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Associação entre o polimorfismo *MAOA*-uVNTR e a suscetibilidade ao TDAH e fenótipos relacionados, com ênfase no transtorno de personalidade antissocial, impulsividade e agressividade

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Orientador(a): Prof. Dr. Claiton Henrique Dotto Bau
Co-orientador(a): Dra. Cibele Edom Bandeira

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RESUMO

A monoamina oxidase A (MAOA) é uma das principais enzimas responsáveis pela catálise de neurotransmissores monoaminérgicos. O polimorfismo de repetição em tandem mais conhecido do gene codificador da MAOA é uma repetição variável de 30 pares de bases na região promotora do gene (uVNTR). O *MAOA*-uVNTR influencia a expressão desse gene de forma que os alelos de 3,5 ou 4 repetições estão relacionados a uma alta expressão gênica (denominados MAOA-*high* ou -H), enquanto os alelos com 2, 3 ou 5 repetições estão associados a uma expressão reduzida (chamados de MAOA-*low* ou -L). Evidências relacionam diferentes alelos do *MAOA*-uVNTR a manifestações comportamentais associadas à impulsividade e agressividade, como ao Transtorno de Déficit de Atenção e Hiperatividade (TDAH) na infância. O presente estudo tem como objetivo ampliar os dados referentes à associação entre *MAOA*-uVNTR, TDAH e fenótipos relacionados à impulsividade e agressão, analisando essa associação em uma amostra extensamente caracterizada de adultos brasileiros do sexo masculino. A amostra incluiu 252 adultos com TDAH recrutados no ambulatório de TDAH do Hospital de Clínicas de Porto Alegre (HCPA) e 303 voluntários sem TDAH, provenientes do Banco de Sangue do HCPA. O diagnóstico de TDAH e a avaliação de comorbidades seguiram os critérios do DSM. O DNA foi extraído usando o método de *salting-out*. O polimorfismo *MAOA*-uVNTR foi amplificado por PCR, e os produtos foram analisados em um gel de acrilamida a 6%. Foi encontrada uma frequência maior do alelo MAOA-L em indivíduos com TDAH (OR = 1,621, p = 0,009). Em indivíduos com TDAH, não houve associação entre os alelos do *MAOA*-uVNTR e o Transtorno de Oposição Desafiante, Transtorno de Conduta, Transtorno de Personalidade Antissocial ou Transtorno por Uso de Substâncias. Também não houve associação entre os alelos do *MAOA* e relatos de problemas legais ou policiais e questões de autoridade e disciplina. Devido à falta de pesquisas abordando esse polimorfismo nesse contexto específico, nossos resultados fornecem uma contribuição significativa para o aprofundamento do entendimento dos aspectos genéticos subjacentes ao TDAH em adultos e comorbidades. Nossos achados abrem caminhos para futuras investigações, oferecendo novas perspectivas sobre os transtornos analisados e os padrões de comportamento associados a eles.

Palavras-chave: *MAOA*-uVNTR, TDAH, comportamentos disruptivos.

ABSTRACT

Monoamine Oxidase A (MAOA) is one of the key enzymes responsible for catalyzing monoaminergic neurotransmitters. The most well-known tandem repeat polymorphism in the MAOA gene, consists of a variable 30-base pair repeat sequence in the gene's promoter region (uVNTR). The *MAOA*-uVNTR influences the gene's expression, where alleles of 3.5 or 4 repeats are associated with high gene expression (referred to as MAOA-high or -H), while alleles with 2, 3, or 5 repeats are linked to reduced expression (referred to as MAOA-low or -L). Evidence links different *MAOA*-uVNTR alleles to behavioral manifestations related to impulsivity and aggression such as childhood Attention-Deficit/Hyperactivity Disorder (ADHD). This study aims to expand our understanding of the association between *MAOA*-uVNTR, ADHD, and phenotypes related to impulsivity and aggression by analyzing this relationship in an extensively characterized sample of Brazilian adult males. The sample included 252 adults with ADHD recruited from the ADHD outpatient clinic at the Hospital de Clínicas de Porto Alegre (HCPA) and 303 volunteers without ADHD from the HCPA Blood Bank. The diagnosis of ADHD and the evaluation of comorbidities followed DSM criteria. DNA extraction was performed using the salting-out method. The *MAOA*-uVNTR polymorphism was amplified through PCR, and the products were analyzed using a 6% acrylamide gel. A higher frequency of the MAOA-L allele was observed in individuals with ADHD (OR = 1.621, p = 0.009). In individuals with ADHD, there was no association between MAOA alleles and Oppositional Defiant Disorder, Conduct Disorder, Antisocial Personality Disorder, or Substance Use Disorder. There was also no association between MAOA alleles and reports of legal or police problems or issues related to authority and discipline. Given the scarcity of studies exploring this polymorphism in this specific context, our findings provide a significant contribution to a deeper understanding of the genetic factors underlying ADHD and comorbidities in adults. Our results pave the way for future investigations, offering new insights into the analyzed disorders and the patterns of behavior associated.

Keywords: *MAOA*-uVNTR, ADHD, disruptive behaviors.

SUMÁRIO

1 INTRODUÇÃO COMPREENSIVA

1.1 Transtornos associados a comportamentos impulsivos e agressivos

A agressão é caracterizada por uma variedade multifacetada de respostas adaptativas destinadas a infligir danos a outro organismo, seja para fins ofensivos ou defensivos (KOLLA; BORTOLATO, 2020). Do ponto de vista evolutivo, os comportamentos agressivos são fundamentais para diversas funções vitais, como a obtenção de recursos, a dissuasão de competidores e a organização de hierarquias sociais (BUSS; SHACKELFORD, 1997). Portanto, é de se esperar que a agressividade em humanos tenha bases genéticas (CERVERA-JUANES et al., 2016). Estudos reportam o papel da herdabilidade da agressão patológica, definida como um conjunto de manifestações hostis mal adaptativas e exageradas, como comportamentos antissociais e violentos (DILALLA; GOTTESMAN, 1991; GROVE et al., 1990; MILES; CAREY, 1997; RHEE; WALDMAN, 2002; TAKAHASHI; MICZEK, 2014). Diversos transtornos estão associados a manifestação patológica de comportamentos agressivos e impulsivos, dentre os quais destacam-se o Transtorno Desafiador Opositivo (TDO), o Transtorno de Conduta (TC), o Transtorno de Personalidade Antissocial, o Transtorno por Uso de Substâncias e o Transtorno do Déficit de Atenção/Hiperatividade (TDAH).

O TDAH é um transtorno do neurodesenvolvimento de início na infância, caracterizado por padrões persistentes de desatenção, hiperatividade e impulsividade que interferem significativamente na função social, acadêmica ou ocupacional do indivíduo (AMERICAN PSYCHIATRIC ASSOCIATION, 2013). Para ser diagnosticado com TDAH de acordo com o Manual Diagnóstico e Estatístico de Transtornos Mentais 5° edição (DSM-5), os sintomas devem estar presentes em múltiplos contextos (por exemplo, em casa, na escola, no trabalho) e causar prejuízo clinicamente significativo nas áreas de funcionamento do indivíduo. Este transtorno possui 3 apresentações, classificadas de acordo com os sintomas presentes: desatenta, hiperativa-impulsiva ou combinada (AMERICAN PSYCHIATRIC ASSOCIATION, 2013).

