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ARRAY AND NGS BASED CHARACTERIZATION OF TRANSLOCATION BREAKPOINTS OF THE t(2:7)(q23;q32),t(5;6)(q23,q26)dn

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Introduction Congenital anomalies, namely caused by chromosome rearrangements, are a leading cause of infant mortality in European countries. The elucidation of the causal relationship between rearrangements and clinical phenotypes requires an efficient approach for identification of breakpoints at nucleotide resolution.

Methods In the last decade we went from conventional FISH based positional mapping of chromosomal breakpoints to sorting and amplification of derivative (der) chromosomes followed by array painting based mapping. Currently we are moving towards the application of Next-Generation Sequencing (NGS) for the identification of chromosome rearrangement breakpoints at nucleotide resolution. By means of these comprehensive molecular techniques we unveil the structural chromosomal alterations at nucleotide resolution in a proband with t(2:7)(q23;q32),t(5;6)(q23,q26)dn. Expression profiling of the proband's LCLs was also carried out.

Results Array painting identified the breakpoints of two balanced chromosome translocations. The disruption of the *PRPF40A* and *SND1* genes by the t(2;7) was identified both by array and NGS analysis. While array analysis identified only t(5;6) breakpoints and the affected *PACRG* gene, NGS revealed further complexity of the breakpoint region. Indeed, der(6) is a complex chromosomal rearrangement (CCR) with three additional breakpoints resulting from an inversion and a *PTPRK* gene excision/insertion.

Discussion Because of the complexity of this rearrangement we are not yet able to establish the candidate genes for the observed clinical phenotype. As shown by the CCR, NGS is currently the only methodology able to identify the full spectrum of balanced structural alterations. Thus, the introduction of NGS technology for high-throughput delineation of chromosomal rearrangements is presently underway.

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