KBG syndrome (ANKRD11)

Gene:
The ANKRD11 gene is located on chromosome 16q24.3 and contains 13 exons. ANKRD11 encodes the Ankyrin repeat domain 11 protein, which belongs to a family of ankyrin repeat-containing cofactors that interact with p160 nuclear receptor coactivators and inhibit ligand-dependent activation of transcription.[1] The protein has a transcriptional activation domain and two transcriptional repression domains.[2]

Clinical Features:
KBG syndrome is characterized by macrodontia of the upper central incisors and a distinct craniofacial appearance, which may include brachycephaly and a round or triangular face. Other features include short stature, skeletal (mainly costovertebral) abnormalities and neurological involvement, such as global developmental delay, seizures and intellectual disabilities. Affected patients may also have a delayed bone age and abnormal hand findings (e.g., 5th finger clinodactyly, brachydactyly, short tubular bones seen on X-ray). Criteria for diagnosing KBG syndrome have been suggested.[3]

16q24.3 microdeletions that involve the ANKRD11 gene as well as surrounding genes have been reported.[4-7] KBG syndrome is a subphenotype of the 16q24.3 microdeletion syndrome because patients with a microdeletion meet some of the diagnostic criteria for KBG syndrome, including the craniofacial appearance, seizures and developmental delay.[4] The 16q24.3 microdeletion syndrome also includes autism and structural and neuronal migration defects of the brain.[5] Besides ANKRD11, other genes are also deleted in this region, which may contribute to the more complex phenotype of the 16q24.3 microdeletion syndrome[4,5].

Inheritance Pattern:
Autosomal dominant with variable expressivity. Most patients with KBG syndrome reported in the literature have been simplex cases with a strong male to female predominance among affected individuals, possibly implying genetic heterogeneity.[8] Familial cases of KBG syndrome (when diagnosed clinically) have been reported. However, all cases that were evaluated on a molecular level had *de novo* findings. Out of approximately 20 patients with ANKRD11 abnormalities, over half had either a *de novo* intragenic variant in the ANKRD11 gene or a *de novo* 16q24.3 microdeletion that involved the ANKRD11 gene.[4,9]

Test Sensitivity:
In a cohort of 71 individuals presenting with clinical characteristics of KBG syndrome who underwent molecular testing, 69% were identified with a pathogenic variant upon sequence analysis and 14% upon deletion/duplication analysis.[10,11]

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

References:

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