

KMT2D (MLL2) Gene Analysis in Kabuki Syndrome (KS)

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

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 reminiscent of the make-up used by actors of traditional Japanese Kabuki theatre and include 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. Other commonly seen features in individuals with KS include high arched/cleft palate, abnormal dentition, and persistence of fetal finger pads and dermatoglyphic abnormalities. Hypotonia and feeding difficulties can be observed during infancy. Individuals with KS have postnatal growth retardation and short stature is frequently observed. Common congenital defects typically involve the heart and/or kidneys. Additionally, individuals with KS can experience recurrent otitis media, immunological defects, seizures, and precocious puberty in affected females. Penetrance appears to be complete, but variable expressivity is observed.^{1,2} KS is caused by variant in the KMT2D (MLL2) gene or the KDM6A gene.

Genetics:

KMT2D-related KS is inherited in an autosomal dominant manner. The majority of identified KMT2D variants are de novo, but there are case reports of parent to child transmission. The KDM6A gene is located on the X chromosome, so while X-linked inheritance is theoretically possible, only de novo cases of KDM6A-related KS have been reported.² KMT2D-associated KS is caused by variants in the KMT2D (MLL2) gene encoding a histone 3 lysine 4 (H3K4) methyltransferase, which methylates the 4th lysine residue of histone H3. Ultimately, the KMT2D gene is involved in regulating cell adhesion, growth impairment, and cell motility during embryogenesis and development. The majority of variants reported in the KMT2D gene are nonsense and frameshift variants (72%), followed by missense (16%), splice site (9%), in-frame deletions and insertions (3%), and rarely whole and partial gene deletions.² In addition, at least three patients mosaic for an KMT2D variant have been reported.³ Haploinsufficiency of KMT2D is the proposed cause of KS, however the exact mechanism is not yet known. KDM6A-associated KS is caused by variants in the KDM6A gene, which encodes an H3K27 demethylase thought to be involved in chromatin activation. Few cases of KDM6A-associated KS have been reported. The variants published thus far include partial gene deletions, nonsense, frameshift, splice-site and missense changes, as well as small deletions.^{2,4,5,6}

Test Sensitivity:

Sequencing of the KMT2D gene identifies variants in approximately 52-76% of individuals with a clinical diagnosis of Kabuki syndrome.^{2,7,8,9,10} The detection frequency of partial and whole deletions of KMT2D is unknown, although it is estimated that large deletions may account for 5% of cases.²

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the KMT2D 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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