O TDAH é um dos transtornos do neurodesenvolvimento mais frequentes entre crianças, com uma prevalência mundial estimada em 5% (WEIBEL et al., 2020). Dados derivados do acompanhamento prospectivo de crianças com TDAH fornecem evidências de persistência de sintomas e/ou prejuízos funcionais na idade adulta para 30 a 60% dos casos (BARBARESI et al., 2018; VAN LIESHOUT et al., 2016), o que está de acordo com estudos

epidemiológicos transversais que estimam a prevalência de TDAH entre adultos entre 2 e 4% (FAYYAD et al., 2017; WEIBEL et al., 2020). No entanto, apesar dessa alta prevalência, poucos adultos com TDAH recebem o diagnóstico e o cuidado apropriados. Isso se deve principalmente às diferenças na apresentação clínica do TDAH em adultos que, assim como na infância, envolve a tríade de sintomas de desatenção, hiperatividade e impulsividade. Em adultos, o TDAH costuma estar associado a outros transtornos psiquiátricos, como transtornos de humor e transtornos de personalidade, tais como TPAS (WEIBEL et al., 2020). Os transtornos por uso de substâncias também são comumente comórbidos com TDAH, provavelmente causados pela tendência a maior impulsividade e desregulação emocional dos indivíduos (SKOGLUND et al., 2015).

O Transtorno por Uso de Substâncias é uma condição clínica caracterizada pelo uso recorrente e prejudicial de substâncias psicoativas, incluindo álcool e drogas, levando a sintomas físicos, psicológicos e sociais adversos (AMERICAN PSYCHIATRIC ASSOCIATION, 2013). Esse transtorno é caracterizado por uma série de critérios específicos que abrangem o consumo compulsivo, a tolerância, a abstinência, a perda de controle sobre o uso, e o tempo gasto em busca da substância (AMERICAN PSYCHIATRIC ASSOCIATION, 2013). O DSM-5 considera 10 classes de substâncias como relacionadas ao TUS. O consumo em excesso de todas essas substâncias têm em comum a ativação direta do sistema de recompensa do cérebro, o qual está envolvido no reforço de comportamentos e na produção de memórias (AMERICAN PSYCHIATRIC ASSOCIATION, 2013).

O TDO, o TC e o TPAS são classificados como transtornos disruptivos do controle do impulso e da conduta, caracterizados por padrões persistentes de comportamento desafiador, agressivo e impulsivo (AMERICAN PSYCHIATRIC ASSOCIATION, 2013). Este grupo de transtornos se diferencia dos demais no sentido de que os problemas na regulação emocional e/ou comportamental se manifestam em comportamentos que violam os direitos dos outros (por exemplo, agressão, destruição de propriedade) e/ou colocam o indivíduo em conflito significativo com normas sociais ou figuras de autoridade (AMERICAN PSYCHIATRIC ASSOCIATION, 2013).

O TDO é caracterizado por um padrão de humor raivoso/irritável, de comportamento questionador/desafiante ou índole vingativa com duração de pelo menos seis meses, evidenciado por pelo menos quatro sintomas de qualquer das categorias definidas pelo DSM V (humor raivoso/irritável, comportamento questionador/desafiante e índole vingativa). Este transtorno é comumente diagnosticado na infância e costuma estar associado a outras patologias comportamentais ou do neurodesenvolvimento (AMERICAN PSYCHIATRIC

ASSOCIATION, 2013). O TC é um padrão de comportamento repetitivo e persistente no qual são violados direitos básicos de outras pessoas ou normas e regras sociais relevantes e apropriadas para a idade, tal como manifestado pela presença de ao menos três dos 15 critérios estabelecidos pelo DSM V, nos últimos 12 meses. Este transtorno costuma ser diagnosticado entre a adolescência e o início da vida adulta e frequentemente está associado a atos criminosos. O TC é considerado um desfecho comum para o TDO, principalmente em situações em que o transtorno não é tratado adequadamente (AMERICAN PSYCHIATRIC ASSOCIATION, 2013). O TPAS é um padrão difuso de desconsideração e violação dos direitos das outras pessoas que ocorre desde os 15 anos de idade, e está bastante relacionado ao fracasso em ajustar-se às normas sociais relativas a comportamentos legais, conforme indicado pela repetição de atos que constituem motivos de detenção, tendência a falsidade, irritabilidade e agressividade, descaso pela segurança de si ou dos outros e ausência de remorso (AMERICAN PSYCHIATRIC ASSOCIATION, 2013). Apesar de o TPAS ser classificado como um transtorno de personalidade, ele também se enquadra como transtorno disruptivo, conforme os critérios do DSM V, levando-se em conta sua relação com o espectro de transtornos relacionados ao controle de comportamentos agressivos e impulsivos

Além de sua etiologia multifatorial e da alta herdabilidade, todos esses transtornos têm uma série de características em comum, tais como fatores genéticos de susceptibilidade e aspectos subjacentes à manifestação clínica, como tendência a comportamentos agressivos e impulsivos (BLAIR; LEIBENLUFT; PINE, 2014). Dados prospectivos mostram uma trajetória de problemas comportamentais, com uma associação frequente entre TDAH, TDO e TC (BLAIR; LEIBENLUFT; PINE, 2014). Embora esse padrão de associações seja comum, ele não é absoluto, ou seja, o TC não se desenvolve na maioria das crianças com TDAH ou TDO, e o tratamento bem-sucedido dessas duas condições pode reduzir o risco de progressão (BONHAM et al., 2021). O TPAS, que tem um prognóstico grave, se desenvolve em um pouco menos de 50% dos pacientes com TC; no entanto, jovens com TC nos quais o TPAS não se desenvolve geralmente têm outros problemas de longo prazo (BONHAM et al., 2021).

