Kabuki Syndrome

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SUMMARY

Disease characteristics. Kabuki syndrome (KS) is characterized by 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; 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 is primarily established by clinical findings. Molecular genetic testing for MLL2, the only gene in which mutations are known to cause KS, is available on a clinical basis.

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 antiepileptic treatment for seizures.

Prevention of secondary complications: Prophylactic antibiotic treatment prior to and during any procedure (such as 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. KS is inherited in an autosomal dominant manner. The proportion of KS caused by de novo mutations is unknown, but is likely high based on clinical experience. Each child of an individual with KS has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing mutation in an affected family member is known.

DIAGNOSIS

Clinical Diagnosis

Consensus clinical diagnostic criteria for Kabuki syndrome (KS) have not been established. Individuals with this condition have characteristic facial features, in addition to a variety of congenital anomalies, which suggest the diagnosis. Listed below are the **five cardinal manifestations** as defined by Niikawa et al [1988].

1. Typical facial features [Niikawa et al 1988, Wilson 1998, Armstrong et al 2005, Schrander-Stumpel et al 2005, Hannibal et al 2011]:

- Elongated palpebral fissures with eversion of the lateral third of the lower eyelid
- Arched and broad eyebrows with the lateral third displaying sparseness or notching
- Short columella with depressed nasal tip
- Large, prominent, or cupped ears

2. Skeletal anomalies:

- Spinal column abnormalities, including sagittal cleft vertebrae, 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 [Matsumoto & Niikawa 2003, Armstrong et al 2005, Schrander-Stumpel et al 2005]:

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

Functional differences can include the following:

- Increased susceptibility to infections and autoimmune disorders
- Seizures

- Endocrinologic abnormalities, including isolated premature thelarche in females
- Feeding problems
- Hearing loss

Molecular Genetic Testing

Gene. MLL2 is the only gene in which mutations are known to cause KS.

Evidence for possible locus heterogeneity. No other loci are known to be involved in causing KS. However, the moderate mutation detection rate (see Sequence analysis) implies possible locus heterogeneity for one or more as-yet unidentified genes [Hannibal et al 2011, Li et al 2011, Micale et al 2011, Paulussen et al 2011].

Clinical testing

- *Sequence analysis*. MLL2 coding region sequencing detects mutations in about 56%-76% of individuals with a clinical diagnosis of KS [Hannibal et al 2011, Li et al 2011, Micale et al 2011, Paulussen et al 2011].
- *Deletion/duplication testing* is available clinically. However, the usefulness of such testing has not been demonstrated, as no large (i.e., exonic or whole-gene) deletions or duplications involving MLL2 have been reported as causative of KS.

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method[1]	Test Availability
MLL2	Sequence analysis	Sequence variants[3]	56%-76%	Clinical Testing
	Deletion / duplication analysis[2]	Exonic or whole-gene deletions	Unknown[4]	

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

Test Availability refers to availability in the GeneTests Laboratory Directory. GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

[1.] The ability of the test method used to detect a mutation that is present in the indicated gene

[2.] Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site mutations.

[3.] Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; a variety of methods including quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), or targeted array GH (gene/segment-specific) may be used. A full array GH analysis that detects deletions/duplications across the genome may also include this gene/segment. See array GH.

[4.] No deletions/duplications reported to date.

Interpretation of test results

- Given the current mutation detection rate, failure to identify a mutation would not preclude the diagnosis of KS.
- For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm/establish the diagnosis in a proband

- The diagnosis is primarily established by clinical findings.
- Molecular testing (sequence analysis) of MLL2 confirms the diagnosis in a majority of cases.
- Array comparative genomic hybridization (aCGH) can be considered to exclude cytogenetic abnormalities that produce phenotypic overlap with KS.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Note: It is the policy of *GeneReviews* to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in MLL2.

CLINICAL DESCRIPTION

Natural History

This section summarizes findings in more than 350 individuals with Kabuki syndrome (KS) [Niikawa et al 1988, Wilson 1998, Kawame et al 1999, Matsumoto & Niikawa 2003, Armstrong et al 2005, Schrander-Stumpel et al 2005].

Growth and feeding. Neonates with KS exhibit normal growth parameters. However, postnatal growth retardation is relatively common (35%-81%). Microcephaly may or may not accompany short stature. Growth hormone deficiency has been reported (see Endocrine) but is not common.

Feeding difficulties are quite common (~70%); however, severity is variable [Kawame et al 1999]. Many individuals with KS have gastroesophageal reflux. Others require gastrostomy tube placement for poorly coordinated suck and swallow. Consequently, some infants with KS exhibit failure to thrive.

