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NEXT-GEN CYTOGENETICS AND THE HIDDEN COMPLEXITY OF GENOMIC OR CHROMOSOMAL REARRANGEMENTS

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Human developmental abnormalities are devastating conditions that account for almost half of all full-term neonatal deaths in developed countries. For individuals who survive, congenital anomalies often confer lifelong disability and their impact on public health is profound. However, the genetic etiology and genomic architecture contributing to the vast majority of these conditions remain unknown. Separately, and in addition, the genetic etiologies of recurrent infertility remain to be elucidated.

The current low resolution diagnostic techniques are insensitive to the full mutational spectrum contributing to human developmental abnormalities and infertility, the poor understanding of the molecular alterations introduced by genomic rearrangements, and the lack of a fully annotated human genome hinders predictive diagnostics.

This study results from collaboration between a Portuguese Consortium including clinical geneticists and the Developmental Genome Anatomy Project (DGAP) from Harvard Medical School.

First, a group of cases were comparatively analyzed using genomic array and Next-Generation Sequencing (NGS). Subsequently, NGS of whole-genome large-insert libraries was applied for the identification of genomic or chromosomal rearrangements at nucleotide resolution in a series of cases, including two prenatal samples. Presently, this high-throughput technology is the only approach able to identify the full spectrum of structural variants, in a time frame that allows its application even for prenatal samples. The introduction of NGS into clinical cytogenetics surely will create a high-throughput, sequence-based Next-Gen Cytogenetics that will catalyze a dramatic advancement in clinical diagnostics. Therefore the understanding of the molecular pathology of these chromosome rearrangement-associated developmental disorders and infertilities will contribute to an improved prediction of the phenotypic consequences of these rearrangements.