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Kabuki Syndrome

Synonyms: Kabuki Make-Up Syndrome, Niikawa-Kuroki Syndrome

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Summary

Clinical characteristics

Kabuki syndrome (KS) is characterized by typical facial features (long palpebral fissures with eversion of the lateral third of the lower eyelid; arched and broad eyebrows; short columella with depressed nasal tip; large, prominent, or cupped ears), minor skeletal anomalies, persistence of fetal fingertip pads, mild-to-moderate intellectual disability, and postnatal growth deficiency. Other findings may include: congenital heart defects, genitourinary anomalies, cleft lip and/or palate, gastrointestinal anomalies including anal atresia, ptosis and strabismus, and widely spaced teeth and hypodontia. Functional differences can include: increased susceptibility to infections and autoimmune disorders, seizures, endocrinologic abnormalities (including isolated premature thelarche in females), feeding problems, and hearing loss.

Diagnosis/testing

The diagnosis of KS is established in a proband of any age with a history of infantile hypotonia, developmental delay, and/or intellectual disability AND one or both of the following:

- Typical dysmorphic features (long palpebral fissures with eversion of the lateral third of the lower eyelid, and ≥2 of the following: arched and broad eyebrows with the lateral third displaying notching or sparseness; short columella with depressed nasal tip; large, prominent, or cupped ears; persistent fingertip pads)
- A heterozygous pathogenic variant in *KMT2D* or a heterozygous or hemizygous pathogenic variant in *KDM6A*

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Management

Treatment of manifestations: Thickened feedings and positioning after meals to treat gastroesophageal reflux; gastrostomy tube placement if feeding difficulties are severe. If cognitive difficulties are evident, psychoeducational testing and special education services to address the individual child's needs. Evaluation by a developmental pediatrician or psychiatrist if behavior suggests autism spectrum disorders. Standard anti-seizure treatment.

Prevention of secondary complications: Prophylactic antibiotic treatment prior to and during any procedure (e.g., dental work) may be indicated for those with specific heart defects.

Surveillance: Monitor height, weight, and head circumference at each well-child visit and, at a minimum, yearly. Developmental milestones should be followed with each well-child visit. Monitor vision and hearing on a yearly basis.

Genetic counseling

KMT2D-related KS is inherited in an autosomal dominant manner; *KDM6A*-related KS is inherited in an X-linked manner.

Autosomal dominant inheritance: The proportion of KS caused by a de novo KMT2D pathogenic variant is unknown but is likely high based on clinical experience. In the rare case that a parent of the proband is affected, the risk to the sibs is 50%.

X-linked inheritance: If the mother of the proband has a KDM6A pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygous and may have features of KS.

Once the causative pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for KS are possible.

Diagnosis

Consensus clinical diagnostic criteria for Kabuki syndrome (KS) have been published [Adam et al 2019].

Suggestive Findings

KS **should be suspected** in individuals with any combination of the **five cardinal manifestations** as defined by Niikawa et al [1988], specific **structural anomalies**, and/or **functional differences**.

Cardinal manifestations

1. Typical facial features:
    - Long palpebral fissures with eversion of the lateral third of the lower eyelid
    - Highly arched and broad eyebrows with the lateral third displaying sparseness or notching
    - Short columella with depressed nasal tip
    - Large, prominent, and/or cupped ears
2. Skeletal anomalies:
    - Spine abnormalities including sagittal clefts, hemivertebrae, butterfly vertebrae, narrow intervertebral disc space, and/or scoliosis
    - Brachydactyly V
    - Brachymesophalangy

- Clinodactyly of fifth digits

3. Dermatoglyphic abnormalities: persistence of fetal fingertip pads

   Note: While absence of digital triradius c and/or d and increased digital loop and hypothenar loop patterns can be observed, this type of analysis is not routinely done in clinical practice in most centers.

4. Mild-to-moderate intellectual disability

5. Postnatal growth deficiency

Structural anomalies in KS can include the following:

- Ophthalmologic anomalies including ptosis and strabismus
- Ear pits (a potentially helpful diagnostic clue when seen with other typical findings)
- Cleft lip and/or palate
- Dental anomalies including widely spaced teeth and hypodontia
- Congenital heart defects
- Gastrointestinal anomalies including anal atresia
- Genitourinary anomalies including cryptorchidism in males

Functional differences can include the following:

- Hearing loss
- Feeding problems
- Endocrinologic abnormalities including isolated premature thelarche in females
- Increased susceptibility to infections and autoimmune disorders
- Seizures

Establishing the Diagnosis

The diagnosis of KS **is established** in a proband of any age with a history of infantile hypotonia, developmental delay, and/or intellectual disability AND one or both of the following [Adam et al 2019]:

- Typical dysmorphic features * at some point of life
- A heterozygous pathogenic (or likely pathogenic) variant in *KMT2D* or a heterozygous or hemizygous pathogenic (or likely pathogenic) variant in *KDM6A* (Table 1)

* Typical dysmorphic features include long palpebral fissures (a palpebral fissure measurement ≥2 SD above the mean for age) with eversion of the lateral third of the lower eyelid AND two or more of the following:

- Arched and broad eyebrows with the lateral third displaying notching or sparseness
- Short columella with depressed nasal tip
- Large, prominent, or cupped ears
- Persistent fingertip pads

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, concurrent or serial single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Kabuki syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Kabuki syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of Kabuki syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

Single-gene testing. Sequence analysis of *KMT2D* and *KDM6A* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected.

