KABUKI SYNDROME: AN INSIDE LOOK

1. While Kabuki syndrome is often thought of as a newer syndrome, it has actually been around for longer than most recognize. The first “case” was seen in 1967 in Japan by Dr. Norio Niikawa and colleagues, when a female infant presented with features not belonging to other known syndromes. In 1968 Dr. Yoshikazu Kuroki and colleagues examined a young boy who also presented with features not confirmed with another syndrome. Additional cases were found in the following years. It was not until 1981 that the combined findings of these cases brought the diagnosis of Kabuki syndrome. Originally known as Kabuki Make-Up Syndrome, after traditional Japanese theater, Make-Up would later be dropped. Kabuki syndrome has evolved over the course of almost 50 years. Once an unknown syndrome, Kabuki syndrome would later be clinically diagnosed and more recently genetic testing would be available to aid in diagnosing many cases.

2. One of the traits of Kabuki syndrome that frequently stands out is the long palpebral fissures and outer eversion of the eyes. Palpebral fissure is the measurement of the opening of the eyes and the long palpebral fissures is the open elongated eyes we see in those with Kabuki syndrome. Hence those beautiful Kabuki eyes. The eversion of the outer third often seen in Kabuki syndrome refers to the eyes being more open (lids turned slightly outward). This can lead to dry eyes and those with Kabuki syndrome often will sleep with their eyes open, or partially open, due to the structure of the eye. When clinically diagnosing Kabuki syndrome, the eyes are one of the features that the physical will look at.

3. Persistent fetal pads are common in Kabuki syndrome. These fetal pads are raised pads on the fingertips and also seen on the toes. This is one of the features that help give a clinical diagnosis of Kabuki syndrome. Persistent fetal pads are also found in various other syndromes. Fetal pads, also called volar pads, are formed when the fetus is around 7 to 8 weeks old and will regress and disappear shortly thereafter in typical development. The same time the volar pads are disappearing, finger ridges/prints are forming. If the finger ridges/prints form when the volar pad is still present, the individual tends to have a whorl fingerprint pattern. These unique features are a blessing in helping to establish a clinical diagnosis.

4. Dysmorphic ears are often seen in those with Kabuki syndrome. Dysmorphic is a Greek word with dys meaning ‘abnormal’ and morphic meaning ‘shape’ or ‘form’. Dysmorphic ears are often an indicator linking to a chromosomal, or genetic disorder. The formation of the ear can be seen on an ultrasound during fetal development and could be a tool to assist with early diagnosis in syndromes. Prominent dysmorphic ears are an identifying feature when clinically diagnosing Kabuki syndrome.

5. As many as 80% of cases of Kabuki syndrome are believed to be caused by a mutation in the KMT2D (also known as MLL2) gene, which is located on the long arm of chromosome 12. This gene is responsible for the production of an enzyme called lysine-specific methyltransferase. In Kabuki syndrome, the mutation causes premature stop signals that cause a short enzyme, making it non-functional. This does not allow for proper activation of certain genes thereby affecting certain organs and tissues, causing Kabuki syndrome. A negative test result does not necessarily mean a person does not have Kabuki syndrome as a small percentage may have the KDM6A gene mutation. There are indications that other genes could also be involved.

6. KDM6A is a second gene found to be associated with Kabuki syndrome. The KMT2D (MLL2) gene was the first gene discovered, and up to 80% of those diagnosed with Kabuki syndrome will have a mutation on this gene. It is estimated that at this time, up to 9% of cases testing negative on KMT2D will test positive on the KDM6A gene mutation. The KDM6A gene is located on the x chromosome and codes a histone demethylase that interacts with the KMT2D. The KDM6A gene provides instruction for making enzyme called lysine-specific demethylase 6A. A mutation on the KDM6A will result in Kabuki syndrome. There are indicators that additional genes are involved.

7. One of the five cardinal traits of Kabuki syndrome is skeletal abnormalities. Some of the typical abnormalities include: short fifth digits, dislocations of the hip, knee and/or shoulders, cranial

*For more information visit: www.AllThingsKabuki.org
abnormalities, vertebrae abnormalities, loose joints, hypotonia, and rib abnormalities. Other skeletal abnormalities may also occur, however not every person with Kabuki syndrome will have all of them.

8. Strabismus is an eye condition that can be associated with Kabuki syndrome. Strabismus is described as the direction of the misalignment of the eyes. There are several types of strabismus, the most common being exotropia, exotropia, hypotropia, and hypertropia. Strabismus is treatable and the goal is to correct it before it causes additional complications. It is important to have an eye exam by a qualified professional to detect strabismus or other eye conditions associated with Kabuki syndrome.

9. Coloboma is a congenital eye condition that can be found in Kabuki syndrome. It involves a defect in either the eyelid, or the structure of the eye. Coloboma can be found in one or both eyes. Depending on the type of coloboma, it may or may not be noticeable or affect vision. Treatment varies by type. Children with coloboma may be sensitive to light.

