

## Kabuki syndrome

### Description

Kabuki syndrome is a disorder that can affect 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 may 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.

### Causes

Kabuki syndrome is caused by variants (also known as 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 variants 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 variants 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 variants associated with Kabuki syndrome lead to the absence of the corresponding functional enzyme. A lack of either 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 variant. These individuals are diagnosed based on the presence of characteristic features of the condition. The cause of Kabuki syndrome in these individuals is unknown.

#### Learn more about the genes associated with Kabuki syndrome

- *KDM6A*
- *KMT2D*

## **Inheritance**

When Kabuki syndrome is caused by variants 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 variants 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 variant 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 variant 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 variant 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 variant from one affected parent.

## **Other Names for This Condition**

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

## **Additional Information & Resources**

### Genetic Testing Information

- 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/>)

### Genetic and Rare Diseases Information Center

- Kabuki syndrome (<https://rarediseases.info.nih.gov/diseases/6810/index>)

### Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (<https://rarediseases.org/>)

### Clinical Trials

- ClinicalTrials.gov ([https://clinicaltrials.gov/search?cond=%22Kabuki syndrome%22](https://clinicaltrials.gov/search?cond=%22Kabuki%20syndrome%22))

### Catalog of Genes and Diseases from OMIM

- KABUKI SYNDROME 1; KABUK1 (<https://omim.org/entry/147920>)
- KABUKI SYNDROME 2; KABUK2 (<https://omim.org/entry/300867>)

### Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?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>)

## References

- Adam MP, Hudgins L, Hannibal M. Kabuki Syndrome. 2011 Sep 1 [updated 2022 Sep15]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews(R) [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from <http://www.ncbi.nlm.nih.gov/books/NBK62111/> Citation on PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/21882399>)
- Banka S, Lederer D, Benoit V, Jenkins E, Howard E, Bunstone S, Kerr B, McKee S, Lloyd IC, Shears D, Stewart H, White SM, Savarirayan R, Mancini GM, Beysen D, Cohn RD, Grisart B, Maystadt I, Donnai D. Novel KDM6A (UTX) mutations and a clinical and molecular review of the X-linked Kabuki syndrome (KS2). *Clin Genet*. 2015 Mar;87(3):252-8. doi: 10.1111/cge.12363. Epub 2014 Mar 27. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/24527667>)
- Barry KK, Tsapalis M, Hoffman D, Hartman D, Adam MP, Hung C, Bodamer OA. From Genotype to Phenotype-A Review of Kabuki Syndrome. *Genes (Basel)*. 2022 Sep 29;13(10):1761. doi: 10.3390/genes13101761. Citation on PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/36292647>)
- Bogershausen N, Wollnik B. Unmasking Kabuki syndrome. *Clin Genet*. 2013 Mar;83(3):201-11. doi: 10.1111/cge.12051. Epub 2012 Nov 26. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/23131014>)
- Bokinni Y. Kabuki syndrome revisited. *J Hum Genet*. 2012 Apr;57(4):223-7. doi: 10.1038/jhg.2012.28. Epub 2012 Mar 22. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/22437206>)
- Dentici ML, Di Pede A, Lepri FR, Gnazzo M, Lombardi MH, Auriti C, Petrocchi S, Pisaneschi E, Bellacchio E, Capolino R, Braguglia A, Angioni A, Dotta A, Digilio MC, Dallapiccola B. Kabuki syndrome: clinical and molecular diagnosis in the first year of life. *Arch Dis Child*. 2015 Feb;100(2):158-64. doi: 10.1136/archdischild-2013-305858. Epub 2014 Oct 3. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/25281733>)
- Kuniba H, Yoshiura K, Kondoh T, Ohashi H, Kurosawa K, Tonoki H, Nagai T, Okamoto N, Kato M, Fukushima Y, Kaname T, Naritomi K, Matsumoto T, Moriuchi H, Kishino T, Kinoshita A, Miyake N, Matsumoto N, Niikawa N. Molecular karyotyping in 17 patients and mutation screening in 41 patients with Kabuki syndrome. *J Hum Genet*. 2009 May;54(5):304-9. doi: 10.1038/jhg.2009.30. Epub 2009 Apr 3. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/19343044>)
- Lederer D, Grisart B, Digilio MC, Benoit V, Crespin M, Ghariani SC, Maystadt I, Dallapiccola B, Verellen-Dumoulin C. Deletion of KDM6A, a histone demethylase interacting with MLL2, in three patients with Kabuki syndrome. *Am J Hum Genet*. 2012 Jan 13;90(1):119-24. doi: 10.1016/j.ajhg.2011.11.021. Epub 2011 Dec 22. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/22197486>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257878/>)
- Liu S, Hong X, Shen C, Shi Q, Wang J, Xiong F, Qiu Z. Kabuki syndrome: a Chinese case series and systematic review of the spectrum of mutations. *BMC Med Genet*. 2015 Apr 21;16:26. doi: 10.1186/s12881-015-0171-4. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/25811111>)