- Perform sequence analysis of *KMT2D* first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- Sequence analysis and gene-targeted deletion/duplication analysis of *KDM6A* can be considered next if no pathogenic variant is found.

Note: Affected individuals with classic features who have a mosaic heterozygous pathogenic variant in *KMT2D* have been reported; therefore, Lepri et al [2017] suggested that targeted next-generation sequencing may be a more appropriate method of mutation detection compared to traditional Sanger sequencing.

A multigene panel that includes *KMT2D*, *KDM6A*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of Kabuki syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Epigenetic signature analysis / methylation array. A distinctive epigenetic signature (disorder-specific genome-wide changes in DNA methylation profiles) in peripheral blood leukocytes has been identified in individuals with Kabuki syndrome [Aref-Eshghi et al 2020, Levy et al 2021]. Epigenetic signature analysis of a peripheral blood sample or DNA banked from a blood sample can therefore be considered to clarify the diagnosis in individuals with: (1) suggestive findings of Kabuki syndrome but in whom no pathogenic variant in *KDM6A or*

KMT2D has been identified via sequence analysis or genomic testing; or (2) suggestive findings of Kabuki syndrome and a *KDM6A or KMT2D* variant of uncertain clinical significance identified by molecular genetic testing. For an introduction to epigenetic signature analysis click here.

Table 1. Molecular Genetic Testing Used in Kabuki Syndrome (KS)

Gene [1, 2]	Proportion of KS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Identified by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
KDM6A	~3%-5% [6]	~80% [6]	~20% [7]
KMT2D	~75% [6]	>99% [8]	5 reported [9]
Unknown [10, 11]	NA		

NA = not applicable
1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Bögershausen et al [2016], Cocciadiferro et al [2018], Yap et al [2019]
7. Van Laarhoven et al [2015], Bögershausen et al [2016], Cocciadiferro et al [2018], Yap et al [2019]
8. Hannibal et al [2011], Li et al [2011], Micale et al [2011], Paulussen et al [2011], Banka et al [2012], Makrythanasis et al [2013], Bögershausen et al [2016]
9. Banka et al [2012], Riess et al [2012], Cocciadiferro et al [2018]
10. For approximately 30% of individuals with a clinical diagnosis of Kabuki syndrome, the genetic cause remains unknown. Therefore, locus heterogeneity for one or more as-yet-unidentified genes remains a possibility [Bögershausen & Wollnik 2013].
11. Further candidate genes for KS or conditions with features that overlap with KS include *RAP1A*, *RAP1B*, and *KDM6C* [Bögershausen et al 2016].

Clinical Characteristics

Clinical Description

This section summarizes findings in more than 400 individuals with a molecularly confirmed diagnosis of Kabuki syndrome (KS).

Growth

Individuals with KS typically exhibit normal growth parameters at birth.

- Infants with KS frequently exhibit failure to thrive for a variety of reasons (see Gastrointestinal).
- In adolescence and adulthood, more than half of individuals with KS develop obesity [Cheon & Ko 2015], which can exacerbate other health issues, such as recurrent patellar dislocation (see Musculoskeletal).
- Without treatment (see Endocrine, **Short stature**), postnatal growth deficiency is evident by age 12 months. Lack of a typical growth spurt during puberty exacerbates short stature [Schott et al 2016a]. Microcephaly may or may not accompany short stature.
- *KMT2D*-related KS-specific growth charts for weight, height, head circumference, and body mass index (BMI) by sex have been published [Ruault et al 2020]. It is unclear if individuals with *KDM6A*-related KS have the same growth pattern as those with *KMT2D*-related KS.

Ophthalmologic

Ocular findings occur in more than one third of individuals with Kabuki syndrome and include blue sclerae, strabismus, ptosis, coloboma, Marcus Gunn phenomenon (also referred to as jaw winking), and corneal abnormalities such as Peters anomaly.

- Rarely, more severe eye anomalies may occur, such as optic nerve hypoplasia, colobomatous microphthalmia, and anophthalmia [Chen et al 2014, McVeigh et al 2015].
- Functional visual problems may include difficulties with motor coordination, visuoperception, and visuomotor integration [Caciolo et al 2018]. Failure to detect and treat these issues can exacerbate learning issues [Lehman et al 2017].
- As a result of the everted lower eyelid, children with KS can demonstrate excessive tearing, which is not usually a significant problem. However, nocturnal lagophthalmos, which occurs in many children with KS, can predispose to corneal abrasion and scarring.

Ears and Hearing

Most individuals with KS have prominent and cup-shaped ears. Ear pits are also relatively common.

From a medical standpoint, chronic otitis media is a major cause of morbidity, including conductive hearing loss. It is not clear, however, whether this finding is related to an underlying susceptibility to infection or to the craniofacial abnormalities, such as palatal insufficiency.

Up to 50% of individuals with KS have hearing loss. Although chronic otitis media is the most common cause, sensorineural hearing loss can rarely occur and some individuals have progressive hearing loss. Inner-ear malformations including Mondini dysplasia, vestibular enlargement, aplastic cochlea and semicircular canals, and aqueductal enlargement have been reported. At least one individual with a clinical diagnosis of Kabuki syndrome who had profound progressive sensorineural hearing loss received a cochlear implant with a reported improvement in quality of life [Vesseur et al 2016].

