF15,GDF6,GRK5,H1F0,HTR2B,IER3,IL20RA,INHBA,ITGA1,KALRN,KCNMA1,KRT18,MAP4K4,MAPK9,MAPT,MAX,NCOA1,NOTCH2,NTRK2,PDIA3,PHLDA1,PIM1,PLAGL1,PLK2,PPARG,PRNP,PSEN1,PSMB8,PTGIS,PTPRH,RARB,RET,RFFL,RRAGC,SCG2,SCN2A,SEMA3A,SERPINE1,SFRP4,SLC40A1,SLIT2,SMAD1,SOCS3,SOX9,SPTAN1,SQSTM1,STAT3,TGM2,TIMP1,TNFRSF19,TRAF3IP2,TRIO,VAV3,YAP1,ZFP36L1
BP	GO:0043086: Negative regulation of catalytic activity	767	49	33.1	0.00389	ABL1,ANXA2,ANXA2P2,ANXA3,ATP2B4,ATPIF1,CAMK2N1,CD44,CDKN1A,CDKN1B,CDKN2C,CNR1,COX11,CRIM1,DLG2,DNAJB6,DNAJC3,DUSP16,DUSP6,EGLN1,ELFN1,ENSA,FARP1,GBA,HEXIM1,NOS1,PI15,PLN,PPARG,PROS1,PRPSAP1,PSEN1,PSMB8,PTX3,RFFL,RGS2,SCG5,SERPINE1,SERPING1,SH3BP4,SLIT2,SOCS3,SPRY1,TAOK3,TIMP1,TIMP2,TIMP3,TRIB2,ZFYVE1
BP	GO:0030326: Embryonic limb morphogenesis	130	13	5.61	0.00407	BCL2L11,CRABP2,CYP26B1,HOXD10,HOXD9,NOTCH2,PBX1,PSEN1,PTCH1,RARB,RDH10,TULP3,WNT3
BP	GO:0035113: Embryonic appendage morphogenesis	130	13	5.61	0.00407	BCL2L11,CRABP2,CYP26B1,HOXD10,HOXD9,NOTCH2,PBX1,PSEN1,PTCH1,RARB,RDH10,TULP3,WNT3
BP	GO:0051384: Response to glucocorticoid	130	13	5.61	0.00407	ADM,ASS1,CCL2,CCND1,CDKN1A,FOS,GBA,HEY1,IGFBP7,MAOB,PLAT,SLIT2,SPARC
BP	GO:0008219: Cell death	1876	104	80.95	0.00411	ABL1,ADM,AIFM2,AKT2,ALK,ANKRD1,APH1A,APLP1,ARHGEF3,ATPIF1,BCL2A1,BCL2L11,BHLHB9,BLCAP,BMPR1B,BTG2,BTK,C8orf4,CADM1,CCL2,CD44,CDKN1A,CDKN1B,CLU,CNR1,CTGF,CTSH,CYFIP2,CYP1B1,CYP26B1,CYR61,DAPL1,DDX5,DNAJB6,DNAJC3,DRAM1,DUSP6,ELL3,ELMO2,FMN2,FOXC1,FOXO3,FRZB,GAL,GDF10,GDF15,GDF6,GRK5,H1F0,HTR2B,IER3,IL20RA,INHBA,ITGA1,KALRN,KCNMA1,KRT18,MAP4K4,MAPK9,MAPT,MAX,MGEA5,NCOA1,NOTCH2,NTRK2,OPTN,PDIA3,PHLDA1,PIM1,PLAGL1,PLK2,PPARG,PRNP,PSEN1,PSMB8,PTGIS,PTPRH,PYGL,RARB,RET,RFFL,RRAGC,SCG2,SCN2A,SEMA3A,SERPINE1,SFRP4,SLC40A1,SLIT2,SMAD1,SNCAIP,SOCS3,SOX9,SPTAN1,SQSTM1,STAT3,TGM2,TIMP1,TNFRSF19,TRAF3IP2,TRIO,VAV3,YAP1,ZFP36L1
BP	GO:1901701: Cellular response to oxygen-containing compound	827	52	35.68	0.00411	ABCA1,ABL1,AKT2,ANKRD1,APLP1,ASS1,ATP2B4,ATP6AP1,ATP6V0D1,ATP6V0E1,ATP6V0E2,ATP6V1A,ATP6V1G2,BTK,CCL2,COL3A1,COLEC12,CYP1B1,CYP24A1,CYP26A1,CYP26B1,FOS,GATA4,GNG2,GNG7,GNG8,IGF2,INHBA,ITPR2,MAPK9,MAX,NRXN1,PAF1,PDGFC,PDGFD,PIM1,PLAT,PPARG,PTCH1,PTGER2,RET,RRAGB,RRAGC,RRAGD,SERPINE1,SH3BP4,SLC8A3,SLIT2,SOCS3,SOX9,STAT3,WNT3
BP	GO:0010604: Positive regulation of macromolecule metabolic process	2423	130	104.55	0.00418	ABL1,AHRR,AKT2,ALK,ANKRD1,ANXA2,ARID1A,ARMCX3,ARRDC3,ATP2B4,ATP6V0D1,ATPIF1,ATXN1,BCL2L11,BPTF,BTG2,CALCA,CAMK1,CCBE1,CCL2,CCND1,CD44,CDK5R2,CDKN1A,CDKN1B,CEBPD,CHRNA3,CHURC1,CIRBP,CLU,CREB5,CREBL2,CREM,CTGF,CTSH,CYFIP2,CYP26B1,CYR61,DDX5,DNAJB11,DNAJC3,EBF1,ELL3,EPAS1,EPM2AIP1,FAM129A,FBXO4,FN1,FOS,FOXC1,FOXO3,GAL,GATA4,GBA,GDF10,GDF15,GDF6,GRIP1,HES1,HEXB,HEY1,HOXD10,HOXD3,HOXD8,HOXD9,HTR2B,IER3,IGF2,INHBA,IRF6,ITGA1,JARID2,LBH,LIF,LUM,MAPK9,MED13,MEIS1,MGEA5,MSN,NANOS1,NCOA1,NCOA3,NCOA7,NFAT5,NOS1,NOTCH4,NSD1,NSF,NTRK2,PACSIN3,PAF1,PBX1,PDGFC,PIM1,PLAGL1,PLK2,PPARG,PSEN1,PSMB8,RAB27A,RAMP1,RARB,RBPMS,RELN,RET,RFWD2,RIMS2,RUNX1,SAMD4A,SDC4,SERPINE1,SFRP4,SLC40A1,SMAD1,SMARCA2,SOAT1,SOX9,SPEN,SQSTM1,STAT3,TAF11,TAOK3,TOM1L1,TPP1,TRIB2,TXK,VANGL2,WNT3,YAP1
BP	GO:1901342: Regulation of vasculature development	209	18	9.02	0.00420	ADM,ANXA3,CCBE1,CCL2,CTSH,CYP1B1,EGLN1,ENPP2,FOXC1,GATA4,HEY1,HIF1AN,NPPB,PTGIS,PTPRM,RUNX1,SERPINE1,SPARC
BP	GO:0009891: Positive regulation of biosynthetic process	1568	89	67.66	0.00422	ABCA1,ADM,AKT2,ANKRD1,ARID1A,ARMCX3,ASS1,ATXN1,BPTF,BTG2,CALCA,CAMK1,CCL2,CEBPD,CHURC1,CIRBP,CLU,CREB5,CREBL2,CREM,CTGF,CYR61,DDX5,EBF1,ELL3,EPAS1,EPM2AIP1,FABP3,FAM129A,FOS,FOXC1,FOXO3,GAL,GATA4,GDF6,GRIP1,GUCA1A,HES1,HEXB,HEY1,HOXD10,HOXD8,HOXD9,HTR2B,IGF2,INHBA,IRF6,LBH,LIF,LUM,MAPK9,MED13,MEIS1,MID1IP1,NCOA1,NCOA3,NCOA7,NFAT5,NOS1,NOTCH4,NSD1,NTRK2,PAF1,PBX1,PDGFC,PLAGL1,PPARG,PSEN1,PTGIR,PTX3,RAB27A,RAMP1,RARB,RET,RUNX1,SAMD4A,SERPINE1,SLC40A1,SMAD1,SMARCA2,SOAT1,SOX9,SPEN,SQSTM1,STAT3,TAF11,TIMP2,TXK,YAP1
BP	GO:0017157: Regulation of exocytosis	146	14	6.3	0.00429	ATP6AP1,CDK5R2,NLGN1,NSF,PCLO,RAB26,RAB27A,RAB3B,RIMS2,SDC4,SDCBP,SYT11,SYT4,SYTL4
BP	GO:0016265: Death	1880	104	81.12	0.00438	ABL1,ADM,AIFM2,AKT2,ALK,ANKRD1,APH1A,APLP1,ARHGEF3,ATPIF1,BCL2A1,BCL2L11,BHLHB9,BLCAP,BMPR1B,BTG2,BTK,C8orf4,CADM1,CCL2,CD44,CDKN1A,CDKN1B,CLU,CNR1,CTGF,CTSH,CYFIP2,CYP1B1,CYP26B1,CYR61,DAPL1,DDX5,DNAJB6,DNAJC3,DRAM1,DUSP6,ELL3,ELMO2,FMN2,FOXC1,FOXO3,FRZB,GAL,GDF10,GDF15,GDF6,GRK5,H1F0,HTR2B,IER3,IL20RA,INHBA,ITGA1,KALRN,KCNMA1,KRT18,MAP4K4,MAPK9,MAPT,MAX,MGEA5,NCOA1,NOTCH2,NTRK2,OPTN,PDIA3,PHLDA1,PIM1,PLAGL1,PLK

						2,PPARG,PRNP,PSEN1,PSMB8,PTGIS,PTPRH,PYGL,RARB,RET,RFFL,RRAGC,SCG2,SCN2A,SEMA3A,SERPINE1,SFRP4,SLC40A1,SLIT2,SMAD1,SNCAIP,SOCS3,SOX9,SPTAN1,SQSTM1,STAT3,TGM2,TIMP1,TNFRSF19,TRAF3IP2,TRIO,VAV3,YAP1,ZFP36L1
BP	GO:0035023: Regulation of Rho protein signal transduction	508	35	21.92	0.00441	ABCA1,ARHGAP20,ARHGAP26,ARHGAP27,ARHGAP31,ARHGAP36,ARHGEF3,ARHGEF37,ASAP1,ASAP2,COL3A1,DOCK9,ELMOD1,FAM13A,FAM13B,FARP1,HTR2B,KALRN,NTRK2,PLXNB1,PSD2,PTGIR,RAB3IP,RABIF,RGL2,RGS13,RGS16,RGS2,RGS7,SH3BGRL3,SH3BP4,SIPA1L1,SIPA1L2,TRIO,VAV3
BP	GO:0001558: Regulation of cell growth	330	25	14.24	0.00468	CDKN1A,CDKN1B,CDKN2C,CRIM1,CTGF,CYR61,DCBLD2,FN1,FRZB,GAL,HBEGF,IGFBP6,IGFBP7,INHBA,MAPT,NPPA,NPPB,PPARG,RND2,SEMA3A,SEMA4F,SH3BP4,SLIT2,SMARCA2,WNT3
BP	GO:0045596: Negative regulation of cell differentiation	641	42	27.66	0.00472	ABCA1,BHLHE41,CALCA,CCND1,CDH2,COL3A1,DPYSL3,EPAS1,FOXC1,FOXO3,FRZB,GAL,HES1,INHBA,KCTD11,KIAA0319,LIF,MEIS1,MMP11,NOTCH2,NOTCH4,NPHP3,NPR2,PAF1,PBX1,PKP2,PLK2,PPARG,PSEN1,PTCH1,RARB,RUNX1,SEMA3A,SEMA4F,SLIT2,SOX9,STAT3,TRIB2,TWSG1,VANGL2,WNT3,YAP1
BP	GO:0014706: Striated muscle tissue development	313	24	13.51	0.00476	ANKRD1,ANKRD33,BTG2,COL11A1,CYP26B1,DCN,DDX5,EGLN1,FLNB,FOS,FOXC1,GATA4,HEY1,HOXD10,HOXD9,ITGA7,NDRG4,NEBL,PKP2,PLAGL1,PLN,RARB,SGCB,SMAD1
BP	GO:0072006: Nephron development	133	13	5.74	0.00495	ACTA2,AQP11,BASP1,CALB1,CD44,HES1,LIF,PBX1,PTCH1,RET,SOX9,VANGL2,YAP1
BP	GO:0006720:Isoprenoid metabolic process	118	12	5.09	0.00496	BCO2,CRABP2,CYP1B1,CYP26A1,CYP26B1,DHRS3,NPC2,PHYH,RBP1,RDH10,SCPEP1,SDC4
BP	GO:0032102: Negative regulation of response to external stimulus	229	19	9.88	0.00498	ANXA2,CCL2,CTNNA2,GBA,IER3,MMP28,NBL1,NRXN1,PLAT,PPARG,PROS1,PTGIS,SEMA3A,SERPINE1,SERPING1,SLIT2,SOCS3,TSPAN8,WNT3
BP	GO:0042127: Regulation of cell proliferation	1414	81	61.01	0.00499	ABL1,ADM,ANXA2,ATPIF1,BMPR1B,BTG2,BTK,CCL2,CCND1,CDKN1A,CDKN1B,CDKN2C,CTGF,CTSH,CYP1B1,CYR61,DACH1,DPT,ELL3,FABP3,FBXO2,FOXO3,FRZB,GAL,GATA4,GPNMB,GRK5,HBEGF,HES1,HLA-E,HTR2B,IGF2,IGFBP6,IGFBP7,INHBA,IRF6,ITGA1,JARID2,KCTD11,LIF,MAB21L1,MCC,NDRG4,NOTCH2,NTRK2,PBX1,PDGFC,PKP2,PLXNB1,PPARG,PRNP,PTCH1,PTGER2,PTGIR,PTPRM,RARB,RARRES1,RBFOX2,RUNX1,SCG2,SERPINE1,SESN1,SFRP4,SH3BP4,SKAP2,SLIT2,SMAD1,SMARCA2,SOX9,SPARC,SPRY1,STAT3,TES,TGM2,TIMP1,TIMP2,TNS3,TSPAN31,TXK,VAV3,YAP1

Ont = Ontology; BP = Biological Process; GO = Gene Ontology

Tabela 4. Representação completa dos processos biológicos e seus respectivos genes enriquecidos no fenótipo das células proliferativas.

Ont	Terms	Annotated	Significant	Expected	Classic	Genes
BP	GO:0050793: Regulation of developmental process	1973	63	23.76	1.0e-13	AGTR1,ARC,ASCL1,ATP11C,BAMBI,BCL11A,BOC,CCDC85B,CDC20,CENPF,CNTN1,CNTN4,CX3CL1,CXCR4,DIO3,DLX5,EGR3,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,ID4,IGFBP3,IGFBP5,IL7,INF2,KIF14,LAMA1,LDB2,LMO4,MGLL,MLLT3,MSX2,MYC,MYO10,NEK6,NELL1,PER2,POLR2F,PRKCA,RORB,SDC2,SERPINF1,SFRP1,SMC3,SNAI1,SOX11,SOX6,STC2,TBX3,TCF4,TERT,TGIF2,TMEM100,TNFRSF21,TRIB3,TRIM67,TSPO,UNC5D,ZFPM1
BP	GO:0045595: Regulation of cell differentiation	1390	50	16.74	1.0e-12	AGTR1,ASCL1,ATP11C,BAMBI,BCL11A,BOC,CCDC85B,CDC20,CNTN1,CNTN4,CXCR4,DLX5,EGR3,FGFR2,GATA3,GLI2,GREM1,HDAC9,HIST1H4J,ID4,IGFBP3,IGFBP5,IL7,LDB2,LMO4,MGLL,MSX2,MYC,NELL1,PER2,POLR2F,PRKCA,RORB,SDC2,SERPINF1,SFRP1,SMC3,SNAI1,SOX11,SOX6,TBX3,TCF4,TGIF2,TMEM100,TNFRSF21,TRIB3,TRIM67,TSPO,UNC5D,ZFPM1
BP	GO:0048856: Anatomical structure development	4769	104	57.42	2.4e-12	ADAM12,AGTR1,ARC,ASCL1,ATP11C,BAMBI,BCL11A,BID,BOC,BRSK2,BYSL,BZW2,CACNA1G,CDC20,CDKN1C,CENPF,CHRDL1,CNTN1,CNTN3,CNTN4,CNTNAP2,COL18A1,CRYAB,CX3CL1,CXCR4,DAND5,DLX5,DOK4,DUSP2,EGFR,EGR3,EIF4EBP1,EPHA8,EYA4,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,HTRA1,ID4,IGFBP3,IGFBP5,IL7,INF2,JPH1,KCNH1,KIF14,LAMA1,LDB2,LHX6,LMO4,LOX,MAP3K1,MGLL,MLLT3,MSX2,MYC,MYLIP,MYO10,NAA15,NELL1,NR4A3,PDE2A,PER2,POLR2F,PPAT,PRKCA,PRRX2,PSD3,RAN,RORB,S100A4,SDC2,SEMA3C,SERPINF1,SFRP1,SIX6,SLC30A1,SLC7A11,SLITRK6,SMAD6,SMC3,SNAI1,SOX11,SOX6,SPRY2,STC2,TBX3,TCF4,TGIF2,TJP2,TLE1,TMEM100,TNFRSF21,TOP1,TPD52,TRIM67,TSPO,UNC5A,UNC5D,ZFPM1
BP	GO:0030154: Cell differentiation	3476	85	41.85	3.1e-12	ADAM12,ADCYAP1R1,AGTR1,ASCL1,ATP11C,BAMBI,BCL11A,BOC,BRSK2,BYSL,BZW2,CACNA1G,CCDC85B,CDC20,CDKN1C,CENPF,CHRDL1,CNTN1,CNTN4,CNTNAP2,COL18A1,CRYAB,CXCR4,DLX5,EGFR,EGR3,EPHA8,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,ID4,IGFBP3,IGFBP5,IL7,KCNH1,KIF14,LAMA1,LDB2,LHX6,LMO4,MAP3K1,MGLL,MSX2,MYC,MYO10,NAA15,NELL1,NR4A3,PDE2A,PER2,POLR2F,PRKCA,PSD3,RAN,RORB,S100A4,SDC2,SEMA3C,SERPINF1,SFRP1,SLC7A11,SLITRK6,SMAD6,SMC3,SNAI1,SOX11,SOX6,SPRY2,TBX3,TCF4,TGIF2,TJP2,TMEM100,TNFRSF21,TPD52,TRIB3,TRIM67,TSPO,UNC5A,UNC5D,ZFPM1
BP	GO:0044767: Single-organism developmental process	5304	110	63.86	8.5e-12	ADAM12,ADCYAP1R1,AGTR1,ARC,ASCL1,ATP11C,BAMBI,BCL11A,BID,BOC,BRSK2,BYSL,BZW2,CACNA1G,CCDC85B,CDC20,CDKN1C,CENPF,CHRDL1,CNTN1,CNTN3,CNTN4,CNTNAP2,COL18A1,CRYAB,CX3CL1,CXCR4,DAND5,DIO3,DLX5,DOK4,DUSP2,EGFR,EGR3,EIF4EBP1,EPHA8,EYA4,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,HTRA1,ID4,IGFBP3,IGFBP5,IL7,JPH1,KCNH1,KIF14,KLF9,LAMA1,LDB2,LHX6,LMO4,LOX,MAP3K1,MGLL,MLLT3,MSX2,MYC,MYLIP,MYO10,NAA15,NEK6,NELL1,NR4A3,PDE2A,PER2,POLR2F,PPAT,PRKCA,PRRX2,PSD3,RAN,RORB,S100A4,SDC2,SEMA3C,SERPINF1,SFRP1,SIX6,SLC30A1,SLC7A11,SLITRK6,SMAD6,SMC3,SNAI1,SOX11,SOX6,SPRY2,STC2,TBX3,TCF4,TERT,TGIF2,TJP2,TLE1,TMEM100,TNFRSF21,TOP1,TPD52,TRIB3,TRIM67,TSPO,UNC5A,UNC5D,ZFPM1
BP	GO:0032502: Developmental process	5390	111	64.9	9.7e-12	ADAM12,ADCYAP1R1,AGTR1,ARC,ASCL1,ATP11C,BAMBI,BCL11A,BID,BOC,BRSK2,BYSL,BZW2,CACNA1G,CCDC85B,CDC20,CDKN1C,CENPF,CHRDL1,CNTN1,CNTN3,CNTN4,CNTNAP2,COL18A1,CRYAB,CX3CL1,CXCR4,DAND5,DIO3,DLX5,DOK4,DUSP2,EGFR,EGR3,EIF4EBP1,EPHA8,EYA4,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,HTRA1,ID4,IGFBP3,IGFBP5,IL7,INF2,JPH1,KCNH1,KIF14,KLF9,LAMA1,LDB2,LHX6,LMO4,LOX,MAP3K1,MGLL,MLLT3,MSX2,MYC,MYLIP,MYO10,NAA15,NEK6,NELL1,NR4A3,PDE2A,PER2,POLR2F,PPAT,PRKCA,PRRX2,PSD3,RAN,RORB,S100A4,SDC2,SEMA3C,SERPINF1,SFRP1,SIX6,SLC30A1,SLC7A11,SLITRK6,SMAD6,SMC3,SNAI1,SOX11,SOX6,SPRY2,STC2,TBX3,TCF4,TERT,TGIF2,TJP2,TLE1,TMEM100,TNFRSF21,TOP1,TPD52,TRIB3,TRIM67,TSPO,UNC5A,UNC5D,ZFPM1
BP	GO:0048869: Cellular developmental process	3696	86	44.5	3.4e-11	ADAM12,ADCYAP1R1,AGTR1,ARC,ASCL1,ATP11C,BAMBI,BCL11A,BOC,BRSK2,BYSL,BZW2,CACNA1G,CCDC85B,CDC20,CDKN1C,CENPF,CHRDL1,CNTN1,CNTN4,CNTNAP2,COL18A1,CRYAB,CXCR4,DLX5,EGFR,EGR3,EPHA8,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,ID4,IGFBP3,IGFBP5,IL7,KCNH1,KIF14,LAMA1,LDB2,LHX6,LMO4,MAP3K1,MGLL,MSX2,MYC,MYO10,NAA15,NELL1,NR4A3,PDE2A,PER2,POLR2F,PRKCA,PSD3,RAN,RORB,S100A4,SDC2,SEMA3C,SERPINF1,SFRP1,SLC7A11,SLITRK6,SMAD6,SMC3,SNAI1,SOX11,SOX6,SPRY2,TBX3,TCF4,TGIF2,TJP2,TMEM100,TNFRSF21,TPD52,TRIB3,TRIM67,TSPO,UNC5A,UNC5D,ZFPM1
BP	GO:0048731: System development	3977	90	47.88	3.9e-11	AGTR1,ASCL1,ATP11C,BAMBI,BCL11A,BID,BOC,BRSK2,BZW2,CACNA1G,CDC20,CDKN1C,CENPF,CHRDL1,CNTN1,CNTN3,CNTN4,CNTNAP2,COL18A1,CRYAB,CX3CL1,CXCR4,DAND5,DLX5,DOK4,EGFR,EGR3,EIF4EBP1,EPHA8,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,HTRA1,ID4,IGFBP5,IL7,JPH1,KIF14,LAMA1,LDB2,LHX6,LMO4,LOX,MAP3K1,MGLL,MLLT3,MSX2,MYC,MYLIP,MYO10,NAA15,NELL1,NR4A3,PDE2A,PER2,PPAT,PRKCA,PRRX2,PSD3,RORB,S100A4,SDC2,SEMA3C,SERPINF1,SFRP1,SIX6,SLC7A11,SLITRK6,SMAD6,SNAI1,SOX11,SOX6,SPRY2,STC2,TBX3,TCF4

