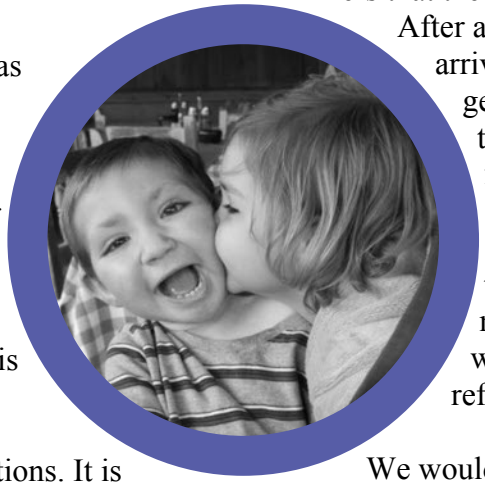
Medical Management of Kabuki Syndrome

Compiled by Margot Schmiedge and Peta Colton

Welcome Families and Professionals

We have come a long way in understanding what it means to have Kabuki syndrome since it was first described in 1981. Studies and their resulting published articles have given us objective data, helping to decipher what is typical for the syndrome and what is simply typical for that individual. Equally important has been the observations and sharing of information between parents and professionals.



The Medical Management Package has been a joint effort between Margot Schmiedge, founder and director of Kabuki Syndrome Network (KSN) and Peta Colton, founder and director of Supporting Aussie Kids with Kabuki Syndrome (SAKKS). It was developed to provide users with an easy to read and print alternative. This package is designed for educational purposes only. It is not intended for diagnosis or advice on medical conditions. It is not meant to endorse particular therapies, treatments and/or medicines. It is paramount that families seek care from the professionals. In addition, this package will only be updated occasionally. The best place for current, up-to-date information is at the respective websites: www.kabukisyndrome.com and http://www.sakks.org.

The articles may use medical terminology. It is difficult to avoid since one medical word often requires ten layman's words. There are many online dictionaries available or, if you prefer, you can use the one at www.kabukisyndrome.com .

The language used to describe varying disability has evolved as society has gained increased knowledge. Some terms have acquired shameful implications because of misuse. We will always refer to a child with Kabuki as just that – not a Kabuki child. The terms cognitive disability and intellectual disability are used interchangeably. 'Developmental delay' is a term often used by professionals. It usually means there are global delays present, including either or both physical and intellectual. It's a 'safe' term because 'delay' infers that the individual will eventually catch-up. After all, a delayed flight does eventually arrive! We are not suggesting that we get hung-up on the terms we use, just that they are respectful and accurate for the situation.

Many families find it helpful to keep their child's medical records and notes in a binder, which they bring with them to appointments for handy reference.

We would like to throw a word of caution, especially to new parents of children with Kabuki. In the coming years you will be inundated with research, advice, and medical procedures. Each family will find it necessary to weed out what is important and what is not for their individual child. Sometimes, though, we need a reminder that it be kept in perspective, that we don't become wholly obsessed with caloric counts, medical procedures and therapies, and in the process, forget to enjoy our children!

Inheritance

On August 15, 2010 researchers at the University of Seattle announced the discovery of the MLL2 gene mutations responsible for approximately 75% of individuals with Kabuki Syndrome. The scientists used a "second generation" technique to examine only the protein-coding gene portion of the human genome, called the exome. Since the exome constitutes only 1 - 2% of the human genome, the cost and time requirement has been greatly reduced, making it more plausible to look for gene mutations.

There are different reasons why a gene may have a mutation. In the case of Kabuki, the MLL2 gene mutations were found to be due to either nonsense or frame-shift mutation which resulted in a shortened, nonfunctional protein. To help families better understand the basics of the discovery please see *Understanding the Genetics of Kabuki*.

It is speculated that Kabuki is a heterogeneous syndrome, meaning that multiple genes could potentially be involved. It is hoped that with continued analysis, other genes will be discovered.

Due to the August 2010 discovery of the MLL2 gene mutations responsible for approximately 75% of individuals with Kabuki Syndrome, a clinical blood test is now available to help with diagnosis. It is currently being performed at the Childrens Hospital in Boston, the Emory University Genetics lab, and the University of Chicago. If you are interested in having an individual with a clinical diagnosis of Kabuki be tested, you can ask your geneticist or another specialist to order the tests, perform the blood work (about 5 cc's of blood draw) and have it sent to those labs. Turnaround time to receive results is approximately 6-8 weeks. The test is called MLL2 Full Gene Sequencing and the test code is SMLL2. If applicable, it may be valuable to call your insurance company to see if the test will be covered. Some insurers cover them because they are diagnostic tests. CPT codes are 83891 (x1), 83894 (x1), 83898 (x76), 83904 (x152), 83909 (x152), 83912 (x1) and cost is approximately $2,000 - $3,000. In Canada, the test is not yet available but there have been situations where a geneticist may send the samples south of the border for testing. Please check with your geneticist to explore the options.

It is important to keep in mind that this test only diagnoses the 75% of cases that are caused by the MLL2 gene. It is possible that your result may be negative for the MLL2, but that the individual may still be believed to have Kabuki syndrome based on other presenting characteristics.

Initially, your geneticist will make a clinical diagnosis of Kabuki based on the recognition of four (out of five) main characteristics, with the distinct facial features being imperative.

- characteristic facies (long palpebral fissures with eversion of outer third, arched eyebrows with sparse outer half, prominent eyelashes, prominent and/or misshapen ears, and depressed nasal tip)
- skeletal anomalies
- dermatoglyphic anomalies
- intellectual disability (mild to moderate)
- postnatal short stature

The characteristic facies is imperative.

Associated features, which are also looked at but which are not cardinal manifestations:

- hypotonia
- feeding difficulties
- recurrent infections
- congenital heart defects
- renal (kidney) / urinary tract anomalies
- small mouth, micrognathia (smallness of the jaws), cleft/high arched palate, hypodontia (missing teeth)
- birth: normal weight, infancy & childhood: underweight, pre-teen onward: possible obesity
- early breast development (girls)
- hearing impaired and/or inner ear malformations

The occurrence of associated conditions, for individuals, varies in number and degree. Though the Kabuki population exhibits a wide spectrum of medical involvement, each patient presents a unique clinical picture.

Dr. Tiong Tan

What Role Does a Clinical Geneticist Play in the Lives of Children and Adults with Kabuki Syndrome

By Dr. Tiong Tan

About Author:
Tiong initially trained as a paediatrician and then as a clinical geneticist working with the fantastic team at Genetic Health Services in Melbourne. His interest lies in helping children and families affected by genetic conditions and birth defects. After doing PhD research in Melbourne, he is now pursuing further research in Hong Kong to understand the mechanisms of congenital changes affecting the head and face, such as clefting. His plan is to rejoin the team in Melbourne with this knowledge and experience and return to clinical work.

Children and adults with Kabuki syndrome often see many health professionals. These may include, but are not limited to, their GP, paediatrician, physiotherapist, heart specialist, speech pathologist, dentist, orthotist, immunologist, and eye specialist. Once every couple of years, they might see a geneticist. What does a geneticist do? And what can a clinical geneticist contribute to the lives of families affected by Kabuki syndrome?

A clinical geneticist is a medical specialist who cares for people with conditions that have a genetic component. A large part of clinical genetics practice is the management of children who are born with multiple birth defects, some of whom are diagnosed with a condition such as Kabuki syndrome. Clinical geneticists usually become involved in the lives of such children when they are asked to make a diagnosis to explain the pattern of medical problems experienced by the child. Kabuki syndrome is a rare condition that is distinctive. Its recognition allows advice and management to be tailored specifically for the affected individual. We base this advice on what we know from our collective medical experience of looking after other individuals with Kabuki syndrome.

Making the diagnosis of Kabuki syndrome does not give us the power of a crystal ball. It does not predict what problems will happen, or when they will happen. But it does allow us to draw up a plan to anticipate some of the problems that might happen, and to avoid them, or at least reduce their impact. It is somewhat like drawing up a road map for the future, to help keep the child on the healthiest route. The clinical geneticist is aware of the possible complications of Kabuki syndrome, and is able to guide the whole care team about how to keep the affected child in the best possible health.

Often a diagnosis of a condition like Kabuki syndrome means that the child will have special needs in the future. The clinical geneticist is in the position to advocate for additional help in school to maximize the learning potential of a child with Kabuki syndrome. The clinical geneticist is also in a position to offer support and care to the entire family, not just the affected child. Often parents have questions about whether they might have another affected child, or whether their other children might have an affected child. These are questions that a clinical geneticist can address. We are also aware of any new research findings, and can provide this information or facilitate involvement in an ongoing research project.

By following a child and his or her family over many years, we learn a great deal about some of the difficulties that have to be overcome, and hopefully contribute in a positive and meaningful way in the management of the family's medical and genetic health.

Margot Schmiedge

Maggie McMillin

Understanding the Genetics of Kabuki

By Margot Schmiedge

Edited by Maggie McMillin

Maggie McMillin is a clinical researcher in Human Genetics, Bamshad Lab at the University of Washington

Every cell in our body contains a full set of chromosomes and identical genes. What then differentiates our cells? What makes some of our cells become muscle and others, say, skin? This happens because only a fraction amount of genes in each cell are 'turned on' or 'expressed'. That's an interesting concept isn't it? That our blood, hormones, bones, and heart all share the exact same building blocks (genes), but only a select few are turned on in each system!

Most of us don't have an insatiable desire to understand genetics, but we all have some basic curiosity as to what our bodies are made of. How does it all work? This is particularly true when things don't work so perfectly.

Let's begin with the smallest most basic elements of the body – DNA. **DNA** is made up of 4 bases (adenine, cytosine, guanine, and thymine), each represented by the letter which they begin with. The bases pair with one another and are attached to sugar and phosphate molecules to make what looks like a ladder. *See Figure 1*

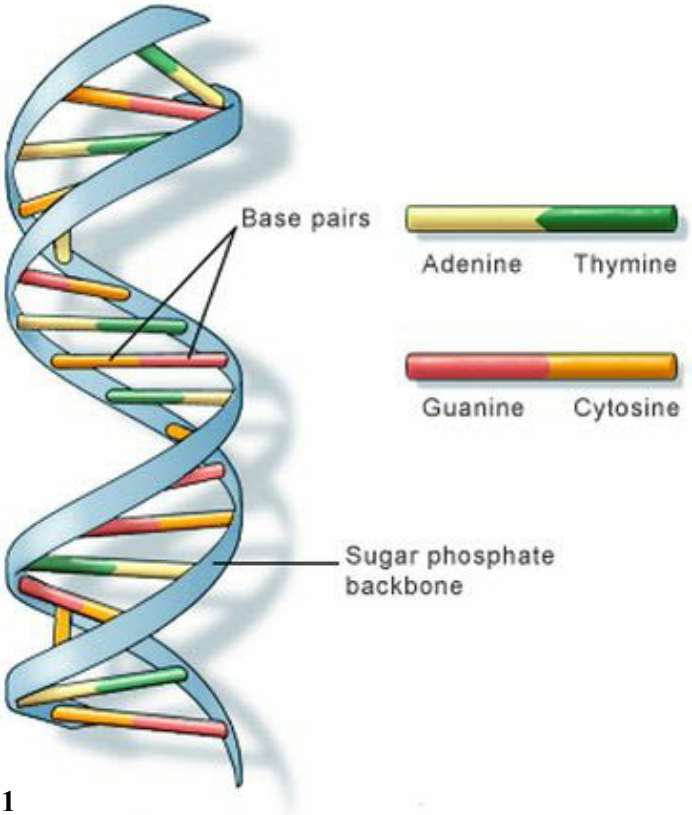


Figure 1

A **gene** is a length of DNA ladders. We have approximately 25,000 genes. The DNA ladders make up a code, similar to our alphabet. Actually, *very* similar to our alphabet. They are read 3 letters at a time to produce amino acids. Think of the amino acids like the words of a sentence. They are read similarly to the way we know that the letters *c-o-l-a* signifies a drink. These same letters put in a different order, *c-o-a-l*, now represents a combustible material. Since there are four different letters (A, C, G, and T), there are 64 different combinations that can be used. However there are only approximately 20 amino acids. That means that different codes can produce the same amino acid. Some of them act as punctuation for the sentence, signalling when a sentence begins and when it ends. *See Figure 2*

An example of an amino acid chain might be: CAT ATT GCA GAT TGT

Use the DNA decoder wheel on the next page to find out what your amino acid chain would look like. Start from the inside of the wheel and work outwards to the second ring for your next letter and so on till you get to the outside ring to find the name of your amino acid.