1.2 Aspectos gerais da Monoamina Oxidase A (MAOA)

A Monoamina Oxidase A (MAOA) é uma enzima mitocondrial responsável por catalisar a desaminação oxidativa de aminas alimentares, neurotransmissores monoaminérgicos e hormônios (BORTOLATO; CHEN; SHIH, 2008). Essa ampla variedade

de substratos inclui várias moléculas biogênicas, em especial a serotonina (5-hidroxitriptamina, 5-HT), a dopamina (DA) e a norepinefrina (NE) (BORTOLATO; CHEN; SHIH, 2008). A rápida degradação de monoaminas cerebrais, como 5-HT, NE e DA, é essencial para o correto funcionamento da neurotransmissão sináptica. A sinalização monoaminérgica é considerada um dos mecanismos-chave para a modulação do humor e das emoções, bem como para o controle das funções motoras, perceptuais e cognitivas (GODAR et al., 2016). Estudos de Ressonância Magnética Funcional (fMRI) indicaram que diferentes alelos de um polimorfismo funcional da MAOA (*MAOA*-uVNTR) podem afetar o funcionamento cerebral durante tarefas cognitivas, de forma que portadores do alelo de baixa atividade da MAOA tem um pior controle inibitório (SUN et al., 2018). A inibição de resposta é o processo cognitivo necessário para cancelar uma função pretendida, e o controle inibitório desempenha um papel importante no controle de comportamentos impulsivos e agressivos (HUNT; KNIGHT; DEPUE, 2023). Processos inibitórios prejudicados podem estar na base das características comportamentais impulsivas associadas a diversos diagnósticos neuropsicológicos, incluindo o TDAH, o TDO, o TC, o TPAS e o TUS (BARI; ROBBINS, 2013; HERBA et al., 2006; HUNT; KNIGHT; DEPUE, 2023).

1.3 MAOA-uVNTR

O gene codificador da MAOA, localizado no braço curto do cromossomo X (Xp11.4-p11.23) (BACH et al., 1988; GRIMSBY et al., 1990), apresenta um polimorfismo de repetição em tandem bastante conhecido, caracterizado por uma repetição de 30 pares de bases na região promotora (uVNTR), na posição -1142 a -1262 em relação ao códon de início da tradução do gene (sequência GenBank: M89636) (ZHU et al., 1992). Várias alelos foram documentados para esse polimorfismo, contendo 2, 3, 3,5, 4, 5 ou 6 repetições da sequência de 30 pares de bases (HUANG et al., 2004; SABOL; HU; HAMER, 1998). Uma variante rara de 1 repetição (1R) também foi descrita recentemente na população iraquiana (AL-TAYIE; ALI, 2019). A sequência de 30 pares de bases (ACCGGCACCG GCACCAGTAC CCGCACCAGT) apresenta cinco repetições do motivo de 6 nucleotídeos ACCVGY (HUANG et al., 2004; SABOL; HU; HAMER, 1998). Cada uma dessas sequências é consistentemente seguida por um motivo de 15 pares de bases (ACCGGCACCG GCACC), correspondendo à primeira metade da repetição (MARTÍNEZ et al., 2022). Essa sequência, contudo, não foi inicialmente incluída na nomenclatura dos alelos (SABOL; HU; HAMER, 1998). Alguns autores defendem o uso de uma classificação mais rigorosa levando em consideração esse ajuste (MARTÍNEZ et

al., 2022); com base nessa convenção alternativa, por exemplo, a variante de 4 repetições (4R) seria chamada de 4,5R, e assim por diante (DAS et al., 2006; IM et al., 2019; JORM et al., 2000). No presente estudo, entretanto, optamos por seguir a nomenclatura original dos alelos, uma vez que ainda é a mais utilizada. Os alelos mais frequentes da MAOA-uVNTR são os de 3 (3R) e quatro repetições (4R). A frequência do alelo 3R é estimada em 51-59% em afro-americanos e 33-37% em caucasianos (BEAVER et al., 2013; HABERSTICK et al., 2014; SABOL; HU; HAMER, 1998). Por outro lado, o alelo 4R é encontrado em 36-43% dos afro-americanos e 60-65% dos caucasianos. Dados de frequência em outras etnias, como asiáticos e hispânicos não brancos, ainda são incertos, pois a maioria das estimativas dessas populações até o momento tem sido baseada em coortes pequenas (KOLLA; BORTOLATO, 2020). Os outros alelos são menos frequentes na população em geral, sendo o de 2 repetições (2R) documentado em cerca de 5% dos afro-americanos (e em 0,1% dos caucasianos) (BEAVER et al., 2013; HABERSTICK et al., 2014) e o de 3,5 repetições (3,5R) encontrado em cerca de 1,5% dos caucasianos e 0,01% dos afro-americanos (HABERSTICK et al., 2014).

Dados *in vitro* têm consistentemente mostrado que as variantes 2R, 3R e 5R estão associadas a uma eficiência transcricional mais baixa (MAOA-L, ou MAOA-*low*) e as variantes 3,5R e 4R, a uma atividade transcricional mais alta (MAOA-H, ou MAOA-*high*) (DENNEY; KOCH; CRAIG, 1999; JÖNSSON et al., 2000; MARTÍNEZ et al., 2022; SABOL; HU; HAMER, 1998). Devido ao seus efeitos funcionais na expressão da MAOA, esse polimorfismo de repetição em tandem têm sido estudado em relação a diversos fenótipos (NILSEN; TULVE, 2020); dentre eles, aspectos comportamentais relacionados a transtornos externalizantes e disruptivos (KOLLA; BORTOLATO, 2020).

1.4 MAOA-uVNTR e fenótipos do comportamento

A primeira descoberta que documentou o envolvimento da MAOA em comportamentos antissociais e agressivos ocorreu com a descrição da síndrome de Brunner, uma síndrome recessiva ligada ao cromossomo X caracterizada por uma mutação *nonsense* no gene *MAOA* (rs72554632) (BRUNNER et al., 1993a, 1993b). A síndrome de Brunner geralmente se encontra associada a deficiências cognitivas e comportamento antisocial (BORTOLATO; FLORIS; SHIH, 2018; BRUNNER et al., 1993b; PITON et al., 2014). Desde então, o polimorfismo *MAOA*-uVNTR tem sido objeto de investigação em relação a um espectro de

distúrbios comportamentais e emocionais, incluindo o TDAH, o TDO, o TC, o TPAS e o TUS (SUN et al., 2018).

Existem evidências que apontam relações entre o polimorfismo *MAOA*-uVNTR e TDAH (LI; LEE, 2012; SUN et al., 2018; ZOHSEL et al., 2015), entretanto, estes estudos são escassos e os resultados são contraditórios. Crianças com TDAH frequentemente exibem uma frequência maior de alelos MAOA-H (KESSI et al., 2022; KIM-COHEN et al., 2006), porém há estudos que apontam associação do alelo MAOA-L ao TDAH na infância (ENOCH et al., 2010). Até onde sabemos, as análises existentes dessa associação não avaliaram outros grupos etários (KESSI et al., 2022; KOLLA; BORTOLATO, 2020). Considerando o envolvimento da enzima MAOA na via dopaminérgica e seu papel na regulação de funções cerebrais como atenção, motivação e recompensa (HONG et al., 2018; KESSI et al., 2022; KLEIN et al., 2019; LIU et al., 2015), a existência da associação entre um polimorfismo funcional MAOA e o diagnóstico de TDAH é uma hipótese coerente a ser considerada, entretanto a escassez de estudos que analisam essa relação não nos permite tirar quaisquer conclusões a respeito.