Craniofacial

Cleft lip and/or palate affects approximately one third of individuals with KS. Submucous cleft palate may be underascertained [Paik & Lim 2016]. Almost three quarters of affected individuals have a high-arched palate. As with all children with palatal abnormalities, feeding difficulties, frequent otitis media, and speech difficulties are more common in this subset of affected individuals. A number of individuals have lower lip pits [Porntaveetus et al 2018].

The typical facial features (elongated palpebral fissures with eversion of the lateral third of the lower eyelid; arched and broad eyebrows; short columella with depressed nasal tip; and large, prominent, or cupped ears) are considered part of the diagnostic criteria of KS and are therefore present in almost all individuals who have a clinical diagnosis of KS. A majority of individuals with a molecularly confirmed diagnosis of KS are also found to have these characteristic facial features [Adam et al 2019].

Dental

A number of different dental anomalies in individuals with KS have been noted [Porntaveetus et al 2018]. Hypodontia is most common, with absent lateral upper incisors, absent lower incisors, ectopic upper six-year molars, and missing second premolars also being described. Abnormally shaped teeth (e.g., flathead-screwdriver-shaped appearance of the upper incisors), small teeth, widely spaced teeth, and malocclusion may also be seen.

Cardiovascular

Approximately 70% of individuals with KS have a congenital heart defect [Digilio et al 2017]. Many heart defects have been described in association with KS, but left-sided obstructive lesions, especially coarctation of the aorta, are the most common. Other defects may include (alone or in combination): septal defects, bicuspid aortic valve, mitral valve anomalies, conotruncal heart defects, and hypoplastic left heart syndrome. Hypertrophic cardiomyopathy and aortic root dilatation have been occasionally reported.

Respiratory

Eventration of the diaphragm has been rarely reported [Zarate et al 2012].

Laryngeal abnormalities may pose problems with anesthesia (see Management, Treatment of Manifestations).

Gastrointestinal

Feeding difficulties are quite common (~70%) and may be related to hypotonia, poor oromotor coordination, and swallowing difficulties [Cheon & Ko 2015] that may require nasogastric or gastrostomy tube placement. Many individuals with KS have gastroesophageal reflux.

Abnormalities involving the gastrointestinal system are not common in KS; however, the following may be seen rarely:

- Anorectal anomalies including imperforate anus, anovestibular fistula, and anteriorly placed anus [Siminas et al 2015]
- Congenital diaphragmatic hernia and eventration of the diaphragm
- Cholestasis from a variety of causes
- Chronic diarrhea from malabsorption and/or celiac disease

Genitourinary

Renal and urinary tract anomalies are seen in more than 25% of affected individuals [Courcet et al 2013]. Common renal findings include anomalies of kidney position and ascent (single fused kidneys, crossed fused renal ectopia) and renal dysplasia; hydronephrosis is the most common urinary tract finding. Other anomalies may include ureteropelvic junction obstruction and duplication of the collecting system. Hypospadias and cryptorchidism can occur in males [Bögershausen & Wollnik 2013].

Musculoskeletal

Joint hypermobility is seen in 50%-75% of individuals with KS. Joint dislocations, especially involving the hips, patellae, and shoulders, are not uncommon. As in most conditions with joint laxity, this finding improves with age.

- Variable degrees of scoliosis and kyphosis are seen and may be associated with vertebral anomalies (hemivertebrae, butterfly vertebrae, sagittal clefts).
- Persistent fetal fingertip pads are considered one of the five cardinal manifestations of KS and are therefore found in a large proportion of affected individuals [Adam et al 2019].
- Absence of digital triradius c and/or d and increased digital loop and hypothenar loop patterns can also be observed, although analysis for these features is not frequently done in current clinical practice.
- Other hand findings (brachydactyly V, brachymesophalangy, and clinodactyly of the 5th digits) can also be seen, but these features rarely lead to clinical issues and are used more as a clue to the diagnosis (see Suggestive Findings).

Endocrine

Premature thelarche in girls is the most common endocrine abnormality described (16%-41%) [Banka et al 2012]. This finding does not represent premature puberty and is likely to resolve with time.

Short stature, even absent growth hormone deficiency, has responded to growth hormone therapy without exacerbating disproportion:

- In a study by Schott et al [2016a], average adult height without growth hormone therapy was between 2.99 and 1.08 standard deviations (SD) below the mean in males and between 5.57 and 1.47 SD below the mean in females.
- After one year of growth hormone treatment, the average height improved from 2.40 to 1.69 SD below the mean [Schott et al 2016b].
- Those who initiated growth hormone therapy at an earlier age received the most benefit in terms of catch-up growth.
- After one year of growth hormone therapy, body proportions were not significantly affected.

Hyperinsulinism is likely underascertained in affected individuals and may be a presenting sign in neonates.

- Failure to recognize and treat hyperinsulinism in a timely fashion can lead to irreversible neurologic damage and exacerbate developmental issues.
- It is estimated that about 1% of neonates with hyperinsulinism have a diagnosis of Kabuki syndrome [Yap et al 2019].

