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P30 | Clinical Genetics

KBG Syndrome: a de novo chromosomal rearrangement in prenatal diagnosis beyond conventional cytogenetics

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Introduction: KBG syndrome (OMIM #148050) is a rare disorder characterized by a typical facial dysmorphism, macrodontia of the upper central incisors, skeletal anomalies, short stature and developmental delay. Cutaneous syndactyly, webbed short neck, cryptorchidism, hearing loss, palatal defects, strabismus and congenital heart defects are less common findings. Although this is an autosomal dominant condition predominant maternal inheritance, mainly due to a milder clinical manifestation in females, is frequently observed. Pathogenic alterations, mainly truncating point mutations and microdeletions, leading to haploinsufficiency of ANKRD11, have been described to be the molecular basis of this syndrome.

Clinical Report: A 39 years old female with irrelevant previous medical history and ongoing 2nd pregnancy was referred to our outpatient clinic due to increased risk for aneuploidies according to 1st trimester screening. Invasive prenatal diagnosis (PND) showed a de novo balanced chromosomal aberration (dnBCA): 46,XX,t(16;17)(q24;q21.3)dn. The 20th week ultrasound revealed hypoplastic nasal bone, atrioventricular septal defect (AVSD) and ventricular septal defect (VSD). Microarray was performed and no clinical relevant CNV's were detected. Large-insert whole-genome sequencing (liWGS) for identification of dnBCA breakpoints at nucleotide resolution was performed. This approach identified the 16q24 and 17q21.3 breakpoints within IVS3 of ANKRD11 and IVS1 of WNT3, respectively. Haploinsufficiency of ANKRD11 causes dominant KBG syndrome, whereas of WNT3 results in recessive tetraamelia syndrome (OMIM #165330). Although the translocation results in fusion genes no evidence of chimeric transcripts was found. Elective C-Section was performed due to fetal distress at 35th week with no complications for the female newborn. Postnatal echocardiography confirmed the AVSD with VSD and at 20 months old she presents mild developmental delay.

Discussion: We here describe the first case of KBG syndrome due to a dnBCA identified in PND. Disruption of both genes by the translocation breakpoints results in their haploinsufficiency. While haploinsufficiency of ANKRD11 leads to the autosomal dominant KBG syndrome the one of WNT3 is benign or subclinical. Additionally, we also demonstrated the importance of whole-genome sequencing for identification of dnBCA breakpoints at nucleotide resolution allowing an improved genetic counseling to the parents. Therefore, we recommend inclusion of this approach into current PND care.