Comportamentos impulsivos, caracterizados pela busca de gratificação imediata e falta de consideração pelas consequências a longo prazo, frequentemente estão associados ao uso de substâncias (CERVERA-JUANES et al., 2016). Devido às evidências de envolvimento da MAOA na regulação de comportamentos impulsivos (DORFMAN; MEYER-LINDENBERG; BUCKHOLTZ, 2014), estudos analisaram as relações entre o polimorfismo *MAOA*-uVNTR e TUS (VANYUKOV et al., 2004). Alguns estudos demonstram uma relação entre alelos da MAOA e comportamentos de dependência de substâncias (CERVERA-JUANES et al., 2016; RIMONDINI et al., 2002; TIKKANEN et al., 2009) inclusive no Brasil, envolvendo mais especificamente o alelo MAOA-L (CONTINI et al., 2006); essa associação, entretanto, não foi consistentemente reportada (KIIVE et al., 2014; MOKROVIĆ et al., 2008). No entanto, isso não implica que o MAOA não esteja envolvido em alguma etapa do processamento do comportamento impulsivo. A influência genética na impulsividade é mediada por uma rede complexa de interações gene-gene e fatores ambientais, incluindo exposição precoce a substâncias, trauma e influências sociais, exigindo assim uma avaliação abrangente desses fatores para compreender a concreta influência do gene *MAOA* nesses fenótipos (KOLLA et al., 2018; NILSSON et al., 2018).

Na literatura, *MAOA*-uVNTR tem sido objeto de investigação em relação a um espectro de distúrbios comportamentais e emocionais associados a agressividade e impulsividade, incluindo TDO, TC e TPAS (SUN et al., 2018). Em um estudo com 237 homens, uma maior gravidade de traços antissociais foi encontrada em portadores de MAOA-L (SADEH;

JAVDANI; VERONA, 2013). Da mesma forma, em um estudo com 4278 indivíduos finlandeses, mulheres homozigotas para MAOA-L exibiram níveis ligeiramente mais elevados de comportamento antissocial do mulheres homozigotas para MAOA-H (HOLLERBACH et al., 2018). Uma investigação observou que as pontuações de traços de TPAS foram mais altas em portadores de MAOA-L em comparação a portadores de MAOA-H em 453 indivíduos caucasianos sem histórico de abuso na infância (RETI et al., 2011). No mesmo estudo também foi observado que indivíduos MAOA-L apresentaram maior raiva/hostilidade e menor afabilidade (RETI et al., 2011), associação replicada posteriormente (GODAR et al., 2016).

Os mecanismos neurobiológicos pelos quais o MAOA-L modula a agressividade não são completamente compreendidos, com as evidências mais consistentes convergindo para influências nas regiões cortico-límbicas (CERASA et al., 2008; LEE; HAM, 2008; MEYER-LINDENBERG et al., 2006; PASSAMONTI et al., 2008). Além disso, análises de conectividade funcional revelaram maior conectividade entre a amígdala e áreas dos córtices pré-frontal ventromedial (BUCKHOLTZ et al., 2008) e do cíngulo anterior (DENSON et al., 2014) em portadores de MAOA-L. Juntos, esses dados sugerem que o alelo de baixa atividade da MAOA facilita alterações nos circuitos cortico-límbicos críticos para a regulação emocional negativa e controle inibitório, provavelmente através de sinalização serotonérgica excessiva durante períodos vulneráveis do desenvolvimento cerebral.

De maneira geral, os estudos que relacionam o alelo MAOA-L com agressividade e comportamentos antissociais consideram a influência de eventos da vida (SUN et al., 2018). A consideração do ambiente, apesar de complexa metodologicamente, pode auxiliar na avaliação do papel da MAOA, uma vez que há uma complexa interação entre expressão gênica e ambiente, que, por sua vez, influencia no fenótipo comportamental (CASPI et al., 2002; POULTON; MOFFITT; SILVA, 2015). Até o momento, três meta-análises independentes (BYRD; MANUCK, 2014; KIM-COHEN et al., 2006; TAYLOR; KIM-COHEN, 2007) validaram a existência dessa interação gene-ambiente. Além das interações gene-ambiente, fatores epigenéticos e outros genes (CHECKNITA et al., 2015, 2021; NILSSON et al., 2014; WATTS; MCNULTY, 2016; ZHANG et al., 2017), idade (LI; LEE, 2012), gênero (ENOCH et al., 2010) e etnia (STETLER et al., 2014) podem afetar a expressão gênica da MAOA e possivelmente influenciar a manifestação de fenótipos comportamentais que possam estar associados a ela.

Embora a maioria das evidências apontem para associação entre MAOA-L e comportamentos agressivos e antissociais em adolescentes e adultos, há estudos que sugerem que esse alelo não confere uma vulnerabilidade inerente a esses comportamentos em meninos.

Um estudo inicial com 50 meninos com comportamento altamente agressivo (com base em relatos dos pais e professores), sugere que esse fenótipo tem uma associação mais forte com o genótipo MAOA-H do que com o MAOA-L (BEITCHMAN et al., 2004). Em conformidade com esse achado, variantes MAOA-H estavam associadas a um aumento leve em problemas globais de saúde mental e comportamento antissocial em meninos de 7 anos (KIM-COHEN et al., 2006). Uma explicação plausível para essa discrepância pode residir na maior associação das variantes MAOA-H com o TDAH em crianças (KIM-COHEN et al., 2006), que, por sua vez, é uma comorbidade chave com comportamento disruptivo na infância (AUGUST et al., 1996). No entanto, os resultados são conflitantes e os mecanismos através dos quais os alelos *MAOA*-uVNTR modulam o comportamento, especialmente entre adultos, não são bem compreendidos.

Portanto, considerando as evidências relacionadas ao papel da MAOA-uVNTR em fenótipos ligados a comportamentos impulsivos e agressivos, e a escassez de estudos que analisam esse polimorfismo em TDAH, especialmente em adultos, pretendemos, com este estudo, ampliar os dados examinando essa associação em uma amostra clínica brasileira de adultos com TDAH.

1.5 JUSTIFICATIVA

O TDAH é um dos transtornos psiquiátricos mais comuns no mundo e amplamente estudado em crianças, porém seu impacto em adultos tem recebido menos atenção na literatura científica. Sua manifestação clínica, bem como a dos transtornos comumente comórbidos ao TDAH costumam estar associados a padrões de comportamentos agressivos e impulsivos, e podem ter repercussões significativas na qualidade de vida dos indivíduos afetados e na sociedade em geral. A etiologia tanto do TDAH quanto das suas comorbidades é multifatorial, de forma que fatores genéticos, ambientais e as interações entre eles contribuem para sua susceptibilidade. Entretanto, nenhum fator de forma isolada é suficiente ou necessário para causar o surgimento de quaisquer dos transtornos.