You should have decoded: Histidine-Isoleucine-Alanine-Aspartic Acid-Cysteine

Proteins are made up of many amino acids. Think of them as the sentences. It is these proteins that perform most of the critical functions of each cell. Again, some proteins will form muscle, some will work as enzymes to regulate hormonal and other chemical processes, and yet others will regulate the genes themselves.

Only about 1% of our DNA is coded by genes, which in turn make proteins. The rest is referred to as non-coding DNA and is not yet well understood. It is believed, among others, that they have an influence on our cells to know when to switch certain genes on and off.

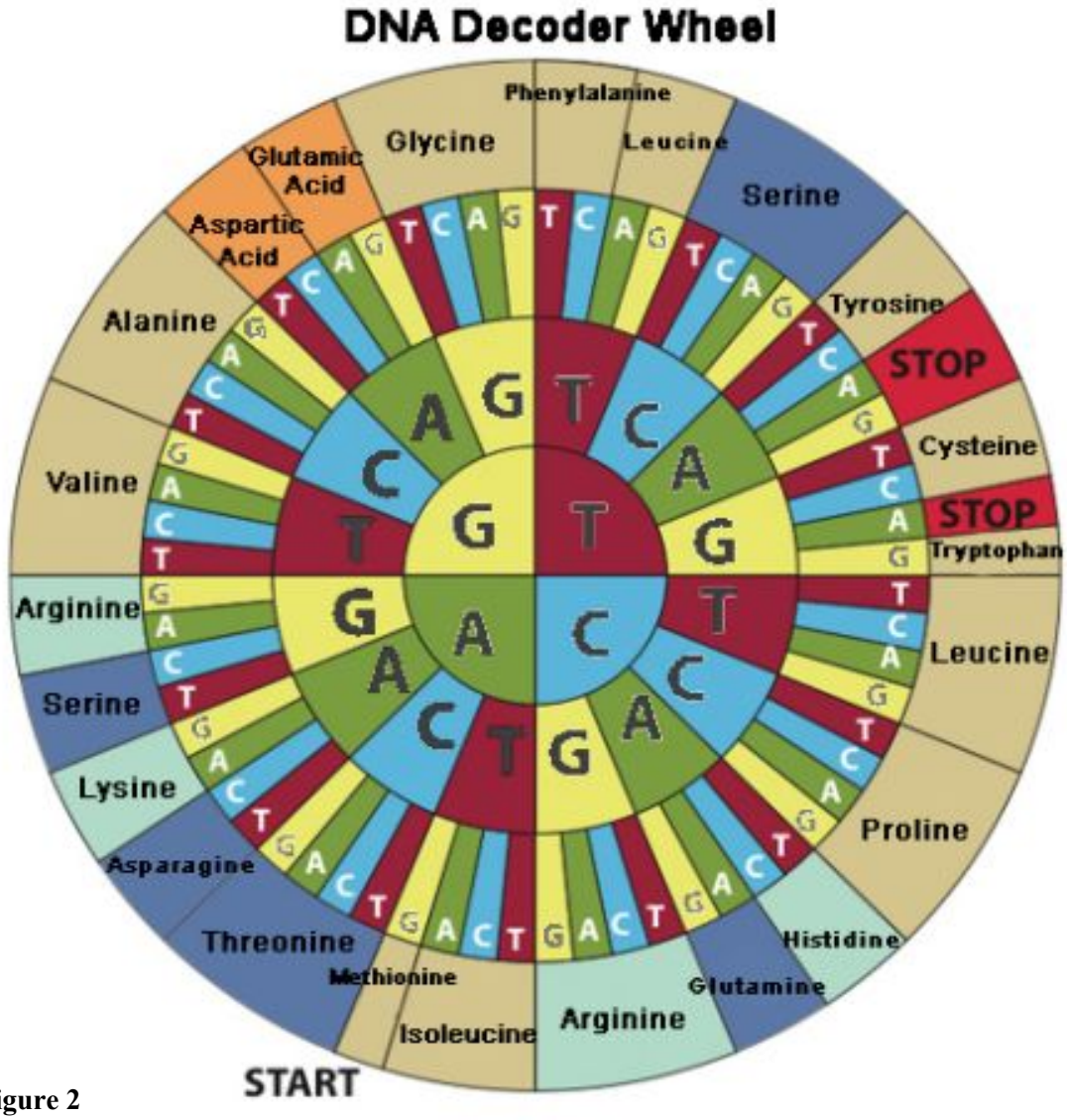


Figure 2

Chromosomes are made up of many genes. Humans have 22 pairs of chromosomes plus one pair that determines our sex. *See Figure 3*

Let's re-cap: DNA consists of 4 bases, and sugar and phosphate molecules to form ladders. Genes consist of DNA ladders and it's all tightly packaged into bundles called chromosomes.

DNA is read 3 bases (letters) at a time to produce amino acids (the words) and stops and starts (the punctuation). Many amino acids make up proteins (the sentences) which are contained in genes (paragraphs or chapters). Proteins do the work in constructing our bodies (which makes the story complete!)

So what happens in the case of disease or a syndrome? Sometimes one of the letters of the DNA is swapped for another. All of us carry some of these errors. So why do we not all have a syndrome? Remember how the four DNA letters could be coded in

64 possible combinations (4x4x4x4) but will only produce about 20 different amino acids? Some combinations can handle an error. For example if the letter T is swapped for an A in the codon GCT the resulting protein would still be the same, since both the old codon (GCT) and new codon (GCA) code for the same amino acid (see for yourself with the DNA decoder). Other error combinations may have very serious effects. Swapping an A for a T in a gene for hemoglobin results in the serious blood condition sickle cell anemia. Think of it like this: it's OK if Jane the waitress doesn't show up because we can move Mary into her position and Jack into Mary's position since they have all performed each other's tasks. However if Jessica the orthopedic surgeon doesn't show up, we can't very well have the OR nurse fill in for her! Other errors can occur as well, such as a bit of the DNA sequence is missed or a bit added, etc.

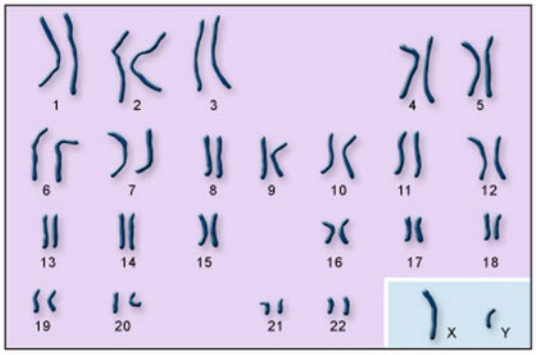


Figure 3

Karyotyping or blood chromosomal analysis is a study of our chromosomes. Cells are stained and examined microscopically to examine the size, shape and number of chromosomes in the sample. Think of it as a view of earth using a satellite. It will clearly show if a continent or country has changed its shape.

Microarray analysis allows scientists to scan the chromosomes, looking more closely at the genes. Different types of microarrays are able to detect different things, for example if there are insertions or deletions of genetic material or compare the expression of genes (remember, this means whether the gene is 'turned on' or not) in a healthy sample versus a diseased one. Think now of a more powerful satellite image that gives you the ability to see cities.

Targeted gene sequencing allows scientists to look very closely at our DNA (about 25,000 genes) to detect small changes in the sequence, or 'letters' in the DNA. Think now of a satellite so powerful that is able to see single homes.

Most individuals with Kabuki will have normal chromosomal study test results. The 'error' is in a letter – a home, not a continent. Even though the change is 'small', that is not to be misunderstood as being a minor error – just a difficult one to see until recently. Increased ability to see smaller and smaller elements of our body and increased understanding of what those elements do, make it possible to more accurately diagnose conditions. But science is a continuous process - one discovery and level of understanding leads to another. Much still needs to be understood, which may even lead to prevention in the future. These are exciting times in the genetic world!

In the case of Kabuki, mutations of the MLL2 gene has been found to occur in 75% of individuals who have been subjectively diagnosed with Kabuki. They were found to be due to either nonsense or frame-shift mutation which resulted in a shortened, nonfunctional protein. A nonsense mutation *(Fig 4)* is a change in one DNA base pair. The altered DNA sequence prematurely signals the cell to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all. In the example below, you can see how the insertion of the base thymine (T) is now read as TAG instead of the intended CAG. Since TAG is read as a STOP, the resulting protein is shortened. Refer back to the DNA Decoder Wheel to see how this happens. A frameshift mutation *(Fig 5)* occurs when the addition or loss of DNA bases changes a gene's reading frame. A reading frame consists of groups of 3 bases that each code for one amino acid. A frameshift mutation shifts the grouping of these bases and changes the code for amino acids. The resulting protein is usually nonfunctional. Insertions, deletions, and duplications can all be frameshift mutations. In the example below you can see how the shift of the first DNA base means that the succeeding bases are all read incorrectly.