						,TGIF2,TLE1,TMEM100,TNFRSF21,TPD52,TRIM67,TSPO,UNC5A,UNC5D,ZFPM1
BP	GO:0007275: Multicellular organismal development	4546	98	54.73	4.3e-11	ADCYAP1R1,AGTR1,ARC,ASCL1,ATP11C,BAMBI,BCL11A,BID,BOC,BRSK2,BYSL,BZW2,CACNA1G,CDC20,CDKN1C,CENPF,CHRDL1,CNTN1,CNTN3,CNTN4,CNTNAP2,COL18A1,CRYAB,CX3CL1,CXCR4,DAND5,DLX5,DOK4,DUSP2,EGFR,EGR3,EIF4EBP1,EPHA8,EYA4,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,HTRA1,ID4,IGFBP5,IL7,JPH1,KIF14,KLF9,LAMA1,LDB2,LHX6,LMO4,LOX,MAP3K1,MGLL,MLLT3,MSX2,MYC,MYLIP,MYO10,NAA15,NELL1,NR4A3,PDE2A,PER2,PPAT,PRKCA,PRRX2,PSD3,RORB,S100A4,SDC2,SEMA3C,SERPINF1,SFRP1,SIX6,SLC30A1,SLC7A11,SLITRK6,SMAD6,SNAI1,SOX11,SOX6,SPRY2,STC2,TBX3,TCF4,TGIF2,TLE1,TMEM100,TNFRSF21,TOP1,TPD52,TRIM67,TSPO,UNC5A,UNC5D,ZFPM1
BP	GO:0048468: Cell development	1920	57	23.12	4.5e-11	ASCL1,BAMBI,BCL11A,BOC,BRSK2,CACNA1G,CDC20,CDKN1C,CNTN1,CNTN4,CNTNAP2,COL18A1,CRYAB,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,GREM1,HDAC9,ID4,KIF14,LAMA1,LDB2,LHX6,MAP3K1,MGLL,MSX2,MYO10,NR4A3,PDE2A,PER2,POLR2F,RAN,RORB,S100A4,SDC2,SEMA3C,SERPINF1,SFRP1,SLITRK6,SMC3,SNAI1,SOX11,SOX6,TBX3,TCF4,TGIF2,TJP2,TNFRSF21,TRIM67,TSPO,UNC5A,UNC5D,ZFPM1
BP	GO:0009653: Anatomical structure morphogenesis	2462	65	29.64	1.9e-10	ADAM12,ARC,BAMBI,BCL11A,BOC,BRSK2,BYSL,CACNA1G,CDKN1C,CNTN1,CNTN4,COL18A1,CRYAB,CX3CL1,CXCR4,DLX5,DUSP2,EGFR,EGR3,EPHA8,EYA4,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HTRA1,IGFBP5,IL7,INF2,KCNH1,KIF14,LAMA1,LMO4,MAP3K1,MGLL,MLLT3,MSX2,MYC,MYO10,NAA15,NR4A3,PRKCA,PRRX2,RORB,S100A4,SDC2,SEMA3C,SERPINF1,SFRP1,SIX6,SLITRK6,SNAI1,SOX11,SOX6,SPRY2,TBX3,TGIF2,TLE1,TMEM100,TPD52,UNC5A,UNC5D,ZFPM1
BP	GO:0009719: Response to endogenous stimulus	1396	44	16.81	2.2e-09	ABCC4,ADCYAP1R1,ASCL1,BAIAP2L1,BAMBI,BID,CARD9,CDKN1C,CRYAB,DAND5,DLX5,EGFR,EGR3,EIF4EBP1,FGFR2,GATA3,HDAC9,HTRA1,IGFBP5,KLF9,LOX,MAP3K1,MSX2,MYC,NR4A3,PDE2A,PPAT,PRKCA,RORB,RUVBL2,SDC2,SERPINF1,SFRP1,SLC7A11,SMAD6,SOX11,SOX6,SPRY2,STC2,TBC1D4,TGIF2,TMEM100,TRIB3,TSPO
BP	GO:2000026: Regulation of multicellular organismal development	1417	44	17.06	3.6e-09	ASCL1,ATP11C,BAMBI,BCL11A,CDC20,CENPF,CNTN1,CNTN4,CX3CL1,CXCR4,EGR3,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,ID4,IL7,KIF14,LAMA1,MGLL,MLLT3,MSX2,MYC,NELL1,PER2,PRKCA,SDC2,SERPINF1,SFRP1,SNAI1,SOX11,SOX6,TBX3,TCF4,TGIF2,TMEM100,TNFRSF21,TRIM67,TSPO,UNC5D,ZFPM1
BP	GO:0000904: Cell morphogenesis involved in differentiation	836	32	10.07	5.7e-09	BAMBI,BCL11A,BOC,BRSK2,CACNA1G,CNTN1,CNTN4,COL18A1,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,GREM1,KIF14,LAMA1,MAP3K1,MGLL,MSX2,MYO10,NR4A3,S100A4,SDC2,SEMA3C,SFRP1,SLITRK6,SNAI1,UNC5A,UNC5D,ZFPM1
BP	GO:0048513: Organ development	2881	68	34.69	7.6e-09	AGTR1,ASCL1,ATP11C,BAMBI,BCL11A,BID,CDKN1C,CENPF,CHRDL1,CNTN1,CNTN4,CNTNAP2,COL18A1,CRYAB,CXCR4,DAND5,DLX5,EGFR,EGR3,EIF4EBP1,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,HTRA1,ID4,IGFBP5,IL7,JPH1,KIF14,LAMA1,LDB2,LHX6,LMO4,LOX,MAP3K1,MLLT3,MSX2,MYC,NELL1,NR4A3,PDE2A,PPAT,PRKCA,PRRX2,RORB,S100A4,SEMA3C,SERPINF1,SFRP1,SIX6,SLC7A11,SLITRK6,SMAD6,SNAI1,SOX11,SOX6,SPRY2,STC2,TBX3,TGIF2,TLE1,TPD52,TSPO,ZFPM1
BP	GO:0051094: Positive regulation of developmental process	993	35	11.96	8.4e-09	AGTR1,ASCL1,ATP11C,BAMBI,BCL11A,BOC,CDC20,CNTN1,CX3CL1,CXCR4,DIO3,DLX5,EGR3,FGFR2,GATA3,GLI2,GREM1,HDAC9,ID4,IGFBP3,IL7,MSX2,MYC,NELL1,PRKCA,SERPINF1,SFRP1,SNAI1,SOX11,SOX6,TCF4,TGIF2,TMEM100,TRIM67,TSPO
BP	GO:0045597: Positive regulation of cell differentiation	725	29	8.73	1.2e-08	AGTR1,ASCL1,ATP11C,BAMBI,BCL11A,BOC,CNTN1,CXCR4,DLX5,EGR3,GATA3,GLI2,GREM1,ID4,IGFBP3,IL7,MSX2,NELL1,PRKCA,SERPINF1,SFRP1,SNAI1,SOX11,SOX6,TCF4,TGIF2,TMEM100,TRIM67,TSPO
BP	GO:0030182: Neuron differentiation	1202	38	14.47	3.3e-08	ASCL1,BCL11A,BOC,BRSK2,CACNA1G,CDC20,CDKN1C,CHRDL1,CNTN1,CNTN4,CNTNAP2,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,ID4,LAMA1,LHX6,LMO4,MGLL,MYO10,NR4A3,PSD3,RORB,SDC2,SEMA3C,SERPINF1,SLITRK6,SOX11,TCF4,TGIF2,TRIM67,TSPO,UNC5A,UNC5D
BP	GO:0048699: Generation of neurons	1309	40	15.76	3.4e-08	ASCL1,BCL11A,BOC,BRSK2,CACNA1G,CDC20,CDKN1C,CHRDL1,CNTN1,CNTN4,CNTNAP2,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,ID4,LAMA1,LHX6,LMO4,MGLL,MYO10,NR4A3,PER2,PSD3,RORB,SDC2,SEMA3C,SERPINF1,SLITRK6,SOX11,TCF4,TGIF2,TNFRSF21,TRIM67,TSPO,UNC5A,UNC5D
BP	GO:0010468: Regulation of gene expression	4014	83	48.33	3.7e-08	AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,CNTN1,CRYAB,DAND5,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP5,IL7,INSM2,ISOC2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,MYLIP,NAA15,NELL1,NR4A3,PDE2A,PER2,PHF5A,POLR2F,PPRC1,PRR16,PRRX2,RAN,RORB,RPS26,RUVBL2,SAMD11,SERPINF1,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,SPRY2,STC2,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TOP1,TRAP1,TRIB3,VARS,ZFPM1,ZNF121
BP	GO:0009888: Tissue development	1708	47	20.56	4.2e-08	ARC,ASCL1,BAMBI,CENPF,COL18A1,CXCR4,DAND5,DLX5,DUSP2,EGFR,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,IGFBP5,LAMA1,LDB2,LMO4,MAP3K1,MLLT3,MSX2,MYC,NELL1,NR4A3,PDE2A,PRKCA,PRRX2,RORB,S100A4,SEMA3C,SERPINF1,SFRP1,SLC7A11,SLITRK6,SMAD6,SNAI1,SOX11,SOX6,SPRY2,STC2,TBX3,TGIF2,TJP2,TMEM100,ZFPM1
BP	GO:0051239:	2243	56	27.01	4.3e-08	AGTR1,ASCL1,ATP11C,BAMBI,BCL11A,CACNA1G,CARD9,CDC20,CENPF,CNTN1,CNTN4,CX3CL1,CXCR4,DIO3,DLX5,EGFR,EGR3,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,ID4,IGFBP5,IL7,KIF14,LAMA1,MGLL,MLLT3,MSX2,

	Regulation of multicellular organismal process					MYC,MYLIP,NELL1,PER2,POLR2F,POLR3D,PRKCA,RORB,SDC2,SERPINF1,SFRP1,SNAI1,SOX11,SOX6,STC2,TBX3,TCF4,TGIF2,TMEM100,TNFRSF21,TRIM67,TSPO,UNC5D,ZFPM1
BP	GO:0022008: Neurogenesis	1385	41	16.68	5.3e-08	ASCL1,BCL11A,BOC,BRSK2,CACNA1G,CDC20,CDKN1C,CHRDL1,CNTN1,CNTN4,CNTNAP2,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,ID4,LAMA1,LHX6,LMO4,MGLL,MYO10,NR4A3,PER2,PSD3,RORB,SDC2,SEMA3C,SERPINF1,SLITRK6,SOX11,SOX6,TCF4,TGIF2,TNFRSF21,TRIM67,TSPO,UNC5A,UNC5D
BP	GO:0007399: Nervous system development	2027	52	24.41	6.5e-08	ASCL1,BCL11A,BID,BOC,BRSK2,BZW2,CACNA1G,CDC20,CDKN1C,CHRDL1,CNTN1,CNTN3,CNTN4,CNTNAP2,CXCR4,DLX5,DOK4,EGFR,EGR3,EPHA8,FGFR2,GATA3,GLI2,ID4,KIF14,LAMA1,LHX6,LMO4,MGLL,MYLIP,MYO10,NELL1,NR4A3,PER2,PSD3,RORB,SDC2,SEMA3C,SERPINF1,SFRP1,SLC7A11,SLITRK6,SOX11,SOX6,TBX3,TCF4,TGIF2,TNFRSF21,TRIM67,TSPO,UNC5A,UNC5D
BP	GO:0042127: Regulation of cell proliferation	1414	41	17.02	9.3e-08	ABCC4,AGTR1,ASCL1,BAMBI,BID,CDC20,CDKN1C,COL18A1,DLX5,EGFR,EGLN3,EGR3,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HTRA1,ID4,IGFBP3,IGFBP5,IL7,KCNH1,KIF14,KLF9,MSX2,MYC,NELL1,PER2,PRKCA,PRRX2,SERPINF1,SFRP1,SMAD6,SOX11,SPRY2,TBX3,TNFRSF21,TPD52,TSPO
BP	GO:0006366: Transcription from RNA polymerase II promoter	1817	48	21.88	1.0e-07	AKNA,ASCL1,BCL11A,CDKN1C,CHRDL1,DAND5,DLX5,EGFR,EGLN3,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HTRA1,ID4,KLF9,LDB2,LMO4,MSX2,MYC,NR4A3,PDE2A,PER2,POLR2F,PPRC1,RORB,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,ZFPM1
BP	GO:0048522: Positive regulation of cellular process	4180	84	50.33	1.1e-07	ABCC4,ACTN2,ADCYAP1R1,AGTR1,AKNA,ASCL1,ATP11C,BAIAP2L1,BAMBI,BCL11A,BCLAF1,BID,BOC,CACNA1G,CARD9,CDC20,CDKN1C,CNTN1,COL18A1,CX3CL1,CXCR4,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,EPHA8,FGFR2,GATA3,GLI2,GNL3,GPC3,GRB14,GREM1,HDAC9,HTRA1,ID4,IGFBP3,IGFBP5,IL7,KIF14,LDB2,LMO4,LRRN3,MAP3K1,MLLT3,MSX2,MYC,MYO10,NAA15,NEK6,NELL1,NR4A3,PHF5A,POLR2F,PPRC1,PRKCA,PRR16,PRRX2,RAN,RORB,RUVBL2,S100A4,SERPINF1,SFRP1,SIX6,SNAI1,SOX11,SOX6,SPRY2,STEAP3,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TMEM100,TPD52,TRIB3,TRIM67,TSPO,UNC5A,ZFPM1
BP	GO:0006357: Regulation of transcription from RNA polymerase II promoter	1651	45	19.88	1.2e-07	AKNA,ASCL1,BCL11A,CDKN1C,CHRDL1,DAND5,DLX5,EGFR,EGLN3,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HTRA1,ID4,KLF9,LDB2,LMO4,MSX2,MYC,NR4A3,PDE2A,PER2,PPRC1,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,ZFPM1
BP	GO:0010467: Gene expression	4770	92	57.43	1.2e-07	AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,CNTN1,CRYAB,DAND5,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP5,IL7,INSM2,ISOC2,KLF9,LDB2,LHX6,LMO4,MARS2,MLLT3,MRPL23,MRPL42,MSX2,MYC,MYLIP,NAA15,NELL1,NR4A3,PDCD11,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPRC1,PRKCA,PRR16,PRRX2,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SERPINF1,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,SPRY2,STC2,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TOP1,TRAP1,TRIB3,VARS,ZFPM1,ZNF121
BP	GO:0010629: Negative regulation of gene expression	1271	38	15.3	1.4e-07	ASCL1,BCL11A,BCLAF1,CCDC85B,CDKN1C,CENPF,CRYAB,EIF4EBP1,FGFR2,GATA3,GLI2,GREM1,HDAC9,HIST1H4J,HR,ID4,IGFBP5,MSX2,MYC,PDE2A,PER2,POLR2F,RORB,RPS26,SAMD11,SERPINF1,SFRP1,SNAI1,SOX11,SOX6,STC2,TBL1X,TBX3,TERT,TGIF2,TLE1,TRIB3,ZFPM1
BP	GO:0044707: Single-multicellular organism process	6400	113	77.06	1.5e-07	ABCC4,ACTG2,ACTN2,ADCYAP1R1,AGTR1,ARC,ASCL1,ATP11C,BAMBI,BCL11A,BID,BOC,BRSK2,BYSL,BZW2,CACNA1G,CALD1,CARD9,CDC20,CDKN1C,CENPF,CHRDL1,CNTN1,CNTN3,CNTN4,CNTNAP2,COL18A1,CRYAB,CX3CL1,CXCR4,DAND5,DIO3,DLX5,DOK4,DUSP2,EGFR,EGR3,EIF4EBP1,EPHA8,EYA4,FAM107B,FGFR2,GATA3,GLI2,GPC3,GRB14,GREM1,HDAC9,HIST1H4J,HTRA1,ID4,IGFBP3,IGFBP5,IL7,JPH1,KIF14,KLF9,LAMA1,LDB2,LHX6,LMO4,LOX,MAP3K1,MGLL,MLLT3,MSX2,MYC,MYLIP,MYO10,NAA15,NELL1,NR4A3,PDE2A,PER2,POLR2F,POLR3D,PPAT,PRKCA,PRRX2,PSD3,RORB,S100A4,SDC2,SEMA3C,SERPINF1,SFRP1,SIX6,SLC30A1,SLC7A11,SLITRK6,SMAD6,SMC3,SNAI1,SOX11,SOX6,SPRY2,STC2,TBL1X,TBX3,TCF4,TFPI2,TGIF2,TJP2,TLE1,TMEM100,TNFRSF21,TOP1,TPD52,TRIM67,TSPO,UNC5A,UNC5D,ZFPM1
BP	GO:0060255: Regulation of macromolecule metabolic process	5326	99	64.13	1.7e-07	ACTN2,AGTR1,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BID,CARD9,CCDC85B,CCNL1,CDC20,CDKN1C,CDYL,CENPF,CHRDL1,CNTN1,CRYAB,CXCR4,DAND5,DLX5,DUSP2,EGFR,EGLN3,EGR3,EIF4EBP1,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP3,IGFBP5,IL7,INSM2,ISOC2,KIF14,KLF9,LDB2,LHX6,LMO4,LRRN3,MAP3K1,MLLT3,MSX2,MYC,MYLIP,NAA15,NEK6,NELL1,NR4A3,PDE2A,PER2,PHF5A,POLR2F,PPRC1,PRKCA,PRR16,PRRX2,RAN,RORB,RPS26,RUVBL2,SAMD11,SERPINF1,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,SPRY2,STC2,TBL1X,TBX3,TCF4,TERT,TFAM,TFPI2,TGIF2,TLE1,TMEM100,TOP1,TRAP1,TRIB3,TRIM67,VARS,ZFPM1,ZNF121
BP	GO:0071495: Cellular response to endogenous stimulus	1030	33	12.4	2.3e-07	BAIAP2L1,BAMBI,CDKN1C,DAND5,DLX5,EGFR,EGR3,EIF4EBP1,FGFR2,GATA3,HDAC9,HTRA1,IGFBP5,KLF9,MAP3K1,MSX2,MYC,NR4A3,PDE2A,PPAT,PRKCA,RORB,RUVBL2,SERPINF1,SFRP1,SMAD6,SOX11,SOX6,SPRY2,TBC1D4,TGIF2,TMEM100,TRIB3
BP	GO:0010605:	2006	50	24.15	3.1e-07	ASCL1,BCL11A,BCLAF1,CCDC85B,CDC20,CDKN1C,CDYL,CENPF,CRYAB,DUSP2,EGFR,EIF4EBP1,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,HR,ID4,IGFBP3,IGFBP5,MSX2,MYC,NELL1,PDE2A,PER2,POLR2F,PRKCA,RORB,RP

