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 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 Methods:

Using genomic DNA from a submitted specimen, bi-directional sequence analysis of the complete coding region (exons 1-54) and splice sites of the KMT2D gene is performed. If no variant is found by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons in the KMT2D gene. The presence of a variant or deletion is confirmed by repeat analysis using sequencing, restriction fragment analysis, or other appropriate method.

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]

References:

1. Wessels et al., (2002) Clinical Dysmorphol 11(2):95–102
2. Adam MP, Hudgins L, Hannibal M. Kabuki Syndrome. 2011 Sep 1 [Updated 2013 May 16]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014
3. Banka et al., (2013) Clin Genet. 83(5):467-71
4. Lederer et al., (2012) Am J Hum Genet 90:119-124
5. Miyake et al., (2013) Am J Med Genet A 161(9):2234-43
6. Micale et al., (2014) Human mutation 35 (7):841-50
7. Ng et al., (2010) Nat Genet 42(9):790-793
8. Paulussen et al., (2010) Hum Mutat 32:E2018-E2025
9. Hannibal et al., (2011) Am J Med Genet A 155(7): 1511-1516
10. Li et al., (2011) Hum Genet 130(6):715-724.