bmed.ncbi.nlm.nih.gov/25896430) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4630853/>)

- Micale L, Augello B, Maffeo C, Selicorni A, Zucchetti F, Fusco C, De Nittis P, Pellico MT, Mandriani B, Fischetto R, Boccone L, Silengo M, Biamino E, Perria C, Sotgiu S, Serra G, Lapi E, Neri M, Ferlini A, Cavaliere ML, Chiurazzi P, Monica MD, Scarano G, Faravelli F, Ferrari P, Mazzanti L, Pilotta A, Patricelli MG, Bedeschi MF, Benedicenti F, Prontera P, Toschi B, Salviati L, Melis D, DiBattista E, Vancini A, Garavelli L, Zelante L, Merla G. Molecular analysis, pathogenic mechanisms, and readthrough therapy on a large cohort of Kabuki syndrome patients. *Hum Mutat.* 2014 Jul;35(7):841-50. doi: 10.1002/humu.22547. Epub 2014 Apr 9. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/24633898/>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4234006/>)
- Miyake N, Koshimizu E, Okamoto N, Mizuno S, Ogata T, Nagai T, Kosho T, Ohashi H, Kato M, Sasaki G, Mabe H, Watanabe Y, Yoshino M, Matsuishi T, Takanashi J, Shotelersuk V, Tekin M, Ochi N, Kubota M, Ito N, Ihara K, Hara T, Tonoki H, Ohta T, Saito K, Matsuo M, Urano M, Enokizono T, Sato A, Tanaka H, Ogawa A, Fujita T, Hiraki Y, Kitanaka S, Matsubara Y, Makita T, Taguri M, Nakashima M, Tsurusaki Y, Saitsu H, Yoshiura K, Matsumoto N, Niikawa N. MLL2 and KDM6A mutations in patients with Kabuki syndrome. *Am J Med Genet A.* 2013 Sep;161A(9):2234-43. doi:10.1002/ajmg.a.36072. Epub 2013 Aug 2. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/23913813/>)
- Miyake N, Mizuno S, Okamoto N, Ohashi H, Shiina M, Ogata K, Tsurusaki Y, Nakashima M, Saitsu H, Niikawa N, Matsumoto N. KDM6A point mutations cause Kabuki syndrome. *Hum Mutat.* 2013 Jan;34(1):108-10. doi: 10.1002/humu.22229. Epub 2012 Oct 17. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/23076834/>)
- Ng SB, Bigham AW, Buckingham KJ, Hannibal MC, McMillin MJ, Gildersleeve HI, Beck AE, Tabor HK, Cooper GM, Mefford HC, Lee C, Turner EH, Smith JD, Rieder MJ, Yoshiura K, Matsumoto N, Ohta T, Niikawa N, Nickerson DA, Bamshad MJ, Shendure J. Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. *Nat Genet.* 2010 Sep;42(9):790-3. doi: 10.1038/ng.646. Epub 2010 Aug 15. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/20711175/>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2930028/>)
- Paulussen AD, Stegmann AP, Blok MJ, Tserpelis D, Posma-Velter C, Detisch Y, Smeets EE, Wagemans A, Schrandt JJ, van den Boogaard MJ, van der Smagt J, van Haeringen A, Stolte-Dijkstra I, Kerstjens-Frederikse WS, Mancini GM, Wessels MW, Hennekam RC, Vreeburg M, Geraedts J, de Ravel T, Fryns JP, Smeets HJ, Devriendt K, Schrandt-Stumpel CT. MLL2 mutation spectrum in 45 patients with Kabuki syndrome. *Hum Mutat.* 2011 Feb;32(2):E2018-25. doi: 10.1002/humu.21416. Epub 2010 Dec 7. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/21280141/>)

**Last updated November 1, 2022**