	Negative regulation of macromolecule metabolic process					S26,SAMD11,SERPINF1,SFRP1,SMAD6,SMC3,SNAI1,SOX11,SOX6,SPRY2,STC2,TBL1X,TBX3,TERT,TFPI2,TGIF2,TLE1,TRIB3,ZFPM1
BP	GO:0032501: Multicellular organismal process	6651	115	80.08	3.4e-07	ABCC4,ACTG2,ACTN2,ADCYAP1R1,AGTR1,ARC,ASCL1,ATP11C,BAMBI,BCL11A,BID,BOC,BRSK2,BYSL,BZW2,CACNA1G,CALD1,CARD9,CDC20,CDKN1C,CDYL,CENPF,CHRDL1,CNTN1,CNTN3,CNTN4,CNTNAP2,COL18A1,CRYAB,CX3CL1,CXCR4,DAND5,DIO3,DLX5,DOK4,DUSP2,EGFR,EGR3,EIF4EBP1,EPHA8,EYA4,FAM107B,FGFR2,GATA3,GLI2,GPC3,GRB14,GREM1,HDAC9,HIST1H4J,HTRA1,ID4,IGFBP3,IGFBP5,IL7,JPH1,KIF14,KLF9,LAMA1,LDB2,LHX6,LMO4,LOX,MAP3K1,MGLL,MLLT3,MSX2,MYC,MYLIP,MYO10,NAA15,NELL1,NR4A3,PDE2A,PER2,POLR2F,POLR3D,PPAT,PRKCA,PRRX2,PSD3,RAN,RORB,S100A4,SDC2,SEMA3C,SERPINF1,SFRP1,SIX6,SLC30A1,SLC7A11,SLITRK6,SMAD6,SMC3,SNAI1,SOX11,SOX6,SPRY2,STC2,TBL1X,TBX3,TCF4,TFPI2,TGIF2,TJP2,TLE1,TMEM100,TNFRSF21,TOP1,TPD52,TRIM67,TSPO,UNC5A,UNC5D,ZFPM1
BP	GO:0009892: Negative regulation of metabolic process	2340	55	28.17	4.5e-07	ASCL1,BCL11A,BCLAF1,CCDC85B,CDC20,CDKN1C,CDYL,CENPF,CRYAB,DUSP2,EGFR,EIF4EBP1,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,HR,ID4,IGFBP3,IGFBP5,IL7,MSX2,MYC,NELL1,PDE2A,PER2,PHACTR1,POLR2F,PPP1R14A,PRKCA,RORB,RPS26,SAMD11,SERPINF1,SFRP1,SMAD6,SMC3,SNAI1,SOX11,SOX6,SPRY2,STC2,TBL1X,TBX3,TERT,TFPI2,TGIF2,TLE1,TRAP1,TRIB3,TSPO,ZFPM1
BP	GO:0031323: Regulation of cellular metabolic process	5581	101	67.2	4.7e-07	ACTN2,ADCYAP1R1,AGTR1,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BID,BOC,CARD9,CCDC85B,CCNL1,CDC20,CDKN1C,CDYL,CENPF,CHRDL1,CRYAB,CXCR4,DAND5,DLX5,DUSP2,EGFR,EGLN3,EGR3,EIF4EBP1,EPHA8,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP3,IGFBP5,INSM2,KIF14,KLF9,LDB2,LHX6,LMO4,LRRN3,MAP3K1,MLLT3,MSX2,MYC,MYLIP,NAA15,NEK6,NELL1,NR4A3,NTHL1,PDE2A,PER2,PHF5A,POLR2F,PPP1R14A,PPRC1,PRKCA,PRR16,PRRX2,RAN,RORB,RPS26,RUVBL2,SAMD11,SERPINF1,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,SPRY2,STC2,TBL1X,TBX3,TCF4,TERT,TFAM,TFPI2,TGIF2,TLE1,TMEM100,TRAP1,TRIB3,TRIM67,TSPO,VARS,ZFPM1,ZNF121
BP	GO:0071840: Cellular component organization or biogenesis	5665	102	68.21	5.0e-07	ACTN2,AGTR1,ARC,ATP11C,BAIAP2L1,BAMBI,BAZ1A,BCL11A,BCLAF1,BID,BOC,BRSK2,BYSL,C10orf2,CACNA1G,CCDC85B,CDC20,CDYL,CENPF,CNTN1,CNTN4,CNTNAP2,COL18A1,CRYAB,CXCR4,DLX5,EGFR,EIF4EBP1,EPB41L4B,EPHA8,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H2BH,HIST1H4J,HTRA1,IGFBP3,IGFBP5,INF2,KIF14,LAMA1,LDB2,LETM1,LMO4,LOX,MAP3K1,MGLL,MRPL23,MRPL42,MSX2,MYC,MYO10,NEK6,NOP16,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PER2,PHACTR1,PPAT,PPRC1,PRKCA,PRR16,RAN,RPL27A,RPS26,RUVBL2,S100A4,SDC2,SEMA3C,SERPINF1,SFRP1,SLITRK6,SMAD6,SMC3,SNAI1,SOX6,SPRY2,SSSCA1,TBC1D4,TBL1X,TCF4,TERT,TFAM,TJP2,TMEM150C,TOP1,TRIM67,TSPO,TUBA1C,UNC5A,UNC5D,WDR3,ZFPM1
BP	GO:0048666: Neuron development	965	31	11.62	5.2e-07	ASCL1,BCL11A,BOC,BRSK2,CACNA1G,CDC20,CDKN1C,CNTN1,CNTN4,CNTNAP2,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,LAMA1,LHX6,MGLL,MYO10,NR4A3,RORB,SDC2,SEMA3C,SERPINF1,SLITRK6,TRIM67,TSPO,UNC5A,UNC5D
BP	GO:0030509: BMP signaling pathway	131	11	1.58	5.3e-07	CHRDL1,DAND5,DLX5,GPC3,GREM1,HTRA1,MSX2,SFRP1,SMAD6,SOX11,TMEM100
BP	GO:0051172: Negative regulation of nitrogen compound metabolic process	1230	36	14.81	5.3e-07	ASCL1,BCL11A,BCLAF1,CCDC85B,CDKN1C,CDYL,CENPF,FGFR2,GATA3,GLI2,GREM1,HDAC9,HIST1H4J,HR,ID4,MSX2,MYC,PDE2A,PER2,PRKCA,RORB,RPS26,SAMD11,SFRP1,SMC3,SNAI1,SOX11,SOX6,TBL1X,TBX3,TERT,TGIF2,TLE1,TRIB3,TSPO,ZFPM1
BP	GO:0051240:Positive regulation of multicellular organismal process	1236	36	14.88	5.9e-07	ASCL1,ATP11C,BAMBI,BCL11A,CARD9,CDC20,CNTN1,CX3CL1,CXCR4,DIO3,DLX5,EGFR,EGR3,FGFR2,GATA3,GLI2,GREM1,HDAC9,ID4,IL7,MSX2,MYC,NELL1,POLR2F,POLR3D,PRKCA,SERPINF1,SNAI1,SOX11,SOX6,TCF4,TGIF2,TMEM100,TRIM67,TSPO,ZFPM1
BP	GO:0080090: Regulation of primary metabolic process	5300	97	63.81	6.0e-07	ACTN2,ADCYAP1R1,AGTR1,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BID,CARD9,CCDC85B,CCNL1,CDC20,CDKN1C,CDYL,CENPF,CHRDL1,CRYAB,CXCR4,DAND5,DLX5,DUSP2,EGFR,EGLN3,EGR3,EIF4EBP1,EPHA8,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP3,IGFBP5,INSM2,KIF14,KLF9,LDB2,LHX6,LMO4,LRRN3,MAP3K1,MLLT3,MSX2,MYC,MYLIP,NAA15,NEK6,NELL1,NR4A3,PDE2A,PER2,PHF5A,POLR2F,PPRC1,PRKCA,PRR16,PRRX2,RAN,RORB,RPS26,RUVBL2,SAMD11,SERPINF1,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,SPRY2,TBL1X,TBX3,TCF4,TERT,TFAM,TFPI2,TGIF2,TLE1,TMEM100,TRAP1,TRIB3,TRIM67,TSPO,VARS,ZFPM1,ZNF121
BP	GO:0010628: Positive regulation of gene expression	1459	40	17.57	6.0e-07	AKNA,ASCL1,BAMBI,BCL11A,BCLAF1,CDKN1C,CNTN1,DLX5,EGFR,FGFR2,GATA3,GLI2,GNL3,GREM1,ID4,LDB2,LMO4,MYC,NAA15,NR4A3,PHF5A,POLR2F,PPRC1,PRR16,RAN,RORB,RUVBL2,SFRP1,SIX6,SNAI1,SOX11,SOX6,SPRY2,TBL1X,TBX3,TCF4,TERT,TFAM,TLE1,ZFPM1
BP	GO:0014070: Response to organic cyclic compound	724	26	8.72	6.1e-07	ABCC4,ADCYAP1R1,ASCL1,BID,CARD9,CRYAB,EGFR,EGR3,GATA3,GLI2,IGFBP5,KLF9,LOX,MSX2,NR4A3,PDE2A,RORB,RUVBL2,SDC2,SERPINF1,SFRP1,SLC7A11,SMAD6,STC2,TERT,TSPO
BP	GO:0009890: Negative regulation of biosynthetic process	1293	37	15.57	6.2e-07	ASCL1,BCL11A,BCLAF1,CCDC85B,CDKN1C,CDYL,CENPF,EIF4EBP1,FGFR2,GATA3,GLI2,GREM1,HDAC9,HIST1H4J,HR,ID4,IGFBP5,MSX2,MYC,PDE2A,PER2,PRKCA,RORB,SAMD11,SFRP1,SMC3,SNAI1,SOX11,SOX6,TBL1X,TBX3,TGIF2,TLE1,TRAP1,TRIB3,TSPO,ZFPM1

BP	GO:0031326: Regulation of cellular biosynthetic process	3983	79	47.96	6.4e-07	ACTN2,ADCYAP1R1,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,CARD9,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP5,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,PPRC1,PRKCA,PRR16,PRRX2,RAN,RORB,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,STC2,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRAP1,TRIB3,TSPO,VARS,ZFPM1,ZNF121
BP	GO:0008219: Cell death	1876	47	22.59	6.8e-07	ACTN2,ADCYAP1R1,ASCL1,BCLAF1,BID,BRSK2,CARD9,COL18A1,CRYAB,CX3CL1,CXCR4,EGFR,EGLN3,EGR3,FAIM3,FGFR2,GATA3,GREM1,IGFBP3,IL7,KIF14,MAP3K1,MSX2,MYC,NAA15,NEK6,NR4A3,PRKCA,SERPINF1,SFRP1,SMAD6,SNAI1,SOX11,SPRY2,STEAP3,TBX3,TERT,TJP2,TLE1,TMEM150C,TNFRSF21,TOP1,TRAP1,TRIB3,TSPO,UNC5A,UNC5D
BP	GO:0060284: Regulation of cell development	681	25	8.2	6.9e-07	ASCL1,BAMBI,BCL11A,CDC20,CNTN1,CNTN4,CXCR4,GATA3,GLI2,GREM1,HDAC9,ID4,MGLL,PER2,SDC2,SERPINF1,SFRP1,SNAI1,SOX11,TCF4,TGIF2,TNFRSF21,TRIM67,TSPO,UNC5D
BP	GO:0016265: Death	1880	47	22.64	7.2e-07	ACTN2,ADCYAP1R1,ASCL1,BCLAF1,BID,BRSK2,CARD9,COL18A1,CRYAB,CX3CL1,CXCR4,EGFR,EGLN3,EGR3,FAIM3,FGFR2,GATA3,GREM1,IGFBP3,IL7,KIF14,MAP3K1,MSX2,MYC,NAA15,NEK6,NR4A3,PRKCA,SERPINF1,SFRP1,SMAD6,SNAI1,SOX11,SPRY2,STEAP3,TBX3,TERT,TJP2,TLE1,TMEM150C,TNFRSF21,TOP1,TRAP1,TRIB3,TSPO,UNC5A,UNC5D
BP	GO:0061564: Axon development	593	23	7.14	7.8e-07	BCL11A,BOC,BRSK2,CACNA1G,CNTN1,CNTN4,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,LAMA1,MGLL,MYO10,NR4A3,SDC2,SEMA3C,SLITRK6,TSPO,UNC5A,UNC5D
BP	GO:0048518: Positive regulation of biological process	4956	92	59.67	8.2e-07	ABCC4,ACTN2,ADCYAP1R1,AGTR1,AKNA,ASCL1,ATP11C,BAIAP2L1,BAMBI,BCL11A,BCLAF1,BID,BOC,CACNA1G,CARD9,CDC20,CDKN1C,CNTN1,COL18A1,CX3CL1,CXCR4,DIO3,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,EPHA8,FGFR2,GATA3,GLI2,GNL3,GPC3,GRB14,GREM1,HDAC9,HTRA1,ID4,IGFBP3,IGFBP5,IL7,KIF14,LDB2,LMO4,LRRN3,MAP3K1,MLLT3,MSX2,MYC,MYLIP,MYO10,NAA15,NEK6,NELL1,NR4A3,PDE2A,PHF5A,POLR2F,POLR3D,PPRC1,PRKCA,PRR16,PRRX2,PSD3,RAN,RORB,RUVBL2,S100A4,SERPINF1,SFRP1,SIX6,SNAI1,SOX11,SOX6,SPRY2,STEAP3,TBC1D4,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TNFRSF21,TPD52,TRIB3,TRIM67,TSPO,UNC5A,ZFPM1
BP	GO:0006928: Movement of cell or subcellular component	1712	44	20.61	8.6e-07	ACTN2,AGTR1,ARC,ASCL1,BAMBI,BOC,CACNA1G,CALD1,CNTN1,CNTN4,COL18A1,CX3CL1,CXCR4,DLX5,EGFR,EGR3,EPHA8,FAM60A,GATA3,GLI2,GRB14,GREM1,HDAC9,IGFBP3,IGFBP5,KIF14,LAMA1,LHX6,MAP3K1,MSX2,MYLIP,MYO10,NR4A3,PHACTR1,PRKCA,SDC2,SEMA3C,SERPINF1,SFRP1,SLC7A11,SNAI1,TSPO,UNC5A,UNC5D
BP	GO:1902680: Positive regulation of RNA biosynthetic process	1257	36	15.13	8.9e-07	AKNA,ASCL1,BAMBI,BCL11A,BCLAF1,CDKN1C,DLX5,EGFR,FGFR2,GATA3,GLI2,GNL3,GREM1,ID4,LDB2,LMO4,MYC,NAA15,NR4A3,PHF5A,POLR2F,PPRC1,RAN,RORB,RUVBL2,SFRP1,SIX6,SNAI1,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,ZFPM1
BP	GO:0045934: Negative regulation of nucleobase-containing compound metabolic process	1207	35	14.53	9.7e-07	ASCL1,BCL11A,BCLAF1,CCDC85B,CDKN1C,CDYL,CENPF,FGFR2,GATA3,GLI2,GREM1,HDAC9,HIST1H4J,HR,ID4,MSX2,MYC,PDE2A,PER2,PRKCA,RORB,RPS26,SAMD11,SFRP1,SMC3,SNAI1,SOX11,SOX6,TBL1X,TBX3,TERT,TGIF2,TLE1,TRIB3,ZFPM1
BP	GO:0016070: RNA metabolic process	4316	83	51.97	1.0e-06	ACTN2,ADAT2,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BYSL,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,DUS3L,EGFR,EGLN3,EGR3,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,INSM2,KLF9,LDB2,LHX6,LMO4,MARS2,MLLT3,MSX2,MYC,NAA15,NR4A3,NSUN5,PDCD11,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPRC1,PRRX2,PUS7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,VARS,WDR3,ZFPM1,ZNF121
BP	GO:0051253: Negative regulation of RNA metabolic process	1103	33	13.28	1.1e-06	ASCL1,BCL11A,BCLAF1,CCDC85B,CDKN1C,CDYL,CENPF,FGFR2,GATA3,GLI2,GREM1,HDAC9,HIST1H4J,HR,ID4,MSX2,MYC,PDE2A,PER2,RORB,RPS26,SAMD11,SFRP1,SNAI1,SOX11,SOX6,TBL1X,TBX3,TERT,TGIF2,TLE1,TRIB3,ZFPM1
BP	GO:0009889: Regulation of biosynthetic process	4034	79	48.57	1.1e-06	ACTN2,ADCYAP1R1,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,CARD9,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP5,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,PPRC1,PRKCA,PRR16,PRRX2,RAN,RORB,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,STC2,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRAP1,TRIB3,TSPO,VARS,ZFPM1,ZNF121
BP	GO:0031327: Negative regulation of cellular biosynthetic process	1275	36	15.35	1.2e-06	ASCL1,BCL11A,BCLAF1,CCDC85B,CDKN1C,CDYL,CENPF,EIF4EBP1,FGFR2,GATA3,GLI2,GREM1,HDAC9,HIST1H4J,HR,ID4,IGFBP5,MSX2,MYC,PDE2A,PER2,PRKCA,RORB,SAMD11,SFRP1,SMC3,SNAI1,SOX11,SOX6,TBL1X,TBX3,TGIF2,TLE1,TRIB3,TSPO,ZFPM1
BP	GO:0040011: Locomotion	1567	41	18.87	1.4e-06	AGTR1,ARC,ASCL1,BAMBI,BOC,CACNA1G,CNTN1,CNTN4,COL18A1,CX3CL1,CXCR4,DLX5,EGFR,EGR3,EPHA8,FAM60A,GATA3,GLI2,GRB14,GREM1,HDAC9,IGFBP3,IGFBP5,KIF14,LAMA1,LHX6,MAP3K1,MSX2,MYO10,NR4A3,PHACTR1,PRKCA,SDC2,SEMA3C,SERPINF1,SFRP1,SLC7A11,SNAI1,TSPO,UNC5A,UNC5D