Development and behavior. In their series of 62 affected individuals, Niikawa et al [1988] reported that intellectual disability, usually in the mild to moderate range, was a cardinal feature, seen in 92%. As more individuals with this condition have been recognized and reported, however, some authors have suggested that as many as one sixth have normal intelligence [Matsumoto & Niikawa 2003]. A more recent review in which authors excluded reports judged to be less thorough or less diagnostically clear calculated an overall frequency of intellectual disability closer to the original estimate [Schrander-Stumpel et al 2005].

Most individuals with KS are able to speak and to ambulate. Rare individuals are non-ambulatory but able to speak; others are nonverbal with no significant motor impairment [Kawame et al 1999]. Vaux et al [2005] report an average age to walk unassisted of 20 months with a range of 15 to 30 months in 15 individuals with Kabuki syndrome. In this series, single words were spoken by 21 months on average, with a range of 10 to 30 months. Thus far, no factors allow for early prognostication.

No clear pattern of specific developmental difficulties has emerged. Limited evidence suggests that tasks such as grammatic construction are of particular difficulty for individuals with KS [Defloor et al 2005]. Mervis et al [2005] performed standardized neuropsychological testing on 11 children and adolescents with Kabuki syndrome and reported relative strengths in verbal and nonverbal reasoning, with relative weakness in visuospatial skills. Receptive language skills were also greatly superior to expressive skills in this study; in contrast, other authors have reported superior expressive language [Vaux et al 2005].

Individuals with KS tend to be described as pleasant and outgoing. In their series of 11 children and adolescents, Mervis et al [2005] report that, overall, the participants' behavioral difficulties did not surpass those expected for their chronologic age.

Autism is a rare but described finding. Ho & Eaves [1997] reported four males with variable cognitive abilities, three of whom had features within the autism spectrum ranging from pervasive developmental disorder to autistic-like to autistic disorder. It is not clear that autism is present at a level above that seen in the general population. As KS becomes more widely recognized, the true incidence of social and communicative difficulties will become apparent.

Neurologic. Many children with KS are hypotonic (25%-89%). Significant joint laxity may be a contributing factor. As with other conditions in which hypotonia is a feature, this finding improves with time.

Seizures are seen more frequently in KS (10%-39%) than in the general population. Good seizure control is generally achieved with medication.

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. Symptomatic Chiari I malformation, however, has been reported in multiple affected individuals [Ciprero et al 2005].

Cardiovascular. Approximately 40%-50% of individuals with KS have congenital heart defects. Left-sided obstructive lesions, especially coarctation of the aorta, are common; interestingly, these lesions are rare in the general population. Septal defects are also common [Kawame et al 1999, Armstrong et al 2005].

Endocrine. Premature thelarche in girls is the most common endocrine abnormality described (7%-50%). This finding does not represent premature puberty and is likely to resolve with time.

Hypoglycemia, congenital hypothyroidism, and growth hormone deficiency are rarely reported findings.

Ophthalmologic. Ocular findings occur in more than one third of individuals with Kabuki syndrome and include blue sclerae, strabismus, ptosis, coloboma, and corneal abnormalities such as Peters anomaly. Optic nerve hypoplasia, cataracts, Duane anomaly, pigmentary retinopathy, and Marcus Gunn phenomenon (also referred to as jaw winking) can also be seen [Ming et al 2003]. Severe visual impairment, however, is rare [Kawame et al 1999].

As a result of the everted lower eyelid, children with KS can demonstrate excessive tearing, which is not usually a significant problem. On the other hand, nocturnal lagophthalmos, which occurs in many children with KS, can predispose to corneal abrasion and scarring [Toriello & Droste 2003].

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 [Matsumoto & Niikawa 2003].

Up to 40% of individuals with KS have hearing loss. Although chronic otitis media is the most common cause, sensorineural hearing loss can rarely occur. Inner ear malformations including Mondini dysplasia, vestibular enlargement, aplastic cochlea and semicircular canals, and aqueductal enlargement have been reported [Tekin et al 2006].

Craniofacial. Cleft lip and/or palate affects approximately one third of individuals with KS. Submucous cleft palate may be underascertained [Iida et al 2006]. 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 with lower lip pits have been reported [Matsumoto & Niikawa 2003].

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.

Dental. A number of different dental anomalies in individuals with KS have been noted. Hypodontia is most common, with missing lateral and central incisors as well as premolars [Matsune et al 2001]. Abnormally shaped teeth, small teeth, widely-spaced teeth, and malocclusion have also been described.