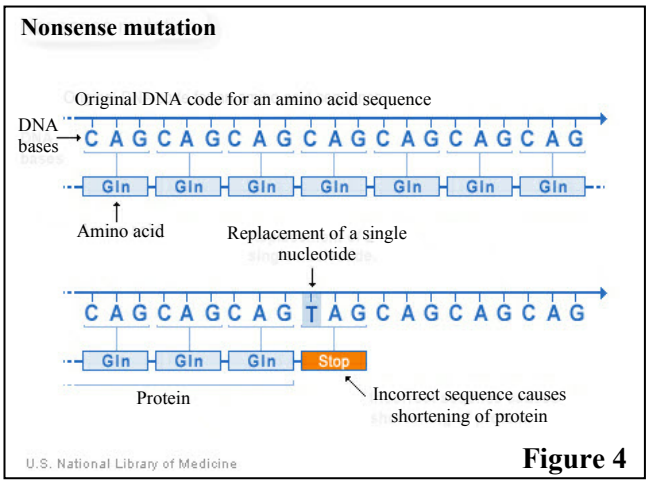


Figure 4

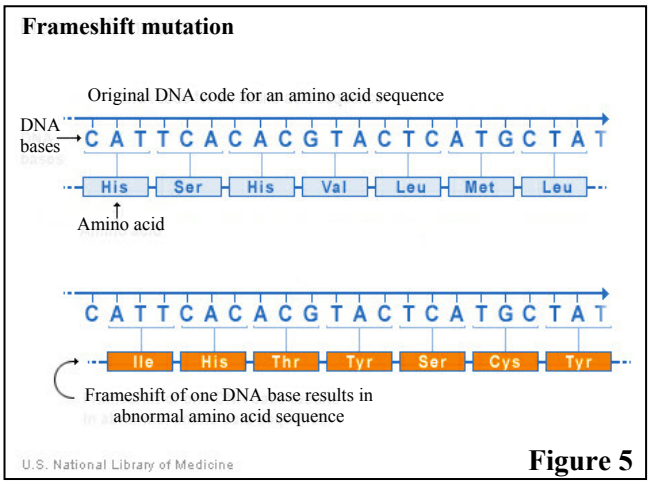


Figure 5

More specifically in the case of Kabuki

Addition by Maggie McMillin

A genome is an individual's entire genetic code. The Human Genome Project was the first time scientists had completely looked at every base (letter) of the genome. There are about 4 billion bases in the entire genome. It is still very difficult and very expensive to sequence an entire genome.
Only about 1% of the genome contains genes. There are about 20,000 genes in the genome. An exome is a newly made-up word to describe targeted sequencing of all the genes. Remember that genes are the part of the genome that code for proteins, and proteins are the things that perform functions in the body. If something does not function or develop properly, a gene is the first place to look to find a change that might cause the disease or dysfunction. So exome sequencing is a way to focus on looking at the most important part of the genome. And because there is much less sequencing than looking at the *entire* genome, the cost is much less.

Recently researchers studying Kabuki syndrome at the University of Washington and Seattle Children's Hospital used exome sequencing to identify the gene causing the syndrome. In the study, researchers sequenced the exomes (all the genes) of 10 individuals with Kabuki Syndrome. Then they compared the information between all 10 individuals to find a gene that contained a change that would be predicted to cause dysfunction of the protein. They found a gene (MLL2 gene*) that had changes, or mutations, in 9 out of the 10 individuals. Then researchers used targeted sequencing to look at the same gene in more individuals with Kabuki and about 75% of individuals had a change in the gene.

The gene provides the instructions, (like a recipe) to make a type of protein called a histone methyltransferase. Histones are proteins that the DNA is tightly wound around, like a spool of thread. This helps to package all the DNA so that it can fit inside the cell nucleus. When a cell needs to "read" the DNA to make a protein and perform a function, it unwinds whatever little part needs to be read. Histone methyltransferase is type of protein, called an enzyme that helps to unwind the DNA from the histone.

There are two clues as to why this gene is a causative agent of Kabuki:

1. The individuals without Kabuki (control individuals) do not have the same types of changes in this particular gene.
2. The parents do not have the change (unless they also have Kabuki). So most of the time the change in an individual with Kabuki is a new, "sporadic" change. This is just something that happens by chance.

This means that researchers have identified a gene that explains a large number of cases of Kabuki syndrome, and now a clinical test can be developed. For individuals with Kabuki that do not have mutations, there is likely another gene that causes the syndrome. The researchers are still conducting the study to look for other genes.

It's not yet known how the changes to the gene change the function of protein or why it causes the features of Kabuki syndrome. It's also not known if different changes within the gene can lead to more or less severe clinical features. But now that the gene has been identified, scientists have the next step in moving forward to try to answer these questions.

* Inserted following Aug 15, 2010 publication release.

Please see *Inheritance* on page 2 for updated information on testing. It's important to note, that with continual new information, the websites are where you will find the most current information available!

Facial Characteristics

Facial characteristics typically include:

- long palpebral fissures
- lower palpebral eversion
- arched eyebrows with sparse outer lateral half
- long eyelashes
- blue sclerae
- ptosis (drooping of upper eye lid)
- depressed nasal tip
- cleft lip/palate or arched palate
- dysmorphic ears
- preauricular pits (dimples in front of ears)
- abnormal dentition

Children with Kabuki have similar facial features, most notably the large eyes, long and thick eyelashes, arched eyebrows, flat nasal tip and prominent ears. Eyebrows can be interrupted in some. Outer lower lid eversion can contribute to sleeping with eyes partially open. Ocular conditions that occur more commonly in KS than the general population are blue sclerae, strabismus, coloboma and ptosis. Less common conditions can include nystagmus, Peters' anomaly, Marcus Gunn phenomenon, and numerous others. Ears are frequently large, cupped, low-set, and incompletely formed. Hearing loss has usually been attributed to both repeated ear infections and sensorineural problems. Cleft palate/lip or high arched palates are commonly found. A thin upper lip has also been noted. Teeth are often wide spaced, irregularly shaped and misaligned. Hypodontia is common, in particular the upper incisors.

Dr. Takuya Iida

Kabuki Syndrome and Cleft Palate

By Takuya Iida, M.D.[1)], Susam Park, M.D[2)] , Eri Iida, M.D.[3)]

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What is a "Cleft Palate"?

The term "cleft" refers to a condition where the two sides of structure did not fuse or join together, and the word "palate" means the roof of the mouth. Thus "cleft palate" means a condition where there is an opening in the roof of the mouth (Fig.1). Cleft palate is a congenital defect, or birth defect, and it is often associated with cleft lip, which means a splitting in the lip.

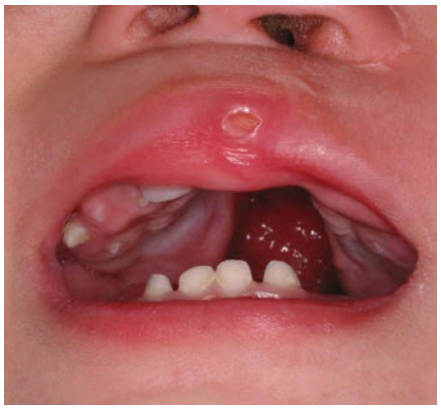

Figure 1

Kabuki syndrome and cleft palate

In general, cleft lips or palates are reported to occur in about 500-700 births worldwide. It is reported that children with Kabuki syndrome have cleft lip/palate at a higher incidence (33-50%).

The chief symptoms of cleft palate are as follows:
Feeding problem: Babies with cleft palate are not able to suck and swallow normally because the opening in the roof of the mouth directly connects the mouth to the nasal cavity, resulting in milk and air escaping from the nose.
Speech and language problems: Children with cleft palates may develop their speech later and have difficulty in pronouncing several kinds of sounds such as "p," "t," and "k" because they cannot raise air pressure in the mouth due to the air leakage through the nose.
Dental problems: Teeth may not erupt normally; some teeth might be absent, malformed, or malpositioned.
Ear infections and hearing difficulties: The function of the auditory tube that connects the middle ear and the throat is often impaired and therefore ear infections can occur easier.

Cleft palate is a treatable condition by multidiciplinary approach. The "Cleft team" will take care of your kids and can help improve not only the function but also the appearance of the child.

Submucous Cleft Plate

Cleft palate is usually diagnosed shortly after birth because it is easy to find the cleft if you look into the baby's mouth. However, there is a special type of cleft palate called submucous cleft palate (SMCP). The term "submucous" means that the cleft is covered by the thin layer of mucosa at the center of the roof of the mouth, although the underlying muscles do not join together. Since there is no apparent opening in the roof of the mouth, SMCP is sometimes difficult to find in infancy (Fig. 2) and might remain undiagnosed until they become older. One of our findings is that SMCP is observed at a much higher rate than has previously been reported. We treated six patients with cleft palate associated with Kabuki Syndrome at Shizuoka Children's Hospital. Three of them had an overt cleft palate and the other three had a submucous cleft palate.

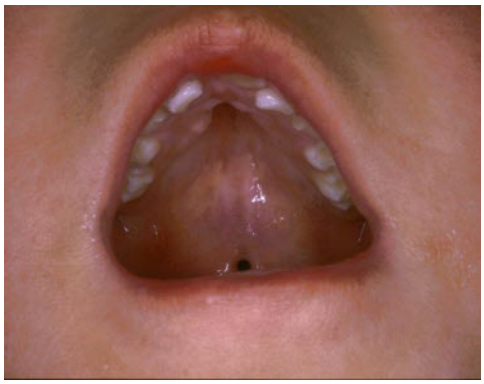

Figure 2

The most important presenting symptom indicating that a child is suspected of having SMCP is abnormal and nasal speech. Another symptom of SMCP is a uvula bifida, which means a splitting "uvula," a small, soft piece of flesh that hangs down at the back of your mouth. If your child has these symptoms, we recommend you consult with a cleft palate specialist.

Treatment

Many medical professionals in different fields are involved in the treatment for your children because the skills of many different areas are necessary to solve the problems caused by cleft palate. A Cleft team, which usually includes a plastic surgeon, a dental surgeon, an ear-nose-throat (ENT) surgeon, a pediatrician, a speech-language pathologist, and a nurse, will take care of your child. Treatments include mainly surgery, speech therapy, and dental therapy.

Surgery

Surgery for cleft palate repair is usually performed between 10 and 18 months after birth. The surgery, which is called " palatoplasty," consists of reconstruction of the splitting palate, including not only the mucosa but also the underlying muscle, which is most important for the speech and swallowing. There are several methods of palatoplasty. One of the most common procedures, "push-back" palatoplasty, is shown in Figure 3. In this procedure, incisions are made on both sides of the palate. Then the palatal tissues, including mucosa and muscle, are moved from each side to the center back, and then sutured. With this procedure, the separated muscles are joined together and the palate can be reconstructed and elongated.

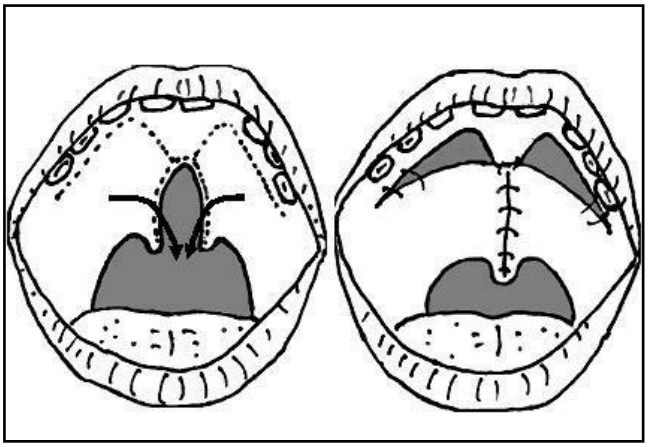

Figure 3

Speech therapy

After palatoplasty, children with cleft palate usually have speech therapy to learn how to use the reconstructed palate properly and acquire the correct pronunciation of sounds and words. The speech-language pathologist will evaluate your child's speech production and language development. The goal of speech therapy is to help them acquire correct sound and good speech habits.

Dental Care and orthodontic treatment

Children with a cleft palate often need dental and orthodontic treatment. Since the growth of the upper jaw is slower and less than the lower jaw, a child's upper teeth may not fit together properly with the lower teeth. In such cases, the orthodontist will help correct the alignment of the teeth and the relationship of the upper jaw to the lower jaw. If the tooth alignments cannot be made normal by orthodontics alone, they may need orthognathic surgery, which is called an osteotomy, to reposition the upper jaw both forward and down.

