Kabuki Syndrome Panel

Disorder also known as: Kabuki Make-up Syndrome (KMS), Niikawa-Kuroki Syndrome

Panel Gene List: *KMT2D (MLL2), KDM6A*

Clinical Features:
Kabuki syndrome (KS) is characterized by a distinct facial appearance, multiple congenital anomalies, and mild-moderate intellectual disability. Affected individuals have facial features consisting of long palpebral fissures, eversion of the lower lateral eyelids, arched eyebrows with sparse hair in outer lateral half, large malformed ears with hypoplastic helices, and a depressed nasal tip. In addition to the distinctive facial features, the cardinal manifestations of KS include skeletal anomalies (spine abnormalities, brachydactyly, clinodactyly), dermatoglyphic abnormalities (persistence of fetal fingertip pads), intellectual disability, and postnatal growth deficiency. Other common characteristics of individuals with KS include high arched/cleft palate, short stature, and abnormal dentition. Common congenital anomolies include heart, genitourinary, and gastrointestinal defects such as, coarctation of the aorta, hydronephrosis, and gastroesophageal reflux. Hypotonia and feeding difficulties can be observed during infancy. Additionally, individuals with KS can experience recurrent otitis media, immunological issues, seizures, and precocious puberty in females. KS is caused by variants in the KMT2D (MLL2) gene and the KDM6A gene.[1,2,3] Neonatal hypoglycemia appears to be more common in patients with KDM6A variants. In general, affected females with KDM6A-related KS present with a milder phenotype compared to their males counterparts (likely due to skewed X-inactivation).[5]

Genetics:
Kabuki syndrome can be inherited in an autosomal dominant (AD) manner (KMT2D), or in an X-linked (XL) manner (KDM6A).[2] The majority of KMT2D variants are *de novo*, but there have been case reports of parent to child transmission and mosaicism.[3,5] Similarly, the majority of KDM6A variants occur *de novo*, however, inheritance from a mildly affected or unaffected mother has been reported.[6]

Approximately 99% of KMT2D variants are sequencing variants, though deletions/duplications have been reported.[2] For the KDM6A gene, about 80% of variants are sequencing variants and about 20% are deletions/duplications.[2] For KMT2D, a variety of pathogenic variant types have been reported, with 70% of pathogenic variants predicted to be protein truncating; those with protein truncating pathogenic variants tend to have more classic Kabuki facies.[4] Pathogenic variants occur throughout KMT2D but are particularly common in exons 39 and 48.[9]

Test Sensitivity

Gene	Protein	Inheritance	Clinical Sensitivity
KMT2D	Lysine-specific methyltransferase 2D	AD	~75% [2,6]
KDM6A	Lysine-specific demethylase 6A	XLD	~3-5% [2,7,8]

Test Methods:

Genomic DNA is extracted from the submitted specimen. For skin punch biopsies, fibroblasts are cultured and used for DNA extraction. The DNA is enriched for the complete coding regions and splice site junctions of the genes on this panel using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons at the exon-level; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data by NGS. 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.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events, but less for deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test identify most deletions and duplications involving coding exons but are less reliable for detecting copy number variants of less than 500 base pairs. Assessment of copy number events also depends on the inherent sequence properties of the targeted regions, including shared homology and exon size. Mosaicism detection is limited and balanced chromosome aberrations cannot be identified.

References:

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