10. Hypotonia is the medical term for low muscle tone and is common in Kabuki syndrome. Low muscle tone is different than muscle weakness, however they can co-exist. Low muscle tone involves the signal from the brain to the muscle. Infants will have a floppy, frog like appearance; older children may have a wider gait for stability. Those with hypotonia also tire easily. Speech therapy, physical therapy and occupational therapy often help.

11. Brachydactyly is common in Kabuki syndrome. Brachydactyly is the shortness of the digits, fingers and toes. In Kabuki syndrome, short fifth digits are one of the skeletal abnormalities seen when using the five cardinal traits for a clinical diagnosis.

12. Clinodactyly is another Kabuki feature. Clinodactyly comes from the Greek word ‘kliner’ (to bend) and ‘dactylos’ (finger). Some people with Kabuki may have a bend in their fifth finger. Clinodactyly is associated with 60 different syndromes. Clinodactyly is not a disease, but rather a sign of something else. Surgery is typically not required unless a significant curve is found to interfere with normal functioning.

13. Congenital Heart Defects (CHD) are seen in approximately 50% of those diagnosed with Kabuki. Studies vary between 31% and 58%. Cardiac malformations seen in Kabuki syndrome are often seen in those with Turner syndrome. Turner syndrome is specific to females missing, in whole or part, the x chromosome. A study conducted by NCBI suggests, “Male preponderance in patients with KS and COA supports the hypothesis that genes located on the x chromosome may be involved in determining KS in some patients.” The most common CHD’s include aortic coarctation, atrial septal defect, and ventricular septal defect.

14. Coarction of the aorta (aka aortic coarctation) is one of the more common heart defects seen in Kabuki syndrome. Aortic Coarctation is the narrowing of the aorta, which pumps blood from the heart to the rest of the body. The narrowing causes the heart to work harder to pump blood. Aortic Coarctation may be mild to severe, and may present with other heart defects. Treatment is usually successful and varies with age and severity.

15. Approximately 30% of persons with Kabuki syndrome have kidney anomalies. Horseshoe kidneys are a common renal fusion anomaly. Persons are usually asymptomatic and are often identified incidentally. Once a person is diagnosed with Kabuki syndrome, a renal ultrasound may be ordered to determine if kidney anomalies are present.

16. Hearing loss is common in Kabuki syndrome. There are three types of hearing loss: conductive, sensorineural and mixed. **Conductive Hearing Loss** occurs when sound is not being conducted through the outer or middle ear. **Sensorineural Hearing Loss** occurs as a result of damage to the inner ear, or impairment of the auditory nerve. **Mixed Hearing Loss**, while less common in Kabuki, is a combination of both conductive and sensorineural hearing loss.

17. Hypodontia and misaligned teeth are common in Kabuki syndrome. Hypodontia is the absence of teeth. Missing and misaligned teeth can affect speech and
bite. There are treatment options to correct missing teeth so it is important to establish routine dental care.

18. Approximately 30% of individuals diagnosed with Kabuki syndrome have kidney anomalies. One of these anomalies includes renal dysplasia, which is the result of the kidney not forming properly in utero. Renal Dysplasia is occasionally detected during a prenatal ultrasound. Most children do well if one kidney is affected, however it becomes more serious if both kidneys are affected.

19. Kabuki children have a happy disposition. There is not a lot research regarding this positive finding, but reports suggest that 87% of children affected by Kabuki syndrome display a happy disposition, despite the challenges they experience.

20. Postnatal growth deficiency is one of the cardinal traits of Kabuki syndrome, though not all persons with Kabuki syndrome are short in stature. Short stature becomes more apparent with age. Growth hormone deficiency has been found in some children with Kabuki syndrome, but is not indicated as a common trait in Kabuki. It is important to work with an endocrinologist to determine if the growth deficiency is due to a growth hormone deficiency and if growth hormone therapy is needed.

21. Blue sclera is an eye condition that can be present in Kabuki syndrome. The sclera is the outer white part of the eye. Blue sclera would indicate a blue tint to the whites of the eyes. This is caused by a thinner sclera. It is important to see an ophthalmologist to rule out any eye conditions that may be associated with Kabuki syndrome.

22. The “scrunchy face” is a common feature seen in Kabuki syndrome. While it is not a cardinal trait, or one you can find scientific literature on, it is a real feature displayed by most with Kabuki. Perhaps it is due to low muscle tone, or facial nerve development. Regardless, it is one of the traits that make Kabuki that much more special, and even provides a common bond among families. Ask a person with Kabuki syndrome to smile and enjoy that beautiful “scrunchy face.”

23. Stimming is self-stimulatory behavior and involves repetition of movement and sound. It is most associated with autism but also seen in Kabuki syndrome. Kabuki syndrome is known to present with ‘autistic like behaviors’.

24. Idiopathic Thrombocytopenic Purpura (ITP) is a condition that can be found in Kabuki syndrome. This condition can lead to excessive bruising and bleeding as a result of low platelet levels. Treatment can depend on age and severity, and if signs and symptoms are present.

25. One of the characteristics of Kabuki syndrome is flat feet. Low muscle tone contributes to hypermobility of the joints. This doesn’t allow enough support to the arch of the foot. Kids with Kabuki syndrome often will roll the foot inward, also called midfoot pronation. Children may also externally rotate the feet. Orthotic devices will assist with correcting issues related to flat feet.