BP	GO:0045893: Positive regulation of transcription, DNA-templated	1228	35	14.79	1.4e-06	AKNA,ASCL1,BAMBI,BCL11A,BCLAF1,CDKN1C,DLX5,EGFR,FGFR2,GATA3,GLI2,GNL3,GREM1,ID4,LDB2,LMO4,MYC,NAA15,NR4A3,PHF5A,PPRC1,RAN,RORB,RUVBL2,SFRP1,SIX6,SNAI1,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,ZFPM1
BP	GO:1903508: Positive regulation of nucleic acid-templated transcription	1228	35	14.79	1.4e-06	AKNA,ASCL1,BAMBI,BCL11A,BCLAF1,CDKN1C,DLX5,EGFR,FGFR2,GATA3,GLI2,GNL3,GREM1,ID4,LDB2,LMO4,MYC,NAA15,NR4A3,PHF5A,PPRC1,RAN,RORB,RUVBL2,SFRP1,SIX6,SNAI1,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,ZFPM1
BP	GO:0007409: Axonogenesis	570	22	6.86	1.5e-06	BCL11A,BOC,BRSK2,CACNA1G,CNTN1,CNTN4,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,LAMA1,MGLL,MYO10,NR4A3,SDC2,SEMA3C,SLITRK6,UNC5A,UNC5D
BP	GO:0051093: Negative regulation of developmental process	812	27	9.78	1.6e-06	ASCL1,BCL11A,CCDC85B,CNTN4,GATA3,GLI2,GREM1,HIST1H4J,ID4,IGFBP5,LDB2,MSX2,MYC,POLR2F,RORB,SERPINF1,SFRP1,SMC3,SNAI1,SOX11,STC2,TBX3,TERT,TNFRSF21,TRIB3,TSPO,ZFPM1
BP	GO:0000902: Cell morphogenesis	1181	34	14.22	1.7e-06	ARC,BAMBI,BCL11A,BOC,BRSK2,CACNA1G,CNTN1,CNTN4,COL18A1,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,GREM1,KIF14,LAMA1,MAP3K1,MGLL,MSX2,MYO10,NR4A3,S100A4,SDC2,SEMA3C,SFRP1,SLITRK6,SNAI1,SOX6,UNC5A,UNC5D,ZFPM1
BP	GO:0007178: Transmembrane receptor protein serine/threonine kinase signaling pathway	321	16	3.86	1.8e-06	BAMBI,CDKN1C,CHRDL1,DAND5,DLX5,GPC3,GREM1,HTRA1,MAP3K1,MSX2,MYC,SFRP1,SMAD6,SOX11,TGIF2,TMEM100
BP	GO:0051254: Positive regulation of RNA metabolic process	1295	36	15.59	1.8e-06	AKNA,ASCL1,BAMBI,BCL11A,BCLAF1,CDKN1C,DLX5,EGFR,FGFR2,GATA3,GLI2,GNL3,GREM1,ID4,LDB2,LMO4,MYC,NAA15,NR4A3,PHF5A,POLR2F,PPRC1,RAN,RORB,RUVBL2,SFRP1,SIX6,SNAI1,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,ZFPM1
BP	GO:0050673: Epithelial cell proliferation	322	16	3.88	1.8e-06	CDKN1C,DLX5,EGFR,EGR3,FGFR2,GATA3,GPC3,HTRA1,IGFBP3,IGFBP5,KLF9,MYC,PRKCA,SERPINF1,SFRP1,SOX11
BP	GO:0031324: Negative regulation of cellular metabolic process	2071	49	24.94	2.0e-06	ASCL1,BCL11A,BCLAF1,CCDC85B,CDC20,CDKN1C,CDYL,CENPF,CRYAB,DUSP2,EIF4EBP1,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,HR,ID4,IGFBP3,IGFBP5,MSX2,MYC,NELL1,PDE2A,PER2,PRKCA,RORB,RPS26,SAMD11,SERPINF1,SFRP1,SMAD6,SMC3,SNAI1,SOX11,SOX6,SPRY2,TBL1X,TBX3,TERT,TFPI2,TGIF2,TLE1,TRAP1,TRIB3,TSPO,ZFPM1
BP	GO:0048523: Negative regulation of cellular process	3881	76	46.73	2.1e-06	ACTN2,ADCYAP1R1,ASCL1,BAMBI,BCL11A,BCLAF1,CCDC85B,CDC20,CDKN1C,CDYL,CENPF,CHRDL1,CNTN4,COL18A1,CRYAB,CX3CL1,DAND5,DUSP2,EGFR,EGR3,EIF4EBP1,FAIM3,FAM60A,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP3,IGFBP5,IL7,KIF14,KLF9,LDB2,LMO4,MGLL,MLLT3,MSX2,MYC,NAA15,NELL1,NR4A3,PDE2A,PER2,POLR2F,PRKCA,RORB,RPS26,SAMD11,SERPINF1,SFRP1,SLC30A1,SMAD6,SMC3,SNAI1,SOX11,SOX6,SPRY2,TBC1D4,TBL1X,TBX3,TERT,TFPI2,TGIF2,TLE1,TNFRSF21,TRAP1,TRIB3,TRIM67,TSPO,ZFPM1
BP	GO:2000113: Negative regulation of cellular macromolecule biosynthetic process	1141	33	13.74	2.2e-06	ASCL1,BCL11A,BCLAF1,CCDC85B,CDKN1C,CENPF,EIF4EBP1,FGFR2,GATA3,GLI2,GREM1,HDAC9,HIST1H4J,HR,ID4,IGFBP5,MSX2,MYC,PDE2A,PER2,RORB,SAMD11,SFRP1,SMC3,SNAI1,SOX11,SOX6,TBL1X,TBX3,TGIF2,TLE1,TRIB3,ZFPM1
BP	GO:0010556: Regulation of macromolecule biosynthetic process	3819	75	45.98	2.3e-06	ACTN2,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,CARD9,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP5,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,PPRC1,PRR16,PRRX2,RAN,RORB,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRAP1,TRIB3,VARS,ZFPM1,ZNF121
BP	GO:0008283: Cell proliferation	1836	45	22.11	2.3e-06	ABCC4,AGTR1,ASCL1,BAMBI,BID,BYSL,CDC20,CDKN1C,CENPF,COL18A1,CXCR4,DLX5,EGFR,EGLN3,EGR3,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HTRA1,ID4,IGFBP3,IGFBP5,IL7,IMPDH1,KCNH1,KIF14,KLF9,MSX2,MYC,NELL1,PER2,PRKCA,PRRX2,SERPINF1,SFRP1,SMAD6,SOX11,SPRY2,TBX3,TNFRSF21,TPD52,TSPO
BP	GO:0007423: Sensory organ development	497	20	5.98	2.5e-06	ASCL1,CDKN1C,CHRDL1,CRYAB,DLX5,EGFR,FGFR2,GATA3,GLI2,LAMA1,MAP3K1,NR4A3,PRRX2,RORB,SERPINF1,SLC7A11,SLITRK6,SOX11,SPRY2,TGIF2
BP	GO:0070848: Response to growth factor	685	24	8.25	2.7e-06	ADCYAP1R1,ASCL1,BAMBI,CDKN1C,DAND5,DLX5,EGFR,EGR3,FGFR2,GATA3,HTRA1,MAP3K1,MSX2,MYC,PDE2A,PRKCA,SFRP1,SMAD6,SOX11,SOX6,SPRY2,TGIF2,TMEM100,TRIB3
BP	GO:0012501: Programmed cell death	1787	44	21.52	2.7e-06	ACTN2,ASCL1,BCLAF1,BID,BRSK2,CARD9,COL18A1,CRYAB,CX3CL1,CXCR4,EGFR,EGLN3,EGR3,FAIM3,FGFR2,GATA3,GREM1,IGFBP3,IL7,KIF14,MAP3K1,MSX2,MYC,NAA15,NEK6,NR4A3,PRKCA,SFRP1,SMAD6,SNAI1,SPRY2,STEAP3,TBX3,TERT,TJP2,TLE1,TMEM150C,TNFRSF21,TOP1,TRAP1,TRIB3,TSPO,UNC5A,UNC5D
BP	GO:0048729: Tissue morphogenesis	593	22	7.14	2.9e-06	CXCR4,EGFR,FGFR2,GATA3,GLI2,GPC3,GREM1,IGFBP5,LAMA1,LMO4,MLLT3,MSX2,MYC,NR4A3,RORB,SEMA3C,SFRP1,SNAI1,SOX11,SPRY2,TBX3,ZFPM1

BP	GO:0045596: Negative regulation of cell differentiation	641	23	7.72	2.9e-06	ASCL1,BCL11A,CCDC85B,CNTN4,GATA3,GLI2,GREM1,HIST1H4J,ID4,IGFBP5,LDB2,MSX2,MYC,POLR2F,RORB,SFRP1,SMC3,SNAI1,SOX11,TBX3,TRIB3,TSPO,ZFPM1
BP	GO:1903507: Negative regulation of nucleic acid-templated transcription	1048	31	12.62	3.0e-06	ASCL1,BCL11A,BCLAF1,CCDC85B,CDKN1C,CDYL,CENPF,FGFR2,GATA3,GLI2,GREM1,HDAC9,HIST1H4J,HR,ID4,MSX2,MYC,PDE2A,PER2,RORB,SAMD11,SFRP1,SNAI1,SOX11,SOX6,TBL1X,TBX3,TGIF2,TLE1,TRIB3,ZFPM1
BP	GO:0031175: Neuron projection development	839	27	10.1	3.0e-06	BCL11A,BOC,BRSK2,CACNA1G,CDC20,CNTN1,CNTN4,CNTNAP2,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,LAMA1,MGLL,MYO10,NR4A3,SDC2,SEMA3C,SERPINF1,SLITRK6,TRIM67,TSPO,UNC5A,UNC5D
BP	GO:0010558: Negative regulation of macromolecule biosynthetic process	1216	34	14.64	3.2e-06	ASCL1,BCL11A,BCLAF1,CCDC85B,CDKN1C,CDYL,CENPF,EIF4EBP1,FGFR2,GATA3,GLI2,GREM1,HDAC9,HIST1H4J,HR,ID4,IGFBP5,MSX2,MYC,PDE2A,PER2,RORB,SAMD11,SFRP1,SMC3,SNAI1,SOX11,SOX6,TBL1X,TBX3,TGIF2,TLE1,TRIB3,ZFPM1
BP	GO:0051960: Regulation of nervous system development	600	22	7.22	3.5e-06	ASCL1,BCL11A,CDC20,CNTN1,CNTN4,CXCR4,GATA3,GLI2,ID4,KIF14,MGLL,PER2,SDC2,SERPINF1,SFRP1,SOX11,TCF4,TGIF2,TNFRSF21,TRIM67,TSPO,UNC5D
BP	GO:0048519: Negative regulation of biological process	4226	80	50.88	3.7e-06	ACTN2,ADCYAP1R1,ASCL1,BAMBI,BCL11A,BCLAF1,CCDC85B,CDC20,CDKN1C,CDYL,CENPF,CHRDL1,CNTN4,COL18A1,CRYAB,CX3CL1,DAND5,DUSP2,EGFR,EGR3,EIF4EBP1,FAIM3,FAM60A,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP3,IGFBP5,IL7,KIF14,KLF9,LDB2,LMO4,MGLL,MLLT3,MSX2,MYC,MYLIP,NAA15,NELL1,NR4A3,PDE2A,PER2,PHACTR1,POLR2F,PPP1R14A,PRKCA,RORB,RPS26,SAMD11,SERPINF1,SFRP1,SLC30A1,SMAD6,SMC3,SNAI1,SOX11,SOX6,SPRY2,STC2,TBC1D4,TBL1X,TBX3,TERT,TFPI2,TGIF2,TLE1,TNFRSF21,TRAP1,TRIB3,TRIM67,TSPO,ZFPM1
BP	GO:0002009: Morphogenesis of an epithelium	467	19	5.62	3.8e-06	CXCR4,EGFR,FGFR2,GATA3,GLI2,GPC3,GREM1,IGFBP5,LAMA1,LMO4,MLLT3,MSX2,MYC,SEMA3C,SFRP1,SNAI1,SOX11,SPRY2,TBX3
BP	GO:0009887: Organ morphogenesis	902	28	10.86	3.8e-06	COL18A1,DLX5,EGFR,FGFR2,GATA3,GLI2,GPC3,GREM1,HTRA1,IGFBP5,IL7,LAMA1,MLLT3,MSX2,MYC,NR4A3,PRRX2,RORB,SEMA3C,SFRP1,SIX6,SLITRK6,SNAI1,SOX11,SPRY2,TBX3,TLE1,ZFPM1
BP	GO:1902679: Negative regulation of RNA biosynthetic process	1063	31	12.8	4.0e-06	ASCL1,BCL11A,BCLAF1,CCDC85B,CDKN1C,CDYL,CENPF,FGFR2,GATA3,GLI2,GREM1,HDAC9,HIST1H4J,HR,ID4,MSX2,MYC,PDE2A,PER2,RORB,SAMD11,SFRP1,SNAI1,SOX11,SOX6,TBL1X,TBX3,TGIF2,TLE1,TRIB3,ZFPM1
BP	GO:0032774: RNA biosynthetic process	3662	72	44.09	4.0e-06	ACTN2,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPRC1,PRRX2,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,ZFPM1,ZNF121
BP	GO:0018130: Heterocycle biosynthetic process	4090	78	49.24	4.0e-06	ACTN2,ADCYAP1R1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IMPDH1,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRRX2,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,TSPO,ZFPM1,ZNF121
BP	GO:0019438: Aromatic compound biosynthetic process	4095	78	49.3	4.2e-06	ACTN2,ADCYAP1R1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IMPDH1,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRRX2,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,TSPO,ZFPM1,ZNF121
BP	GO:0034654: Nucleobase-containing compound biosynthetic process	4023	77	48.44	4.2e-06	ACTN2,ADCYAP1R1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IMPDH1,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRRX2,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,ZFPM1,ZNF121
BP	GO:0045892: Negative regulation of transcription, DNA-templated	1015	30	12.22	4.5e-06	ASCL1,BCL11A,BCLAF1,CCDC85B,CDKN1C,CENPF,FGFR2,GATA3,GLI2,GREM1,HDAC9,HIST1H4J,HR,ID4,MSX2,MYC,PDE2A,PER2,RORB,SAMD11,SFRP1,SNAI1,SOX11,SOX6,TBL1X,TBX3,TGIF2,TLE1,TRIB3,ZFPM1
BP	GO:0050678: Regulation of epithelial cell proliferation	268	14	3.23	4.7e-06	CDKN1C,DLX5,EGFR,EGR3,FGFR2,GATA3,GPC3,HTRA1,KLF9,MYC,PRKCA,SERPINF1,SFRP1,SOX11
BP	GO:0097659:	3539	70	42.61	4.8e-06	ACTN2,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,

	Nucleic acid-templated transcription					GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPRC1,PRRX2,RAN,RORB,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,ZFPM1,ZNF121
BP	GO:0001649: Osteoblast differentiation	197	12	2.37	4.8e-06	DLX5,FGFR2,GLI2,ID4,IGFBP3,IGFBP5,MSX2,NELL1,RORB,SFRP1,SNAI1,SOX11
BP	GO:0006915: Apoptotic process	1769	43	21.3	5.0e-06	ACTN2,ASCL1,BCLAF1,BID,BRSK2,CARD9,COL18A1,CRYAB,CX3CL1,CXCR4,EGFR,EGLN3,EGR3,FAIM3,FGFR2,GATA3,GREM1,IGFBP3,IL7,KIF14,MAP3K1,MSX2,MYC,NAA15,NEK6,NR4A3,PRKCA,SFRP1,SMAD6,SNAI1,SPRY2,STEAP3,TBX3,TERT,TJP2,TLE1,TMEM150C,TNFRSF21,TRAP1,TRIB3,TSPO,UNC5A,UNC5D
BP	GO:0072358: Cardiovascular system development	868	27	10.45	5.6e-06	COL18A1,CX3CL1,CXCR4,DAND5,EGR3,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,LAMA1,LMO4,LOX,MSX2,NAA15,PRKCA,PRRX2,SEMA3C,SERPINF1,SFRP1,SNAI1,SOX11,SOX6,TBX3,TMEM100,ZFPM1
BP	GO:0072359: Circulatory system development	868	27	10.45	5.6e-06	COL18A1,CX3CL1,CXCR4,DAND5,EGR3,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,LAMA1,LMO4,LOX,MSX2,NAA15,PRKCA,PRRX2,SEMA3C,SERPINF1,SFRP1,SNAI1,SOX11,SOX6,TBX3,TMEM100,ZFPM1
BP	GO:0045667: Regulation of osteoblast differentiation	107	9	1.29	5.7e-06	DLX5,FGFR2,ID4,IGFBP5,MSX2,NELL1,RORB,SFRP1,SOX11
BP	GO:0071363: Cellular response to growth factor stimulus	668	23	8.04	5.8e-06	ADCYAP1R1,BAMBI,CDKN1C,DAND5,DLX5,EGFR,EGR3,FGFR2,GATA3,HTRA1,MAP3K1,MSX2,MYC,PDE2A,PRKCA,SFRP1,SMAD6,SOX11,SOX6,SPRY2,TGIF2,TMEM100,TRIB3
BP	GO:0061138: Morphogenesis of a branching epithelium	201	12	2.42	5.9e-06	CXCR4,FGFR2,GLI2,GPC3,GREM1,LAMA1,MSX2,MYC,SEMA3C,SFRP1,SPRY2,TBX3
BP	GO:0010557: Positive regulation of macromolecule biosynthetic process	1423	37	17.13	5.9e-06	AKNA,ASCL1,BAMBI,BCL11A,BCLAF1,CDKN1C,DLX5,EGFR,FGFR2,GATA3,GLI2,GNL3,GREM1,ID4,LDB2,LMO4,MYC,NAA15,NR4A3,PHF5A,POLR2F,PPRC1,PRR16,RAN,RORB,RUVBL2,SFRP1,SIX6,SNAI1,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,ZFPM1
BP	GO:0019222: Regulation of metabolic process	6417	108	77.26	6.0e-06	ACTN2,ADCYAP1R1,AGTR1,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BID,BOC,CARD9,CCDC85B,CCNL1,CDC20,CDKN1C,CDYL,CENPF,CHRDL1,CNTN1,CRYAB,CXCR4,DAND5,DLX5,DUSP2,EGFR,EGLN3,EGR3,EIF4EBP1,EPHA8,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP3,IGFBP5,IL7,INSM2,ISOC2,KIF14,KLF9,LDB2,LHX6,LMO4,LRRN3,MAP3K1,MLLT3,MSX2,MYC,MYLIP,NAA15,NEK6,NELL1,NR4A3,NTHL1,PDE2A,PER2,PHACTR1,PHF5A,POLR2F,PPP1R14A,PPRC1,PRKCA,PRR16,PRRX2,PSD3,RAN,RORB,RPS26,RUVBL2,SAMD11,SERPINF1,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,SPRY2,STC2,TBC1D4,TBL1X,TBX3,TCF4,TERT,TFAM,TFPI2,TGIF2,TLE1,TMEM100,TOP1,TRAP1,TRIB3,TRIM67,TSPO,VARS,ZFPM1,ZNF121
BP	GO:2000112: Regulation of cellular macromolecule biosynthetic process	3701	72	44.56	6.0e-06	AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP5,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,PPRC1,PRR16,PRRX2,RAN,RORB,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRAP1,TRIB3,VARS,ZFPM1,ZNF121
BP	GO:0031328: Positive regulation of cellular biosynthetic process	1542	39	18.57	6.1e-06	ADCYAP1R1,AKNA,ASCL1,BAMBI,BCL11A,BCLAF1,CDKN1C,DLX5,EGFR,FGFR2,GATA3,GLI2,GNL3,GREM1,ID4,LDB2,LMO4,MYC,NAA15,NR4A3,PHF5A,POLR2F,PPRC1,PRKCA,PRR16,RAN,RORB,RUVBL2,SFRP1,SIX6,SNAI1,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,ZFPM1
BP	GO:0060548: Negative regulation of cell death	872	27	10.5	6.1e-06	ADCYAP1R1,ASCL1,CRYAB,CX3CL1,EGFR,EGR3,FAIM3,FGFR2,GATA3,GREM1,IL7,KIF14,MSX2,MYC,NAA15,NR4A3,PRKCA,SERPINF1,SFRP1,SMAD6,SNAI1,SOX11,SPRY2,TBX3,TERT,TLE1,TRAP1
BP	GO:0010941: Regulation of cell death	1425	37	17.16	6.1e-06	ACTN2,ADCYAP1R1,ASCL1,BCLAF1,BID,CARD9,COL18A1,CRYAB,CX3CL1,EGFR,EGLN3,EGR3,FAIM3,FGFR2,GATA3,GREM1,IGFBP3,IL7,KIF14,MSX2,MYC,NAA15,NR4A3,PRKCA,SERPINF1,SFRP1,SMAD6,SNAI1,SOX11,SPRY2,STEAP3,TBX3,TERT,TLE1,TRAP1,TSPO,UNC5A
BP	GO:0009790: Embryo development	978	29	11.78	6.2e-06	BYSL,CDKN1C,DLX5,DUSP2,EGFR,FGFR2,GATA3,GLI2,GPC3,GREM1,LAMA1,LMO4,MSX2,NR4A3,PRRX2,SEMA3C,SFRP1,SLC30A1,SLITRK6,SMAD6,SNAI1,SOX11,SOX6,SPRY2,TBX3,TGIF2,TMEM100,TOP1,ZFPM1
BP	GO:0007167: Enzyme linked receptor protein signaling pathway	1092	31	13.15	6.9e-06	ADAM12,ADCYAP1R1,BAIAP2L1,BAMBI,CDKN1C,CHRDL1,DAND5,DLX5,DOK4,EGFR,EIF4EBP1,EPHA8,FGFR2,GATA3,GPC3,GREM1,HTRA1,IGFBP3,IGFBP5,MAP3K1,MSX2,MYC,PRKCA,SDC2,SFRP1,SMAD6,SOX11,SPRY2,TGIF2,TMEM100,TRIB3
BP	GO:2001141: Regulation of RNA biosynthetic process	3434	68	41.35	6.9e-06	ACTN2,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,PPRC1,PRRX2,RAN,RORB,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,ZFPM1,ZNF121