Other. The following findings have been described in a small subset of individuals with KS in the literature:

- Adrenal insufficiency
- Combined pituitary hormone deficiency
- Diabetes insipidus
- Frank growth hormone deficiency
- Hypothyroidism
- Primary ovarian dysfunction
- True precocious puberty

Immunologic

Immune dysfunction including both humoral immune deficiency and autoimmune disease has been described [Lindsley et al 2016]. Clinical findings in affected individuals may mimic those seen in individuals with common variable immune deficiency.

- Frequent and recurrent infections, such as frequent sinopulmonary infections and recurrent otitis media, are found in a majority of affected individuals [Lin et al 2015].
- Hypogammaglobulinemia and IgA deficiency are common.
- Diminished B-cell populations have also been reported [Lindsley et al 2016].
- Autoimmune conditions such as vitiligo, immune thrombocytopenia (ITP), hemolytic anemia, and even diabetes mellitus have also been described in affected individuals, most commonly in childhood or adolescence [Brackmann et al 2013, Giordano et al 2014, Lindsley et al 2016].

Neurologic

Most children with KS are hypotonic and joint laxity may be a contributing factor.

- Hypotonia may contribute to significant feeding problems in infancy (see Growth). As with other conditions in which hypotonia is a feature, this finding tends to improve with age.

- Seizures are seen more frequently in KS (10%-39%) than in the general population and represent a spectrum of findings including infantile spasms [Liu et al 2015]. Good seizure control is generally achieved with standard anti-seizure medications.

Neuroimaging

Although most people with Kabuki syndrome undergo brain imaging at some point for indications such as seizures and/or developmental delay, major structural brain anomalies are rare. Reported findings have included the following [Banka et al 2015, Liu et al 2015, Teranishi et al 2018]:

- Cerebellar and brain stem atrophy
- Dandy-walker malformation
- Delayed myelination
- Mild ventriculomegaly

Note: Prior to the identification of the genetic causes of KS, symptomatic Chiari I malformation was reported in multiple affected individuals [Ciprero et al 2005]. This specific finding has not been highlighted in recent publications on individuals with a confirmed molecular diagnosis. However, this does not preclude symptomatic Chiari I malformation as a clinical feature in individuals with molecularly confirmed KS.

Development

Intellectual disability, usually in the mild to moderate range, has been reported in a majority of individuals; however, reports of rare individuals with pathogenic variants in either *KMT2D* or *KDM6A* who have IQ levels above 70 have been published [Lederer et al 2012, Cheon et al 2014, Lederer et al 2014, Morgan et al 2015, Butcher et al 2017, Lehman et al 2017, Sakata et al 2017, Caciolo et al 2018]. Most individuals with KS are able to speak and to ambulate.

- Average IQ scores in individuals with *KMT2D* pathogenic variants range from the high 50s to high 60s [Lehman et al 2017, Caciolo et al 2018]. Rare case reports of affected individuals who are basically nonverbal have been published [Lindgren et al 2013, Miyake et al 2013].
- Neuropsychiatric testing has identified deficits in both comprehension and production of verbal language, but this may be related, in part, to hearing, neurologic, orofacial, and cognitive deficits [Morgan et al 2015].
    - No specific language profile has been identified. However, all language subdomains including syntax, morphology, pragmatics, and semantics may be affected.
    - Dysarthria (reduced rate and stress, distorted pitch, harsh vocal quality, hypernasality, and imprecise consonants) has also been described.
    - On formal neuropsychiatric testing, individuals with KS tend to score better in the areas of vocabulary comprehension and working memory and score lower in the areas of nonverbal reasoning and processing speed [Lehman et al 2017].
- In terms of adaptive skills, individuals with KS have more difficulties with daily living than with communication.
- An educational environment that stresses audio-verbal learning over visual learning may beneficial (see Ophthalmologic).

Behavior

Individuals with KS tend to be described as pleasant and outgoing.

- Attention-deficit disorder and/or hyperactivity are present in a subset of affected individuals. Other behavioral findings including anxiety disorder, self-harm, and sleep disturbance have been rarely reported [Banka et al 2015, Caciolo et al 2018].

- Autism continues to be a rare but described finding in affected individuals [Paděrová et al 2016, Sertçelik et al 2016]. Whether this is truly part of the spectrum of KS or is a coincidental secondary diagnosis as a result of the frequency of autism spectrum disorders in the general population remains to be seen.

Benign Tumors

Pilomatricomas, benign tumors of the hair shaft that commonly occur on the head and neck, have been described rarely in those with Kabuki syndrome [Bernier et al 2017]. In most cases, removal by a dermatologist is sufficient.

Malignancies

Although pathogenic somatic variants in *KMT2D* and *KDM6A* have been seen in a variety of sporadic tumors [Huether et al 2014], malignancies (primarily as case reports) have only been described in a few individuals with KS. There is no clear evidence of a significant predisposition to the development of cancer in individuals with KS [Roma et al 2015, Karagianni et al 2016]. Therefore, no tumor screening protocol for individuals with KS has been developed.