26. Long eyelashes are a sign of beauty in many cultures. They are also a characteristic of Kabuki syndrome. While the exact reason for this may not be completely understood, eyelashes are a characteristic in many syndromes and diseases that can offer clues in diagnosing, whether they be missing, long, short or odd in color.

27. Ectodermal issues are common in Kabuki syndrome. Those with Kabuki often have missing, thin or fragile nails, or nails incompletely formed.

28. Ptosis is a condition associated with Kabuki syndrome. It is the drooping of the upper eye lids. In severe cases, it can block or restrict vision. Ptosis can be corrected with surgery if severe enough.

29. Dental anomalies are often present in Kabuki syndrome. The central incisors (two front teeth) are often misshaped with the lower part of the tooth narrower than the mid. This is a condition rarely found in other children and can be used as a diagnostic tool for Kabuki syndrome. Working with a dentist to reshape the tooth can improve tooth function.
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30. How common is Kabuki syndrome? It was originally estimated that Kabuki syndrome occurs in approximately 1 in 32,000 births. Newer estimates suggest that number to be 1:10,000 to 1:32,000. With quicker diagnosis, significantly more physicians having heard of Kabuki, genes discovered to explain the majority of Kabuki cases, there is some evidence suggesting there are more cases than originally believed. Since Kabuki syndrome is a relatively new syndrome (from a medical perspective), in time clearer estimates may be given. While statistics are important for many reasons, Kabuki syndrome is still an individual diagnosis for each family, and the extent of complications varies greatly for each person.

31. Micrognathia can be found in Kabuki syndrome. Micrognathia means having a small lower jaw. This can interfere with feeding and normal dental development. On occasion the jaw may correct itself with growth (in typical children), this may not be the case with those with a syndrome such as Kabuki. It is important to work with your healthcare provider to determine the severity of micrognathia and determine a plan of action.

32. Polycythemia is a condition that can be found in Kabuki syndrome, though not as common as in other syndromes. Polycythemia is a condition in which the red blood cells are increased in the blood volume either by reduced plasma or increased red blood cells.

33. Duplicated ureter is a condition that can be found in Kabuki syndrome. It occurs when two ureters are formed draining a single kidney. Prognosis is excellent with medical management.

34. While Kabuki syndrome has been around for decades, it has only been in the past decade that advances have been made. Another promising breakthrough for Kabuki syndrome can found in an article titled ‘Special Diet Found to Alleviate Inherited Form of Intellectual Disability in Mice’ – 10/07/15. Web: www.hopkinsmedicine.org

35. Syndactyly, or webbing of the digits, is associated with Kabuki syndrome, though unusually mild. This occurs when the digits fail to completely separate in utero, around the sixth to eighth week. Treatment depends on the severity of the webbing; mild webbing does not usually require treatment.

36. Gastroesophageal Reflux Disease (GERD) is common in Kabuki syndrome, especially those of younger age. GERD is a digestive disorder affecting the lower esophagus sphincter muscle. Low muscle tone is an obvious contributing factor, but other uncommon underlying issues can contribute as well.

37. Microphthalmia is an eye condition where one or both eyes are abnormally small and can be found in Kabuki syndrome. There is no treatment for severe cases, however, milder cases may benefit with surgery.

38. Certain eye conditions may be present with Kabuki syndrome. One of the less common conditions seen is Marcus Gunn Phenomenon. This involves one of the upper eye lids involuntarily rising with movement of the lower jaw. While the exact cause is not known, it could be linked to nerve and/or muscle coordination.

39. Microcephaly is a condition in which the head is a smaller circumference than a normally developed head. Microcephaly is seen in many, but not all, with Kabuki syndrome. Microcephaly is associated with developmental delays and there is no treatment other than early intervention through multiple forms of therapy. Developmental delays are often seen in Kabuki syndrome, whether one has microcephaly or not.

40. A sacral sinus or dimple is often seen in Kabuki syndrome. It is an indentation located on the lower back, just above the crease of the buttocks. It is usually harmless. If accompanied by a hairy tuft, discoloration, or other unusual skin condition, it should be evaluated by a healthcare provider. These could indicate rare conditions such as spina bifida occulta, or tethered cord.

41. Optic Nerve Hypoplasia is a condition that can be found in Kabuki syndrome. This is a congenital condition in which the optic nerve is under developed. There is no medical treatment or surgery that can be done to correct this condition. Support by an eye doctor is important with any vision issues.

All Things Kabuki’s 2015 Awareness Project: Kabuki Syndrome: An Inside Look. * For more information visit: www.AllThingsKabuki.org

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SOURCES:

The majority of the facts listed in Kabuki Syndrome: An Inside Look come directly from families raising children with Kabuki syndrome. Additional sources include:

www.rarediseases.org/rare-disease-information/rare-diseases/byID/920/viewFullReport


www.ncbi.nlm.nih.gov/pmc/articles/PMC2930028/

www.kabukisyndrome.com

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