THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Genetic Testing for Kabuki Syndrome

Clinical Features:

Patients with Kabuki syndrome [OMIM #147920] have characteristic facial features, short stature, congenital heart defects, skeletal anomalies, immunological abnormalities, and mild to moderate mental retardation. Facial features include long palpebral fissures with eversion of the lower lateral eyelid, sparse and arched eyebrows, depressed nasal tip, and large prominent earlobes. Other features include joint laxity, dental abnormalities, finger-tip pads, and renal/urinary tract anomalies. Some individuals have been reported with normal intelligence (1).

Molecular Genetics:

Mutations of the *KMT2D* (*MLL2)* [OMIM #602113] gene were reported in 35/53 (66%) patients with Kabuki syndrome by Ng *et al*, 2010 (2). More recently, Banka *et al*, 2012 identified *KMT2D* mutations in 55-80% of patients with Kabuki syndrome (3). *KMT2D* encodes a Trithorax-group histone methyltransferase that belongs to the SET family. The SET domain of KMT2D has strong histone 3 lysine 4 methyltransferase activity and plays a role in the epigenic control of active chromatin states. *KMT2D* has 54 coding exons and is located at 12q12-14. Most mutations reported to date are truncating mutations that occur before the SET domain.

Mutations of the *KDM6A* (lysine specific demethylase 6A) [OMIM#300128] gene were reported in 3/32 (9%) patients with Kabuki syndrome that were negative for mutations in the *KMT2D* gene (4). Pathogenic sequence changes detected included two nonsense mutations and 1 frameshift mutation. In addition, exonic deletions of *KDM6A* have also been previously reported (5). The *KDM6A* gene codes for a residue protein that contains two functional domains and one of its functions is working with KMT2D in the epigenetic control of transcriptionally active chromatin. *KDM6A* has 29 coding exons and is located at Xp11.3 and largely escapes X-inactivation.

Inheritance:

KMT2D-related Kabuki syndrome is an autosomal dominant condition that occurs in 1 in approximately 32,000 live births (1). Most cases appear to be *de novo*, but familial cases are reported. Recurrence risk for unaffected parents of an isolated case is approximately 0.1%. Recurrence risk for affected individuals with a *KMT2D* mutation is 50%. To date, all cases of *KDM6A*-related Kabuki syndrome have been *de-novo*. While X-linked inheritance is theoretically possible, no familial cases of *KDM6A*-related Kabuki syndrome have been reported.

Additional Resources:

Kabuki Syndrome Network
Website: kabukisyndrome.com
Phone: 306-543-8715
Email: margot@kabukisyndrome.com

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *KMT2D* and/or *KDM6A* genes is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Kabuki syndrome Panel (*KMT2D* and *KDM6A* sequencing and del/dup)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2500
CPT codes:	81406, 81407
Turn-around time:	8 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Matsumoto N, Niikawa N. Kabuki make-up syndrome: a review. Am J Med Genet C Semin Med Genet 2003: 117C: 57-65.
2. Ng SB, Bigham AW, Buckingham KJ et al. Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. Nat Genet 2010: 42: 790-793.
3. Banka S, Veeramachaneni R, Reardon W et al. How genetically heterogeneous is Kabuki syndrome?: MLL2 testing in 116 patients, review and analyses of mutation and phenotypic spectrum. Eur J Hum Genet 2012: 20: 381-388.
4. Miyake N, Mizuno S, Okamoto N et al. KDM6A point mutations cause Kabuki syndrome. Hum Mutat 2013: 34: 108-110.
5. Lederer D, Grisart B, Digilio MC et al. Deletion of KDM6A, a histone demethylase interacting with MLL2, in three patients with Kabuki syndrome. Am J Hum Genet 2012: 90: 119-124.

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS' NEEDS