Phenotype Correlations by Gene

KMT2D

- Those with a *KMT2D* pathogenic variant are more likely to have the distinctive Kabuki facial phenotype, which may reflect the fact that a portion of those without a *KMT2D* pathogenic variant may indeed have been misdiagnosed.
- In general, those with a *KMT2D* pathogenic variant are also more likely to have renal anomalies, feeding problems, premature thelarche in females, joint dislocations, and palatal anomalies than are those without a *KMT2D* pathogenic variant [Bögershausen & Wollnik 2013, Courcet et al 2013].

***KDM6A*.** The following are more common in individuals with a pathogenic variant in *KDM6A* [Banka et al 2015, Yap et al 2019]:

- Hypoglycemia as a result of hyperinsulinism
- Hypertrichosis
- Long halluces
- Large central incisors

Affected males are more likely to have moderate-to-severe developmental delay / cognitive impairment than are females, who may have mild-to-moderate intellectual disability. In general, females with a pathogenic variant in *KDM6A* tend to have milder features than affected males, despite the fact that *KDM6A* escapes X-chromosome inactivation [Banka et al 2015].

Genotype-Phenotype Correlations

KMT2D

- Individuals with KS caused by a heterozygous pathogenic missense variants in the terminal regions of *KMT2D* may have an increased risk for autoimmune disease [Lindsley et al 2016].
- Individuals with KS caused by a whole-gene deletion of *KMT2D* or pathogenic truncating variants that occur in the first half of the gene may have more severe intellectual disability [Lehman et al 2017].

Note: Individuals with a heterozygous pathogenic variant involving exons 38 or 39 potentially resulting in a gain of function may have some features similar to KS but otherwise have a phenotype that is noticeably different from KS (see Genetically Related Disorders).

KDM6A

- Based on small numbers of individuals with *KDM6A*-related KS, pathogenic variants at the 3' end of the gene are more common than those at the 5' end [Bögershausen et al 2016].
- Splice site variants, as compared to nonsense, missense, and small in/dels, are the most common type of single-nucleotide variant in individuals with *KDM6A*-related KS [Bögershausen et al 2016].

Penetrance

Penetrance for pathogenic variants in *KMT2D* appears to be complete; not enough information is available to make any conclusions regarding penetrance for those with pathogenic variants in *KDM6A*. Variable expressivity may lead to underascertainment of mildly affected individuals.

Prevalence

The prevalence of KS in Japan is estimated at 1:32,000 live births [Niikawa et al 1988]. The live birth prevalence outside Japan presumably approximates that seen in the Japanese population.

White et al [2004] calculated a minimum birth incidence of 1:86,000 in Australia and New Zealand.

Genetically Related (Allelic) Disorders

***KMT2D*-related disorder.** Individuals with a heterozygous pathogenic missense variant that involves exons 38 or 39 and that generally falls within an approximately 56-amino-acid region flanked by Leu3525 and Lys3583 have features that are not typical for KS [Baldridge et al 2020, Cuvertino et al 2020]. Reported individuals may have choanal atresia, hypoplastic or absent nipples, external and internal ear anomalies with hearing loss, brachial sinus abnormalities, interstitial lung disease, hypothyroidism, hypoparathyroidism, variable developmental delay/intellectual disability (although some have normal intelligence), and dysmorphic features that are distinct from what is typically seen in individuals with KS. Although these individuals may technically meet the international consensus diagnostic criteria for KS as a result of having a history of infantile hypotonia, developmental delay, and/or intellectual disability AND a heterozygous pathogenic variant in *KMT2D*, the reports by Baldridge et al [2020] and Cuvertino et al [2020] suggest that the phenotype is noticeably different from KS. Furthermore, a possible gain-of-function mechanism has been hypothesized for this phenotype, as opposed to a loss-of-function mechanism for KS.

***KDM6A*.** No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *KDM6A*.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of Kabuki Syndrome (KS)

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping w/KS	Distinguishing from KS
CHARGE syndrome	*CHD7*	AD	• Cleft palate • Congenital heart defects • Ocular coloboma • Growth restriction	In CHARGE syndrome: • Square face • Short, wide ear w/little or no earlobe • Prominent columella • Broad nasal root In KS: fingertip pads

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping w/KS	Distinguishing from KS
22q11.2 deletion syndrome	See footnote 1.	AD	• Cleft palate • Congenital heart defects • Urinary tract anomalies	In 22q11 deletion syndrome: • Short & narrow palpebral fissures w/hooded eyelids • Bulbous nasal tip • Small, C-shaped ears w/ overfolded superior &/or lateral helices
IRF6-related disorders [2]	*IRF6*	AD	• Cleft lip & palate • Lip pits	• *IRF6*-related disorders are not assoc w/atypical growth & development, cardiac malformations, or typical Kabuki syndrome facies. • Pterygia is not expected in KS.
Branchiootorenal (BOR) syndrome	*EYA1* *SIX5* *SIX1*	AD	• Ear pits • Cupped ears • Hearing loss • Renal anomalies	In BOR syndrome: • Otherwise normal craniofacies, growth, & development • Common renal anomalies incl renal hypoplasia &/or agenesis; (vs in KS: common renal anomalies incl hydronephrosis & malposition). • Branchial cleft cysts may be present (not reported in KS).
Hypermobile Ehlers-Danlos syndrome (EDS)	Unknown	AD	• Significant joint hypermobility (incl congenital hip dislocation & patellar dislocations) • Blue sclerae	Hypermobile EDS & Larsen syndrome are not assoc w/major malformations involving other organ systems or the typical minor anomalies seen in KS.
Larsen syndrome (See *FLNB*-Related Disorders.)	*FLNB*	AD		
X-chromosome anomalies / variety of other chromosome anomalies	NA	See footnote 3.	• Similar facial features • Congenital heart defects • Growth restriction	Chromosome anomalies can easily be distinguished from KS by chromosome analysis or CMA.
Hardikar syndrome (OMIM 612726)	Unknown		• Prolonged hyperbilirubinemia • Cleft lip & palate	Persons w/KS do not typically develop pigmentary retinopathy or sclerosing cholangitis, as seen in Hardikar syndrome.