Ear treatment

Children with a cleft palate are susceptible to ear infections, so it is important to have an regular examination by an ENT doctor for your child's ears. Since Children with severe ear infections are not able to hear language normally due to fluid collection in the middle ear, there is a risk for language delays and speech problems To obtain proper drainage of the fluid in the middle ear, a small plastic tube is often inserted into the eardrum by an ENT surgeon.

Figures:
1 Appearance of cleft palate
2 Appearance of a submucous cleft palate (cited from The Cleft Palate-Craniofacial Journal, Allen Press Publishing Services. 2006, Iida T et. al. Cleft palate in Kabuki syndrome: a report of six cases)
3 Schematic illustration of "push-back" palatoplasty

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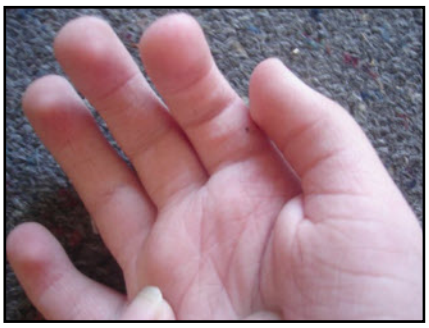
Musculoskeletal Characteristics

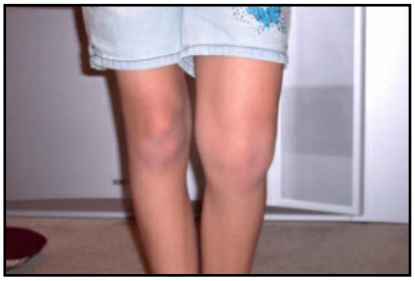
Musculoskeletal characteristics typically include:

- short fingers
- short middle phalanx of fifth finger
- syndactyly - mild webbing between fingers
- cranial abnormalities
- vertebral abnormalities
- rib anomalies
- scoliosis
- Hypotonia
- joint laxity
- dislocations of hip, patella and shoulders

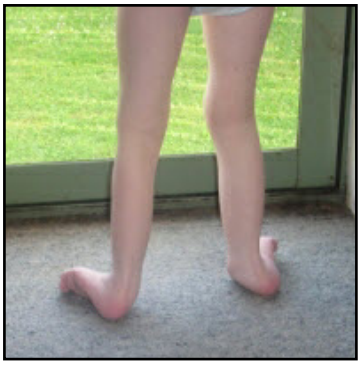
Vertebral anomalies can include butterfly vertebra, sagittal cleft, narrow intervertebral disc space, spina bifida occulta, and scoliosis.
Joint hypermobility is very common, in particular in the younger child. The hypermobility, exacerbated by hypotonia, can lead to dislocation of joints, in particular the hip, knees and shoulders. It is yet unclear whether joint laxity is neurogenic or due to a connective tissue disorder.
Short fingers, in particular the fifth finger, is common. Webbing between the fingers is less commonly seen.



Fetal pads and short fifth finger



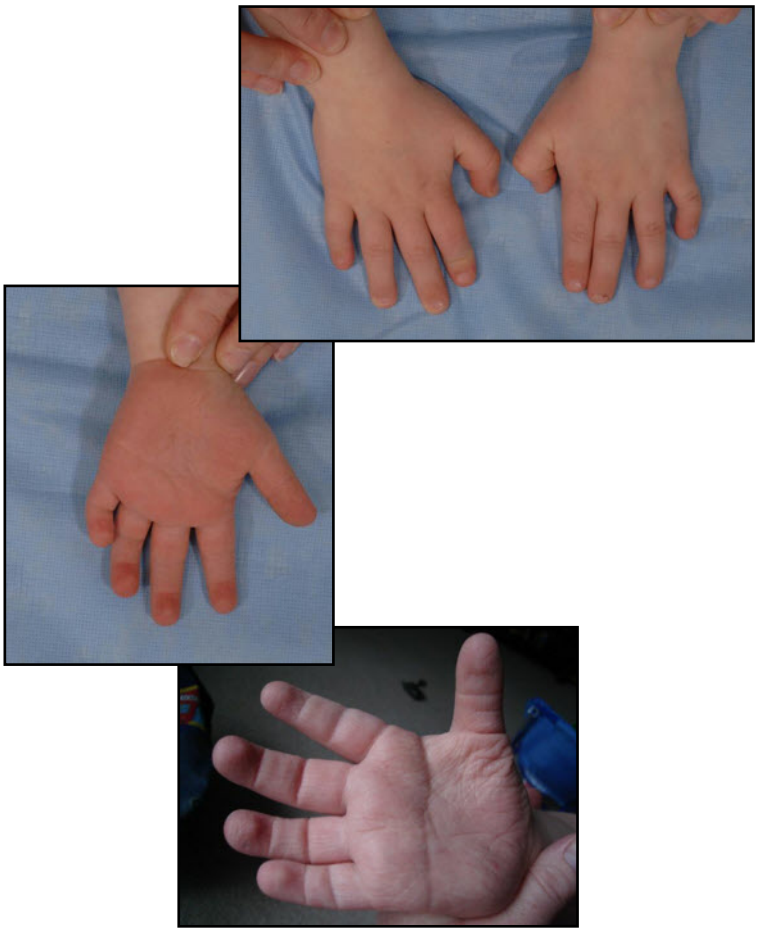
Dislocated Left Knee Cap

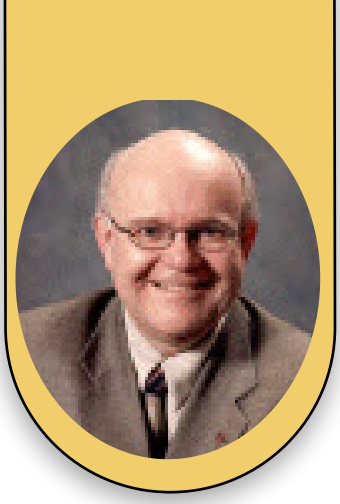


Severe pronation with active overuse of the foot everters in attempt to aquire stability

Dermatoglyphic Characteristics

With the recent genetic discovery for Kabuki, there will be less need to use dermatoglyphics for diagnosis. However, as one of the five cardinal characteristics, it may still be used as a contributing factor for diagnosis.





Dermatoglyphics and Kabuki Syndrome

By Dr. Albert Chudley

About Author:
Dr. Chudley is a medical geneticist and pediatrician. He is a professor at the University of Manitoba , at Winnipeg Children's Hospital.

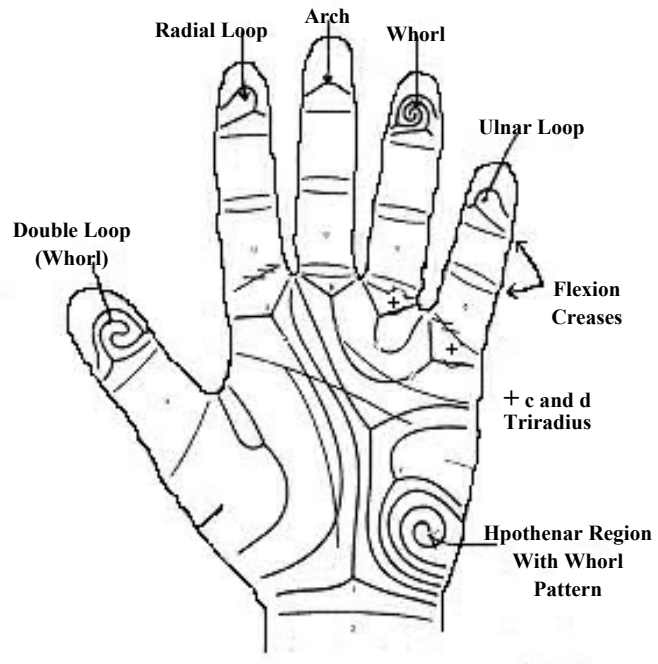
Dermatoglyphics (writing on the skin in Greek) is the study of epidermal ridges. Epidermal ridges form early in fetal life, and are unique to each individual. They consist of patterns of ridges on the finger pads, palms and soles of all individuals. They form different patterns, and are unique to individuals. This means they can be used for personal identification in criminal investigations. In genetics and medicine, they are useful in diagnosis, since recurring abnormal patterns are often seen in a variety of genetic syndromes. In addition, creases are formed on palms and soles that are also altered in syndromes. Although creases are not part of epidermal ridges, which require a magnifying glass or an ink impression to examine thoroughly, creases are part of what a geneticist looks at during his or her dermatoglyphic analysis and examination.

In Down syndrome, the creases are frequently abnormal on the palms with two of the three large creases forming what appears to be a single palmar crease (31% compared to 2% of controls). Also, individuals with Down syndrome have tibial arch patterns on the soles near the base of the great toes (60% compared to 0.5% of controls) and they tend to have 10 ulnar loops on their finger pads (30% compared to 7% of controls).

For Down syndrome, there is a diagnostic test, the chromosome analysis, that confirms the presence of 3 chromosome # 21's, instead of the usual 2. Therefore, dermatoglyphic analysis has become less important for the diagnosis of Down syndrome than for syndromes in which the genetic alteration has not been identified, such as for Kabuki syndrome (KS).

In many children with KS (over 75%), there are prominent fetal fingerpads. Usually these fingerpads become flat by the time of delivery, but in KS individuals, they remain prominent. This is not specific for KS, as they have been described in other syndromes, and can also be present in individuals without a genetic syndrome. Dr. Niikawa and co-authors brought our attention to the fact that in most people with KS, there are dermatoglyphic findings that separate affected individuals from unaffected. His findings showed that there was an increase in ulnar loops (63%); absence of digital triradius c (48%); absence of digital triradius d (30%); increase of hypothenar loops; and a single flexion crease of the 5th finger. Overall, in his study of dozens of KS individuals, about 93% showed some unusual dermatoglyphic findings. (See illustration).

Geneticists use dermatoglyphic analysis to help support the diagnosis of KS. However, as in Down syndrome, eventually the genetic cause of KS will be established, and the use of dermatoglyphic analysis will become less important



This illustration shows the various landmarks related to dermatoglyphics and some common patterns or formations. In Kabuki syndrome, there are at least five commonly seen changes: (1) increase in ulnar loops (2) absent of the digital c or d triradius –region highlighted with asterix (3) increase in hypothenar patterns (4) single flexion crease in 5th digit (5) prominent fingerpads (not shown).

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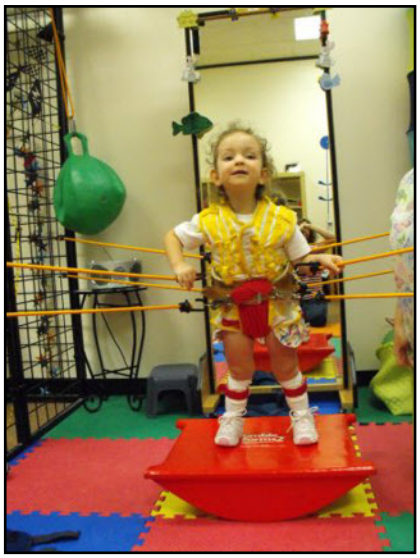
Intellectual, Sensory and Behavioral

Many individuals with Kabuki syndrome have sensory processing disorder. This inability to accurately organize sensory information can lead to behavior problems.

