

Kabuki Syndrome ICD-10-CM Code Request

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Kabuki Syndrome (KS)

- Multiple malformation syndrome associated with cognitive impairment and a specific learning profile
- Prevalence estimates range from 1:32,000-86,000 live births, but newer diagnostic methods suggest it may be closer to 1:20,000-1:25,000
- Due to either:
 - Heterozygous pathogenic variants in *KMT2D* (~75%)
 - Heterozygous or hemizygous pathogenic variants in *KDM6A* (~3%-5%)



Definitive Clinical Diagnosis

The diagnosis of KS is established in a person 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* at some point of life
- A heterozygous pathogenic variant in *KMT2D* or a heterozygous or hemizygous pathogenic variant in *KDM6A*

* What are considered “typical dysmorphic features”



“Typical Dysmorphic Features”

- Long palpebral fissures (a palpebral fissure measurement greater than or equal to 2 standard deviations above the mean for age) with eversion of the lateral third of the lower eyelid



[Kabuki syndrome - Wikipedia](#)



Adam MP et al. J Med Genet. 56:89-95, 2019



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Cardinal Dysmorphic Facial Features

Arched and broad eyebrows with lateral sparseness or notching



Short columella with depressed nasal tip



Cardinal Dysmorphic Facial Features/Hand Findings

Large, prominent,
or cupped ears



Persistent fetal
fingertip pads



[persistent fetal fingertip pads - Search Images \(bing.com\)](#)



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Roles of KMT2D and KDM6A

Both work to regulate transcription

KMT2D is a histone methyltransferase that adds mono- and trimethylation to the fourth lysine (K4) of histone 3, promoting open chromatin



KDM6A is a histone demethylase that removes trimethylation of H3K27 (a closed chromatin mark)

Gene Expression



Mendelian Disorders of Epigenetic Machinery (MDEMs)

- There is a specific epigenetic signature for Kabuki syndrome to support a diagnosis of KS if there is a variant of unknown clinical significance identified on genetic testing or no genetic change identified in *KMT2D* or *KDM6A*
- May also be used as a biomarker in research



Central Nervous System/Learning

- Learning profiles:
 - 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
 - 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 be beneficial



Immunologic Features

Suggested evaluations at time of diagnosis:

- T cell count, T cell subsets, & serum immunoglobulin levels at time of diagnosis or at age 1 year (whichever is later)

Treatment:

- Intravenous immunoglobulin therapy may be considered in those w/documentated immunoglobulin deficiency.

Surveillance

- Assessment of completed blood count every 2-3 years



Endocrinologic Features

Suggested evaluations and monitoring:

- Monitor for persistent hypoglycemia in neonates and infants

Treatment:

- Growth hormone for short stature may be considered
- No treatment warranted for premature thelarche

Surveillance

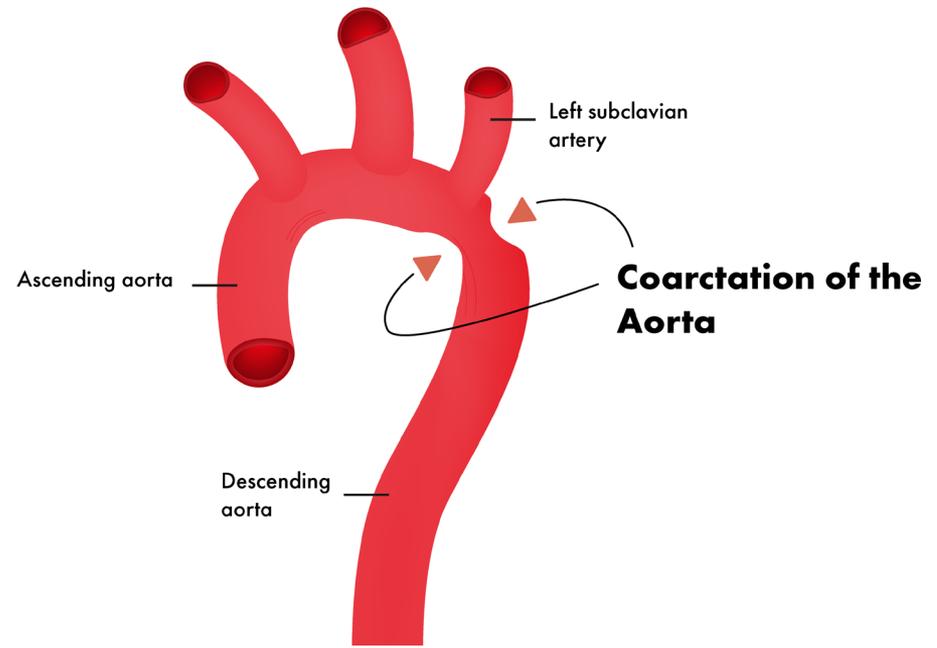
- Thyroid function tests every 2-3 years



Cardiac Features

Suggested evaluations at time of diagnosis:

- Echocardiogram with visualization of the aortic arch



Targeted Therapies

- Mouse model of KS (loss of function of *KMT2D*)
 - Memory deficits due to anomalies seen in parts of the mouse brain (involved in adult neurogenesis)
 - Given histone deacetylase inhibitors (HDACi)
 - Normalization of the structural and functional areas of this part of the brain
 - Improved neurogenesis and memory



https://www.yourgenome.org/sites/default/files/images/photos/Black%20mouse_Credit_Wellcome%20Library,%20London_cropped.jpg

Bjornsson HT et al. *Sci Transl Med*, 6(256):256ra135, 2014.



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Emerging Targeted Therapies

- Diet
 - Ketosis also acts as an endogenous HDACi
 - Ketogenic diet: low carb, high fat diet
- Currently 8 targeted therapies are in development
 - One has received rare pediatric disease and orphan drug designation from the FDA (RSC-57)
 - Another treatment being developed for KS also received orphan drug designation from the FDA and European Commission (TAK-418)



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Appropriate Diagnosis Leads to Best Treatment

- Prevalence of Kabuki syndrome is similar (or even more prevalent in some cases) to other rare disorders that have been provided codes, including
 - Prader-Willi syndrome (Q87.11)
 - CDKL5 Deficiency (G40.42)
 - SYNGAP1 Encephalopathy (F78.A1)
 - Angelman syndrome (Q93.51)
- Having a specific code as soon as possible will enable us to capture all cases accurately, which is critical to improving patient care, accelerating research and promoting health equity.