BP	GO:0010604: Positive regulation of macromolecule metabolic process	2423	53	29.17	7.0e-06	AGTR1,AKNA,ASCL1,BAMBI,BCL11A,BCLAF1,BID,CDC20,CDKN1C,CNTN1,CXCR4,DLX5,EGFR,EGLN3,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,ID4,KIF14,LDB2,LMO4,LRRN3,MAP3K1,MYC,MYLIP,NAA15,NR4A3,PHF5A,POLR2F,PPRC1,PRKCA,PRR16,RAN,RORB,RUVBL2,SFRP1,SIX6,SNAI1,SOX11,SOX6,SPRY2,TBL1X,TBX3,TCF4,TERT,TFAM,TLE1,TRIB3,TRIM67,ZFPM1
BP	GO:0016477: Cell migration	1093	31	13.16	7.0e-06	AGTR1,ARC,ASCL1,BAMBI,COL18A1,CX3CL1,CXCR4,EGFR,EGR3,EPHA8,FAM60A,GATA3,GRB14,GREM1,HDAC9,IGFBP3,IGFBP5,KIF14,LAMA1,LHX6,MAP3K1,MSX2,PRKCA,SDC2,SEMA3C,SERPINF1,SFRP1,SLC7A11,SNAI1,TSPO,UNC5D
BP	GO:0001503: Ossification	358	16	4.31	7.2e-06	CHRDL1,DLX5,EGFR,FGFR2,GLI2,GPC3,GREM1,ID4,IGFBP3,IGFBP5,MSX2,NELL1,RORB,SFRP1,SNAI1,SOX11
BP	GO:0032989: Cellular component morphogenesis	1264	34	15.22	7.4e-06	ARC,BAMBI,BCL11A,BOC,BRSK2,CACNA1G,CNTN1,CNTN4,COL18A1,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,GREM1,KIF14,LAMA1,MAP3K1,MGLL,MSX2,MYO10,NR4A3,S100A4,SDC2,SEMA3C,SFRP1,SLITRK6,SNAI1,SOX6,UNC5A,UNC5D,ZFPM1
BP	GO:0050767: Regulation of neurogenesis	536	20	6.45	7.7e-06	ASCL1,BCL11A,CDC20,CNTN1,CNTN4,CXCR4,GATA3,GLI2,ID4,MGLL,PER2,SDC2,SERPINF1,SOX11,TCF4,TGIF2,TNFRSF21,TRIM67,TSPO,UNC5D
BP	GO:0006351: Transcription, DNA-templated	3519	69	42.37	8.0e-06	AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPRC1,PRRX2,RAN,RORB,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,ZFPM1,ZNF121
BP	GO:0035239: Tube morphogenesis	364	16	4.38	8.8e-06	CXCR4,EGFR,FGFR2,GATA3,GLI2,GPC3,GREM1,LAMA1,LMO4,MSX2,MYC,NR4A3,SFRP1,SOX11,SPRY2,TBX3
BP	GO:0009891: Positive regulation of biosynthetic process	1568	39	18.88	9.0e-06	ADCYAP1R1,AKNA,ASCL1,BAMBI,BCL11A,BCLAF1,CDKN1C,DLX5,EGFR,FGFR2,GATA3,GLI2,GNL3,GREM1,ID4,LDB2,LMO4,MYC,NAA15,NR4A3,PHF5A,POLR2F,PPRC1,PRKCA,PRR16,RAN,RORB,RUVBL2,SFRP1,SIX6,SNAI1,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,ZFPM1
BP	GO:0045935: Positive regulation of nucleobase-containing compound metabolic process	1511	38	18.19	9.4e-06	ADCYAP1R1,AKNA,ASCL1,BAMBI,BCL11A,BCLAF1,CDKN1C,DLX5,EGFR,FGFR2,GATA3,GLI2,GNL3,GREM1,ID4,LDB2,LMO4,MYC,NAA15,NR4A3,PHF5A,POLR2F,PPRC1,PRKCA,RAN,RORB,RUVBL2,SFRP1,SIX6,SNAI1,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,ZFPM1
BP	GO:0051252: Regulation of RNA metabolic process	3536	69	42.57	9.5e-06	ACTN2,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,PPRC1,PRRX2,RAN,RORB,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,ZFPM1,ZNF121
BP	GO:0048667: Cell morphogenesis involved in neuron differentiation	640	22	7.71	9.6e-06	BCL11A,BOC,BRSK2,CACNA1G,CNTN1,CNTN4,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,LAMA1,MGLL,MYO10,NR4A3,SDC2,SEMA3C,SLITRK6,UNC5A,UNC5D
BP	GO:0044271: Cellular nitrogen compound biosynthetic process	4182	78	50.35	9.7e-06	ACTN2,ADCYAP1R1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IMPDH1,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRRX2,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,TSPO,ZFPM1,ZNF121
BP	GO:0007411: Axon guidance	410	17	4.94	9.9e-06	BOC,CACNA1G,CNTN1,CNTN4,CXCR4,DLX5,EGFR,EPHA8,GATA3,GLI2,LAMA1,MYO10,NR4A3,SDC2,SEMA3C,UNC5A,UNC5D
BP	GO:0097485: Neuron projection guidance	410	17	4.94	9.9e-06	BOC,CACNA1G,CNTN1,CNTN4,CXCR4,DLX5,EGFR,EPHA8,GATA3,GLI2,LAMA1,MYO10,NR4A3,SDC2,SEMA3C,UNC5A,UNC5D
BP	GO:0035295: Tube development	593	21	7.14	1.0e-05	ASCL1,CXCR4,EGFR,EIF4EBP1,FGFR2,GATA3,GLI2,GPC3,GREM1,LAMA1,LMO4,LOX,MSX2,MYC,NR4A3,SEMA3C,SFRP1,SMAD6,SOX11,SPRY2,TBX3
BP	GO:0001763: Morphogenesis of a branching structure	212	12	2.55	1.0e-05	CXCR4,FGFR2,GLI2,GPC3,GREM1,LAMA1,MSX2,MYC,SEMA3C,SFRP1,SPRY2,TBX3
BP	GO:0060429: Epithelium development	1061	30	12.77	1.1e-05	ASCL1,COL18A1,CXCR4,DLX5,EGFR,FGFR2,GATA3,GLI2,GPC3,GREM1,IGFBP5,LAMA1,LDB2,LMO4,MAP3K1,MLLT3,MSX2,MYC,PDE2A,SEMA3C,SFRP1,SLC7A11,SLITRK6,SMAD6,SNAI1,SOX11,SPRY2,TBX3,TJP2,TMEM100
BP	GO:0048870: Cell motility	1176	32	14.16	1.1e-05	AGTR1,ARC,ASCL1,BAMBI,COL18A1,CX3CL1,CXCR4,EGFR,EGR3,EPHA8,FAM60A,GATA3,GRB14,GREM1,HDAC9,IGFBP3,IGFBP5,KIF14,LAMA1,LHX6,MAP3K1,MSX2,PHACTR1,PRKCA,SDC2,SEMA3C,SERPINF1,SFRP1,SLC7A11,SNAI1,TSPO,UNC5D
BP	GO:0051674: Localization of cell	1176	32	14.16	1.1e-05	AGTR1,ARC,ASCL1,BAMBI,COL18A1,CX3CL1,CXCR4,EGFR,EGR3,EPHA8,FAM60A,GATA3,GRB14,GREM1,HDAC9,IGFBP3,IGFBP5,KIF14,LAMA1,LHX6,MAP3K1,MSX2,PHACTR1,PRKCA,SDC2,SEMA3C,SERPINF1,SFRP1,SLC7A11,SNAI1,TSPO,UNC5D

BP	GO:1903506: Regulation of nucleic acid-templated transcription	3414	67	41.1	1.1e-05	ACTN2,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,PPRC1,PRRX2,RAN,RORB,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,ZFPM1,ZNF121
BP	GO:0009725: Response to hormone	852	26	10.26	1.2e-05	ADCYAP1R1,BAIAP2L1,BID,CRYAB,EGFR,EGR3,EIF4EBP1,FGFR2,GATA3,HDAC9,IGFBP5,KLF9,LOX,MSX2,NR4A3,PPAT,PRKCA,RORB,RUVBL2,SERPINF1,SFRP1,SMAD6,STC2,TBC1D4,TRIB3,TSPO
BP	GO:0090304: Nucleic acid metabolic process	4800	86	57.79	1.2e-05	ACTN2,ADAT2,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BYSL,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,DUS3L,EGFR,EGLN3,EGR3,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,INSM2,KLF9,LDB2,LHX6,LMO4,MARS2,MLLT3,MSX2,MYC,NAA15,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPRC1,PRRX2,PUS7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TOP1,TRIB3,VARS,WDR3,ZFPM1,ZNF121
BP	GO:0048812: Neuron projection morphogenesis	652	22	7.85	1.3e-05	BCL11A,BOC,BRSK2,CACNA1G,CNTN1,CNTN4,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,LAMA1,MGLL,MYO10,NR4A3,SDC2,SEMA3C,SLITRK6,UNC5A,UNC5D
BP	GO:1901362: Organic cyclic compound biosynthetic process	4215	78	50.75	1.3e-05	ACTN2,ADCYAP1R1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IMPDH1,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRRX2,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,TSPO,ZFPM1,ZNF121
BP	GO:0031325: Positive regulation of cellular metabolic process	2547	54	30.67	1.4e-05	ADCYAP1R1,AGTR1,AKNA,ASCL1,BAMBI,BCL11A,BCLAF1,BID,CARD9,CDC20,CDKN1C,CXCR4,DLX5,EGFR,EGLN3,EPHA8,FGFR2,GATA3,GLI2,GNL3,GREM1,ID4,IGFBP3,KIF14,LDB2,LMO4,LRRN3,MAP3K1,MYC,NAA15,NR4A3,PHF5A,POLR2F,PPRC1,PRKCA,PRR16,RAN,RORB,RUVBL2,SFRP1,SIX6,SNAI1,SOX11,SOX6,SPRY2,TBL1X,TBX3,TCF4,TERT,TFAM,TRIB3,TRIM67,TSPO,ZFPM1
BP	GO:0035107: Appendage morphogenesis	150	10	1.81	1.4e-05	DLX5,FGFR2,GLI2,GPC3,GREM1,MSX2,PRRX2,SEMA3C,SOX11,TBX3
BP	GO:0035108: Limb morphogenesis	150	10	1.81	1.4e-05	DLX5,FGFR2,GLI2,GPC3,GREM1,MSX2,PRRX2,SEMA3C,SOX11,TBX3
BP	GO:0051173: Positive regulation of nitrogen compound metabolic process	1542	38	18.57	1.5e-05	ADCYAP1R1,AKNA,ASCL1,BAMBI,BCL11A,BCLAF1,CDKN1C,DLX5,EGFR,FGFR2,GATA3,GLI2,GNL3,GREM1,ID4,LDB2,LMO4,MYC,NAA15,NR4A3,PHF5A,POLR2F,PPRC1,PRKCA,RAN,RORB,RUVBL2,SFRP1,SIX6,SNAI1,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,ZFPM1
BP	GO:0001822: Kidney development	258	13	3.11	1.5e-05	AGTR1,CDKN1C,FGFR2,GATA3,GLI2,GPC3,GREM1,MYC,PPAT,SERPINF1,SFRP1,SMAD6,SOX11
BP	GO:0048863: Stem cell differentiation	339	15	4.08	1.6e-05	ASCL1,BAMBI,FGFR2,GREM1,LDB2,MSX2,POLR2F,S100A4,SEMA3C,SFRP1,SMC3,SNAI1,SOX11,SOX6,TBX3
BP	GO:0071559: Response to transforming growth factor beta	222	12	2.67	1.6e-05	BAMBI,CDKN1C,DAND5,HTRA1,MAP3K1,MYC,PDE2A,SFRP1,SMAD6,SOX11,SOX6,TGIF2
BP	GO:0071560: Cellular response to transforming growth factor beta stimulus	222	12	2.67	1.6e-05	BAMBI,CDKN1C,DAND5,HTRA1,MAP3K1,MYC,PDE2A,SFRP1,SMAD6,SOX11,SOX6,TGIF2
BP	GO:0008285: Negative regulation of cell proliferation	613	21	7.38	1.6e-05	CDKN1C,COL18A1,FGFR2,GATA3,GPC3,GREM1,IGFBP3,IGFBP5,KLF9,MSX2,MYC,NELL1,PER2,PRKCA,SERPINF1,SFRP1,SMAD6,SOX11,SPRY2,TNFRSF21,TSPO
BP	GO:0006355: Regulation of transcription, DNA-templated	3389	66	40.8	1.8e-05	AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,PPRC1,PRRX2,RAN,RORB,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,ZFPM1,ZNF121
BP	GO:0022612: Gland morphogenesis	125	9	1.51	2.0e-05	EGFR,FGFR2,GLI2,IGFBP5,LAMA1,MSX2,SEMA3C,SFRP1,TBX3
BP	GO:0003205: Cardiac chamber development	126	9	1.52	2.2e-05	DAND5,FGFR2,GATA3,LMO4,MSX2,SEMA3C,SOX11,TBX3,ZFPM1
BP	GO:0009059: Macromolecule biosynthetic process	4793	85	57.71	2.2e-05	ACTN2,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,C10orf2,CARD9,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP5,INSM2,KLF9,LDB2,LHX6,LMO4,MARS2,MLLT3,MRPL23,MRPL42,MSX2,MYC,NAA15,NR4A3,PD

						E2A,PER2,PHF5A,POLR2F,POLR3D,PPRC1,PRR16,PRRX2,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SDC2,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,ST6GAL1,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TOP1,TRAP1,TRIB3,VARS,ZFPM1,ZNF121
BP	GO:0000122: Negative regulation of transcription from RNA polymerase II promoter	676	22	8.14	2.2e-05	ASCL1,BCL11A,CDKN1C,FGFR2,GATA3,GLI2,HDAC9,ID4,MSX2,MYC,PDE2A,PER2,SAMD11,SNAI1,SOX11,SOX6,TBL1X,TBX3,TGIF2,TLE1,TRIB3,ZFPM1
BP	GO:0010033: Response to organic substance	2465	52	29.68	2.4e-05	ABCC4,ADCYAP1R1,ASCL1,BAIAP2L1,BAMBI,BID,BRSK2,CARD9,CDKN1C,CRYAB,CX3CL1,CXCR4,DAND5,DLX5,EGFR,EGR3,EIF4EBP1,FGFR2,GATA3,GLI2,HDAC9,HTRA1,IGFBP5,KLF9,LOX,MAP3K1,MGLL,MSX2,MYC,NR4A3,PDE2A,PPAT,PRKCA,RORB,RUVBL2,SDC2,SERPINF1,SFRP1,SLC7A11,SMAD6,SOX11,SOX6,SPRY2,STC2,TBC1D4,TERT,TGIF2,TJP2,TMEM100,TNFRSF21,TRIB3,TSPO
BP	GO:0019219: Regulation of nucleobase-containing compound metabolic process	3848	72	46.33	2.4e-05	ACTN2,ADCYAP1R1,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,PPRC1,PRKCA,PRRX2,RAN,RORB,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,ZFPM1,ZNF121
BP	GO:0048732: Gland development	398	16	4.79	2.7e-05	ASCL1,CDKN1C,EGFR,FGFR2,GATA3,GLI2,IGFBP5,LAMA1,LMO4,MSX2,PPAT,SEMA3C,SERPINF1,SFRP1,TBX3,TSPO
BP	GO:0072001: Renal system development	273	13	3.29	2.7e-05	AGTR1,CDKN1C,FGFR2,GATA3,GLI2,GPC3,GREM1,MYC,PPAT,SERPINF1,SFRP1,SMAD6,SOX11
BP	GO:0042981: Regulation of apoptotic process	1346	34	16.21	2.8e-05	ACTN2,ASCL1,BCLAF1,BID,CARD9,COL18A1,CRYAB,CX3CL1,EGFR,EGLN3,EGR3,FAIM3,FGFR2,GATA3,GREM1,IGFBP3,IL7,KIF14,MSX2,MYC,NAA15,NR4A3,PRKCA,SFRP1,SMAD6,SNAI1,SPRY2,STEAP3,TBX3,TERT,TLE1,TRAP1,TSPO,UNC5A
BP	GO:0042472: Inner ear morphogenesis	100	8	1.2	2.8e-05	DLX5,FGFR2,GATA3,GLI2,NR4A3,PRRX2,SLITRK6,SPRY2
BP	GO:0006935: Chemotaxis	688	22	8.28	2.9e-05	AGTR1,BOC,CACNA1G,CNTN1,CNTN4,CX3CL1,CXCR4,DLX5,EGFR,EGR3,EPHA8,GATA3,GLI2,GREM1,LAMA1,MYO10,NR4A3,PRKCA,SDC2,SEMA3C,UNC5A,UNC5D
BP	GO:0042330: Taxis	688	22	8.28	2.9e-05	AGTR1,BOC,CACNA1G,CNTN1,CNTN4,CX3CL1,CXCR4,DLX5,EGFR,EGR3,EPHA8,GATA3,GLI2,GREM1,LAMA1,MYO10,NR4A3,PRKCA,SDC2,SEMA3C,UNC5A,UNC5D
BP	GO:0048864: Stem cell development	275	13	3.31	3.0e-05	BAMBI,FGFR2,GREM1,LDB2,MSX2,POLR2F,S100A4,SEMA3C,SFRP1,SMC3,SNAI1,SOX11,TBX3
BP	GO:0006139: Nucleobase-containing compound metabolic process	5364	92	64.58	3.1e-05	ACTN2,ADAT2,ADCYAP1R1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BYSL,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,DUS3L,EGFR,EGLN3,EGR3,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IMPDH1,INSM2,KLF9,LDB2,LHX6,LMO4,MARS2,MLLT3,MSX2,MYC,NAA15,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRRX2,PUS7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TJP2,TLE1,TMEM100,TOP1,TRIB3,VARS,WDR3,ZFPM1,ZNF121
BP	GO:0051171: Regulation of nitrogen compound metabolic process	3948	73	47.53	3.2e-05	ACTN2,ADCYAP1R1,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,INSM2,KLF9,LDB2,LHX6,LMO4,MLLT3,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,PPRC1,PRKCA,PRRX2,RAN,RORB,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TRIB3,TSPO,ZFPM1,ZNF121
BP	GO:0043067: Regulation of programmed cell death	1355	34	16.31	3.2e-05	ACTN2,ASCL1,BCLAF1,BID,CARD9,COL18A1,CRYAB,CX3CL1,EGFR,EGLN3,EGR3,FAIM3,FGFR2,GATA3,GREM1,IGFBP3,IL7,KIF14,MSX2,MYC,NAA15,NR4A3,PRKCA,SFRP1,SMAD6,SNAI1,SPRY2,STEAP3,TBX3,TERT,TLE1,TRAP1,TSPO,UNC5A
BP	GO:0034645: Cellular macromolecule biosynthetic process	4627	82	55.71	3.6e-05	AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP5,INSM2,KLF9,LDB2,LHX6,LMO4,MARS2,MLLT3,MRPL23,MRPL42,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPRC1,PRR16,PRRX2,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,ST6GAL1,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TOP1,TRAP1,TRIB3,VARS,ZFPM1,ZNF121
BP	GO:0097305: Response to alcohol	281	13	3.38	3.7e-05	ADCYAP1R1,BID,CRYAB,EGFR,EIF4EBP1,GATA3,KLF9,MSX2,RUVBL2,SERPINF1,SFRP1,STC2,TSPO
BP	GO:0048736: Appendage development	169	10	2.03	3.9e-05	DLX5,FGFR2,GLI2,GPC3,GREM1,MSX2,PRRX2,SEMA3C,SOX11,TBX3

