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Disruption of WDR26 by a translocation breakpoint confirms its causal role in Skraban-Deardorff and 1q41q42 microdeletion syndromes

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Introduction: Microdeletions or contiguous gene syndromes (CGSs) are characterized by variable complex clinical phenotypes caused by hemizygosity of contiguous genes, defined mainly by a common deletion region, or of a major causal gene locus. Delineation of the pathogenic genes within these CGS regions is a major challenge. Identification of breakpoints at nucleotide resolution of balanced chromosomal rearrangements localized within these regions constitutes a key strategy for definition of the phenotypically important genes. The aim of this study is the identification of molecular alterations responsible for an extremely complex clinical phenotype resembling 1q41q42 microdeletion syndrome (coarse facial features, severe developmental delay, congenital heart disease and congenital microcephaly) presented by an individual with the t(1;3)(q42.11;p25.3)dn.
Methods: Translocation breakpoints were localized by large-insert whole-genome sequencing. Nucleotide-level resolution of the breakpoints was carried out by amplification of the junction fragments and Sanger sequencing.
Results: The 1q42.11 breakpoint disrupts exon 12 of WD repeat domain 26 (WDR26), reported in 2017 as the causative gene of the autosomal dominant Skraban-Deardorff syndrome (SKDEAS, OMIM #617616), with clinical features that almost completely overlap the 1q41q42 microdeletion syndrome. WDR26 is WD40 repeat-containing protein presumably involved in multiple disease-associated signalling pathways. The 3p25.3 breakpoint disrupts IVS 1 of the ATPase, Ca++ transporting, plasma membrane 2 (ATP2B2, OMIM *108733), reported as a modifier of the autosomal recessive deafness-12.
Discussion: The proband's clinical features basically confirm the phenotypical overlaps between SKDEAS and 1q41q42 microdeletion syndromes. Nevertheless, deep phenotyping showed clinical features dissimilar to both syndromes, namely, aggravated congenital heart disease, hyperactivity, enuresis and encopresis. Although genes from both breakpoint regions may well contributed to the observes additional clinical features, surprisingly, their overall contribution seems marginal. In conclusion, disruption of WDR26 by the 1q42.11 breakpoint most likely leads to its haploinsufficiency due to nonsense mediated RNA decay, resulting in an extremely severe complex clinical phenotype basically matching both SKDEAS and 1q41q42 microdeletion syndromes. Therefore, we confirm its major causative role in these phenocopic syndromes.