Devido ao envolvimento do *MAOA*-uVNTR nos níveis de neurotransmissores fundamentais para a regulação do comportamento, a relação desse polimorfismo com transtornos disruptivos, tais como TDO, TC e TPAS vem sendo bastante estudado. No entanto, existem poucos estudos que analisam a relação do *MAOA*-uVNTR com TDAH, e as análises são feitas majoritariamente em amostras de crianças. É fundamental ressaltar que o TDAH e suas comorbidades não são condições estáticas, e sua manifestação pode variar

substancialmente entre crianças e adultos. Essa diferença na apresentação clínica, e provavelmente na etiologia, é muitas vezes subestimada e merece uma análise mais aprofundada. A variabilidade genética entre grupos étnicos pode influenciar a frequência e a expressão de polimorfismos genéticos, incluindo o *MAOA*-uVNTR. Portanto, o estudo dessas relações em uma amostra brasileira, caracterizada por sua diversidade étnica e miscigenação, é especialmente relevante.

Assim, o presente estudo tem como objetivo expandir os dados acerca das possíveis relações entre *MAOA*-uVNTR, TDAH e comorbidades associadas a comportamentos agressivos e impulsivos, em uma amostra de adultos brasileiros. Isso pode fornecer *insights* importantes sobre as bases genéticas desses transtornos, bem como abrir caminho para investigações futuras dessas associações em diferentes contextos.

1.6 OBJETIVOS

1.6.1 Objetivo geral

Investigar a associação entre o polimorfismo *MAOA*-uVNTR e a suscetibilidade ao TDAH e fenótipos relacionados, com ênfase no transtorno de personalidade antissocial, impulsividade e agressividade.

1.6.2 Objetivos específicos

a) verificar as relações entre o polimorfismo *MAOA*-uVNTR e o TDAH em uma amostra clínica;
b) testar a associação entre *MAOA*-uVNTR e transtornos relacionados a impulsividade (TUS) e transtornos disruptivos (TOD, TC e TPAS) em uma amostra de homens com TDAH;
c) verificar a associação entre o polimorfismo *MAOA*-uVNTR e características dimensionais (número de sintomas de TDAH e problemas com autoridade, disciplina, lei e polícia).

2 ARTIGO CIENTÍFICO

Em preparação para submissão na revista *Genetics and Molecular Biology* (IF = 2.087)

Effects of MAOA-uVNTR polymorphism in externalizing and disrupted behaviors in a brazilian clinical sample of men with ADHD

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ABSTRACT

The polymorphism of variable number tandem repeats in the Monoamine Oxidase A gene (*MAOA*-uVNTR) have functional effects, where alleles containing 3.5 or 4 repeats are associated with high gene expression (MAOA-H), and alleles with 2, 3, or 5 repeats, with low gene expression (MAOA-L). Evidence links different *MAOA*-uVNTR alleles to impulsive and aggressive behaviors, as well as childhood attention-deficit/hyperactivity disorder (ADHD). The present study aims to expand the available data by analyzing the *MAOA*-uVNTR in an extensively characterized sample of Brazilian men. The sample included 252 adults from the ADHD outpatient clinic at the Hospital de Clínicas de Porto Alegre (HCPA) and 303 controls. The *MAOA*-uVNTR polymorphism was amplified by PCR, and the products were analyzed on a 6% acrylamide gel. MAOA-L allele was associated with ADHD (OR = 1.621, p = 0.009). In individuals with ADHD, there was no association between *MAOA*-uVNTR and Oppositional Defiant Disorder, Conduct Disorder, Antisocial Personality Disorder or Substance Use Disorder, as well as reports of legal or police problems and authority and discipline issues. Given the scarcity of studies exploring this polymorphism in clinical samples of adults, our findings provide significant contributions in the topic, paving the way for future investigations.

Keywords: *MAOA*-uVNTR, ADHD, disruptive behaviors, externalizing disorders, adults.

Introduction

Impulsive and aggressive behaviors represent a major public health concern, frequently leading to negative outcomes including harm to others or self-harm. The prevalence of these behaviors is increased in clinical psychiatric samples (Girasek et al. 2022), including attention-deficit/hyperactivity disorder (ADHD) (Saylor and Amann 2016). These phenotypes are influenced by multiple variables, involving complex interactions between genetic and environmental risk factors (Sun et al. 2018). Among the genetic factors most commonly associated with impulsive and aggressive behaviors, the gene encoding Monoamine Oxidase A (MAOA) (Xp11.3) stands out (Godar et al. 2016). MAOA is a mitochondrial enzyme involved in the catalysis of several monoaminergic neurotransmitters implicated in the regulation of aggression and impulsivity, including serotonin and the catecholamines norepinephrine and dopamine (Bortolato et al. 2008; Xu et al. 2017; Bendre et al. 2018).

The first association established between the *MAOA* gene and behavior patterns was in relation to Brunner syndrome, a recessive X-linked syndrome characterized by a nonsense mutation (*MAOA* rs72554632). The syndrome typically manifests with intellectual disability and antisocial behavior (Brunner et al. 1993; Piton et al. 2014; Bortolato et al. 2018). Since then, MAOA has been investigated across a broad spectrum of traits related to impulsive and aggressive behaviors (Kuepper et al. 2013; Bendre et al. 2018; Nilsson et al. 2018; Hollerbach et al. 2021), with reports of findings concerning its role in modulating the impact of environmental factors on susceptibility to disruptive behaviors (Caspi et al. 2002; Kim-Cohen et al. 2006; Frazzetto et al. 2007; McDermott et al. 2009; Enoch et al. 2010; Aslund et al. 2011; Kolla et al. 2018).

Most association studies involving the *MAOA* predominantly focus on the *MAOA*-uVNTR polymorphism, which consists of 2, 3, 3.5, 4, or 5 repetitions of a 30-base pair sequence (ACCGGCACCG GCACCAGTAC CCGCACCAGT) located in the gene's promoter region (Zhu et al. 1992). This sequence is consistently followed by a 15-base pair motif (ACCGGCACCG GCACC), corresponding to the first half of the repeat (Das et al. 2006; Martínez et al. 2022); which was not initially included in the nomenclature (Sabol et al. 1998). Some authors advocate for a more stringent classification, taking this adjustment into account; based on this alternative convention, for example, the 4-repeat variant (4R) has sometimes been referred to as 4.5R, and so forth (Jorm et al. 2000; Das et al. 2006; Im et al. 2019). However, in this study, we will adhere to the conventional nomenclature for the alleles.

The various alleles of this polymorphism exert an influence on MAOA gene expression, with alleles containing 3.5 or 4 repetitions being associated with higher enzyme expression (MAOA-H), and alleles with 2, 3, or 5 repetitions, with lower expression (MAOA-L) (Sabol et al. 1998; Guo et al. 2008; Zhang et al. 2011; Martínez et al. 2022). Evidence links low-expression alleles (2R, 3R, or 5R) to antisocial traits and behaviors (Kim-Cohen et al. 2006; Mertins et al. 2011), primarily in males (Tiihonen et al. 2015), and to psychiatric disorders with impulsive characteristics and alcohol dependence (Contini et al. 2006). There are studies associating MAOA alleles with childhood ADHD (Enoch et al. 2010; Li and Lee 2012; Zohsel et al. 2015), which, in turn, often co-occurs with disruptive disorders such as antisocial personality disorder (ASPD), conduct disorder (CD), and oppositional defiant disorder (ODD) (Manor et al. 2002; Kolla et al. 2018; Bonham et al. 2021) and with impulsive-related disorders such as substance use disorder (SUD) (Vanyukov et al. 2004; Skoglund et al. 2015). However, results are conflicting, and the mechanisms through which *MAOA*-uVNTR alleles modulate behavior, especially among adults, are not fully understood.