BP	GO:0048754: Branching morphogenesis of an epithelial tube	169	10	2.03	3.9e-05	CXCR4,FGFR2,GLI2,GPC3,GREM1,LAMA1,MSX2,MYC,SPRY2,TBX3
BP	GO:0060173: Limb development	169	10	2.03	3.9e-05	DLX5,FGFR2,GLI2,GPC3,GREM1,MSX2,PRRX2,SEMA3C,SOX11,TBX3
BP	GO:0090092: Regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	205	11	2.47	3.9e-05	BAMBI,CDKN1C,CHRDL1,DAND5,GPC3,GREM1,HTRA1,MSX2,SFRP1,SMAD6,SOX11
BP	GO:0016043: Cellular component organization	5550	94	66.82	3.9e-05	ACTN2,AGTR1,ARC,ATP11C,BAIAP2L1,BAMBI,BAZ1A,BCL11A,BCLAF1,BID,BOC,BRSK2,C10orf2,CACNA1G,CCDC85B,CDC20,CDYL,CENPF,CNTN1,CNTN4,CNTNAP2,COL18A1,CRYAB,CXCR4,DLX5,EGFR,EIF4EBP1,EPB41L4B,EPHA8,EYA4,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,HIST1H2BH,HIST1H4J,HTRA1,IGFBP3,IGFBP5,INF2,KIF14,LAMA1,LETM1,LMO4,LOX,MAP3K1,MGLL,MRPL23,MRPL42,MSX2,MYC,MYO10,NEK6,NR4A3,NTHL1,PDE2A,PER2,PHACTR1,PPAT,PPRC1,PRKCA,PRR16,RAN,RPL27A,RPS26,RUVBL2,S100A4,SDC2,SEMA3C,SERPINF1,SFRP1,SLITRK6,SMAD6,SMC3,SNAI1,SOX6,SPRY2,SSSCA1,TBC1D4,TBL1X,TCF4,TERT,TFAM,TJP2,TMEM150C,TOP1,TRIM67,TSPO,TUBA1C,UNC5A,UNC5D,ZFPM1
BP	GO:0060562: Epithelial tube morphogenesis	325	14	3.91	4.1e-05	CXCR4,FGFR2,GATA3,GLI2,GPC3,GREM1,LAMA1,LMO4,MSX2,MYC,SFRP1,SOX11,SPRY2,TBX3
BP	GO:0048545: Response to steroid hormone	368	15	4.43	4.1e-05	ADCYAP1R1,BID,CRYAB,EGFR,GATA3,KLF9,LOX,MSX2,NR4A3,RORB,RUVBL2,SERPINF1,SFRP1,SMAD6,TSPO
BP	GO:0006725: Cellular aromatic compound metabolic process	5555	94	66.88	4.1e-05	ACTN2,ADAT2,ADCYAP1R1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BYSL,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DIO3,DLX5,DUS3L,EGFR,EGLN3,EGR3,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IMPDH1,INSM2,KLF9,LDB2,LHX6,LMO4,MARS2,MLLT3,MSX2,MYC,NAA15,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRRX2,PUS7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TJP2,TLE1,TMEM100,TOP1,TRIB3,TSPO,VARS,WDR3,ZFPM1,ZNF121
BP	GO:0042221: Response to chemical	3833	71	46.15	4.1e-05	ABCC4,ADCYAP1R1,AGTR1,ASCL1,BAIAP2L1,BAMBI,BID,BOC,BRSK2,CACNA1G,CARD9,CDKN1C,CENPF,CNTN1,CNTN4,COL18A1,CRYAB,CX3CL1,CXCR4,DAND5,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,EPHA8,FGFR2,GATA3,GLI2,GREM1,HDAC9,HTRA1,IGFBP5,KLF9,LAMA1,LOX,MAP3K1,MGLL,MPST,MSX2,MYC,MYO10,NR4A3,PDE2A,PPAT,PRKCA,RORB,RUVBL2,SDC2,SEMA3C,SERPINF1,SFRP1,SLC30A1,SLC7A11,SMAD6,SOX11,SOX6,SPRY2,STC2,TBC1D4,TERT,TGIF2,TJP2,TMEM100,TNFRSF21,TOP1,TRAP1,TRIB3,TSPO,UNC5A,UNC5D
BP	GO:0060485: Mesenchyme development	207	11	2.49	4.3e-05	BAMBI,DAND5,FGFR2,GREM1,MSX2,MYC,S100A4,SEMA3C,SFRP1,SNAI1,SOX11
BP	GO:0043066: Negative regulation of apoptotic process	814	24	9.8	4.6e-05	ASCL1,CRYAB,CX3CL1,EGFR,EGR3,FAIM3,FGFR2,GATA3,GREM1,IL7,KIF14,MSX2,MYC,NAA15,NR4A3,PRKCA,SFRP1,SMAD6,SNAI1,SPRY2,TBX3,TERT,TLE1,TRAP1
BP	GO:0030278: Regulation of ossification	173	10	2.08	4.7e-05	DLX5,FGFR2,GREM1,ID4,IGFBP5,MSX2,NELL1,RORB,SFRP1,SOX11
BP	GO:0060541: Respiratory system development	212	11	2.55	5.3e-05	ASCL1,DLX5,EGFR,EIF4EBP1,FGFR2,GLI2,GPC3,LAMA1,LOX,SOX11,SPRY2
BP	GO:0043069: Negative regulation of programmed cell death	823	24	9.91	5.5e-05	ASCL1,CRYAB,CX3CL1,EGFR,EGR3,FAIM3,FGFR2,GATA3,GREM1,IL7,KIF14,MSX2,MYC,NAA15,NR4A3,PRKCA,SFRP1,SMAD6,SNAI1,SPRY2,TBX3,TERT,TLE1,TRAP1
BP	GO:0014031: Mesenchymal cell development	142	9	1.71	5.6e-05	BAMBI,FGFR2,GREM1,MSX2,S100A4,SEMA3C,SFRP1,SNAI1,SOX11
BP	GO:0045165: Cell fate commitment	253	12	3.05	5.8e-05	ASCL1,FGFR2,GATA3,GLI2,IL7,LHX6,LMO4,SFRP1,SOX6,SPRY2,TBX3,ZFPM1
BP	GO:0044260: Cellular macromolecule metabolic process	7711	120	92.84	6.4e-05	ACTN2,ADAT2,AGTR1,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BID,BRSK2,BYSL,C10orf2,CAMKV,CCDC85B,CCNL1,CDC20,CDKN1C,CDYL,CENPF,CHRDL1,CRYAB,CXCR4,DAND5,DLX5,DUS3L,DUSP2,EGFR,EGLN3,EGR3,EIF4EBP1,EPHA8,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP3,IGFBP5,INSM2,KIF14,KLF9,LDB2,LHX6,LMO4,LOX,LRRN3,MAP3K1,MARS2,MLLT3,MRPL23,MRPL42,MSX2,MYC,MYLIP,NAA15,NEK6,NELL1,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPRC1,PRKCA,PRR16,PRRX2,PUS7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SDC2,SERPINF1,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,SPRY2,ST6GAL1,STK32C,TBL1X,TBX3,TCF4,TERT,TFAM,TFPI2,TGIF2,TLE1,TMEM100,TOP1,TRAP1,T

						RIB3,TRIM67,TTLL12,TUBA1C,UBE2QL1,VARS,WDR3,ZFPM1,ZNF121
BP	GO:0046483: Heterocycle metabolic process	5540	93	66.7	6.6e-05	ACTN2,ADAT2,ADCYAP1R1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BYSL,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,DUS3L,EGFR,EGLN3,EGR3,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IMPDH1,INSM2,KLF9,LDB2,LHX6,LMO4,MARS2,MLLT3,MSX2,MYC,NAA15,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRRX2,PUS7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TJP2,TLE1,TMEM100,TOP1,TRIB3,TSPO,VARS,WDR3,ZFPM1,ZNF121
BP	GO:0048598: Embryonic morphogenesis	574	19	6.91	6.7e-05	CDKN1C,DLX5,DUSP2,FGFR2,GATA3,GLI2,GPC3,GREM1,LMO4,MSX2,NR4A3,PRRX2,SFRP1,SLITRK6,SNAI1,SOX11,SPRY2,TBX3,TGIF2
BP	GO:0008284: Positive regulation of cell proliferation	780	23	9.39	6.7e-05	ABCC4,ASCL1,BAMBI,CDC20,COL18A1,DLX5,EGFR,EGR3,FGFR2,GLI2,GREM1,HTRA1,ID4,IL7,KIF14,MYC,PRKCA,PRRX2,SFRP1,SOX11,TBX3,TPD52,TSPO
BP	GO:0071310: Cellular response to organic substance	1906	42	22.95	7.0e-05	ADCYAP1R1,BAIAP2L1,BAMBI,BRSK2,CDKN1C,CX3CL1,CXCR4,DAND5,DLX5,EGFR,EGR3,EIF4EBP1,FGFR2,GATA3,GLI2,HDAC9,HTRA1,IGFBP5,KLF9,MAP3K1,MSX2,MYC,NR4A3,PDE2A,PPAT,PRKCA,RORB,RUVBL2,SERPINF1,SFRP1,SMAD6,SOX11,SOX6,SPRY2,STC2,TBC1D4,TERT,TGIF2,TMEM100,TNFRSF21,TRIB3,TSPO
BP	GO:0050679: Positive regulation of epithelial cell proliferation	147	9	1.77	7.3e-05	DLX5,EGFR,EGR3,FGFR2,HTRA1,MYC,PRKCA,SFRP1,SOX11
BP	GO:0030324: Lung development	183	10	2.2	7.6e-05	ASCL1,EGFR,EIF4EBP1,FGFR2,GLI2,GPC3,LAMA1,LOX,SOX11,SPRY2
BP	GO:0043170: Macromolecule metabolic process	8437	128	101.58	8.9e-05	ACTN2,ADAM12,ADAMTS19,ADAT2,AGTR1,AKNA,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BID,BRSK2,BYSL,C10orf2,CAMKV,CARD9,CCDC85B,CCNL1,CDC20,CDKN1C,CDYL,CENPF,CHRDL1,CNTN1,COL18A1,CRYAB,CXCR4,DAND5,DLX5,DUS3L,DUSP2,EGFR,EGLN3,EGR3,EIF4EBP1,EPHA8,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP3,IGFBP5,IL7,INSM2,ISOC2,KIF14,KLF9,LDB2,LHX6,LMO4,LOX,LRRN3,MAP3K1,MARS2,MLLT3,MRPL23,MRPL42,MSX2,MYC,MYLIP,NAA15,NEK6,NELL1,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPRC1,PRKCA,PRR16,PRRX2,PUS7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SDC2,SERPINF1,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,SPRY2,ST6GAL1,STC2,STK32C,TBL1X,TBX3,TCF4,TERT,TFAM,TFPI2,TGIF2,TLE1,TMEM100,TOP1,TRAP1,TRIB3,TRIM67,TTLL12,TUBA1C,UBE2QL1,VARS,WDR3,ZFPM1,ZNF121
BP	GO:0044249: Cellular biosynthetic process	5658	94	68.12	8.9e-05	ACTN2,ADCYAP1R1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,C10orf2,CARD9,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP5,IMPDH1,INSM2,KLF9,LDB2,LHX6,LMO4,MARS2,MCAT,MGLL,MLLT3,MPST,MRPL23,MRPL42,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRR16,PRRX2,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,ST6GAL1,STC2,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TOP1,TRAP1,TRIB3,TSPO,VARS,ZFPM1,ZNF121
BP	GO:0030323: Respiratory tube development	187	10	2.25	9.1e-05	ASCL1,EGFR,EIF4EBP1,FGFR2,GLI2,GPC3,LAMA1,LOX,SOX11,SPRY2
BP	GO:0042471: Ear morphogenesis	119	8	1.43	9.6e-05	DLX5,FGFR2,GATA3,GLI2,NR4A3,PRRX2,SLITRK6,SPRY2
BP	GO:0042493: Response to drug	398	15	4.79	9.8e-05	ABCC4,ADCYAP1R1,CARD9,CENPF,COL18A1,EGFR,GATA3,LOX,MYC,PDE2A,PPAT,SEMA3C,SFRP1,TOP1,TSPO
BP	GO:0001655: Urogenital system development	312	13	3.76	0.00011	AGTR1,CDKN1C,FGFR2,GATA3,GLI2,GPC3,GREM1,MYC,PPAT,SERPINF1,SFRP1,SMAD6,SOX11
BP	GO:0048762: Mesenchymal cell differentiation	155	9	1.87	0.00011	BAMBI,FGFR2,GREM1,MSX2,S100A4,SEMA3C,SFRP1,SNAI1,SOX11
BP	GO:0048646: Anatomical structure formation involved in morphogenesis	1031	27	12.41	0.00011	ADAM12,BYSL,COL18A1,CX3CL1,CXCR4,DLX5,DUSP2,EGR3,FGFR2,GATA3,GLI2,GREM1,HDAC9,KCNH1,LMO4,MSX2,NAA15,NR4A3,PRKCA,SEMA3C,SERPINF1,SFRP1,SNAI1,SOX11,TBX3,TMEM100,ZFPM1
BP	GO:1901360: Organic cyclic compound metabolic process	5770	95	69.47	0.00011	ACTN2,ADAT2,ADCYAP1R1,AGTR1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BYSL,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DIO3,DLX5,DUS3L,EGFR,EGLN3,EGR3,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IMPDH1,INSM2,KLF9,LDB2,LHX6,LMO4,MARS2,MLLT3,MSX2,MYC,NAA15,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRRX2,PUS7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TJP2,TLE1,TMEM100,TOP1,TRIB3,TSPO,VARS,WDR3,ZFPM1,ZNF121

BP	GO:0009058: Biosynthetic process	5849	96	70.42	0.00012	ACTN2,ADCYAP1R1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A, BCL11A,BCLAF1,C10orf2,CARD9,CCDC85B,CCNL1,CDKN1 C,CDYL,CENPF,CHRDL1,DAND5,DIO3,DLX5,EGFR,EGLN3 ,EGR3,EIF4EBP1,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GR EM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP5,IMPDH1,INS M2,KLF9,LDB2,LHX6,LMO4,MARS2,MCAT,MGLL,MLLT3, MPST,MRPL23,MRPL42,MSX2,MYC,NAA15,NR4A3,PDE2A, PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRR16, PRRX2,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SDC2, SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,ST 6GAL1,STC2,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,T MEM100,TOP1,TRAP1,TRIB3,TSPO,VARS,ZFPM1,ZNF121
BP	GO:0001568: Blood vessel development	549	18	6.61	0.00012	COL18A1,CX3CL1,CXCR4,EGR3,FGFR2,GPC3,GREM1,HDA C9,LAMA1,LOX,NAA15,PRKCA,PRRX2,SEMA3C,SERPINF1 ,SFRP1,TBX3,TMEM100
BP	GO:0045944: Positive regulation of transcription from RNA polymerase II promoter	921	25	11.09	0.00012	AKNA,ASCL1,BCL11A,DLX5,EGFR,FGFR2,GATA3,GLI2,G NL3,GREM1,ID4,LDB2,LMO4,MYC,NR4A3,PPRC1,RUVBL2, SIX6,SOX11,SOX6,TBL1X,TCF4,TERT,TFAM,ZFPM1
BP	GO:0009893: Positive regulation of metabolic process	3181	60	38.3	0.00013	ADCYAP1R1,AGTR1,AKNA,ASCL1,BAMBI,BCL11A,BCLA F1,BID,CARD9,CDC20,CDKN1C,CNTN1,CXCR4,DLX5,EGF R,EGLN3,EPHA8,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,I D4,IGFBP3,KIF14,LDB2,LMO4,LRRN3,MAP3K1,MYC,MYLI P,NAA15,NR4A3,PHF5A,POLR2F,PPRC1,PRKCA,PRR16,PSD 3,RAN,RORB,RUVBL2,SFRP1,SIX6,SNAI1,SOX11,SOX6,SPR Y2,TBC1D4,TBL1X,TBX3,TCF4,TERT,TFAM,TLE1,TRIB3,T RIM67,TSPO,ZFPM1
BP	GO:0043627: Response to estrogen	161	9	1.94	0.00015	ADCYAP1R1,BID,CRYAB,EGFR,GATA3,MSX2,RUVBL2,SF RP1,SMAD6
BP	GO:0001654: Eye development	326	13	3.93	0.00017	CDKN1C,CHRDL1,CRYAB,FGFR2,GATA3,LAMA1,MAP3K1 ,RORB,SERPINF1,SLC7A11,SLITRK6,SOX11,TGIF2
BP	GO:0043010: Camera-type eye development	284	12	3.42	0.00017	CDKN1C,CRYAB,FGFR2,GATA3,LAMA1,MAP3K1,RORB,S ERPINF1,SLC7A11,SLITRK6,SOX11,TGIF2
BP	GO:0071407: Cellular response to organic cyclic compound	328	13	3.95	0.00018	EGFR,EGR3,GLI2,IGFBP5,KLF9,MSX2,NR4A3,PDE2A,ROR B,RUVBL2,SERPINF1,SFRP1,TERT
BP	GO:0001944: Vasculature development	569	18	6.85	0.00018	COL18A1,CX3CL1,CXCR4,EGR3,FGFR2,GPC3,GREM1,HDA C9,LAMA1,LOX,NAA15,PRKCA,PRRX2,SEMA3C,SERPINF1 ,SFRP1,TBX3,TMEM100
BP	GO:0071383: Cellular response to steroid hormone stimulus	132	8	1.59	0.00020	EGFR,KLF9,MSX2,NR4A3,RORB,RUVBL2,SERPINF1,SFRP1
BP	GO:0071214: Cellular response to abiotic stimulus	246	11	2.96	0.00020	ASCL1,CRYAB,EGFR,GATA3,MAP3K1,MYC,PDE2A,PRKC A,RUVBL2,SFRP1,TSPO
BP	GO:0001657: Ureteric bud development	100	7	1.2	0.00021	FGFR2,GATA3,GPC3,GREM1,MYC,SFRP1,SMAD6
BP	GO:0045664: differentiation	427	15	5.14	0.00021	ASCL1,BCL11A,CDC20,CNTN1,CNTN4,GATA3,GLI2,ID4,M GLL,SDC2,SERPINF1,SOX11,TCF4,TGIF2,TRIM67
BP	GO:0072163: Mesonephric epithelium development	101	7	1.22	0.00022	FGFR2,GATA3,GPC3,GREM1,MYC,SFRP1,SMAD6
BP	GO:0072164: Mesonephric tubule development	101	7	1.22	0.00022	FGFR2,GATA3,GPC3,GREM1,MYC,SFRP1,SMAD6
BP	GO:0023051: Regulation of signaling	2891	55	34.81	0.00023	ACTN2,ARC,ASCL1,BAIAP2L1,BAMBI,BCLAF1,BID,BRSK2 ,CARD9,CDC20,CDKN1C,CHRDL1,CNTN4,CX3CL1,CXCR4, DAND5,DLX5,DUSP2,EGFR,EPHA8,FGFR2,GATA3,GLI2,GP C3,GRB14,GREM1,HTRA1,IGFBP3,IGFBP5,IL7,KIF14,MAP3 K1,MGLL,MLLT3,MSX2,MYC,NEK6,PER2,PRKCA,PRRX2,P SD3,S100A4,SFRP1,SLC30A1,SMAD6,SNAI1,SOX11,SPRY2, STEAP3,TBC1D4,TERT,TLE1,TRAP1,TRIB3,TRIM67
BP	GO:0034641: Cellular nitrogen compound metabolic process	5874	95	70.72	0.00024	ACTN2,ADAT2,ADCYAP1R1,AKNA,AMD1,ASCL1,BAMBI, BAZ1A,BCL11A,BCLAF1,BYSL,C10orf2,CCDC85B,CCNL1,C DKN1C,CDYL,CENPF,CHRDL1,DAND5,DIO3,DLX5,DUS3L, EGFR,EGLN3,EGR3,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GN L3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IMPDH1 ,INSM2,KLF9,LDB2,LHX6,LMO4,MARS2,MLLT3,MPST,MS X2,MYC,NAA15,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PE R2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRRX2,P US7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,S FRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,TBL 1X,TBX3,TCF4,TERT,TFAM,TGIF2,TJP2,TLE1,TMEM100,TO P1,TRIB3,TSPO,VARS,WDR3,ZFPM1,ZNF121
BP	GO:0010646: Regulation of cell communication	2903	55	34.95	0.00026	ACTN2,ARC,ASCL1,BAIAP2L1,BAMBI,BCLAF1,BID,BRSK2 ,CARD9,CDC20,CDKN1C,CHRDL1,CNTN4,CX3CL1,CXCR4, DAND5,DLX5,DUSP2,EGFR,EPHA8,FGFR2,GATA3,GLI2,GP C3,GRB14,GREM1,HTRA1,IGFBP3,IGFBP5,IL7,KIF14,MAP3 K1,MGLL,MLLT3,MSX2,MYC,NEK6,PER2,PRKCA,PRRX2,P