Some of the more commonly reported sensory issues include need for oral stimulation (chewing on non-food items), tactile defensiveness towards various sensations and stimuli, panic-like reactions to certain noises, and aversion to textures and/or smells of select foods. Anxiety, obsessive/compulsive traits and autistic-type behaviors are commonly observed. Individuals with Kabuki syndrome often have an obsessive need for routine. Mild depression has been reported in young adults.

Parents frequently report an excellent memory for face recognition, song lyrics, dates of events, etc.



Margot Schmiedge

Kabuki and Autistic Behaviors

By Margot Schmiedge and Jen Morton

The spectrum of characteristics associated with Kabuki syndrome is extremely varied. As with any newly described syndrome it is initially difficult to know if certain presenting characteristics are typical of the syndrome or simply typical for that individual. However, it has become increasingly evident that many individuals with Kabuki display autistic-type behaviors. Although few children have been officially diagnosed with autism, virtually all children have some degree of sensory processing disorder.

What is autism?

Autism is a spectrum disorder. This means the symptoms and characteristics can present themselves in a wide range of combinations and from mild to severe. In other words, two children with the same diagnosis can be very different from each other and have varying abilities/disabilities. Autism is a combination of several developmental challenges.

According to the Autism Society of America, the following areas are among those that may be affected:

Communication

- language develops slowly or not at all
- uses words without attaching the usual meaning to them
- communicates with gestures instead of words
- short attention span

Social Interaction

- spends time alone rather than with others
- shows little interest in making friends
- less responsive to social cues such as eye contact or smiles

Sensory Impairment

- may have sensitivities in the areas of sight, hearing, touch, smell, and taste to a greater or lesser degree

Play

- lack of spontaneous or imaginative play
- does not imitate others' actions
- does not initiate pretend games

Behaviors

- may be overactive or very passive
- throws tantrums for no apparent reason
- perseverates (shows an obsessive interest in a single item, idea, activity or person)
- apparent lack of common sense
- may show aggression to others or self
- often has difficulty with changes in routine

Behaviors often associated with children with Kabuki

Communication

- almost all families report language delays

Social Interaction

- some families report their child as being very social, others report their child as having little interest in friendships, preferring to play alone, often able to speak more freely with adults than peers
- poor eye contact (50% according to survey done by KSN)
- poor at understanding the unspoken "rules" of socialization
- poor at understand the give-and-take of a conversation or how to end one
- very literal thinkers, have difficulty thinking abstractly
- unable to 'read between the lines'

Sensory Impairment

- hypersensitive to touch (such as play dough, walking barefoot, etc)
- aversion to loud noises
- aversion to particular smells (cooking smells, etc)
- hypersensitive to visual stimuli
- aversion to particular food tastes and textures (often causing gagging)
- self-stimulatory behaviors such as hand flapping, head shaking, rocking, repeating phrases over and over (over 50% according to survey done by KSN)
- self injurious behaviors such as biting self and head banging
- very oral, many chew on non-food items (over 60% according to survey done by KSN)

Play

- some do not seek out friendships, preferring to play alone or with adults
- others seek friendships but prefer younger children
- many like to play the same thing or watch the same videos over and over

Behaviors

- extreme need to know what to expect throughout the day and exact schedule of events (about 60% according to survey done by KSN)
- repeating of questions over and over
- difficulty waiting
- interrupting often
- talking to self (about 60% according to survey done by KSN)

What does this mean for the child with Kabuki?

It is important to know that developmental delay in general can be accompanied by several types of symptoms and behaviors that one sees with autism (speech and language delay, self-stimulatory behaviors, social impairment, inappropriate behavior). It is true that autism is more easily recognized today and if a child fits into a set of criterion, a diagnosis of autism may come about. This is not to say that the autistic diagnosis is permanent or that it conflicts with the Kabuki diagnosis. With skill development and ongoing intervention, a child may mature and gain ground in an area so that they no longer 'fit' into the autism heading. The fact that our children have Kabuki syndrome is the reason they are demonstrating autistic-like tendencies in the first place. Autism is not necessarily a separate label. More than likely, ALL of our children at some point or other are demonstrating behaviors that could be considered autistic-like. Whether our children have been given an autism label or not, the types of therapy and intervention that we would seek to assist with their areas of need are the same. Many autism treatment approaches are very beneficial for all children facing issues in any of these functional areas.

Growth

Twins Hannah and Zachary on 10th Birthday

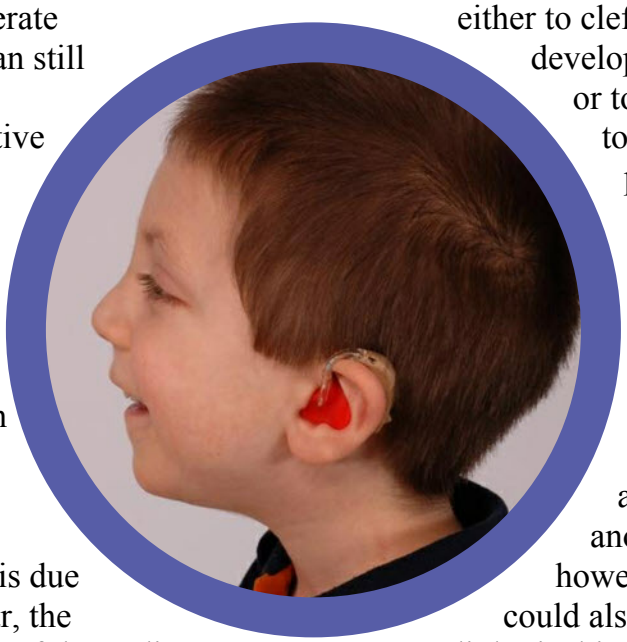
Postnatal short stature is one of the cardinal features of Kabuki Syndrome. It is still unclear as to what extent growth hormone deficiency contributes to this characteristic.

Although birth weight and length are generally normal, growth delay often starts during the first year of life. Poorly coordinated sucking & swallowing, reflux, recurrent infections, cardiac defects, and hypotonia may all be contributing factors. Although growth hormone levels are in the normal range for most children, a significant number have a partial or complete deficiency. Obesity seems to be a common problem during puberty years. The adult with Kabuki will be shorter than the norm – two or more standard deviations below the mean.

Hearing

Hearing loss is a common finding in Kabuki syndrome and can be of three basic types: conductive, sensorineural or mixed.

Conductive hearing loss occurs when sound is not conducted properly through the outer ear, middle ear, or both, such as in ear canal obstruction or in acute otitis media (ear infection). It is generally a mild to moderate impairment because sound can still be detected by the inner ear. Generally, with pure conductive hearing loss, the quality of hearing (speech discrimination) is good, as long as the sound is amplified loud enough to be easily heard. This type of hearing impairment can often be medically or surgically treated.



Sensorineural hearing loss is due to the damage of the inner ear, the cochlea, or to the impairment of the auditory nerve. It can be mild, moderate, severe, or profound, to the point of total deafness. It is a permanent loss and it doesn't only affect sound intensity such as the ability to hear faint sounds but also makes it more difficult for you to recognize complex sounds, to understand speech and to hear clearly.

Mixed hearing loss - In some cases, such as in complication of recurrent/chronic otitis media, a conductive hearing loss occurs in combination with damage of the inner ear or of the auditory nerve. When this occurs the hearing loss is referred to as a mixed hearing loss.

Conductive hearing loss, mainly due to recurrent otitis media, is reported with a frequency ranging from 24% to 82%. In fact chronic otitis media is extremely frequent in individuals with Kabuki syndrome during childhood. It is probably related either to cleft palate and abnormal development of the Eustachian tube or to immune deficiency. It has to be cured in order to limit permanent hearing loss sequelae (mixed hearing loss).

Sensorineural hearing loss is very rare in Kabuki syndrome. Only a few cases are reported in the literature and are mainly caused by anomalies of the inner ear, however this low prevalence could also be due to incomplete neuro-radiological investigations (CT brain) reported up to now in the medical literature.

Some children may utilize a personal or classroom soundfield FM system, either in conjunction with aids or without. The FM system enhances the distance to noise ratio, in the typical classroom, so that environmental/background noise is decreased while the voice of the speaker is amplified.

Dr. Stefania Barozzi

Dr. Di Berardino

Audiological and Vestibular Findings in Kabuki Syndrome

By S. Barozzi [1], F. Di Berardino [1], A. Selicorni [2]

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[2] Department of Pediatrics, Fondazione Ospedale Maggiore, Mangiagalli e Regina Elena, Milan, Italy

Note: *For complete study results see: Audiological and vestibular findings in the Kabuki syndrome - Am J Med Genet A Jan15;149A(2):171-6 2009 Author: Barozzi S, Di Berardino F, Atzeri F, Filipponi E, Cerutti M, Selicorni A, Cesarani A*

In Kabuki syndrome there is a high prevalence of otolaryngologic problems such as ear diseases (92%), hearing loss (82%) and airways problems (58%) only partially due to the prevalence of cleft palate. *See Fig. 1*

Concerning the external ear, which consists of pinna and external auditory meatus, minor anomalies are typical of this syndrome and have been described by most authors. Prominent large and cup-shaped ears are the most common findings (85-100%) and one of the diagnostic criteria of the Kabuki facies. However aural atresia (absence of the pinna), small external ears or preauricular fistula can also be present along with accessory auricular appendages (preauricular pits).

Hearing loss is also a common finding in Kabuki syndrome and can be of three basic types: conductive, sensorineural or mixed.

- *Conductive hearing loss* occurs when sound is not conducted properly through the outer ear, middle ear, or both, such as in ear canal obstruction or in acute otitis media. It is generally a mild to moderate impairment because sound can still be detected by the inner ear. Generally, with pure conductive hearing loss, the quality of hearing (speech discrimination) is good, as long as the sound is amplified loud enough to be easily heard. This type of hearing impairment can often be medically or surgically treated.

- *Sensorineural hearing loss* is due to the damage of the inner ear, the cochlea, or to the impairment of the auditory nerve. It can be mild, moderate, severe, or profound, to the point of total deafness. It is a permanent loss and it doesn't only affect sound intensity such as the ability to hear faint sounds but also makes it more difficult for you to recognise complex sounds, to understand speech and to hear clearly.

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Conductive hearing loss, mainly due to recurrent otitis media, is reported with a frequency ranging from 24% to 82%. In fact chronic otitis media is extremely frequent in patients with Kabuki syndrome during childhood. It is probably related either to cleft palate and abnormal development of the Eustachian tube or to immune deficiency. It has to be cured in order to limit permanent hearing loss sequelae (mixed hearing loss).

Sensorineural hearing loss is very rare in Kabuki syndrome. Only a few cases are reported in the literature and are mainly caused by anomalies of the inner ear, such as bilateral absence of cochlea with dilated dysplastic vestibule and unilateral enlarged vestibule. This low prevalence could also be due to incomplete neuro-radiological investigations (CT brain) reported up to now in the medical literature.

In our study of ten patients affected by Kabuki syndrome, seven males and three females, with ages ranging from 10 to 25 years, only three showed normal hearing. We found that a slight mild or moderate hearing loss was extremely frequent since it was evident in 70% of the affected ears.