Therefore, considering the evidence regarding the role of the *MAOA*-uVNTR in phenotypes related to impulsive and aggressive behaviors, and the relative scarcity of studies in ADHD, especially among adults, we aim to test these associations in a Brazilian clinical sample of adults with and without ADHD.

Material and Methods

Sample

This study includes a total of 555 men recruited in the Hospital de Clínicas de Porto Alegre (HCPA), divided in 252 subjects with ADHD diagnosed at the adult division of the ADHD outpatient program (ProDAH-A) and 303 blood-donors without ADHD. Subjects were native-Brazilians of predominantly European descent aged 18 years or older. The exclusion criteria were: a) evidence of clinically significant neurological diseases (e.g., delirium, dementia, epilepsy, head trauma, multiple sclerosis); b) current or past history of psychosis and c) IQ $\leq$ 70 (Kaplan et al. 1991). All subjects included in this study signed an informed consent approved by the Ethics Committees of the Hospital and the Universidade Federal do Rio Grande do Sul (IRB 0000921).

The diagnostic procedures for ADHD and comorbidities in our unit have been described elsewhere (Grevet et al. 2007; Fischer et al. 2007; Karam et al. 2009). Briefly, the protocol

included the following semi-structured interviews: (a) K-SADS-E (Schedule for Affective Disorders and Schizophrenia for School-Age Children - Epidemiologic Version) (Mercadante et al. 1995), adapted to adults (Matte et al. 2015), for ADHD and ODD diagnoses; (b) SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders, and (c) M.I.N.I (Mini-International Psychiatric Interview) for the diagnosis of SUD and ASPD, respectively. For subjects recruited from 2001 to 2012, DSM-IV diagnostic criteria was used to assess ADHD (applied through K-SADS-E) (American Psychiatric Association 1994) and SCID-I was used to evaluate other psychiatric disorders (First et al. 1998). Subjects evaluated in 2013 or later were diagnosed following DSM-5 criteria (American Psychiatric Association 2013) and comorbidities were assessed with SCID-5 (First et al. 2015).

Genotyping

DNA was extracted from peripheral blood by salting out method (Lahiri and Nurnberger 1991)) and the *MAOA*-uVNTR polymorphism was amplified using the polymerase chain reaction (PCR) conditions adapted from Manor et al. (2002). The PCR products were analyzed on a 6% acrylamide gel stained with ethidium bromide. The gel was visualized under UV light to determine the fragment sizes by comparison with a 100 bp DNA ladder. The 2-, 3-, and 5-repeats alleles were classified as "low-activity" (MAOA-L) and the 3.5- and 4-repeats alleles were classified as "high-activity" (MAOA-H) (Sabol et al. 1998; Guo et al. 2008; Zhang et al. 2011; Kolla and Bortolato 2020).

Statistical analyses

The relationships between the *MAOA*-uVNTR polymorphism and phenotypes related to impulsive or aggressive behaviors were analyzed with logistic regression. To evaluate the associations between *MAOA*-uVNTR and the number of ADHD symptoms, linear regression was used. All analyses included age as covariate and were conducted using SPSS version 18.0 software (SPSS Inc., USA). Bonferroni multiple testing correction was applied considering the disorders evaluated (ADHD, ODD, CD/ASPD, and SUD), but not the other phenotypes, since they are significantly correlated and therefore not independent.

Results

The descriptive characteristics of the sample can be found in **Table 1**. A higher frequency of MAOA-L was observed in individuals with ADHD compared to the frequency of MAOA-L in controls (OR = 1.621, p = 0.009, $p_{Bonferroni}$=0.036, **Table 2**). There was no significant association between the number of ADHD symptoms and *MAOA*-uVNTR alleles (**Table 2**).

Within subjects with ADHD, there was no association between *MAOA*-uVNTR and ODD (p = 0.551), CD or ASPD (p = 0.180), and SUD (p = 0.965). Similarly, disruptive-related phenotypes such as problems with authority and discipline, and problems with law and the police did not present significant associations with *MAOA*-uVNTR (**Table 2**).

Discussion

In our clinical sample, men with ADHD exhibited a higher frequency of the MAOA-L allele. No association was found between the alleles and the number of ADHD symptoms or other impulsive/disruptive phenotypes. Here, we explored the well-established relationship between MAOA and externalizing and disruptive phenotypes in a sample of Brazilian adults. Given the significant role of the environment in the associations reported for MAOA and several behaviors, it was necessary to replicate these findings in a sample with a different exposome. Furthermore, the phenotypic manifestations of ADHD are notably different across different age groups. Therefore, our study contributes to understanding the relationships between *MAOA*-uVNTR alleles and phenotypes related to ADHD. To our knowledge, this is the first study to analyze this polymorphism in a sample of adults with ADHD.

Considering the involvement of the MAOA enzyme in the dopaminergic pathway and its role in regulating brain functions such as attention, motivation, and reward (Liu et al. 2015; Hong et al. 2018; Klein et al. 2019; Kessi et al. 2022), the association between a functional MAOA polymorphism and the diagnosis of ADHD observed in our study is expected. Studies relating ADHD to the *MAOA*-uVNTR polymorphism, however, are quite scarce, and existing results are contradictory (Kolla and Bortolato 2020; Kessi et al. 2022). Children with ADHD often exhibit a higher frequency of MAOA-H alleles, but the existing analyses of this association did not evaluate other age groups (Kolla and Bortolato 2020; Kessi et al. 2022). The conflicting results underscore the complexity of the relationship between the *MAOA*-uVNTR polymorphism and behavior. In our sample, we did not find significant differences in

the number of ADHD symptoms between carriers of MAOA-L or MAOA-H alleles. The potential influence that *MAOA* alleles may have on ADHD-related phenotypes could be associated with the overall manifestation of ADHD and not with more subtle aspects of the disorder such as its severity.

Although no significant associations were found between *MAOA*-uVNTR alleles and ODD, CD/ASPS, or SUD, a higher frequency of the MAOA-L was observed among individuals with these disorders. The fact that we could not replicate previous associations could be attributed to a variety of factors, including the possibility that these phenotypes were not as severe in our sample as they may be when considering them as the main diagnoses. However, it is important to note that studies examining the association between the *MAOA*-uVNTR polymorphism and aggressive/impulsive behaviors do not always demonstrate significant results, often suggesting that other factors play a significant role in behavior, such as genetic effects, environmental factors, ethnicity, and gender (Byrd and Manuck 2014; Kolla and Bortolato 2020).

