R.C.P.U. NEWSLETTER

R.C. Philips Research and Education Unit

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Kabuki Syndrome

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Introduction

Kabuki syndrome is a rare genetic disorder that affects multiple systems within the body. The syndrome is named after the facial features of many affected children that resembled the makeup used by actors in kabuki, a form of Japanese theater. The specific symptoms associated with Kabuki syndrome can vary greatly from one person to another, however, features often include the characteristic facial appearance, skeletal abnormalities, short stature, heart defects, and intellectual disability. Kabuki Syndrome has historically been difficult to diagnose, but it is estimated that 1 in 32,000 births are affected by this condition across all ethnic backgrounds. Currently, there is no cure for Kabuki syndrome, therefore medical management is focused on treating the unique symptoms of each patient.

Clinical Features

- Facial features:
  - Arched or interrupted eyebrows
  - Long eyelids
  - Low eyelids that are turned outward
  - Prominent eyelashes
  - Broad nose with a depressed nasal tip
  - Large, low set ears without ear pits
- Eye findings:
  - Blue sclerae
  - Strabismus
  - Ptosis
  - Vision loss
- Mild to moderate intellectual disability
- Speech delays
- Anxiety or behavioral concerns
- Growth deficiencies
- Small head size (microcephaly)
- Weak muscle tone (hypotonia)
- Short stature
- Skeletal abnormalities
- Cleft lip and/or palate
- Dental problems
- Frequent ear infections
- Hearing loss
- Heart abnormalities
- Joint hypermobility
- Immune deficiencies
- Endocrine complications such as hyperinsulinism or early puberty
- GERD
- Feeding difficulties
- Urogenital and kidney problems
- Seizures
- Thick, fleshy fingertip pads
- Absent mid finger creases on 3rd and 4th fingers

Diagnosis
Diagnosis of Kabuki syndrome can be established in a patient, regardless age or biological sex, with a history of hypotonia, developmental delay and/or intellectual disability, AND one or both of the following:

- Typical Kabuki facial features
- A genetic change in the *KMT2D* or *KDM6A* genes

Roughly 20% of individuals with Kabuki syndrome will not be found to have a genetic cause in either gene. However, clinical diagnosis can still be made based on symptoms, a detailed family history, and physical exam. Specifically, physicians should look for characteristic facial features, fingertip pads or abnormal finger creases, low tone, developmental delay, and intellectual disability. Further testing, such as chromosomal studies or blood work may be used to rule out other possible disorders.

Molecular Etiology
There are currently two known genes associated with Kabuki syndrome: *KMT2D* (formerly *MLL2*) and *KDM6A*. The *KMT2D* gene is found on chromosome 12q13.12 and plays a role in histone methylation and provides the instructions for a transcription factor that is critical for cell differentiation during embryonic development. The *KDM6A* gene is found on Xp11.2 and plays a role in histone demethylation. By adjusting the methylation and demethylation of histone proteins on their respective chromosomes, these genes work together to regulate gene expression. Along with Kabuki syndrome, genetic changes in these genes have been associated with congenital heart disease and various forms of cancer.

Genetic Testing
The common genetic testing approach when finding a molecular diagnosis of Kabuki syndrome includes single-gene targeted testing. This approach analyzes for both the gene sequence and possible intragenic deletions/duplications in either *KMT2D* or *KDM6A*. The recommended guidelines for genetic testing suggest performing a single-gene analysis of *KMT2D* first since roughly 75% of disease-causing changes occur within this gene. If no change is found, analysis of *KDM6A* should follow.

It is possible that a genetic cause for Kabuki syndrome is not found in either *KMT2D* or *KDM6A*. In these instances, broader tests should be considered. Multi-gene panels that include other genes of interest, as well as whole exome sequencing are recommended.

Genetic Counseling
Most cases of Kabuki syndrome, particularly those caused by a change in *KMT2D*, occur *de novo*, meaning they occur for the first time in an affected individual with no family history of the condition. However, familial occurrence of Kabuki syndrome has been reported. In *KMT2D* Kabuki syndrome, the condition is passed from parent to child in a dominant pattern. In dominant patterns, only a single copy of an abnormal genetic change is necessary for the

condition to be seen in an individual. The risk of passing the condition on from parent to child is 50% or 1/2 for each pregnancy. This risk is the same for both males and females. In *KDM6A* Kabuki syndrome, the condition is passed in an X-linked pattern. In this pattern, it is possible for a woman with a change in *KDM6A* to pass on the condition to her children. The risk for a woman carrying a *KMD6A* change to pass it on to her children is 50% or 1/2 with each pregnancy. Female children who inherit the change may have mild or absent symptoms and may continue to pass down the change to their children. Male children who inherit the change will have Kabuki syndrome and will continue to pass the change on to their daughters, but not their sons. Due to the intricacies of the inheritance of Kabuki syndrome, genetic counseling is recommended.

The penetrance for *KMT2D* Kabuki syndrome appears to be complete, however the penetrance for *KDM6A* is currently unknown. It is possible variable expressivity leads to more mildly affected individuals and thus an under-ascertainment of penetrance data.

Management

There is currently no cure for Kabuki syndrome. Treatment is dependent on an individual's specific features. Treatment typically requires a multidisciplinary approach, often involving pediatricians, surgeons, cardiologists, endocrinologists, geneticists, and other specialists. Special services that may be beneficial to affected children include remedial education, physical and occupational therapy, and speech therapy. Early intervention is key to ensuring individuals with Kabuki syndrome receive the best healthcare management and highest quality of life.

Concern	Treatment and Referrals
Ophthalmological	Standard treatment Refer to an ophthalmologist
Hearing loss	Treatment may include pressure equalizing tubes or hearing aids Refer to an ENT specialist
Cleft lip and/or palate	Standard treatment Management through specialized craniofacial clinic
Dental	Refer to an orthodontist
Heart defects or arrhythmia	Refer to a cardiologist If catheterization or angioplasty is being considered, a potential increased risk of aortic aneurysm should be communicated
Feeding difficulties or GERD	Treatment may include pharmaceuticals, thickened formulas, or a gastrostomy tube if difficulties are severe or there is poorly coordinated suck and swallow
Gastrointestinal or urogenital	Refer to a gastroenterologist or urologist
Hyperinsulinism or hypothyroidism	Standard treatment Refer to an endocrinologist
Short stature	Possible growth hormone therapy Refer to an endocrinologist
Seizures	Antiepileptic treatment Refer to a neurologist

Developmental delay and/or intellectual disability	Refer to an early intervention program for access to occupational, physical, speech, and feeding therapies Evaluation for an individualized education plan when entering school Consultation with a developmental pediatrician is recommended

Support Networks

- All Things Kabuki
  www.allthingskabuki.org
- Kabuki Syndrome Network
  www.kabukisyndrome.com
- Kabuki Syndrome Foundation
  www.kabukisyndromefoundation.org
- The Arc
  www.thearc.org

Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health.

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About the RCPU:

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate disorders of intellectual disability through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects. Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-