In this group of ten subjects, all hearing losses were conductive or mixed. We didn't find any sensorineural hearing loss, thus confirming that it is a rare disorder in Kabuki patients.

Otomicroscopy was mandatory to study the condition of tympanic membrane and chronic otitis media complications. Pure tone audiometry was easily performed in seven patients, while three non-cooperative individuals required behavioural audiometry (audiometry used in young children).

In the ears with hearing loss the most frequent finding was otitis media and its consequences (otitis media with effusion, serous adhesive otitis media, antroatticotomy and tympanomastoidectomy).

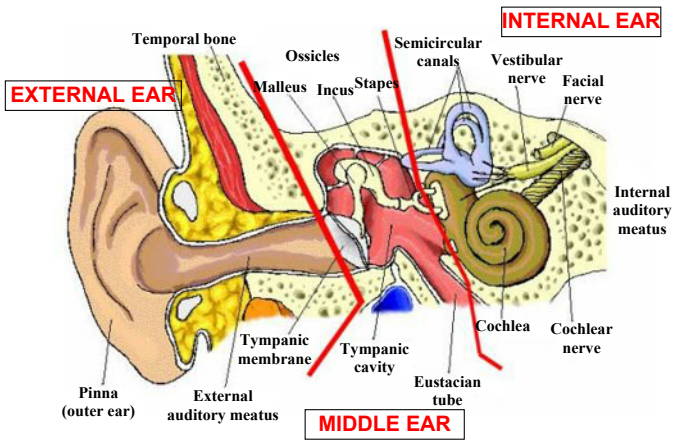


Fig 1

In Kabuki patients, the frequency of otitis media is likely related both to the high incidence of infections and to the Eustachian tube impairment. In our study, none of the seven patients affected by otitis media and its complications had had a cleft palate. These findings support Peterson-Falzone et al. (1977) who indicated that the prevalence of ear disease in Kabuki syndrome cannot be explained solely on cleft palate and suggested that hearing loss in Kabuki syndrome requires the diagnosis and treatment expertise of audiologist and otolaryngologists.

The hearing loss in the other impaired ears was related to aural atresia in one ear and, in 5 ears, it was associated with a normal otomicroscopy and, in immittance audiometry tympanometry, with the absence of stapedial reflexes suggesting a possible ossicular fixation. As reported in literature, the skeletal anomalies frequently observed in Kabuki patients might also involve the middle ear ossicles with a fixation of the joints. Therefore we suggest to always perform a complete hearing test that includes pure tone and immittance (tympanometry and stapedial reflex determination) audiometry.

In our experience the vestibular evaluation was difficult in the Kabuki subjects since they cannot offer the cooperation needed for caloric examination. Caloric test is used to evaluate the peripheral vestibular function through the irrigation of cold and warm water into the external auditory canal. This test can be carried out exclusively in cooperative patients with no anomalies of the external ears, tympanic membrane perforation, or oto-surgical outcomes. In our patients, caloric tests have been possible only in six subjects.

In the restricted group of patients examined for the vestibular function, 92% showed normal results. In particular, all the ears studied with caloric tests were normoreflective. As the vestibular caloric stimulation was impossible in the patient with aural atresia, the implementation of bone VEMPs was useful, revealing a saccular impairment on the side of the abnormal ear. Vestibular Evoked Myogenic potentials can be used to investigate saccular function, measured from the tonically contracted sternocleidomastoid muscles in response to bone conducted sound stimuli at 70 dB SPL. The saccule is a small labyrinthic sac situated between the cochlea and the semicircular canals. Also this test requires patient cooperation to keep the head elevated in order to contract the sternocleidomastoid muscles.

In view of these findings, it would be advisable to study each patient affected by Kabuki syndrome through audiological examinations and reserve the vestibular assessment for selected patients with vestibular symptoms, with sensorineural hearing loss or inner ear abnormalities.

In conclusion we recommend audiological evaluation in all patients with Kabuki syndrome and vestibular assessment in selected individuals.

Speech

Delay in speech and language acquisition is very common, exacerbated by craniofacial anomalies, hypotonia, and poor coordination.

Articulation errors are common and are likely due to oral-motor hypotonia and general poor coordination. It is not felt that structural abnormalities such as velopharyngeal insufficiency, dental malocclusion and cleft palate are major contributors.

Also common is abnormal oral resonance, again likely due to oral-motor hypotonia and not structural abnormalities. Resonance is the quality of the voice as the result of sound vibrations in the pharnyx (throat), oral cavity (mouth) and nasal cavity (nose).

Abnormal prosody, defined as the the rhythm, stress and intonation of speech, is evident in many children. One study showed that the prosody and articulation errors became more pronounced when spontaneous speech increased in length and complexity. It also found that pitch, loudness and prosody did not mature significantly over time, despite ongoing speech services, resulting in inappropriate and difficult to understand speech production by adolescence. More long term follow-up studies of the distinctive speech patterns of Kabuki Syndrome are needed. This will hopefully lead to better tailoring of speech-language therapies, specific for Kabuki.

Theresa Cinotti

Kim Tillery

The CAPD Model and Kabuki Syndrome

By Theresa Cinotti, M.A., CCC-SLP & Kim Tillery, Ph.D., CCC-A

What is Central Auditory Processing Disorder (CAPD)?

CAPD is not how one hears, but rather "what one does with what they hear". Clients with a CAPD display a wide range of functional behavioral limitations: difficulty understanding or remembering auditory information, weak phonemic skills, intolerance to noise, difficulty understanding speech in background noise, frequently require directions to be repeated, substitute improper speech sounds, display weak reading, spelling, organization and comprehension skills, and often act as if they have a hearing loss.

There are different types of CAPD that dictate specific therapy regimens. Decoding type of CAPD involves a breakdown at the phonemic level where the client struggles in understanding each sound, displays weak reading and spelling skills and requires a long time to respond. A second type of CAPD is known as Tolerance-Fading Memory (TFM) which involves weak short-term memory resulting in poor reading comprehension and weak expressive language skills. Often those with TFM forget the first set of information verses the final set. A third type of CAPD is known as Organization, as weak sequencing and organization abilities are characteristic of this type. A fourth CAPD subtype is Integration, involving poor language and phonemic ability and severe reading and spelling delays.

While an audiologist is the professional who diagnosis the types of CAPD, it is usually the speech-language pathologist who provides therapy and who also evaluates language skills. Most individuals with a CAPD exhibit normal hearing. The etiology is unknown although it is speculated that a history of ear infections and genetic links may be related.

LIZ

Liz was first diagnosed at 14 years of age with Kabuki Syndrome. Currently at age 22 years, she presents with several characteristics related to the syndrome, such as a submucous cleft of the palate, hypotonia, visual perceptual difficulty and mild-to-moderate cognitive challenges. Hearing problems include sensorineural (inner ear) and conductive (middle ear) hearing impairment with recurrent bouts of ear infections. In addition she exhibits speech-language delays and increased nasality of speech.

Liz was first referred for a CAPD evaluation at 16 years of age by a reading specialist as Liz could write the grapheme (letters), but was unable to make the sound-symbol relationship. For example, Liz was able to write her name, but did not understand the relationship of the sounds to the letters, an essential precursor to reading, rhyming and spelling. The reading teacher reported a lack of understanding of left to right scanning of words across the page and also noted that Liz was unable to perform on preschool literacy testing.

The CAPD evaluation indicated two subtypes of CAPD: TFM and Decoding and Liz was referred for CAPD therapy. She received two 50-minute therapy sessions, per week for one and half years, targeting the Decoding CAPD subtype. Therapy consisted of Phonemic Synthesis Training Program (Katz and Fletcher, 1982), Visual-Rhyming Therapy, and general auditory training exercises.

Phonemic Synthesis Training Program consists of 15 lessons to expose the client to the concept of sounds in words by auditorily presenting one sound at a time for which the client is instructed to properly blend the sounds into the target word. For example, the client hears: "b-oa-t" and should respond "boat" without any form of delay or struggle. The goal of this program is to enhance the client's ability to properly perceive sounds in words and utilize that skill in higher level of comprehension, reading and spelling tasks.

Visual-Rhyming Therapy is a technique derived from Soundabet, a training activity in the Processing Power program (Ferre, 1997), which assists the client to recognize sounds and sound patterns represented by all graphemes (letters), thus enhancing rhyming skill. For example the

client is presented a target pattern such as "at" and must rhyme this provided word or nonsense word using all probable consonant sounds. The client would respond with, "bat, dat, fat, gat, hat, jat, kat, lat, mat", etc. with the visual cue provided in left-to-right format.

b d f g h j k l m

n p r s t v w y z

Upon the success of accurately blending the above consonants with the target pattern, the chart is expanded to include consonant blends, such as br, bl, dr, fl, fr, and st, etc.
This therapy enhances knowledge of left-to-right reading, phonemic and phonological awareness, rhyming, and sound-symbol awareness, again all skills needed for comprehension, reading and spelling. General auditory training exercises were used to supplement the above therapies. Therapies utilized would be considered aural rehabilitation (AR) therapies, although the impact is often seen in language and written language development.

After completing the above therapies, Liz demonstrated progress in the areas of focus. On the Phonemic Synthesis Test (Katz and Fletcher, 1981), a measure of Liz's sound blending skills, Liz's progress was follows:

Pre Therapy:
4 accurate responses
1 year later:
19 accurate responses

Lesson 12 of the Phonemic Synthesis Training Program was administered as a baseline measure prior to beginning the entire Phonemic Synthesis Program (lessons 1 through 15). On Lesson 12 Liz performed as follows:

Pre Therapy:
2 accurate responses
3 months later:
21 proper responses
1 year later:
39 proper responses

In August of 2002, at 19 years of age, Liz entered a therapy program which focused on further enhancing auditory decoding and phonological awareness skills while concurrently fostering language abilities, in essence combining aural rehabilitation and language therapy techniques for functional generalization of skills learned.

With this new therapy program, sound blending was a continued focus with sound segmentation added to the challenge. Sound segmenting tasks involve an individual hearing a word, perceiving the sounds in the word, and then being able to identify the sounds individually and in sequence, the inverse of a blending task. For example, if asked to segment the word "tent" the individual would be verbally presented with the word and then required to say the sounds "t-e-n-t".

Being able to perceive the sounds in a word is a precursor to actual spelling abilities and an aid to fluent reading. As segmenting skills develop, an individual is then challenged to represent sounds with symbols. At first arbitrary symbols such as blocks may be used and, later, the actual graphemes (letters) will be added. As an example, when segmenting the word "ten" an individual may verbally respond "t-e-n" and place three different colored blocks on the table, representing the three different sounds heard. They then could assign letters to correspond to the blocks to actually spell the word. As segmenting skills and sound symbol association skills increase, an individual's spelling as well as reading skills should subsequently improve. The aforementioned methodology is similar to that advocated in programs such as the Lindamood Phoneme Sequencing Program (Lindamood and Lindamood, 1998), the Phonological Awareness Kit (Robertson and Salter, 1997), and the Ortan Gillingham Program (Institute for Multi-sensory Education), to name a few.