Our study should be viewed in the light of several limitations. Although our clinical sample is one of the largest samples of adults with ADHD that evaluated *MAOA*-uVNTR, it is still a relatively small sample size to draw definitive conclusions. The clinical setting from our sample also increases the chance to detect impulsive and aggressive behaviors. However, the prevalence of some phenotypes was still relatively low. The homogeneity regarding sex can be advantageous when looking at phenotypes (and genotypes) with different relations according to sex. The analysis of women, though, is needed to help clarify the big puzzle of MAOA and behavior. Finally, our cross-sectional study design prevents the analysis of gene-by-environmental interactions, frequently reported in the literature.

The effects of the *MAOA*-uVNTR on aggressive and impulsive behaviors may be modulated by intricate interactions with other genetic variants and environmental factors. This pattern of small additive genetic effects aligns with the overall findings of modern genomic analysis methods, such as Genome-Wide Association Studies (GWAS) in complex behaviors. Additionally, phenotypic differences among groups of individuals, such as ethnicity, gender, and age, appear to exert a significant influence on the expression of MAOA variants and related phenotypes. Ultimately, a considerable lack of investigations addressing X chromosome polymorphisms through GWASs persists. This gap in GWASs can be attributed to methodological complexities that must be carefully applied, both in terms of quality control and statistical analyses. Specifically, the investigation of VNTRs presents additional challenges due to their minority presence in GWAS analyses. Given the functional relevance of *MAOA*-

uVNTR, it is imperative to continue research examining its effects in clinical samples characterized by distinct exposomes from those previously explored in the literature.

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Conflict of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicial to the impartiality of the reported research.

Authors Contributions

G.L.R.S Formal Analysis, Research, Methodology, Writing; E.H.G. Conceptualization, Resource Acquisition; M.E.A.T. Conceptualization, Resource Acquisition, C. E. B. Conceptualization, Formal Analysis, Resource Acquisition, Methodology, Writing, Supervision, C.H.D.B. Conceptualization, Formal Analysis, Resource Acquisition, Methodology, Writing, Supervision. All authors read and approved the final version.

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Table 1. Sample characteristics.

	Cases (n=252)	**Controls** (n=303)
	Mean (SD)	
Age (years)	32.5 (10.6)	29.28 (8.6)
Education (years of study)	13.54 (2.8)	12.76 (3.0)
	n (%)	
Oppositional Defiant Disorder	146 (57.9)	9 (3.0)
CD/ASPD[1]	65 (25.8)	1 (0.3)
Alcohol Use Disorder	51 (20.2)	10 (3.3)
Tobacco Use Disorder	119 (47.2)	58 (19.1)

[1]Lifetime presence of Conduct Disorder (CD) or Antisocial Personality Disorder (ASPD).

Table 2. Results for the analysis with *MAOA*-uVNTR and externalizing/disruptive phenotypes.

	MAOA-H	**MAOA-L**	**Total N**	**P-value**
ADHD (yes)	155 (41.2%)	97 (54.2%)	252	**0.009**[1]
ADHD (no)	221 (58.8%)	82 (45.8%)	303	
Only cases (n=252)				
Oppositional Defiant Disorder	87 (56.5%)	59 (60.8%)	146	0.571
CD/ASPD[2]	36 (23.2%)	29 (32.2%)	65	0.180
Tobacco Use Disorder[3]	72 (46.5%)	47 (48.5%)	119	0.965
Alcohol Use Disorder[3]	29 (18.7%)	22 (22.9%)	51	0.567
Number of ADHD symptoms	12.68 (3.0)	12.77 (2.7)	-	0.772
Number of inattention symptoms	7.52 (1.3)	7.19 (1.5)	-	0.166
Number of hyperactivity/impulsivity symptoms	5.16 (2.6)	5.59 (2.3)	-	0.255
Problems with authority and discipline	76 (49.0%)	46 (47.4%)	122	0.731
Problems with law and police	26 (16.8%)	13 (13.4%)	39	0.451

[1]PBonf=0.036; [2]Lifetime presence of Conduct Disorder (CD) or Antisocial Personality Disorder (ASPD); [3]Substance Use Disorder (SUD) was analyzed separately for Alcohol and Tobacco. For categoric measures, values are described as n (%). For continuous traits, values are represented as mean (SD). For the analyses in cases sample, percentages refer to the frequency of the disorders in subjects with MAOA-H (n=155) or MAOA-L (n=97).

3 CONCLUSÃO E PERSPECTIVAS

Com base nos achados descritos na seção 2, observou-se que os homens com TDAH exibiram uma frequência mais elevada do alelo low. Esta descoberta é notável, pois sugere a possibilidade de uma diferenciação entre os alelos de risco para o TDAH na fase adulta em comparação com a infância. Isso porque nossos resultados divergem das informações documentadas na literatura, que tipicamente associam a maior frequência do alelo high ao TDAH, embora essas associações tenham sido predominantemente identificadas em análises realizadas apenas em crianças, conforme nosso conhecimento atual.

Não foi encontrada associação entre os alelos e o número de sintomas de TDAH ou outros fenótipos impulsivos/disruptivos. Entretanto, observou-se uma frequência mais elevada do alelo MAOA-L entre indivíduos com TDO, TC/TPAS e TUS. A maioria dos estudos que analisam a associação entre *MAOA*-uVNTR e estes distúrbios costumam encontrar associação significativa com o alelo MAOA-L, principalmente em análises realizadas em indivíduos do sexo masculino. O fato de não termos conseguido replicar essas descobertas pode ser atribuído a fatores intrínscecos a nossa amostra, porém é importante ressaltar que estudos que relacionam o polimorfismo *MAOA*-uVNTR a fenótipos agressivos/impulsivos nem sempre apresentam associações significativas, indicando a influência de outros fatores nessa relação, como outras variáveis genéticas, fatores ambientais, faixa etária, etnia e sexo. Em geral, nossos resultados indicam que a influência que o polimorfismo *MAOA*-uVNTR exerce no comportamento é mais relevante quando considerado juntamente com outros fatores do que se for analisado individualmente.

Em estudos futuros, com o objetivo de compreender melhor a relação do polimorfismo *MAOA*-uVNTR com o TDAH e outros fenótipos associados a impulsividade/agressividade, temos como perspectiva realizar as análises em mulheres para verificar as possíveis diferenças que o sexo pode ter nessa relação. Pretendemos explorar as relações gene-gene analisando a interação desse polimorfismo com escores de risco poligênico de comportamentos disruptivos/externalizantes. Ainda, abordagens com neuroimagem deverão ser realizadas para avaliar o *MAOA*-uVNTR em relação a aspectos estruturais (espessura cortical, área cortical e volume subcortical de areas relacionadas a impulsididade/agressividade) e conectividade funcional em redes relacionadas a controle inibitório e a tomada de decisões.

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ANEXO – Normas de publicação da revista *Genetics and Molecular Biology*

Instructions to authors

There is a publication charge for manuscripts once they are accepted. For price information, exemptions and waiver policies, please consult the journal homepage http://www.gmb.org.br.

