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. Deletion/duplication analysis of the KMT2D and KDM6A genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.
**KMT2D (MLL2) sequence analysis**
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1000
CPT codes: 81408
Turn-around time: 4 weeks

**KMT2D (MLL2) deletion/duplication analysis**
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1000
CPT codes: 81407
Turn-around time: 4 weeks

**KDM6A sequence analysis**
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1000
CPT codes: 81407
Turn-around time: 4 weeks

**KDM6A deletion/duplication analysis**
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1000
CPT codes: 81406
Turn-around time: 4 weeks

**Comprehensive Kabuki syndrome Panel (KMT2D and KDM6A sequencing and del/dup)**
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $2500
CPT codes: 81406, 81407
Turn-around time: 4 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:**