AD = autosomal dominant; CHARGE = *c*oloboma, *h*eart defects, choanal *a*tresia, *r*etarded growth and development, *g*enital abnormalities, and *e*ar anomalies; CMA = chromosomal microarray; MOI = mode of inheritance

1. Deletion of genes within the DiGeorge chromosome region is the only genetic abnormality known to be associated with 22q11.2 deletion syndrome.

2. IRF6-related disorders span a spectrum from isolated cleft lip and palate and Van der Woude syndrome at the mild end to popliteal pterygium syndrome at the more severe end.

3. Dependent on anomaly

Management

Comprehensive management guidelines for Kabuki syndrome (KS) were developed in 2010 but have not been updated; these guidelines are available online (pdf).

Evaluations Following Initial Diagnosis

To establish the extent of disease and the needs of an individual diagnosed with KS, the following evaluations are recommended if they have not already been completed:

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Kabuki Syndrome

System/Concern	Evaluation	Comment
Growth	Measurement of height, weight, & head circumference	• Consider plotting growth on *KMT2D*-related KS-specific growth charts. [1] • Growth restriction & poor weight gain are common sequela of feeding difficulties.
Ophthalmologic	Ophthalmology eval	For assessment of strabismus, refractive error, ptosis, & corneal abnormalities
Hearing	Baseline audiology eval	To assess for conductive &/or sensorineural hearing loss
Mouth	Directed evaluation of the palate for palatal anomalies	Consider referral to a craniofacial specialist if palatal anomalies are suspected.
	Consider dental eval for those age >3 yrs.	
Cardiac	Echocardiogram w/visualization of the aortic arch	To assess for congenital heart defects incl coarctation of the aorta
	Consider EKG.	If arrhythmia is suspected
Respiratory	Consider chest radiographs to assess for diaphragmatic eventuation.	In those w/respiratory issues, chronic cough, or recurrent pneumonia
Gastrointestinal/ Feeding	Assess nutritional status, feeding, GERD.	• Consider assessment by feeding team &/or VFSS for those w/suspected dysphagia. • Infants may have FTT; adolescents & adults may have obesity.
Genitourinary	Baseline renal ultrasound	To evaluate for renal anomalies & hydronephrosis
	Physical exam for hypospadias &/or cryptorchidism in males	
Musculoskeletal	Consider radiographs of the spine in those w/scoliosis.	To assess for vertebral anomalies
Endocrinologic	Assess for hyperinsulinism. [2]	In neonates & infants w/persistent hypoglycemia
	Assess for hypothyroidism & growth hormone deficiency. [3]	In those w/abnormal growth velocity
Immunologic	T cell count, T cell subsets, & serum immunoglobulin levels at time of diagnosis or at age 1 yr (whichever is later)	Refer to immunologist if: • Levels are abnormal; or • Person has history of recurrent infections.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	EEG	In those w/suspected seizures
	Head MRI	To evaluate for: • Structural brain malformation in those w/ seizures • Chiari I malformation in those w/ suggestive symptoms [4]
Psychiatric/ Behavioral	Neuropsychiatric eval	Screen persons age >12 mos for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD.
Miscellaneous/ Other	Developmental assessment	Evaluate motor, speech-language, general cognitive, & vocational skills.
	Consultation w/clinical geneticist &/or genetic counselor	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; FTT = failure to thrive; GERD = gastroesophageal reflux disease; KS = Kabuki syndrome; VFSS = videofluoroscopic swallowing study

1. *KMT2D*-related KS-specific growth charts have been published [Ruault et al 2020]. While these charts were developed using data from individuals with *KMT2D*-related KS, individuals with *KDM6A*-related KS or with KS and no identifiable pathogenic variant are more likely to follow the same growth pattern as children with *KMT2D*-related KS than a typical growth pattern. Plotting such individuals on the *KMT2D*-related KS-specific growth charts may give the provider a better idea of their true growth potential than plotting these individuals on a typical growth chart, which may accentuate or exaggerate their growth deficiency compared to others with KS.

2. This may include collection of a "critical sample," such as obtaining plasma levels of insulin, free fatty acids, beta-hydroxybutyrate, and glycemic response to glucagon during a period of low plasma glucose [Yap et al 2019].

3. Thyroid function tests may include free T4 and TSH levels. Assessment for growth hormone deficiency can be challenging and is best directed by an endocrinologist. Tests may include measurement of insulin-like growth factor 1 (IGF-1) and IGF binding protein 3, in addition to consideration of a growth hormone stimulation test using either arginine or clonidine [Schott et al 2016b].