1. Manuscripts must be submitted through our online submission platform hosted at: https://mc04.manuscriptcentral.com/gmb-scielo

The cover letter should be addressed to:

Carlos C. F. Menck and Márcia Pinheiro Margis,

Editors-in-Chief, Genetics and Molecular Biology

2. For submission the following instructions must be observed:

a) The manuscript must be submitted by the Corresponding Author, identified as such in the title page of the manuscript. This is the person who will also check the page proofs, and arranges for any payment that may incur during the editorial process. The submitting author must provide an ORCID ID (Open Researcher and Contributor ID, http://orcid.org/), with public information available, at the time of submission by entering it in the user profile in the submission system. **Multiple submissions from the same computer of manuscripts from different institutions will not be accepted.**

b) Entering the following metadata is required: (i) the manuscript title, (ii) a short running title (max. 35 characters), (iii) the Abstract, and (iv) up to five keywords. All these items must be exactly the same as those figuring in the first two pages of the manuscript file.

c) Statements are required informing that the data have not been published and are not under consideration elsewhere, and that all authors have approved the submission of the manuscript. Furthermore, possible conflicts of interest (e.g. due to funding, consultancies) must also be disclosed. For statements on ethical issues in research see below (3.1.m).

d) The names of all co-authors, including institutional affiliations and e-mail addresses must be entered, as contact information for the Editorial Office. We strongly encourage co-authors to also provide their ORCID iDs at the time of submission.

e) In the referee suggestions field, up to five reviewer names can be entered by the author(s); valid e-mail contact addresses for these are required, in case they are selected by the editor. These suggestions can be made separately as preferred and opposed reviewer(s).

f) Files must be uploaded separately and identified according to file types, respecting the following sequence: main text document (title page as page 1), tables, figures and, if applicable, supplementary material. The main text file must include the title page, Abstract, References and, if applicable, figure legends, which must be typed on a separate page following the References and Internet Resources sections. Each table, figure and element containing supplementary material must be saved and uploaded in a separate file. Formats for text and tables are Word or RTF in Windows platform. Figures should be in TIFF or JPEG formats (see detailed instructions in 3.1.i).

g) Manuscripts including photos or any other identifiable data of human subjects must be accompanied by a copy of the signed consent by the individual or his/her guardian.

Failure to adhere to these guidelines can delay the handling of your contribution and manuscripts may be returned before being reviewed.

Special attention should be given to the structuring of the manuscript and correct language usage. These are important factors in the smooth running of the editorial and peer-review process, and can result in faster publication.

3. Categories of Contribution

3.1. Research Articles

Manuscripts must be written in English in double-spaced, 12-point type throughout; marked with consecutive line and page numbers, beginning with the cover page.
The following elements must start on a new page and be ordered as they are listed below:

a) **The title page** must contain: a concise and informative title; the authors' names (first name at full length); the authors' institutional affiliation, including department, institution, city, state or province, and country; different affiliations indicated with superscript Arabic numbers; a short running title of up to 35 characters (including spaces); up to five key words; the corresponding author's name, full postal, postal, email address and ORCID ID.

b) **The Abstract** must be a single paragraph that does not exceed 200 words and summarizes the main results and conclusions of the study. It should not contain references.

c) **The text** must be as succinct as possible. Text citations: articles should be referred to by authors' surnames and date of publication; citations with two authors must include both names; in citations with three or more authors, name the first author and use et al. List two or more references in the same citation in chronological order, separated by semi-colons. When two or more works in a citation were published in the same year, list them alphabetically by the first author surname. For two or more works by the same author(s) in a citation, list them chronologically, with the years separated by commas. (Example: Freire-Maia et al., 1966a, 1966b, 2000). Only articles that are published or in press should be cited. In the case of personal communications or unpublished results, all contributors must be listed by initials and last name (et al. should not be used). Numbers: In the text, numbers nine or less must be written out except as part of a date, a fraction or decimal, a percentage, or a unit of measurement. Use Arabic numerals for numbers larger than nine.Binomial Names: Latin names of genera, species and infraspecific taxa must be printed in italics; names of orders and families should appear in the Title and also when first mentioned in the text. URLs for programs, data or other sources should be listed in the Internet Resources Section, immediately following the References Section, not in the text.

The text includes the following elements:

Introduction - Description of the background that led to the study.
Material (or Subjects) and Methods - Details relevant to the conduct of the study. Statistical methods should be explained at the end of this section.
Results - Undue repetition in text and tables should be avoided. Statistical analyses should be presented as complete as possible, i.e. not only P-values should be shown, but also all other test variables required for full appreciation of the results by the reviewers and readers.

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d) **The Acknowledgments** must be a single paragraph that immediately follows the discussion and includes references to grant support.

e) **Conflict of Interest:** Any possible conflict of interest must be disclosed here. If there is none, please state: The authors declare that there is no conflict of interest that could be perceived as prejudicial to the impartiality of the reported research.

f) **Authors Contributions:** The contributions of each author must be specified here; identify authors by their initials. The style of this section may be as follows:

author initials> conceived and the study, <author initials> conducted the experiments (detail if necessary), <author initials> analyzed the data, <author initials> wrote the manuscript, <author initials> (other contributions if applicable), all authors read and approved the final version.

In case of doubts concerning contribution definitions, we suggest to consult the CRediT taxonomy at https://casrai.org/credit.

g) **The References Section:** References must be ordered alphabetically by the first author surname; references with the same first author should be ordered as follows: first, as single author in chronological order; next, with only one more co-author in alphabetical order by the second author; and finally followed by references with more than two co-authors, in chronological order, independent of the second author surnames. In references with more than 10 authors only the first ten should be listed, followed by et al. Use standard abbreviations for journal titles as suggested by NCBI (http://www.ncbi.nlm.nih.gov/journals/).
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LEM Software, http://dir.niehs.nih.gov/dirbb/weinbergfiles/hybrid_design.htm (September 4, 2009)

i) **Tables:** must be in Word format prepared with the table tool (do not use space bar or tabulator). A concise title should be provided above the table. Tables must be numbered consecutively in Arabic numerals. Each column must have a title in the box head. Footnotes typed directly below the table should be indicated in lowercase superscript letters. Tables that are to appear in the printed version must be saved in Word format and not as figures, so that they can later be fitted during typesetting. Each table must be saved and uploaded as a separate file.

j) **Figures** must be numbered consecutively using Arabic numerals. Images should be in TIFF or JPEG format. Figures in Word, PowerPoint or Excel format cannot be published. Only sequence data can be presented in Word format. Journal quality reproduction will require grayscale resolution yielding 300 dpi, color figures should be at 600 dpi. These resolutions refer to the output size of the file, that is the size in which it will appear printed in the journal; if it is anticipated that images will be enlarged or reduced, the resolutions should be adjusted accordingly. Figures composed of several elements should be sent as a single panel, obeying the print size definitions of the journal (single or two columns width). Scanned figures should not be submitted. Color illustrations are accepted. Each figure/panel must be saved and uploaded as a separate file. When uploading, identify each illustration by the first author name and the number of the respective figure.
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