Gastrointestinal. Abnormalities involving the gastrointestinal system are not common in KS; however, anorectal anomalies including imperforate anus, anovestibular fistula, and anteriorly placed anus have been reported in a number of individuals, primarily in females [Matsumura et al 1992]. Congenital diaphragmatic hernia and eventration of the diaphragm have also been described [Niikawa et al 1981, Kawame et al 1999]. The risk of neonatal cholestasis from a variety of causes is increased [Isidor et al 2007].

Genitourinary. Renal and urinary tract anomalies are seen in more than 25% of affected individuals [Matsumoto & Niikawa 2003]. Common renal findings include anomalies of kidney position and ascent (single fused kidneys, crossed fused renal ectopia), ureteropelvic junction obstruction, duplication of the collecting system, and hydronephrosis [Kawame et al 1999]. Hypospadias, cryptorchidism, and (more rarely) micropenis can occur in males; females can demonstrate hypoplastic labia [Armstrong et al 2005].

Musculoskeletal. Joint hypermobility is seen in 50%-75% of individuals with KS [Kawame et al 1999, Matsumoto & Niikawa 2003]. 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) [Niikawa et al 1988].

Persistent fetal fingertip pads are considered one of the five cardinal manifestations of KS and are therefore found in a large proportion of individuals with a clinical diagnosis of KS.

Immunologic. Immune dysfunction has been described, mostly in adolescents. Hoffman et al [2005] found that 16 of 19 individuals with KS had some form of hypogammaglobulinemia. Low levels of serum IgA have been

reported in association with idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and recurrent sinopulmonary infections [Kawame et al 1999, Ming et al 2005].

Genotype-Phenotype Correlations

Because the gene that is mutated in Kabuki syndrome was only identified in 2011, few studies to date have investigated genotype-phenotype correlation.
Comparisons of the clinical features of MLL2 mutation-positive versus MLL2 mutation-negative individuals with a clinical diagnosis of Kabuki syndrome have found little difference.

- In general, those with an MLL2 mutation are more likely to have renal anomalies and short stature than are those without an MLL2 mutation [Hannibal et al 2011, Li et al 2011, Paulussen et al 2011].
- Not surprisingly, those with an MLL2 mutation are more likely to have the distinctive Kabuki facial phenotype, which may reflect the fact that a portion of those without an MLL2 mutation may indeed have been misdiagnosed.

Penetrance

Penetrance appears to be complete. Variable expressivity may lead to underascertainment of mildly affected individuals.

Anticipation

To date, anticipation has not been observed.

Prevalence

Initially, the majority of individuals reported with KS were Japanese; the prevalence in Japan is estimated at approximately 1:32,000 [Niikawa et al 1988].

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

KS has been reported in almost all ethnic groups; its prevalence outside Japan presumably approximates that seen in the Japanese population.

DIFFERENTIAL DIAGNOSIS

For current information on availability of genetic testing for disorders included in this section, see Gene Tests Laboratory Directory. —ED.

Disorders that have overlapping features with Kabuki syndrome (KS) include the following:

- CHARGE syndrome, particularly cleft palate, heart defects, coloboma, and growth retardation. However, the typical facial features and prominent fingertip pads in KS are distinct from those in CHARGE syndrome. Mutations in CHD7 are causative; inheritance is autosomal dominant.
- 22q11 deletion syndrome, particularly cleft palate, congenital heart defects, and urinary tract anomalies. However, the different characteristic facial features seen in the two conditions should distinguish them.
- IRF6-related disorders (Van der Woude syndrome and popliteal pterygium syndrome), particularly cleft lip and palate, cleft palate, and lip pits. Individuals with IRF6-related disorders do not have atypical

growth and development, cardiac malformations, or the typical Kabuki syndrome facies. Pterygia are not expected in people with KS.

- Branchiootorenal (BOR) syndrome, particularly ear pits, cupped ears, hearing loss, and renal anomalies. However, individuals with BOR syndrome have otherwise normal craniofacies, normal growth, and normal development. In BOR syndrome the common renal anomalies are renal hypoplasia and/or agenesis, while in KS renal anomalies commonly include hydronephrosis and malposition. Branchial cleft cysts may be present in BOR but have not been reported in KS.
- Ehlers-Danlos syndrome, hypermobility type or Larsen syndrome (see FLNB-Related Disorders), particularly significant joint hypermobility (including congenital hip dislocation and patellar dislocations) and blue sclerae. These conditions are not associated with major malformations involving other organ systems or the typical minor anomalies seen in KS.
- X-chromosome anomalies and a variety of other chromosome anomalies, which can present with similar facial features, congenital heart defects, and growth retardation. These can easily be distinguished from KS by a chromosome analysis or chromosomal microarray (CMA).
- Hardikar syndrome (OMIM 612726), particularly prolonged hyperbilirubinemia with cleft lip and palate. However, individuals with KS do not typically develop pigmentary retinopathy or sclerosing cholangitis, as seen in Hardikar syndrome.