4. Symptoms may include headaches, ocular disturbances, otoneurologic disturbances, lower cranial nerve signs, cerebellar ataxia, spasticity, or seizures.

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Kabuki Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Strabismus, refractive error, ptosis, lagophthalmos	Standard treatment per ophthalmologist	
Hearing loss	Consider: • Pressure-equalizing tubes for those w/ conductive hearing loss; • Hearing aids for those w/sensorineural hearing loss. [1]	Refer to an ENT specialist & audiologist; see Genetic Hearing Loss Overview.
Cleft lip &/or palate	Standard treatment	• Management through a specialized craniofacial clinic is ideal. • The palate may be shorter, which can lead to velopharyngeal insufficiency after typical cleft repair.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Dental anomalies	Orthodontic referral if hypodontia or significant malocclusion is noted	
Congenital heart defects &/or arrhythmia	Standard treatment per cardiologist	It is unclear whether risk for aortic aneurysm is ↑; however, if catheterization or angioplasty is being considered, a potential ↑ risk of aortic aneurysm should be communicated to treating team.
Feeding difficulties / GERD	Standard treatment, which may incl thickening feeds & appropriate positioning after meals in infants & toddlers	Pharmacologic treatment for GERD may be considered.
	Consider gastrostomy tube.	In those w/severe feeding difficulties &/or poorly coordinated suck & swallow
Chronic diarrhea	Refer to gastroenterologist.	Consider eval for malabsorption &/or celiac disease.
Hypospadias/ Cryptorchidism	Standard treatment per urologist	
Hyperinsulinism & hypothyroidism	Standard treatment per endocrinologist	
Short stature	Consider growth hormone therapy.	Refer to endocrinologist.
Recurrent infections	Intravenous immunoglobulin therapy may be considered in those w/documented immunoglobulin deficiency.	Refer to immunologist.
Seizure disorder	Standard anti-seizure treatment per neurologist	
Short stature	Growth hormone treatment may be considered. [2]	Refer to endocrinologist.
Premature thelarche	No treatment warranted if no other signs of premature puberty	
Need for anesthesia	Care in positioning during intubation because of joint laxity, which can affect the cervical spine	Educate regarding potential structural airway anomalies that could make intubation difficult.

1. Cochlear implants can also be considered, as per ENT and audiologist recommendations.
2. Schott et al [2016a]

See Therapies Under Investigation for discussion of histone deacetylase inhibitors and ketogenic diet as hypothesized treatments for individuals with KS. Currently neither of these therapies is recommended as a primary treatment for individuals with KS, outside of a clinical trial.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

Neurodevelopmental therapies should target language and motor abilities to improve daily living skills and behaviors [Caciolo et al 2018].

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility.
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding because of poor oral motor control.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat ADHD, when necessary.

Surveillance

Table 5. Recommended Surveillance for Individuals with Kabuki Syndrome

System/Concern	Evaluation	Frequency
Growth	Measurement of at least height & weight [1]	At each appointment
Ophthalmologic	Ophthalmology or optometry to assess vision	At least annually
Hearing	Hearing assessment	
Musculoskeletal	Clinical eval for scoliosis	At each appointment until skeletal maturity
Endocrinologic	Thyroid function tests	Every 2-3 yrs
Immunologic	Assessment of complete blood count	
Miscellaneous/ Other	Monitor developmental progress & educational needs.	At each visit during childhood & adolescence

1. Adolescents and adults may develop obesity.

Agents/Circumstances to Avoid

In those with joint laxity, activities that increase the risk of joint damage (e.g., bouncing on a trampoline) should be avoided.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Based on the function of *KMT2D* and *KDM6A* as regulators of chromatin expression (see Molecular Genetics), it has been hypothesized that histone deacetylase inhibitors (HDACi) could have a beneficial effect on individuals with Kabuki syndrome. Bjornsson et al [2014] created a mouse model of KS and found that treatment with HDACi normalized the structural and functional differences seen in certain brain areas in these affected mice, leading to improved neurogenesis and memory. This has yet to be tested in humans with KS, but clinical trials based on these mouse studies are in the planning phase.

Since ketosis acts as an endogenous HDACi, others have hypothesized that placing individuals with KS on a ketogenic diet could improve their cognitive issues [Benjamin et al 2017]. This is NOT currently a recommended treatment for KS, although some families and physicians have trialed this diet independently. Since the ketogenic diet as a treatment for KS has not been studied as part of a clinical trial, no results of these types of experimental treatments are available in the peer-reviewed literature.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

KMT2D-related Kabuki syndrome is inherited in an autosomal dominant manner.

KDM6A-related Kabuki syndrome is inherited in an X-linked manner.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- A minority of individuals diagnosed with *KMT2D*-related KS have an affected parent.
- A proband with *KMT2D*-related KS may have the disorder as the result of a *de novo* pathogenic variant. Because simplex cases (i.e., a single occurrence in a family) have not been evaluated sufficiently to determine if the pathogenic variant was *de novo*, the proportion of *KMT2D*-related KS caused by a *de novo* pathogenic variant is unknown. However, based on clinical experience, the proportion of *KMT2D*-related KS caused by a *de novo* variant is likely high.
- Recommended evaluations for the parents of a proband include:
  - Molecular genetic testing if the pathogenic variant in the proband has been identified. If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Although no instances of germline mosaicism have been reported, it remains a possibility.
  - If the pathogenic variant in the proband is not known, clinical evaluation of the proband's parents, including a thorough physical examination by a clinical geneticist, is indicated to evaluate for any phenotypic features consistent with KS.
- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected [Banka et al 2013, Lepri et al 2017].

