

## ANKRD11 Gene Analysis in KBG Syndrome and 16q24.3 Microdeletion Syndrome

### Clinical Features:

KBG syndrome is characterized by macrodontia of the upper central incisors, distinct craniofacial appearance, which may include brachycephaly, a round or triangular face, short stature, skeletal abnormalities (mainly costovertebral) and neurological involvement that includes global developmental delay, seizures and intellectual disabilities. Other clinical features reported in affected patients include delayed bone age and abnormal hand findings (e.g., 5<sup>th</sup> finger clinodactyly, brachydactyly, short tubular bones seen on X-ray). Criteria for diagnosing KBG syndrome have been suggested.<sup>1</sup>

16q24.3 microdeletions that involve ANKRD11 as well as surrounding genes have been reported.<sup>2-5</sup> 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.<sup>2</sup> The 16q24.3 microdeletion syndrome also includes autism and structural and neuronal migrational brain abnormalities.<sup>3</sup> Additional genes besides ANKRD11 are also deleted in this region and may contribute to the more complex phenotype of the 16q24.3 microdeletion syndrome<sup>2,3</sup>.

### Inheritance Pattern/Genetics:

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.<sup>6</sup> Familial cases of KBG syndrome (when diagnosed clinically) have been reported. However in the literature to date, out of approximately 20 patients who have reported to have an abnormality in the ANKRD11 gene, 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.<sup>2,7</sup>

### Test Methods:

Using genomic DNA obtained from the submitted biological material, bi-directional sequence analysis of 11 coding exons (exons 3-13) and the flanking exon/intron boundaries of the ANKRD11 gene is obtained and analyzed. If gene sequencing is negative, array CGH analysis is available to detect deletions involving ANKRD11 in 16q24.3. Variants found in the first person of a family to be tested are confirmed by repeat sequence analysis using sequencing, restriction fragment analysis, array CGH, or another appropriate method.

## Test Sensitivity:

In one study of 10 individuals with clinical characteristics of KBG syndrome, 5 had an intragenic variant in the ANKRD11 gene<sup>5</sup>. However, due to the small sample size and the paucity of case reports describing intragenic variants in the ANKRD11 gene associated with KBG syndrome or the 16q23.4 microdeletion syndrome, the precise clinical sensitivity is not clear.

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.<sup>8</sup> The protein has a transcriptional activation domain and two transcriptional repression domains.<sup>9</sup>

## References:

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