Kabuki syndrome

Kabuki syndrome is a disorder that affects many parts of the body. It is characterized by distinctive facial features including arched eyebrows; long eyelashes; long openings of the eyelids (long palpebral fissures) with the lower lids turned out (everted) at the outside edges; a flat, broadened tip of the nose; and large protruding earlobes. The name of this disorder comes from the resemblance of its characteristic facial appearance to stage makeup used in traditional Japanese Kabuki theater.

People with Kabuki syndrome have mild to severe developmental delay and intellectual disability. Affected individuals may also have seizures, an unusually small head size (microcephaly), or weak muscle tone (hypotonia). Some have eye problems such as rapid, involuntary eye movements (nystagmus) or eyes that do not look in the same direction (strabismus).

Other characteristic features of Kabuki syndrome include short stature and skeletal abnormalities such as abnormal side-to-side curvature of the spine (scoliosis), short fifth (pinky) fingers, or problems with the hip and knee joints. The roof of the mouth may have an abnormal opening (cleft palate) or be high and arched, and dental problems are common in affected individuals. People with Kabuki syndrome may also have fingerprints with unusual features and fleshy pads at the tips of the fingers. These prominent finger pads are called fetal finger pads because they normally occur in human fetuses; in most people they disappear before birth.

A wide variety of other health problems occur in some people with Kabuki syndrome. Among the most commonly reported are heart abnormalities, frequent ear infections (otitis media), hearing loss, and early puberty.

Frequency

Kabuki syndrome occurs in approximately 1 in 32,000 newborns.

Genetic Changes

Kabuki syndrome is caused by mutations in the *KMT2D* gene (also known as *MLL2*) or the *KDM6A* gene.

Between 55 and 80 percent of cases of Kabuki syndrome are caused by mutations in the *KMT2D* gene. This gene provides instructions for making an enzyme called lysine-specific methyltransferase 2D that is found in many organs and tissues of the body. Lysine-specific methyltransferase 2D functions as a histone methyltransferase. Histone methyltransferases are enzymes that modify proteins called histones. Histones are structural proteins that attach (bind) to DNA and give chromosomes their shape. By

adding a molecule called a methyl group to histones (a process called methylation), histone methyltransferases control (regulate) the activity of certain genes. Lysine-specific methyltransferase 2D appears to activate certain genes that are important for development.

Between 2 and 6 percent of cases of Kabuki syndrome are caused by mutations in the *KDM6A* gene. This gene provides instructions for making an enzyme called lysine-specific demethylase 6A. This enzyme is a histone demethylase, which means that it helps to remove methyl groups from certain histones. Like lysine-specific methyltransferase 2D, lysine-specific demethylase 6A regulates the activity of certain genes, and research suggests that the two enzymes work together to control certain developmental processes.

The *KMT2D* and *KDM6A* gene mutations associated with Kabuki syndrome lead to the absence of the corresponding functional enzyme. A lack of the enzymes produced from these genes disrupts normal histone methylation and impairs proper activation of certain genes in many of the body's organs and tissues, resulting in the abnormalities of development and function characteristic of Kabuki syndrome.

Some people with Kabuki syndrome have no identified *KMT2D* or *KDM6A* gene mutation. The cause of the disorder in these individuals is unknown.

Inheritance Pattern

When Kabuki syndrome is caused by mutations in the *KMT2D* gene, it is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

When Kabuki syndrome is caused by mutations in the *KDM6A* gene, it is inherited in an X-linked dominant pattern. The *KDM6A* gene is located on the X chromosome, which is one of the two sex chromosomes. In females (who have two X chromosomes), a mutation in one of the two copies of the gene in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), a mutation in the only copy of the gene in each cell causes the disorder. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Most cases of Kabuki syndrome result from a new mutation in one of these genes and occur in people with no history of the disorder in their family. In a few cases, an affected person is believed to have inherited the mutation from one affected parent.

Other Names for This Condition

- Kabuki make-up syndrome
- Kabuki makeup syndrome
- KMS
- Niikawa-Kuroki syndrome

Diagnosis & Management

Formal Treatment/Management Guidelines

- European Network of Centers of Expertise for Dysmorphology: Management of Kabuki Syndrome
  http://kabukisyndrome.com/sites/default/files/Kabuki%20Guidelines_0.pdf

Genetic Testing

- Genetic Testing Registry: Kabuki syndrome 1
  https://www.ncbi.nlm.nih.gov/gtr/conditions/CN030661/
- Genetic Testing Registry: Kabuki syndrome 2
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C3275495/

Other Diagnosis and Management Resources

- GeneReview: Kabuki Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK62111

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Health Topic: Developmental Disabilities
  https://medlineplus.gov/developmentaldisabilities.html

Genetic and Rare Diseases Information Center

- Kabuki syndrome
  https://rarediseases.info.nih.gov/diseases/6810/kabuki-syndrome

Additional NIH Resources

- National Institutes of Health: Discovered Gene Causes Kabuki Syndrome
  https://www.nih.gov/news-events/news-releases/discovered-gene-causes-kabuki-syndrome

Educational Resources

- Disease InfoSearch: Kabuki syndrome
  http://www.diseaseinfosearch.org/Kabuki+syndrome/3945
- Disease InfoSearch: KABUKI SYNDROME 2
  http://www.diseaseinfosearch.org/KABUKI+SYNDROME+2/8701
- Genetics Education Materials for School Success: Kabuki Syndrome
  https://www.gemssforschools.org/sites/www.gemssforschools.org/files/library/pdfs_for_printing-dec2015/printable_kabuki-12.10.15.pdf
- MalaCards: kabuki syndrome 1
  http://www.malacards.org/card/kabuki_syndrome_1
- MalaCards: kabuki syndrome 2
  http://www.malacards.org/card/kabuki_syndrome_2
- My46 Trait Profile
  https://www.my46.org/trait-document?trait=Kabuki%20syndrome&type=profile
- Orphanet: Kabuki syndrome
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=2322
- Raising Children Network (Australia): Kabuki Syndrome
  http://raisingchildren.net.au/articles/kabuki_syndrome.html
- Swedish Information Centre for Rare Diseases
  http://www.socialstyrelsen.se/rarediseases/kabukisyndrome
- University of Arizona Database of Hereditary Ocular Disease: Kabuki Syndrome 1
  http://disorders.eyes.arizona.edu/disorders/kabuki-syndrome-1
- University of Arizona Database of Hereditary Ocular Disease: Kabuki Syndrome 2
  http://disorders.eyes.arizona.edu/handouts/kabuki-syndrome-2
- Victoria (Australia) State Department of Health
  https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/kabuki-syndrome

Patient Support and Advocacy Resources

- All Things Kabuki
  http://allthingskabuki.org/home/index
- Contact a Family (UK)
  https://www.cafamily.org.uk/medical-information/conditions/k/kabuki-syndrome/
- Kabuki Syndrome Network
  http://kabukisyndrome.com/
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/kabuki-syndrome/
- University of Kansas Genetics Education Center
  http://www.kumc.edu/gec/support/kabuki.html

GeneReviews

- Kabuki Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK62111

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22Kabuki+syndrome%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Abnormalities,+Multiple%5BMAJR%5D%29+AND+%28kabuki+syndrome%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- KABUKI SYNDROME 1
  http://omim.org/entry/147920
- KABUKI SYNDROME 2
  http://omim.org/entry/300867

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Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/condition/kabuki-syndrome

Reviewed: January 2017
Published: September 12, 2017

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