When Liz first began attempting segmenting tasks she required maximal support to separate the sounds in two phoneme (sound) words (ie. no = n-o). As therapy progressed, she was able to consistently identify the sounds in two sound words and also represent the number of sounds heard using arbitrary symbols (colored blocks). Liz continued to progress in segmenting and is currently able to segment four phoneme words using colored blocks and match blocks to appropriate letters with some consistency. Liz is able to match sounds to corresponding consonants approximately 90% of the time with less consistency with matching vowel sounds to letters. However, using this structured system with a speech-language pathologist to guide her through the process, Liz is able to spell two, three, and four sound words with minimal error. Some carryover is seen in spontaneous spelling of words outside of the clinic setting, however, Liz has not fully generalized her skills and continues to work toward independence in this area.

Given that the development of decoding and phonological awareness skills begins in infancy and continues through a child's school years, LS has made remarkable progress in "catching up" over the last six years of her life to reach a level of phonological processing consistent with early readers. Her most recent testing, using the Phonological Awareness Test (Roberson and Salter, 1997) revealed rhyming skills to be at a 5 year 2 month level and segmentation skills to be at a 5 year, 4 month level. Liz's ability to isolate sounds in words (determining what sound

was heard at the beginning, middle, or end of the word) was found to be at a 6 year, 0 month level, and her deletion skills(ability to determine what the remaining sounds in a word are when a sound or set of sounds are deleted – say "bat", say "bat" again without the "b") were found to be at a 5 year, 10 month level.

As Liz continues on her journey toward enhanced skills it is a goal to have her consistently make sound symbol associations for functional vocabulary that she will encounter in her environment or during her daily routine. In addition to using decoding therapies to enhance spelling and reading ability, sight word reading is also a focus to enhance comprehension and use of written words pertinent to Liz's vocational, academic, and personal life. Visualization, association, and first letter cuing strategies are currently utilized to develop Liz's recognition of words. Although Liz requires several weeks for the establishment of each new set of sight word vocabulary, this practice has allowed Liz to use, recognize, and read words too complex at this point in her development to sound out independently. Recently, in addition to sight word recognition, common phrases have been targeted for recognition. The goal is to have Liz recognize common phrases from a list of phrases that she will use as a cue to independently create appropriate written language, particularly targeting e-mail communication with friends and relatives.

(L to R)Theresa Cinotti, Liz S, and Dr. Kim Tillery

In addition to written language (spelling, reading, and writing), Liz's understanding and use of language has been targeted through the years. Particularly, Liz has made outstanding progress in compensating for auditory comprehension issues resulting from language delay and hearing loss and compounded by her auditory recall difficulty and perception related to her auditory processing disorder. Liz has developed and frequently utilizes strategies such as attending to visual cues (body language and lip reading), recognizing comprehension breakdowns, and repairing breakdowns through asking for repetition or clarification.

Liz's expressive language has continued to blossom with therapy targeting expansion of simple utterances to form complex. In addition, pragmatic skills, which are interaction abilities have flourished as Liz's practice and maturity have resulted in improved conversational abilities. As language and auditory processing skills have developed, Liz has been able partake in functional activities geared to enhance daily living through improved organization and problem solving. For example, medication recognition and organization, calendar planning, event planning, and situational problem solving and role-playing have contributed to enhancement of Liz's overall independence. Liz has made outstanding progress through the years in all aspects of her communication and overall development. Liz's successes are likely a function of her positive attitude and the outstanding support that she receives from each of her family members. Liz consistently attends and participates in scheduled sessions, and carryover of skills is facilitated by family as her mother regularly attends sessions and continually communicates with Liz's speech-pathologist, audiologist, and ENT to optimize care. Continued success is projected for Liz's future. Liz's story has been shared at numerous conferences and serves as an inspiration to professionals, conveying the message that those with multiple challenges can achieve amazing feats with the appropriate therapies and supports. Central auditory processing therapies have been integral in Liz's skill development, particularly related to her comprehension skills and her reading, writing, and spelling development. The first step in proper treatment planning is appropriate evaluation. Those suspecting an auditory processing disorder, should consult a qualified audiologist with verbal and written language skills assessed by a speech-language pathologist. It has been an honor to work with Liz and her family. They are truly an inspiration to all.

About The Authors

Theresa M. Cinotti, M.A., CCC-SLP
Clinical Assistant Professor at the University at Buffalo

Theresa is currently the Speech-Language Coordinator and one of the clinical supervisors at the University at Buffalo Speech-Language and Hearing Clinic, a training clinic for graduate students pursuing their master's degree in speech-

language pathology. Theresa runs the Intensive Language and Auditory Processing Program at the University, an intensive summer program which addresses the language and auditory processing needs of children ages 5 years and older. In addition, Theresa coordinates the adult language and auditory processing program at the University, a program which focuses on optimizing processing skills and functional communication for adults with auditory processing and related issues.

Kim L. Tillery, Ph.D., CCC-A
Associate Professor and Chairperson of the Speech Department at SUNY of Fredonia

Dr. Kim Tillery has authored one chapter and co-authored four chapters and several peer-reviewed journal publications regarding Auditory Processing Disorders (APDs) and it's relationship with Attention Deficit Hyperactivity Disorders (ADHD). Invited international, national and state presentations include her research of 1) Ritalin's effects on APD, 2) therapeutic measures for Decoding and Integration types of ADP, 3) the co-morbidity of attention, learning and auditory processing deficits, and 4) how reliable differential diagnosis improves effective management of ADHD, LD and APD. Besides her teaching and research Dr. Tillery maintains a private practice, has served as the Co-President of the Speech-Language and Hearing Association of Western NY (SHAWNY) for two-years, received the 2003 SHAWNY Award for her dedication and service to the communicatively disabled of WNY, and serves on other Professional Advisory Boards and Committees.

Visual

More common ocular conditions can include:

- blue sclerae
- strabismus
- coloboma
- ptosis
- micropthalmia

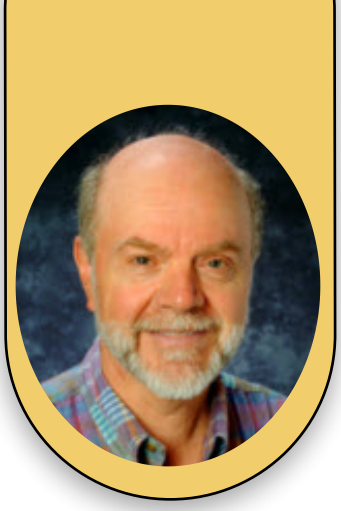
Less common conditions can include:

- nystagmus
- Peters' anomaly
- Marcus Gunn phenomenon
- optic nerve hypoplasia
- obstructed nasolacrimal ducts
- refractive anomalies

Dental

Teeth are often wide spaced, irregularly shaped and/or misaligned. Hypodontia is common, in particular missing upper incisors.

Sensitivity to oral stimulus frequently interferes with proper oral hygiene.



Important Dental and Orthodontic Issues for Children with Kabuki Syndrome

By Bryan J. Williams DDS, MSD, MEd

Pediatric Dentisty and Orthodontics

Oral health is important for all children but is especially important for children with special medical and/or developmental challenges. Children with Kabuki Syndrome have a complex array of special features and functional challenges. Good oral health and proper dental follow up is an important element in the overall care pathway for these children. This paper outlines important issues in dental development, oral health care, facial growth and development and orthodontic care.

Facial Growth Patterns

Children with Kabuki Syndrome have characteristic facial features that have been well documented and described in the literature and this paper will not describe these in detail. As we well know, there is classically some flatness in the cheek areas below the eyes and lack of forward projection of the cheek bones. The lower portion of the face is often disproportionately long compared to typically developing children. This pattern of facial features is rooted in the growth patterns of the jaw structures and the neuromuscular environment. In this paper we will focus on the underlying facial development which has implications for facial pattern, jaw alignment, dental development, and oral health.

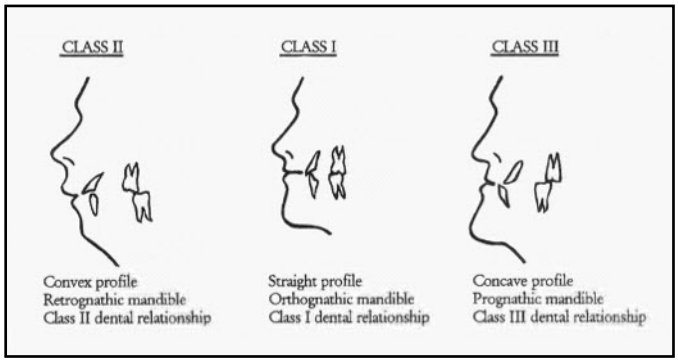


Figure 1: Common Patterns of Facial and Jaw Development

Overall jaw growth and bite relationships are classified into three patterns (Class I, II and III). These patterns result from the relative growth of the two jaws and can be seen in Figure 1. If the upper and lower jaws are in balance this is called a Class I pattern. The bite will be ideal in the molars and the front teeth with the lower front teeth biting slightly behind the upper front teeth. The facial profile will be ideal as well. A Class II pattern occurs when the lower jaw is shorter than the upper which alters the bite on the molars and front teeth. In these children the lower front teeth fit well behind the upper front teeth and commonly these children are said to have an "overbite". These children have a profile where the chin seems receded and/or the upper front teeth appear to protrude. A Class III pattern occurs when either the upper jaw is too short or the lower jaw is too long or both. In children with a Class III pattern the lower front teeth are in front of the upper front teeth and this is called a crossbite. The facial profile will seem like the chin is protrusive. Jay Leno is a good example of a person with a Class III jaw growth pattern.

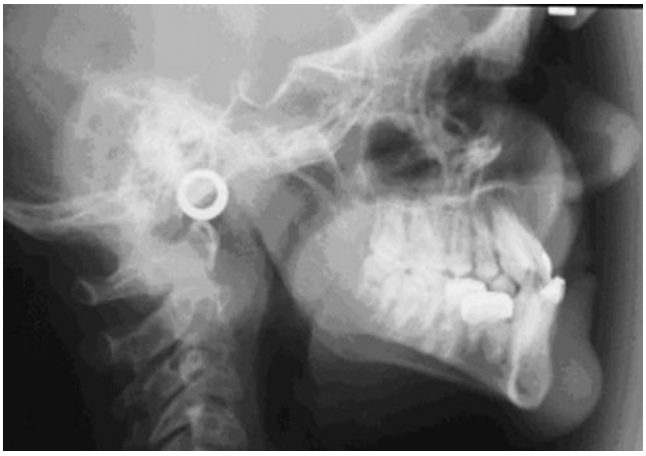


Figure 2: Lateral Jaw Xray of 12 Year Old Male with Kabuki Syndrome

In the Caucasian population Class III patterns are seen in between 1 and 3% of the population. For children with Kabuki Syndrome this is much more common and is the most frequent jaw development pattern. In many children with Kabuki Syndrome this is due to underdevelopment of the upper jaw relative to the lower. Children who have this pattern of jaw growth have less projection in the cheek bone area and the face may appear flatter than ideal in this area. Due to the jaw growth pattern it is also more common to see a crossbite of the front teeth with the lower front teeth in front of the upper. Figures 2 and 3 show a lateral jaw x ray and tracing of a 12 year old male with Kabuki Syndrome. His Class III pattern shows the upper jaw

behind the lower and lower front teeth which are ahead of the upper front teeth. Children with Kabuki Syndrome also often have a tendency to a long lower facial proportion. This relates to a lower jaw which is canted downwards more steeply than ideal. The feeling is that this relates to the neuromuscular pattern where the jaw muscles are more lax allowing the lower jaw to develop at a steeper angle. Figure 4 shows a jaw x ray tracing of a 7 year old girl with Kabuki Syndrome. The lower jaw angle is steep when compared to a tracing of a typically developing child (Figure 5).