Note to clinicians: For a patient-specific 'simultaneous consult' related to this disorder, go to SimulConsult, an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

MANAGEMENT

Evaluations Following Initial Diagnosis

To establish the extent of disease and the needs of an individual diagnosed with Kabuki syndrome (KS), the following evaluations are recommended:

- Height, weight, and head circumference are measured and plotted on standard growth charts. Evaluation for a hormone deficiency, including hypothyroidism or growth hormone deficiency, is recommended in children with abnormal growth velocity.
- If feeding problems are severe and/or failure to thrive is apparent, an esophageal pH probe study can be considered. A barium swallow study may assist in determining whether the suck and swallow mechanism is normal.
- Evaluation for developmental milestones is recommended and referral for formal developmental evaluation is indicated if delays are identified.
- A physical therapy evaluation is indicated in those children with KS who exhibit hypotonia.
- Evaluation by a neurologist is recommended in those individuals with suspected seizure activity.
- Brain imaging at the time of diagnosis (if not already performed) is recommended in those with headaches, ocular disturbances, otoneurologic disturbances, lower cranial nerve signs, cerebellar ataxia, spasticity, or seizures to evaluate for a Chiari 1 malformation or for a brain malformation.
- As the incidence of cardiac malformations is high, echocardiogram with good visualization of the aortic arch is indicated in all individuals at the time of diagnosis. Referral to a pediatric cardiologist for management should be considered if a cardiac defect is present.
- Because of the frequency of ocular findings, formal ophthalmologic examination at the time of diagnosis is recommended for all individuals with KS.

- A directed evaluation of the palate at the time of diagnosis is indicated. Individuals with cleft lip, cleft palate, submucous cleft palate, or any evidence of velopharyngeal insufficiency should be referred for otorhinolaryngology evaluation.
- A directed physical examination to evaluate for evidence of gastrointestinal abnormalities is indicated in neonates with KS. Evidence of cholestasis should prompt a full workup, as it would in any other child. By recognizing that eventration of the diaphragm is seen in this condition, the medical care provider can avoid further evaluation for possible phrenic nerve paralysis.
- Because of the frequency of renal/urinary tract anomalies, renal ultrasound examination is indicated in all individuals with KS at the time of diagnosis. Referral to a nephrologist and/or urologist is recommended for those individuals with hydronephrosis. Referral to a urologist is indicated in those individuals with cryptorchidism.
- Referral for evaluation by an orthopedic surgeon in those children with congenital dislocation of the hip(s) and other joints is recommended.
- Spine radiographs at the time of diagnosis are indicated in all individuals with KS. If scoliosis is noted and/or vertebral abnormalities are detected, orthopedic evaluation should be considered.
- Obtaining T cell count, T cell subsets, and serum immunoglobulin levels in all individuals with KS at the time of diagnosis or at one year of age (whichever comes second) is recommended. An evaluation by an immunologist is indicated if the levels are abnormal or if the affected individual has a history of recurrent infections.
- Medical genetics consultation is appropriate.

Comprehensive management guidelines are also available from DYSCERNE. See Guidelines (pdf).

Treatment of Manifestations

Thickened feedings and appropriate positioning after meals may improve reflux symptoms.

Gastrostomy tube placement is typically considered in those with severe feeding difficulties, especially if a poorly coordinated suck and swallow are noted.

Thorough psychoeducational testing is indicated for all children who exhibit cognitive difficulties in order to determine strengths and weaknesses and to tailor special education services. Special education services are tailored to address strengths and weaknesses for each child with KS since no characteristic pattern of disabilities has been identified.

Formal evaluation by a developmental pediatrician or psychiatrist may be helpful in those children who exhibit features suggestive of autism spectrum disorders, since educational interventions may be influenced by the result.

Standard antiepileptic treatment is efficacious in treating seizures in individuals with KS.

Evidence of sensorineural hearing loss is typically followed up with referral to an otorhinolaryngologist and imaging to screen for inner ear anomalies.

Persistent, unexplained head and neck pain or other evidence of intracranial abnormality could be secondary to Chiari I malformation and is a clear indication for brain imaging in affected individuals.

