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EXCLUSION OF inv(2)(p16.1;q14.3) AS THE CAUSE OF A SEVERE CONGENITAL DISEASE BY NEXT-GENERATION SEQUENCING

Cardoso MP[1] (manuela.cardoso@insa.min-saude.pt), Talkowski ME[2], Freixo J[3], Gonçalves RM[3], Morton CC[4], David D[1]

1 *Departamento de Genética Humana, Instituto Nacional de Saúde Dr. Ricardo Jorge, INSA IP, Lisboa, Portugal*
2 *Center for Human Genetic Research, Massachusetts General Hospital, Boston, United States of America*
3 *Serviço de Genética, Centro Hospitalar de Lisboa Central, Lisboa, Portugal*
4 *Department of Obstetrics and Gynecology, and Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, United States of America*

Introduction Congenital anomalies, a leading cause of infant mortality in developed countries, are usually caused by genomic and/or chromosome rearrangements. Such rearrangements, like inversions, disrupt the genomic architecture at the breakpoint regions and can be either subclinical or pathogenic. Currently, the lack of a fully annotated genome hinders the prediction of phenotypical consequences of these anomalies.

Methods We report a familial pericentric inversion, inv(2)(p16.1;q14.3), in a proband presenting multiple psychomotor and developmental anomalies, dismorphism and autistic features, with phenotypically normal parents. Traditional analysis methods are labor intensive and of low resolution. Here we employed Next-Generation Sequencing (NGS) to identify breakpoints at nucleotide resolution in the proband, followed by familial segregation analysis by Sanger sequencing. Genomic and transcriptome array analysis were performed, for exclusion of further genomic alterations and for gene expression profiling.

Results The inversion breakpoints, at chr2:55,707,929 and chr2:123,010,109 (GRCh38), did not disrupt any gene or regulatory element and are flanked by *PNPT1* and *EFEMP1*, and *TSN* and *CNTNAP5*, respectively. No significant alteration in the expression level of possible candidate genes were observed. Aside from a polymorphic duplication, inherited from his father, no other pathogenic genomic imbalances were identified in the proband.

Discussion Based on these data, the causal relationship between clinical phenotype and the inversion is most likely excluded, as the inversion probably is nonpathogenic. It was yet not possible to establish the cause of the observed phenotype. The introduction of NGS represents a hallmark in the characterization of congenital disorders associated with chromosomal rearrangements.

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