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
  - If a parent of the proband is affected, the risk to the sibs is 50%.
  - If the *KMT2D* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism.
- If both parents are clinically unaffected but have not been tested for the *KMT2D* pathogenic variant (or molecular genetic testing is not appropriate because a pathogenic variant has not been identified in the proband), the risk to the sibs of a proband appears to be low.

Offspring of a proband. Each child of an individual with *KMT2D*-related Kabuki syndrome has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at risk.

X-Linked Inheritance – Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *KDM6A* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *KDM6A* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo KDM6A* pathogenic variant, in which case the mother is not a heterozygote. About 80% of affected males represent simplex cases [Bögershausen et al 2016].

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a *KDM6A* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and may have features of KS, although features in females tend to be milder than those in males (see Phenotype Correlations by Gene).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *KDM6A* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of maternal germline mosaicism.

Offspring of a male proband. Because of the small number of affected males and the relatively recent identification of *KDM6A* as a gene implicated in KS, no reports in the literature have described an affected male who has reproduced.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes for the pathogenic variant and the aunts' offspring, depending on their sex, may be at risk of being heterozygotes (carriers) for the pathogenic variant and/or being affected.

Heterozygote detection. Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband. Note: Females who are heterozygous for this X-linked disorder can have a range of clinical manifestations (see Phenotype Correlations by Gene).

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or are carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for Kabuki syndrome are possible.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **All Things Kabuki**
  www.allthingskabuki.org
- **Kabuki Syndrome Foundation**
  Northbrook IL 60065
  Email: info@kabukisyndromefoundation.org
  www.kabukisyndromefoundation.org
- **SAKKS: Supporting Aussie Kids with Kabuki Syndrome**
  Email: petal@sakks.org
  www.sakks.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Kabuki Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
KDM6A	Xp11.3	Lysine-specific demethylase 6A	UTX @ LOVD	KDM6A	KDM6A
KMT2D	12q13.12	Histone-lysine N-methyltransferase 2D	KMT2D database	KMT2D	KMT2D

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Kabuki Syndrome (View All in OMIM)

147920	KABUKI SYNDROME 1; KABUK1
300128	LYSINE DEMETHYLASE 6A; KDM6A
300867	KABUKI SYNDROME 2; KABUK2
602113	LYSINE-SPECIFIC METHYLTRANSFERASE 2D; KMT2D

Molecular Pathogenesis

Both KDM6A and KMT2D work as part of a complex of proteins termed the ASCOM complex. The function of this complex is to remove repressive epigenetic marks and deposit activating methylation marks on chromatin. This then recruits RNA polymerase II complex, resulting in an activated chromatin state [Bögershausen & Wollnik 2013]. KDM6A is an H3K27 demethylase that removes repressive polycomb-derived methylation marks [Agger et al 2007, Hong et al 2007]. KMT2D is a histone 3 lysine 4 (H3K4) N-methyltransferase that specifically

modifies the lysine residue at the fourth amino acid position of the histone H3 protein, catalyzing the conversion from nonmethylated to mono-, di-, and trimethylated H3K4. The SET domain of KMT2D is responsible for the methyltransferase activity [Kouzarides 2007]. However, most target genes (and their respective functions) of the regulatory pathways in which KMT2D and KDM6A play a role are not yet known.

Mechanism of disease causation. Loss of function of KDM6A or KMT2D causes Kabuki syndrome.

***KDM6A*- or *KMT2D*-specific laboratory considerations.** Of note, *KDM6A* escapes X-chromosome inactivation.

Cancer and Benign Tumors

***KDM6A*.** Somatic variants in this gene have been described most commonly in urothelial carcinoma, T-cell acute lymphoblastic leukemia, and breast cancer, although a variety of cancers may contain somatic variants in this gene [Schulz et al 2019].

***KMT2D*.** Deleterious somatic variants in this gene have been described in a variety of different cancers including central nervous system, gastrointestinal, and hematopoietic malignancies [Ford & Dingwall 2015, Rao & Dou 2015].

Chapter Notes

Revision History

- 25 April 2024 (ma) Revision: *KMT2D*-related KS-specific growth charts published [Ruault et al 2020]
- 15 September 2022 (sw) Revision: epigenetic signature analysis (Establishing the Diagnosis, Option 2)
- 15 July 2021 (ma) Revision: added *KMT2D*-related disorder (Genetically Related Disorders; Genotype-Phenotype Correlations) and associated references (Cuvertino and Baldridge)
- 21 October 2019 (aa) Revision: X-linked inheritance added to Summary
- 28 January 2019 (sw) Comprehensive update posted live
- 16 May 2013 (aa) Revision: mutations in *KDM6A* associated with Kabuki syndrome; large *KMT2D* (formerly *MLL2*) deletions/duplications reported as causative of Kabuki syndrome; addition of proposed phenotypic scoring system
- 1 September 2011 (me) Review posted live
- 8 July 2011 (ma) Original submission

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