Monitoring for nocturnal lagophthalmos by parents or caregivers is recommended. If present, evaluation by an ophthalmologist is indicated.

A dental evaluation as a toddler is indicated in every child with KS. Referral for orthodontic assessment should be arranged if abnormalities such as hypodontia or significant malocclusion are noted at any point in childhood.

Individuals with documented immunoglobulin deficiency may benefit from scheduled intravenous immunoglobulin infusions.

Treatment of premature thelarche is not warranted unless other signs of premature puberty are apparent.

At least one individual has shown no change in linear rate of growth when treated with human growth hormone [Kawame et al 1999].

Prevention of Secondary Complications

As with many cases of congenital heart disease, prophylactic antibiotic treatment may be indicated prior to and during any procedure (e.g., dental work) that could lead to bacteremia.

Surveillance

The following are recommended for individuals with KS:

- Frequent monitoring of height, weight, and head circumference (at each well-child visit and, at a minimum, yearly)
- Evaluation of developmental milestones at each well child visit; referral for formal developmental evaluation if delays are identified
- Following prepubertal girls expectantly for possible premature thelarche, so that the healthcare provider can reassure parents if this finding becomes apparent
- Annual monitoring of vision
- Annual hearing evaluation
- Expectant monitoring for otitis media in children. An ear examination is indicated at all well-child visits; prompt evaluation for all children with symptoms suggestive of otitis media.
- Regular follow up by an immunologist for those with abnormal immunologic studies or those who have recurrent infections

Testing of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the Gene Tests Clinic Directory.

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

GENETIC COUNSELING

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Kabuki syndrome (KS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- A minority of individuals diagnosed with KS have an affected parent.
- A proband with KS may have the disorder as the result of a new mutation. Because simplex cases (i.e., a single occurrence in a family) have not been evaluated sufficiently to determine if the mutation was de novo, the proportion of KS caused by de novo mutations is unknown. However, based on clinical experience, the proportion of KS caused by de novo mutations is likely high.
- If the disease-causing mutation found in the proband cannot be detected in leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or a de novo mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.
- If the proband's disease-causing mutation has been identified, both parents can be offered testing. If no disease-causing mutation is found in the proband, clinical evaluation of the proband's parents, including a thorough physical examination by a medical 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 mutation first occurred s/he may have somatic mosaicism for the mutation and may be mildly/minimally affected.

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%.
- When the parents are apparently unaffected (as evaluated by molecular genetic testing or by thorough clinical evaluation in those families in which no MLL2 mutation has been identified), the risk to the sibs of a proband appears to be low.
- If the disease-causing mutation found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low, but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Each child of an individual with Kabuki syndrome has a 50% chance of inheriting the mutation.

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

Related Genetic Counseling Issues

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

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing mutation of an affected family member must have been identified in the family before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Note: It is the policy of GeneReviews to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

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.

Gene Symbol	Chromosomal Locus	Protein Name
MLL2	12q12-q14	Histone-lysine N-methyltransferase MLL2

Table A. Kabuki Syndrome: Genes and Databases

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) linked to, click here.

147920	Kabuki Syndrome
602113	Myeloid/Lymphoid or Mixed Lineage Leukemia 2; MLL2

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

Normal allelic variants. MLL2 is 36.3 kb in size and comprises 54 exons. It encodes a protein with 5537 amino acids.

Pathologic allelic variants. The majority of mutations are nonsense and frameshift. Mutations are distributed throughout the gene but are more prevalent in the 3' exons. Missense mutations have been reported but are relatively infrequent [Hannibal et al 2011, Li et al 2011, Micale et al 2011, Paulussen et al 2011].

Normal gene product. MLL2 is a histone 3 lysine 4 (H3K4) N-methyltransferase, one of at least ten proteins that have been identified to specifically modify the lysine residue at the fourth amino acid position of the histone H3 protein [Kouzarides 2007]. MLL2 has a SET domain near its C terminus that is shared by yeast Set1, Drosophila Trithorax (TRX), and human MLL1 [FitzGerald & Diaz 1999]. MLL2 appears to regulate gene transcription and chromatin structure in early development [Prasad et al 1997]. It forms part of the MLL2/MLL3 complex, also known as the ASCOM complex, which is thought to regulate the beta-globin and ESR1 loci [Demers et al 2007].

Abnormal gene product. In the majority of affected individuals, haploinsufficiency of MLL2 is likely the underlying basis of Kabuki syndrome.

RESOURCES

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.—ED.

REFERENCES

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page PubMed.

Published Guidelines/Consensus Statements

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CHAPTER NOTES

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