						SD3,S100A4,SFRP1,SLC30A1,SMAD6,SNAI1,SOX11,SPRY2,STEAP3,TBC1D4,TERT,TLE1,TRAP1,TRIB3,TRIM67
BP	GO:0045444: Fat cell differentiation	175	9	2.11	0.00027	CCDC85B,GATA3,ID4,MSX2,PER2,SFRP1,SMAD6,TRIB3,ZFPM1
BP	GO:0001823: Mesonephros development	105	7	1.26	0.00028	FGFR2,GATA3,GPC3,GREM1,MYC,SFRP1,SMAD6
BP	GO:0090287: Regulation of cellular response to growth factor stimulus	176	9	2.12	0.00029	BAMBI,CDKN1C,DAND5,FGFR2,GATA3,HTRA1,SMAD6,SOX11,SPRY2
BP	GO:0003206: Cardiac chamber morphogenesis	106	7	1.28	0.00029	FGFR2,GATA3,MSX2,SEMA3C,SOX11,TBX3,ZFPM1
BP	GO:0072089: Stem cell proliferation	140	8	1.69	0.00029	ASCL1,FGFR2,GPC3,ID4,MYC,PRRX2,SOX11,TBX3
BP	GO:0003002: Regionalization	347	13	4.18	0.00030	ARC,ASCL1,FGFR2,GLI2,GPC3,GREM1,MLLT3,MSX2,SEMA3C,SFRP1,SMAD6,SNAI1,TBX3
BP	GO:0007389: Pattern specification process	443	15	5.33	0.00031	ARC,ASCL1,CXCR4,DAND5,FGFR2,GLI2,GPC3,GREM1,MLLT3,MSX2,SEMA3C,SFRP1,SMAD6,SNAI1,TBX3
BP	GO:0007507: Heart development	443	15	5.33	0.00031	DAND5,FGFR2,GATA3,GLI2,GPC3,GREM1,HDAC9,LMO4,MSX2,SEMA3C,SNAI1,SOX11,SOX6,TBX3,ZFPM1
BP	GO:0010243: Response to organonitrogen compound	758	21	9.13	0.00033	ABCC4,ASCL1,BAIAP2L1,CARD9,EGFR,EGR3,EIF4EBP1,FGFR2,HDAC9,IGFBP5,NR4A3,PDE2A,PPAT,PRKCA,SDC2,SFRP1,SLC7A11,STC2,TBC1D4,TRIB3,TSPO
BP	GO:1901576: Organic substance biosynthetic process	5766	93	69.42	0.00033	ACTN2,ADCYAP1R1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,C10orf2,CARD9,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP5,IMPDH1,INSM2,KLF9,LDB2,LHX6,LMO4,MARS2,MCAT,MGLL,MLLT3,MRPL23,MRPL42,MSX2,MYC,NAA15,NR4A3,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRR16,PRRX2,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SDC2,SFRP1,SIX6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,ST6GAL1,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TLE1,TMEM100,TOP1,TRAP1,TRIB3,TSPO,VARS,ZFPM1,ZNF121
BP	GO:0090101: Negative regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	109	7	1.31	0.00035	BAMBI,CHRDL1,DAND5,GREM1,HTRA1,SFRP1,SMAD6
BP	GO:0040007: Growth	876	23	10.55	0.00036	AGTR1,BCL11A,CCDC85B,CDKN1C,CRYAB,DIO3,FGFR2,GATA3,GLI2,GPC3,GREM1,HTRA1,IGFBP3,IGFBP5,IL7,KIF14,MGLL,MSX2,RUVBL2,SFRP1,SLITRK6,SPRY2,STC2
BP	GO:0044237: Cellular metabolic process	9700	140	116.79	0.00037	ACTN2,ADAT2,ADCYAP1R1,AGTR1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BID,BOC,BRSK2,BYSL,C10orf2,CAMKV,CARD9,CCDC85B,CCNL1,CDC20,CDKN1C,CDYL,CENPF,CHRDL1,CPPED1,CRYAB,CXCR4,DAND5,DIO3,DLX5,DOK4,DUS3L,DUSP2,EGFR,EGLN3,EGR3,EIF4EBP1,EPHA8,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP3,IGFBP5,IMPDH1,INSM2,KCNH1,KIF14,KLF9,LDB2,LHX6,LMO4,LOX,LRRN3,MAP3K1,MARS2,MCAT,MGLL,MLLT3,MPST,MRPL23,MRPL42,MSX2,MYC,MYLIP,NAA15,NEK6,NELL1,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPP1R14A,PPRC1,PRKCA,PRR16,PRRX2,PUS7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SDC2,SERPINF1,SFRP1,SIX6,SLC27A6,SLC6A6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,SPRY2,ST6GAL1,STC2,STK32C,TBL1X,TBX3,TCF4,TERT,TFAM,TFPI2,TGIF2,TJP2,TLE1,TMEM100,TNFRSF21,TOP1,TRAP1,TRIB3,TRIM67,TSPO,TTLL12,TUBA1C,UBE2QL1,VARS,WDR3,ZFPM1,ZNF121
BP	GO:0032870: Cellular response to hormone stimulus	558	17	6.72	0.00043	BAIAP2L1,EGFR,EGR3,EIF4EBP1,FGFR2,HDAC9,KLF9,MSX2,NR4A3,PPAT,PRKCA,RORB,RUVBL2,SERPINF1,SFRP1,TBC1D4,TRIB3
BP	GO:1901700: Response to oxygen-containing compound	1303	30	15.69	0.00044	ADCYAP1R1,ASCL1,BAIAP2L1,BID,BRSK2,CARD9,COL18A1,CRYAB,EGFR,EGR3,EIF4EBP1,FGFR2,GATA3,HDAC9,IGFBP5,KLF9,MGLL,MSX2,NR4A3,PDE2A,PPAT,PRKCA,RORB,RUVBL2,SERPINF1,SFRP1,STC2,TBC1D4,TRIB3,TSPO
BP	GO:0048858: Cell projection morphogenesis	831	22	10.01	0.00044	BCL11A,BOC,BRSK2,CACNA1G,CNTN1,CNTN4,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,LAMA1,MGLL,MYO10,NR4A3,SDC2,SEMA3C,SLITRK6,UNC5A,UNC5D
BP	GO:1901698: Response to nitrogen compound	832	22	10.02	0.00045	ABCC4,ASCL1,BAIAP2L1,CARD9,EGFR,EGR3,EIF4EBP1,FGFR2,HDAC9,IGFBP5,NR4A3,PDE2A,PPAT,PRKCA,SDC2,SFRP1,SLC7A11,STC2,TBC1D4,TERT,TRIB3,TSPO
BP	GO:0030030: Cell projection organization	1184	28	14.26	0.00045	ACTN2,BCL11A,BOC,BRSK2,CACNA1G,CDC20,CNTN1,CNTN4,CNTNAP2,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,LAMA1,MGLL,MYO10,NR4A3,SDC2,SEMA3C,SERPINF1,SLITRK6,TRIM67,TSPO,UNC5A,UNC5D
BP	GO:0030334:	562	17	6.77	0.00047	COL18A1,CXCR4,EGFR,FAM60A,GATA3,GREM1,HDAC9,IGFBP3,IGFBP5,KIF14,LAMA1,MAP3K1,PRKCA,SERPINF1,SFRP1,SNAI1,UNC5D

	Regulation of cell migration					
BP	GO:0050680: Negative regulation of epithelial cell proliferation	115	7	1.38	0.00048	CDKN1C,FGFR2,GATA3,GPC3,KLF9,SERPINF1,SFRP1
BP	GO:0007179: Transforming growth factor beta receptor signaling pathway	190	9	2.29	0.00050	BAMBI,CDKN1C,DAND5,HTRA1,MAP3K1,MYC,SMAD6,SOX11,TGIF2
BP	GO:0008152: Metabolic process	11485	159	138.28	0.00051	ABCC4,ABHD14A,ACTN2,ADAM12,ADAMTS19,ADAT2,ADCYAP1R1,AGTR1,AKNA,AMD1,ASCL1,ATP11C,BAMBI,BAZ1A,BCL11A,BCLAF1,BID,BOC,BRSK2,BYSL,C10orf2,CAMKV,CARD9,CCDC85B,CCNL1,CDC20,CDKN1C,CDYL,CENPF,CHRDL1,CNTN1,COL18A1,COMTD1,CPPED1,CRYAB,CXCR4,DAND5,DIO3,DLX5,DOK4,DUS3L,DUSP2,EGFR,EGLN3,EGR3,EIF4EBP1,ENOX1,EPHA8,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP3,IGFBP5,IL7,IMPDH1,INSM2,ISOC1,ISOC2,KCNH1,KIF14,KLF9,LDB2,LHX6,LMO4,LOX,LRRN3,MAP3K1,MARS2,MCAT,MGLL,MLLT3,MPST,MRPL23,MRPL42,MSX2,MYC,MYLIP,MYO10,NAA15,NEK6,NELL1,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PER2,PHACTR1,PHF5A,POLR2F,POLR3D,PPAT,PPP1R14A,PPRC1,PRKCA,PRR16,PRRX2,PSD3,PUS7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SDC2,SERPINF1,SFRP1,SIX6,SLC25A37,SLC27A6,SLC30A1,SLC6A6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,SPRY2,ST6GAL1,STC2,STEAP3,STK32C,TBC1D4,TBL1X,TBX3,TCF4,TERT,TFAM,TFPI2,TGIF2,TJP2,TLE1,TMEM100,TNFRSF21,TOP1,TRAP1,TRIB3,TRIM67,TSPO,TTLL12,TUBA1C,UBE2QL1,VARS,WDR3,ZFPM1,ZNF121
BP	GO:0030855: Epithelial cell differentiation	568	17	6.84	0.00052	ASCL1,COL18A1,DLX5,FGFR2,GATA3,GLI2,GREM1,LAMA1,MAP3K1,MSX2,PDE2A,SLC7A11,SLITRK6,SOX11,TBX3,TJP2,TMEM100
BP	GO:0040008: Regulation of growth	569	17	6.85	0.00054	AGTR1,BCL11A,CCDC85B,CRYAB,DIO3,FGFR2,GPC3,GREM1,HTRA1,IGFBP3,IGFBP5,IL7,KIF14,MGLL,RUVBL2,SFRP1,STC2
BP	GO:0009967: Positive regulation of signal transduction	1258	29	15.15	0.00054	ASCL1,BAMBI,BCLAF1,BID,CARD9,CDKN1C,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GPC3,GRB14,GREM1,IGFBP3,IGFBP5,MAP3K1,MLLT3,MSX2,NEK6,PRKCA,PRRX2,S100A4,SFRP1,SOX11,SPRY2,STEAP3,TERT
BP	GO:0070887: Cellular response to chemical stimulus	2365	46	28.47	0.00055	ADCYAP1R1,AGTR1,BAIAP2L1,BAMBI,BRSK2,CDKN1C,CX3CL1,CXCR4,DAND5,DLX5,EGFR,EGLN3,EGR3,EIF4EBP1,FGFR2,GATA3,GLI2,GREM1,HDAC9,HTRA1,IGFBP5,KLF9,MAP3K1,MSX2,MYC,NR4A3,PDE2A,PPAT,PRKCA,RORB,RUVBL2,SERPINF1,SFRP1,SMAD6,SOX11,SOX6,SPRY2,STC2,TBC1D4,TERT,TGIF2,TMEM100,TNFRSF21,TRAP1,TRIB3,TSPO
BP	GO:0048568: Embryonic organ development	421	14	5.07	0.00059	CDKN1C,DLX5,EGFR,FGFR2,GATA3,GLI2,NR4A3,PRRX2,SLITRK6,SNAI1,SOX11,SPRY2,TBX3,ZFPM1
BP	GO:0032990: Cell part morphogenesis	850	22	10.23	0.00060	BCL11A,BOC,BRSK2,CACNA1G,CNTN1,CNTN4,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GLI2,LAMA1,MGLL,MYO10,NR4A3,SDC2,SEMA3C,SLITRK6,UNC5A,UNC5D
BP	GO:0022603: Regulation of anatomical structure morphogenesis	796	21	9.58	0.00062	ARC,BAMBI,BCL11A,CX3CL1,FGFR2,GATA3,GPC3,GREM1,HDAC9,INF2,MGLL,MLLT3,MYC,MYO10,PRKCA,SDC2,SERPINF1,SFRP1,SNAI1,TGIF2,TMEM100
BP	GO:0009966: Regulation of signal transduction	2595	49	31.24	0.00068	ACTN2,ASCL1,BAIAP2L1,BAMBI,BCLAF1,BID,CARD9,CDKN1C,CHRDL1,CX3CL1,CXCR4,DAND5,DLX5,DUSP2,EGFR,EPHA8,FGFR2,GATA3,GLI2,GPC3,GRB14,GREM1,HTRA1,IGFBP3,IGFBP5,IL7,KIF14,MAP3K1,MGLL,MLLT3,MSX2,MYC,NEK6,PRKCA,PRRX2,PSD3,S100A4,SFRP1,SMAD6,SNAI1,SOX11,SPRY2,STEAP3,TBC1D4,TERT,TLE1,TRAP1,TRIB3,TRIM67
BP	GO:0006807: Nitrogen compound metabolic process	6193	97	74.56	0.00069	ACTN2,ADAT2,ADCYAP1R1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BYSL,C10orf2,CCDC85B,CCNL1,CDKN1C,CDYL,CENPF,CHRDL1,DAND5,DIO3,DLX5,DUS3L,EGFR,EGLN3,EGR3,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IMPDH1,INSM2,KLF9,LDB2,LHX6,LMO4,MARS2,MLLT3,MPST,MSX2,MYC,NAA15,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRRX2,PUS7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SDC2,SFRP1,SIX6,SLC6A6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,TBL1X,TBX3,TCF4,TERT,TFAM,TGIF2,TJP2,TLE1,TMEM100,TOP1,TRIB3,TSPO,VARS,WDR3,ZFPM1,ZNF121
BP	GO:0051128: Regulation of cellular component organization	1985	40	23.9	0.00069	AGTR1,ARC,BAIAP2L1,BAMBI,BCL11A,BCLAF1,BID,BOC,CCDC85B,CDC20,CENPF,CNTN1,CRYAB,EIF4EBP1,FGFR2,GATA3,GPC3,GREM1,HTRA1,IGFBP3,IGFBP5,INF2,KIF14,LMO4,MAP3K1,MGLL,MSX2,MYC,MYO10,NEK6,NTHL1,PER2,RUVBL2,SDC2,SERPINF1,SFRP1,SMAD6,SNAI1,TBC1D4,TRIM67
BP	GO:0023057: Negative regulation of signaling	1099	26	13.23	0.00073	BAMBI,CHRDL1,CX3CL1,DAND5,DUSP2,EGFR,GATA3,GPC3,GREM1,HTRA1,IGFBP3,IGFBP5,IL7,MGLL,MLLT3,MYC,PRKCA,SFRP1,SLC30A1,SMAD6,SNAI1,SPRY2,TERT,TLE1,TRAP1,TRIM67
BP	GO:0051962:	336	12	4.05	0.00079	ASCL1,BCL11A,CDC20,CNTN1,CXCR4,GLI2,SERPINF1,SOX11,TCF4,TGIF2,TRIM67,TSPO

	Positive regulation of nervous system development					
BP	GO:0002521: Leukocyte differentiation	434	14	5.23	0.00080	ATP11C,BCL11A,EGR3,GATA3,GLI2,GPC3,HDAC9,IL7,MYC,PDE2A,PRKCA,SFRP1,TPD52,ZFPM1
BP	GO:0010648: Negative regulation of cell communication	1106	26	13.32	0.00080	BAMBI,CHRDL1,CX3CL1,DAND5,DUSP2,EGFR,GATA3,GPC3,GREM1,HTRA1,IGFBP3,IGFBP5,IL7,MGLL,MLLT3,MYC,PRKCA,SFRP1,SLC30A1,SMAD6,SNAI1,SPRY2,TERT,TLE1,TRAP1,TRIM67
BP	GO:0051726: Regulation of cell cycle	870	22	10.47	0.00081	ASCL1,BID,CCNL1,CDC20,CDKN1C,CENPF,EGFR,EIF4EBP1,FGFR2,GATA3,KIF14,MSX2,MYC,NEK6,NELL1,NR4A3,PER2,PRKCA,SFRP1,SMC3,SOX11,TBX3
BP	GO:0010720: Positive regulation of cell development	387	13	4.66	0.00085	ASCL1,BAMBI,BCL11A,CNTN1,CXCR4,GLI2,SERPINF1,SNAI1,SOX11,TCF4,TGIF2,TRIM67,TSPO
BP	GO:2000145: Regulation of cell motility	593	17	7.14	0.00085	COL18A1,CXCR4,EGFR,FAM60A,GATA3,GREM1,HDAC9,IGFBP3,IGFBP5,KIF14,LAMA1,MAP3K1,PRKCA,SERPINF1,SFRP1,SNAI1,UNC5D
BP	GO:0061061: Muscle structure development	540	16	6.5	0.00085	ADAM12,BOC,CENPF,CRYAB,EGR3,FGFR2,GREM1,HDAC9,IGFBP3,IGFBP5,JPH1,KCNH1,SOX11,SOX6,TBX3,ZFPM1
BP	GO:0007219: Notch signaling pathway	166	8	2	0.00091	ASCL1,CNTN1,HDAC9,MYC,SNAI1,TBL1X,TLE1,TMEM100
BP	GO:0021543: Pallium development	129	7	1.55	0.00096	ASCL1,CNTNAP2,EGFR,ID4,KIF14,LHX6,NR4A3
BP	GO:0090596: Sensory organ morphogenesis	252	10	3.03	0.00098	DLX5,FGFR2,GATA3,GLI2,NR4A3,PRRX2,RORB,SLITRK6,SOX11,SPRY2
BP	GO:0071704: Organic substance metabolic process	9953	141	119.84	0.00100	ACTN2,ADAM12,ADAMTS19,ADAT2,ADCYAP1R1,AGTR1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BID,BRSK2,BYSL,C10orf2,CAMKV,CARD9,CCDC85B,CCNL1,CDC20,CDKN1C,CDYL,CENPF,CHRDL1,CNTN1,COL18A1,CRYAB,CXCR4,DAND5,DIO3,DLX5,DUS3L,DUSP2,EGFR,EGLN3,EGR3,EIF4EBP1,EPHA8,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP3,IGFBP5,IL7,IMPDH1,INSM2,ISOC2,KIF14,KLF9,LDB2,LHX6,LMO4,LOX,LRRN3,MAP3K1,MARS2,MCAT,MGLL,MLLT3,MPST,MRPL23,MRPL42,MSX2,MYC,MYLIP,NAA15,NEK6,NELL1,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRR16,PRRX2,PUS7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SDC2,SERPINF1,SFRP1,SIX6,SLC27A6,SLC6A6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,SPRY2,ST6GAL1,STC2,STK32C,TBL1X,TBX3,TCF4,TERT,TFAM,TFPI2,TGIF2,TJP2,TLE1,TMEM100,TNFRSF21,TOP1,TRAP1,TRIB3,TRIM67,TSPO,TTLL12,TUBA1C,UBE2QL1,VARS,WDR3,ZFPM1,ZNF121
BP	GO:0030326: Embryonic limb morphogenesis	130	7	1.57	0.00100	DLX5,GLI2,GPC3,GREM1,MSX2,PRRX2,TBX3
BP	GO:0035113: Embryonic appendage morphogenesis	130	7	1.57	0.00100	DLX5,GLI2,GPC3,GREM1,MSX2,PRRX2,TBX3
BP	GO:0009968: Negative regulation of signal transduction	1005	24	12.1	0.00104	BAMBI,CHRDL1,CX3CL1,DAND5,DUSP2,EGFR,GATA3,GPC3,GREM1,HTRA1,IGFBP3,IGFBP5,IL7,MLLT3,MYC,PRKCA,SFRP1,SMAD6,SNAI1,SPRY2,TERT,TLE1,TRAP1,TRIM67
BP	GO:0050769: Positive regulation of neurogenesis	303	11	3.65	0.00114	ASCL1,BCL11A,CNTN1,CXCR4,GLI2,SERPINF1,SOX11,TCF4,TGIF2,TRIM67,TSPO
BP	GO:0048584: Positive regulation of response to stimulus	1771	36	21.32	0.00114	AGTR1,ASCL1,BAMBI,BCLAF1,BID,CARD9,CDKN1C,CX3CL1,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GPC3,GRB14,GREM1,IGFBP3,IGFBP5,MAP3K1,MLLT3,MSX2,MYC,MYO10,NEK6,PDE2A,POLR3D,PRKCA,PRRX2,S100A4,SFRP1,SOX11,SPRY2,STEAP3,TERT,TNFRSF21
BP	GO:0030879: Mammary gland development	134	7	1.61	0.00119	FGFR2,GATA3,GLI2,IGFBP5,MSX2,PPAT,TBX3
BP	GO:0001775: Cell activation	900	22	10.84	0.00126	ABCC4,ACTN2,ATP11C,BCL11A,CX3CL1,CXCR4,EGFR,EGR3,GATA3,GLI2,HDAC9,IL7,IMPDH1,LMO4,MGLL,PRKCA,SFRP1,SLC7A11,SOX11,TNFRSF21,TPD52,ZFPM1
BP	GO:0034660: NcRNA metabolic process	407	13	4.9	0.00134	ADAT2,BYSL,DUS3L,EXOSC5,MARS2,NSUN5,PDCD11,POLR2F,PUS7,PUS7L,SNAPC4,VARS,WDR3
BP	GO:1902105: Regulation of leukocyte differentiation	219	9	2.64	0.00137	ATP11C,EGR3,GATA3,GLI2,IL7,MYC,PRKCA,SFRP1,ZFPM1
BP	GO:0048839: Inner ear development	177	8	2.13	0.00138	DLX5,FGFR2,GATA3,GLI2,NR4A3,PRRX2,SLITRK6,SPRY2
BP	GO:0017015:	101	6	1.22	0.00139	BAMBI,CDKN1C,DAND5,HTRA1,SMAD6,SOX11

