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CYTOGENOMIC EVALUATION OF CHROMOSOME REARRANGEMENTS BY ARRAY-CGH IN THE IDURONATE-2 SULPHATASE (IDS) GENE REGION

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Introduction: The majority of cases of Hunter syndrome are caused by point mutations, small deletions and insertions in the iduronate-2-sulphatase (IDS) gene which spans about 24kb in the Xq28 region. In 20% of cases major structural alterations occur, including large deletions and rearrangements (Froissart et al., 2002). In ~6-8% of cases the disease results of a complete deletion of the IDS gene (Hopwood et al., 1993). During the last decade it has become apparent that the molecular genetic mechanisms for many disease traits often involve complex genomic rearrangements that leads to small or large deletions of one or more genes. Individuals may present large segment rearrangements of their genome, with evidence for both decreased and increased copy number. This finding has been enabled by array technologies that allow high-resolution screening of the entire human genome. Aims: To evaluate the use of high-resolution array-based Comparative Genomic Hybridization (array-CGH) in the determination of genomic rearrangements in the IDS gene region. Material and methods: Chromosome microarray analysis was performed on DNA samples with known deletions within the IDS gene region. The customized oligonucleotide-based microarray using the 1 million array (Agilent Technologies Inc., Santa Clara, CA) was applied in each of the samples test and controls in order to better delineate the chromosomal rearrangement in the Xq28 region. The arrays were analyzed through the Agilent Feature Extraction for CytoGenomics (v9.5.1). Graphical overview was obtained using the Agilent CytoGenomics (v.2.0.6.0) analytics software. Results: The array-CGH data confirmed the previous exon-by-exon IDS PCR results which demonstrated partial or complete deletions. Additionally, the microarray analysis revealed a contiguous duplicated region on Xq28 in one of the samples, encompassing approximately 476 Kb. Conclusion: The spectrum of human genetic variation ranges from a single base pair to large chromosome events, but it has become apparent that human genomes differ more as a consequence of structural variation than of single base pair differences. In our study, the arraybased method enabled the detection of genomic gains and losses and the determination of the extension of the rearrangements in and around the IDS region. A comprehensive molecular analysis in patients affected by MPS II, especially in the ones with large deletions, is crucial for the understanding of the molecular mechanisms of rearrangements in the IDS gene region and the related phenotypic traits. Possibly rearrangements of the IDS gene region occur in greater extent than estimated so far, as part Xq28 chromosome variation, with potentially involvement of contiguous genes. The array-based methods have proven to be powerful tools in genomewide detection of copy number changes of different sizes and gene content in MPS II patients. FIPE/HCPA 10560; CNPq 402012/2010-0.