	Regulation of transforming growth factor beta receptor signaling pathway					
BP	GO:1903844: Regulation of cellular response to transforming growth factor beta stimulus	101	6	1.22	0.00139	BAMBI,CDKN1C,DAND5,HTRA1,SMAD6,SOX11
BP	GO:0021700: Developmental maturation	221	9	2.66	0.00146	ASCL1,CDC20,CDKN1C,CNTNAP2,EPHA8,GATA3,GREM1,LHX6,MSX2
BP	GO:0042303: Molting cycle	102	6	1.23	0.00146	EGFR,FGFR2,IGFBP5,LDB2,MSX2,SNAI1
BP	GO:0042633: Hair cycle	102	6	1.23	0.00146	EGFR,FGFR2,IGFBP5,LDB2,MSX2,SNAI1
BP	GO:0090288: Negative regulation of cellular response to growth factor stimulus	102	6	1.23	0.00146	BAMBI,DAND5,GATA3,HTRA1,SMAD6,SPRY2
BP	GO:0051248: Negative regulation of protein metabolic process	852	21	10.26	0.00147	CDC20,CDKN1C,CENPF,CRYAB,DUSP2,EGFR,EIF4EBP1,GPC3,GREM1,IGFBP3,IGFBP5,NELL1,PER2,PRKCA,SERPINF1,SFRP1,SMAD6,SPRY2,TFPI2,TRIB3,ZFPM1
BP	GO:0097285: Cell-type specific apoptotic process	416	13	5.01	0.00163	ASCL1,BID,COL18A1,EGLN3,FGFR2,GATA3,KIF14,MSX2,MYC,NR4A3,PRKCA,SFRP1,TNFRSF21
BP	GO:0048534: Hematopoietic or lymphoid organ development	743	19	8.95	0.00163	ATP11C,BCL11A,CDKN1C,EGR3,FGFR2,GATA3,GLI2,GPC3,HDAC9,HIST1H4J,IL7,LMO4,MYC,PDE2A,PRKCA,SFRP1,SOX6,TPD52,ZFPM1
BP	GO:0060070: Canonical Wnt signaling pathway	270	10	3.25	0.00164	BAMBI,DLX5,FGFR2,GATA3,GPC3,GREM1,MLLT3,MYC,SFRP1,TBL1X
BP	GO:0055123: Digestive system development	142	7	1.71	0.00167	ASCL1,CDKN1C,EGFR,FGFR2,GLI2,SFRP1,SOX11
BP	GO:0072073: Kidney epithelium development	142	7	1.71	0.00167	FGFR2,GATA3,GPC3,GREM1,MYC,SFRP1,SMAD6
BP	GO:0007155: Cell adhesion	1365	29	16.43	0.00191	ACTN2,ADAM12,BCL11A,BOC,BYSL,CNTN1,CNTN3,CNTN4,CNTNAP2,COL18A1,CX3CL1,CXCR4,EGFR,EGR3,EPHA8,GATA3,GLI2,GREM1,IL7,KIF14,LAMA1,MYO10,PCDH17,PRKCA,SFRP1,SLC7A11,SMAD6,TNFRSF21,ZFPM1
BP	GO:0022610: Biological adhesion	1372	29	16.52	0.00206	ACTN2,ADAM12,BCL11A,BOC,BYSL,CNTN1,CNTN3,CNTN4,CNTNAP2,COL18A1,CX3CL1,CXCR4,EGFR,EGR3,EPHA8,GATA3,GLI2,GREM1,IL7,KIF14,LAMA1,MYO10,PCDH17,PRKCA,SFRP1,SLC7A11,SMAD6,TNFRSF21,ZFPM1
BP	GO:0048514: Blood vessel morphogenesis	482	14	5.8	0.00215	COL18A1,CX3CL1,CXCR4,EGR3,FGFR2,GREM1,HDAC9,LAMA1,NAA15,PRKCA,PRRX2,SERPINF1,SFRP1,TMEM100
BP	GO:0042254: Ribosome biogenesis	190	8	2.29	0.00216	BYSL,EXOSC5,GNL3,NOP16,NSUN5,PDCD11,RAN,WDR3
BP	GO:0051098: Regulation of binding	235	9	2.83	0.00222	BAMBI,GATA3,MSX2,PER2,RAN,RUVBL2,SOX11,TRIB3,ZFPM1
BP	GO:0040012: Regulation of locomotion	649	17	7.81	0.00223	COL18A1,CXCR4,EGFR,FAM60A,GATA3,GREM1,HDAC9,IGFBP3,IGFBP5,KIF14,LAMA1,MAP3K1,PRKCA,SERPINF1,SFRP1,SNAI1,UNC5D
BP	GO:0030097: Hemopoiesis	706	18	8.5	0.00223	ATP11C,BCL11A,CDKN1C,EGR3,FGFR2,GATA3,GLI2,GPC3,HDAC9,HIST1H4J,IL7,MYC,PDE2A,PRKCA,SFRP1,SOX6,TPD52,ZFPM1
BP	GO:0001501: Skeletal system development	484	14	5.83	0.00223	CDKN1C,DLX5,FGFR2,GLI2,GREM1,MSX2,PRKCA,PRRX2,SFRP1,SNAI1,SOX11,SOX6,TBX3,ZFPM1
BP	GO:0001558: Regulation of cell growth	330	11	3.97	0.00224	AGTR1,BCL11A,CCDC85B,CRYAB,GREM1,HTRA1,IGFBP3,IGFBP5,KIF14,MGLL,SFRP1
BP	GO:0023056: Positive regulation of signaling	1380	29	16.62	0.00224	ASCL1,BAMBI,BCLAF1,BID,CARD9,CDKN1C,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GPC3,GRB14,GREM1,IGFBP3,IGFBP5,MAP3K1,MLLT3,MSX2,NEK6,PRKCA,PRRX2,S100A4,SFRP1,SOX11,SPRY2,STEAP3,TERT
BP	GO:0016331: Morphogenesis of embryonic epithelium	150	7	1.81	0.00228	FGFR2,GATA3,GLI2,GREM1,LMO4,SFRP1,SOX11
BP	GO:0045666: Positive regulation of neuron differentiation	236	9	2.84	0.00228	ASCL1,BCL11A,CNTN1,GLI2,SERPINF1,SOX11,TCF4,TGIF2,TRIM67

BP	GO:0051241: Negative regulation of multicellular organismal process	884	21	10.64	0.00229	ASCL1,BCL11A,CNTN4,GATA3,GLI2,GREM1,HIST1H4J,ID4,IGFBP5,MSX2,MYC,MYLIP,RORB,SERPINF1,SFRP1,SNAI1,SOX11,STC2,TNFRSF21,TSPO,ZFPM1
BP	GO:0043933: Macromolecular complex subunit organization	2324	43	27.98	0.00234	ACTN2,AGTR1,BAIAP2L1,BAZ1A,BCL11A,BCLAF1,BID,C10orf2,CDYL,CENPF,CRYAB,EIF4EBP1,EYA4,GATA3,GREM1,HDAC9,HIST1H2BH,HIST1H4J,KIF14,LMO4,LOX,MAP3K1,MRPL23,MRPL42,MYC,NEK6,PER2,PHACTR1,PPAT,PRKCA,RAN,RPL27A,RPS26,RUVBL2,SFRP1,SMAD6,SMC3,TBL1X,TCF4,TFAM,TOP1,TUBA1C,ZFPM1
BP	GO:0030098: Lymphocyte differentiation	284	10	3.42	0.00237	ATP11C,BCL11A,EGR3,GATA3,GLI2,HDAC9,IL7,SFRP1,TPD52,ZFPM1
BP	GO:1901701: Cellular response to oxygen-containing compound	827	20	9.96	0.00237	BAIAP2L1,BRSK2,EGFR,EGR3,EIF4EBP1,FGFR2,HDAC9,IGFBP5,KLF9,MSX2,PDE2A,PPAT,PRKCA,RORB,RUVBL2,SERPINF1,SFRP1,TBC1D4,TRIB3,TSPO
BP	GO:0048562: Embryonic organ morphogenesis	285	10	3.43	0.00243	DLX5,FGFR2,GATA3,GLI2,NR4A3,PRRX2,SLITRK6,SOX11,SPRY2,TBX3
BP	GO:0010647: Positive regulation of cell communication	1388	29	16.71	0.00244	ASCL1,BAMBI,BCLAF1,BID,CARD9,CDKN1C,CXCR4,DLX5,EGFR,EPHA8,FGFR2,GATA3,GPC3,GRB14,GREM1,IGFBP3,IGFBP5,MAP3K1,MLLT3,MSX2,NEK6,PRKCA,PRRX2,S100A4,SFRP1,SOX11,SPRY2,STEAP3,TERT
BP	GO:0007517: Muscle organ development	335	11	4.03	0.00251	CENPF,CRYAB,EGR3,FGFR2,GREM1,HDAC9,IGFBP5,JPH1,SOX11,SOX6,ZFPM1
BP	GO:0001933: Negative regulation of protein phosphorylation	287	10	3.46	0.00256	CDKN1C,DUSP2,GREM1,IGFBP3,NELL1,PRKCA,SFRP1,SMAD6,SPRY2,TRIB3
BP	GO:0033993: Response to lipid	717	18	8.63	0.00263	ADCYAP1R1,ASCL1,BID,CRYAB,EGFR,GATA3,KLF9,LOX,MSX2,NR4A3,PRKCA,RORB,RUVBL2,SERPINF1,SFRP1,SMAD6,STC2,TSPO
BP	GO:0007417: Central nervous system development	838	20	10.09	0.00276	ASCL1,BID,CNTN1,CNTN4,CNTNAP2,CXCR4,EGFR,FGFR2,GLI2,ID4,KIF14,LHX6,LMO4,NR4A3,SLC7A11,SOX11,SOX6,TBX3,TNFRSF21,UNC5D
BP	GO:0051270: Regulation of cellular component movement	663	17	7.98	0.00278	COL18A1,CXCR4,EGFR,FAM60A,GATA3,GREM1,HDAC9,IGFBP3,IGFBP5,KIF14,LAMA1,MAP3K1,PRKCA,SERPINF1,SFRP1,SNAI1,UNC5D
BP	GO:0032269: Negative regulation of cellular protein metabolic process	781	19	9.4	0.00285	CDC20,CDKN1C,CENPF,CRYAB,DUSP2,EIF4EBP1,GPC3,GREM1,IGFBP3,IGFBP5,NELL1,PER2,PRKCA,SERPINF1,SFRP1,SMAD6,SPRY2,TFPI2,TRIB3
BP	GO:0002520: Immune system development	782	19	9.42	0.00289	ATP11C,BCL11A,CDKN1C,EGR3,FGFR2,GATA3,GLI2,GPC3,HDAC9,HIST1H4J,IL7,LMO4,MYC,PDE2A,PRKCA,SFRP1,SOX6,TPD52,ZFPM1
BP	GO:0043009: Chordate embryonic development	610	16	7.34	0.00295	BYSL,CDKN1C,EGFR,FGFR2,GATA3,GLI2,LMO4,PRRX2,SEMA3C,SFRP1,SLC30A1,SNAI1,SOX11,SOX6,TBX3,TMEM100
BP	GO:0002064: Epithelial cell development	201	8	2.42	0.00305	COL18A1,FGFR2,GATA3,GREM1,MAP3K1,PDE2A,SLITRK6,TJP2
BP	GO:0042063: Gliogenesis	201	8	2.42	0.00305	ASCL1,CXCR4,EGFR,ID4,SOX11,SOX6,TNFRSF21,TSPO
BP	GO:0043583: Ear development	202	8	2.43	0.00314	DLX5,FGFR2,GATA3,GLI2,NR4A3,PRRX2,SLITRK6,SPRY2
BP	GO:0065008: Regulation of biological quality	3220	55	38.77	0.00315	ABCC4,ACTN2,ADCYAP1R1,AGTR1,ARC,ATP11C,BAIAP2L1,BAMBI,BCL11A,BID,BRSK2,CACNA1G,CDC20,CNTN4,CXCR4,DIO3,EGFR,GATA3,GRB14,HIST1H4J,IGFBP5,IL7,INF2,ISOC2,JPH1,KCNH1,KCNK10,LDB2,MAP3K1,MGLL,MYC,MYLIP,MYO10,NAA15,PDE2A,PER2,PPAT,PRKCA,PRR16,SERPINF1,SFRP1,SLC25A37,SLC30A1,SLC7A11,SOX11,SOX6,STC2,STEAP3,TBX3,TERT,TFPI2,TJP2,TSPO,VARS,ZFPM1
BP	GO:0009792: Embryo development ending in birth or egg hatching	616	16	7.42	0.00324	BYSL,CDKN1C,EGFR,FGFR2,GATA3,GLI2,LMO4,PRRX2,SEMA3C,SFRP1,SLC30A1,SNAI1,SOX11,SOX6,TBX3,TMEM100
BP	GO:1902107: Positive regulation of leukocyte differentiation	120	6	1.44	0.00331	ATP11C,EGR3,GATA3,GLI2,IL7,PRKCA
BP	GO:1903706: Regulation of hemopoiesis	299	10	3.6	0.00343	ATP11C,EGR3,GATA3,GLI2,HIST1H4J,IL7,MYC,PRKCA,SFRP1,ZFPM1
BP	GO:0016055: Wnt signaling pathway	401	12	4.83	0.00346	BAMBI,DLX5,FGFR2,GATA3,GPC3,GREM1,MLLT3,MYC,SFRP1,TBL1X,TERT,TLE1

BP	GO:0030177: Positive regulation of Wnt signaling pathway	162	7	1.95	0.00350	BAMBI,DLX5,FGFR2,GPC3,MLLT3,SFRP1,TERT
BP	GO:0044087: Regulation of cellular component biogenesis	565	15	6.8	0.00354	BAIAP2L1,BCL11A,BCLAF1,BID,EIF4EBP1,GREM1,KIF14,LDB2,LMO4,MAP3K1,MYO10,PRKCA,SFRP1,SMAD6,SNAI1
BP	GO:0007224: Smoothened signaling pathway	122	6	1.47	0.00360	BOC,FGFR2,GLI2,GPC3,PRRX2,SFRP1
BP	GO:0010001: Glial cell differentiation	163	7	1.96	0.00362	ASCL1,CXCR4,EGFR,ID4,SOX11,SOX6,TNFRSF21
BP	GO:0032879: Regulation of localization	2102	39	25.31	0.00368	ACTN2,ADCYAP1R1,AGTR1,BAMBI,BID,BRSK2,CACNA1G,CNTN1,COL18A1,CRYAB,CXCR4,EGFR,FAM60A,GATA3,GPC3,GREM1,HDAC9,IGFBP3,IGFBP5,JPH1,KCNH1,KCNK10,KIF14,LAMA1,MAP3K1,PDE2A,PER2,PRKCA,SERPINF1,SFRP1,SLC30A1,SNAI1,SOX11,STC2,TBC1D4,TNFRSF21,TRIB3,TSPO,UNC5D
BP	GO:2000027: Regulation of organ morphogenesis	164	7	1.97	0.00375	FGFR2,GATA3,GPC3,GREM1,MLLT3,MYC,SFRP1
BP	GO:0001525: Angiogenesis	405	12	4.88	0.00375	COL18A1,CX3CL1,CXCR4,EGR3,FGFR2,GREM1,HDAC9,NAA15,PRKCA,SERPINF1,SFRP1,TMEM100
BP	GO:0032268: Regulation of cellular protein metabolic process	1970	37	23.72	0.00386	AGTR1,BID,CCNL1,CDC20,CDKN1C,CENPF,CRYAB,CXCR4,DUSP2,EGFR,EGLN3,EIF4EBP1,GATA3,GPC3,GREM1,IGFBP3,IGFBP5,KIF14,LRRN3,MAP3K1,MYC,MYLIP,NEK6,NELL1,PER2,PRKCA,PRR16,RUVBL2,SERPINF1,SFRP1,SMAD6,SPRY2,TFPI2,TRAP1,TRIB3,TRIM67,VARS
BP	GO:0048589: Developmental growth	407	12	4.9	0.00390	BCL11A,DIO3,FGFR2,GATA3,GLI2,IGFBP5,IL7,MGLL,MSX2,SFRP1,SPRY2,STC2
BP	GO:0051276: Chromosome organization	987	22	11.88	0.00391	BAZ1A,C10orf2,CDC20,CDYL,CENPF,EYA4,GATA3,HDAC9,HIST1H2BH,HIST1H4J,KIF14,MYC,NEK6,PER2,PRKCA,RUVBL2,SMC3,TBL1X,TERT,TFAM,TOP1,ZFPM1
BP	GO:0042326: Negative regulation of phosphorylation	356	11	4.29	0.00399	CDKN1C,DUSP2,GREM1,IGFBP3,MYC,NELL1,PRKCA,SFRP1,SMAD6,SPRY2,TRIB3
BP	GO:0044238: Primary metabolic process	9598	134	115.56	0.00411	ACTN2,ADAM12,ADAMTS19,ADAT2,ADCYAP1R1,AGTR1,AKNA,AMD1,ASCL1,BAMBI,BAZ1A,BCL11A,BCLAF1,BID,BRSK2,BYSL,C10orf2,CAMKV,CARD9,CCDC85B,CCNL1,CDC20,CDKN1C,CDYL,CENPF,CHRDL1,CRYAB,CXCR4,DAND5,DLX5,DUS3L,DUSP2,EGFR,EGLN3,EGR3,EIF4EBP1,EPHA8,EXOSC5,EYA4,FGFR2,GATA3,GLI2,GNL3,GPC3,GREM1,HDAC9,HIST1H4J,HR,HTRA1,ID4,IGFBP3,IGFBP5,IMPDH1,INSM2,KIF14,KLF9,LDB2,LHX6,LMO4,LOX,LRRN3,MAP3K1,MARS2,MCAT,MGLL,MLLT3,MRPL23,MRPL42,MSX2,MYC,MYLIP,NAA15,NEK6,NELL1,NR4A3,NSUN5,NTHL1,PDCD11,PDE2A,PER2,PHF5A,POLR2F,POLR3D,PPAT,PPRC1,PRKCA,PRR16,PRRX2,PUS7,PUS7L,RAN,RORB,RPL27A,RPS26,RUVBL2,SAMD11,SDC2,SERPINF1,SFRP1,SIX6,SLC27A6,SLC6A6,SMAD6,SMC3,SNAI1,SNAPC4,SOX11,SOX6,SPRY2,ST6GAL1,STK32C,TBL1X,TBX3,TCF4,TERT,TFAM,TFPI2,TGIF2,TJP2,TLE1,TMEM100,TNFRSF21,TOP1,TRAP1,TRIB3,TRIM67,TSPO,TTLL12,TUBA1C,UBE2QL1,VARS,WDR3,ZFPM1,ZNF121
BP	GO:0044344: Cellular response to fibroblast growth factor stimulus	212	8	2.55	0.00421	EGFR,EGR3,FGFR2,GATA3,PRKCA,SFRP1,SPRY2,TRIB3
BP	GO:0045619: Regulation of lymphocyte differentiation	126	6	1.52	0.00421	ATP11C,EGR3,GATA3,GLI2,IL7,SFRP1
BP	GO:0001701: In utero embryonic development	359	11	4.32	0.00424	BYSL,CDKN1C,EGFR,FGFR2,GATA3,GLI2,SLC30A1,SNAI1,SOX6,TBX3,TMEM100
BP	GO:0061351: Neural precursor cell proliferation	127	6	1.53	0.00438	ASCL1,CXCR4,FGFR2,GLI2,ID4,KIF14
BP	GO:0071901: Negative regulation of protein serine/threonine kinase activity	127	6	1.53	0.00438	CDKN1C,DUSP2,NELL1,PRKCA,SFRP1,SPRY2
BP	GO:1901699: Cellular response to nitrogen compound	524	14	6.31	0.00453	BAIAP2L1,EGFR,EGR3,EIF4EBP1,FGFR2,HDAC9,IGFBP5,PDE2A,PPAT,PRKCA,SFRP1,TBC1D4,TERT,TRIB3
BP	GO:0071774: Response to fibroblast growth factor	215	8	2.59	0.00458	EGFR,EGR3,FGFR2,GATA3,PRKCA,SFRP1,SPRY2,TRIB3
BP	GO:0021953:	171	7	2.06	0.00471	ASCL1,FGFR2,GLI2,ID4,LHX6,LMO4,UNC5D

	Central nervous system neuron differentiation					
BP	GO:0014706: Striated muscle tissue development	313	10	3.77	0.00472	CENPF,FGFR2,GREM1,HDAC9,IGFBP5,SEMA3C,SOX11,SOX6,TBX3,ZFPM1
BP	GO:0048583: Regulation of response to stimulus	3356	56	40.41	0.00478	ACTN2,AGTR1,ASCL1,BAIAP2L1,BAMBI,BCLAF1,BID,BRSK2,CARD9,CDKN1C,CHRDL1,CX3CL1,CXCR4,DAND5,DLX5,DUSP2,EGFR,EPHA8,FGFR2,GATA3,GLI2,GPC3,GRB14,GREM1,HTRA1,IGFBP3,IGFBP5,IL7,KIF14,MAP3K1,MGLL,MLLT3,MSX2,MYC,MYO10,NEK6,PDE2A,POLR3D,PRKCA,PRRX2,PSD3,S100A4,SERPINF1,SFRP1,SMAD6,SNAI1,SOX11,SPRY2,STEAP3,TBC1D4,TERT,TLE1,TNFRSF21,TRAP1,TRIB3,TRIM67
BP	GO:0048565: Digestive tract development	130	6	1.57	0.00490	ASCL1,EGFR,FGFR2,GLI2,SFRP1,SOX11

Ont = Ontology; BP = Biological Process; GO = Gene Ontology