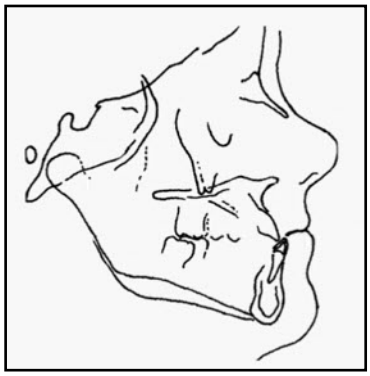


Figure 3: Lateral Jaw X Ray Tracing of 12 Year Old Male with Kabuki Syndrome

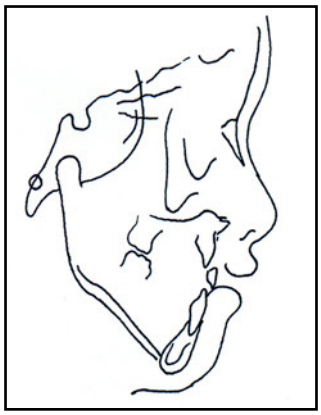


Figure 4: Lateral Jaw X Ray Tracing Showing Steep Angle of Lower Jaw

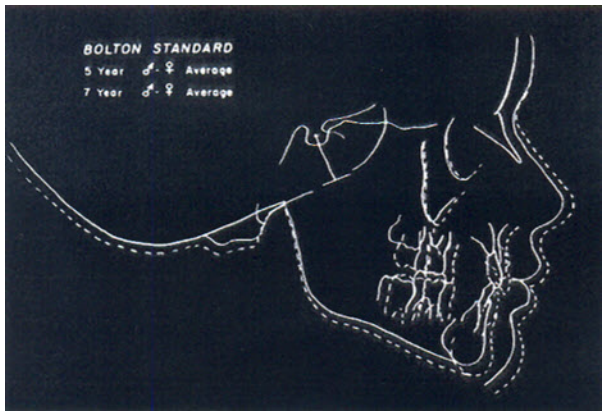


Figure 5: Typical Jaw Development from the Bolton Growth Study - Cleveland OH

The tendencies to have length and angular imbalances in jaw development have significant implications for facial growth, the bite and for potential orthodontic treatment. From the parents perspective it can cause a disconcerting change in the bite as the child matures. Often when the baby teeth are present the bite may look fine to the parent but as the jaw development progresses the bite may become more noticeably irregular. This usually becomes more obvious when the permanent teeth are beginning to erupt. Often this is when the child will be taken for a consultation with an orthodontist. For children with Kabuki syndrome, it is especially important that the orthodontist do a thorough evaluation of the underlying jaw development pattern in advance of initiating any orthodontic treatment. The biting pattern of the teeth is most often a result of the growth pattern of the jaws and not just malposition of the teeth. Treatment options must be carefully assessed in order to optimize outcome. Given the pattern of the neuromuscular environment, children with Kabuki Syndrome may not have the same options for orthodontic treatment as typically developing children where sometimes during growth muscle forces can be harnessed to improve the bite and jaw positions. In children with Kabuki Syndrome with significant jaw length abnormality or vertical jaw imbalance ideal correction may necessitate integrating jaw repositioning surgery into the orthodontic management plan. Obviously careful evaluation of the child's overall medical and developmental status is important prior to considering significant treatment like jaw repositioning surgery.

Other Important Oral Findings

Once there is an understanding of the overall jaw development pattern there are other important oral and dental development issues.

First it is important to realize that over 50% of children with Kabuki Syndrome have some significant cardiac anomaly. For certain dental procedures and with certain types of cardiac issues it will be necessary to provide prophylactic antibiotic coverage in advance of many dental appointments. The American Heart Association has recently revised the guidelines for antibiotic premedication for children with cardiac irregularities (April 2007). It is important that your dentist be familiar with the new guidelines.

The literature shows that high arched palate is common in children with Kabuki syndrome. Cleft Palate occurs in excess of 50% of the children. Cleft Palate has significant implications for breathing, feeding, speech, jaw development and dental development. Optimum management for children with cleft palate requires a coordinated management plan from the time of birth. The management plan should involve a team of specialists who

will provide well coordinated care for all of these significant issues.

In addition to some degree of laxity of the muscles that position the lower jaw, children with Kabuki Syndrome also have a higher risk of laxity in the ligament and muscular structures that position the temporomandibular joint (TMJ) which is the hinge between the base of the skull and the lower jaw. Although the literature doesn't indicate that a high proportion of the children have problems with dysfunction of the TMJ it is important for the child's dental professional to monitor the function of the joint during routine checkup visits.

Children with Kabuki Syndrome commonly have dental anomalies that can affect the shape, size and number of teeth. The two upper front teeth (central incisors) often have a characteristic shovel shape where the lower edge of the tooth is narrower than the mid portion. This is opposite to the normal shape of this tooth where the lower edge is the widest part of the tooth. This is a dental anomaly that is very rarely found in other children and the presence of shovel shaped central incisors is one diagnostic sign that is helpful in formulation of a diagnosis of Kabuki Syndrome. The dentist can improve the shape of the central incisors with simple cosmetic bonding materials. Children with Kabuki Syndrome often have agenesis or lack of formation of one or more permanent teeth resulting in missing permanent teeth. This most commonly involves the upper lateral incisors which are the teeth next to the big front ones (central incisors). When permanent teeth are missing there are a number of management options that your dentist can consider and discuss with you.

Maintaining Basic Dental Health

For any children with special health needs the maintenance of good dental health is very important. Children with Kabuki Syndrome can have intellectual and behavioral parameters which make dental treatment difficult. For these children it is extremely important to prevent dental disease in order to avoid the need for treatment which could be difficult to accomplish.

In simple terms there are two dental diseases that should concern any parent. One is dental caries or what is commonly referred to as decay or cavities. The second is inflammation or infection of the gum tissue which is periodontal disease. Usually in children severe periodontal disease is uncommon but gingivitis which is an early stage of the disease is much more common. Both cavities and gingivitis have a common cause in that certain types of bacteria in the mouth digest sugar containing foods and secrete acids and toxins which attack the teeth and the gum tissue.

Preventing cavities and gingivitis is therefore relatively straightforward with three key actions by parents and children being important. One is to disrupt the bacteria and food that is left around the teeth by at least twice daily tooth brushing. Also in a child who is cooperative, flossing is of great value in cleaning the areas between the teeth that can't be reached by the toothbrush. Second, teeth can be strengthened by the use of fluoride which hardens the tooth enamel and makes it more resistant to decay. The fluoride can come in many forms including community water fluoridation, fluoride in toothpaste, fluoride supplements by prescription if you live in an area where the water is not fluoridated, or professionally applied fluoride treatments. The third factor in preventing dental disease relates to control of the diet. Sugar containing foods provide food for the bacteria and also if a child snacks frequently (or constantly) there are some natural cavity healing mechanisms in the mouth that don't have a chance to work. Many of the dietary habits that increase a child's risk for cavities also are unhealthy for other concerns like childhood obesity.

Regular ongoing dental care is an important part of good medical care for a child with Kabuki syndrome. The American Academy of Pediatric Dentistry recommends the first dental visit be around one year of age. This provides an opportunity to have a base line evaluation, have your questions addressed and with the dentist develop a long term plan to assure the child will grow with good dental health. In a child with complex long term health and developmental needs it is even more important to get a very solid and early start on good oral health.

Immunity and Blood Disorders

Virtually all children are more susceptible to recurrent ear infections in their early childhood years. It is unclear whether the infections are secondary to underlying immune deficiencies. Craniofacial abnormalities, including cleft palates, may also be a contributing factor. It is significant to point out that the typical toddler has approximately 11 upper respiratory infections a year.

Recurring renal tract infections have been reported. Other disorders can include Idiopathic Thrombocytopenic Purpura (ITP), autoimmune hemolytic anemia, polycythemia, hypogammaglobulinemia, and selective IgA deficiency.

Immune and Autoimmune Issues in Kabuki Syndrome

By Jeffrey E. Ming, MD, PhD

About Author:
Jeffrey E. Ming, MD, PhD, is in the Division of Human Genetics at the Children's Hospital of Philadelphia. He has seen over 35 children with KS and has written medical articles on immune issues and other aspects of KS. He is also conducting research studies in order to understand the genes that cause KS.

We all get exposed every day to many things that can cause infections, and we all know how easy it is to catch a cold if a family member or co-worker is sick. The body relies on the immune system to fight infections from germs such as viruses, bacteria, or fungi. But if the body's immune system is not working well, a person can get infections more often and have a harder time getting better.

Many children with Kabuki syndrome get an increased number of infections. Although not all of these children have a problem with the immune system, some children with KS do have an immune system that is not working completely properly. For example, an immune problem, or immunodeficiency, can be a cause of more frequent and/or more serious infections. The extent and severity of the infections depends on the degree to which the immune system is affected. There are medications that can be given if a child is found to have an immunodeficiency.

A number of doctors have seen that there can be immune problems in children with KS, and in children that we have evaluated at The Children's Hospital of Philadelphia, many have decreased antibody levels. Antibodies (also called immunoglobulins) are made by immune cells and are found in the blood. Antibodies are critical for the body to handle infections effectively. If the antibody levels fall very low, there is a much greater chance that a person will get an infection, and it will be harder for the body to fight off the infection. There are several different types, or classes, of antibodies. The major classes are IgG, IgM, IgA, and IgE. When the antibody levels are low, usually only some, not all, of the antibody classes are decreased. The severity of infections will depend on which of these classes are low, and how low the levels are. The levels of each class of antibody can be easily measured with a blood test. We do not know exactly why the immune problems happen in KS, although it is probably due to a change in a gene that is different in individuals with KS.

We also know that autoimmune conditions seem to occur more often in children with KS. However, most children with KS do not develop an autoimmune condition. An autoimmune condition is a disease in which the body's immune system causes damage to its own cells and tissues. Autoimmune conditions that have been seen in children with KS include those that affect the thyroid, the skin (vitiligo, a localized decrease in skin pigment), and blood cells (anemia, low platelets). The fact that autoimmune problems occur more often in people with KS is probably related to the fact that immune problems may also be seen in children with KS, although a person does not have to have a known immune problem to have an autoimmune disease.

In order for the immune system to work properly, it has to be able to detect an infection and send the right cells into action to fight off that particular infection. That is, the immune system is regulated in a very precise way. The immune system is also regulated so that it does not attack the body. So, problems with regulation of the immune system can cause the immune system to not function properly, either by not responding well to infections or by failing to ensure that the immune system does not attack the body. Therefore, it is likely that suboptimal regulation of the immune system underlies the immune and autoimmune issues that can be seen in children with KS.

Checking of antibody levels should be considered for children with KS who are more than one year old or if there are symptoms of an immunodeficiency. If there are any deficiencies, the child should be seen by a pediatric immunologist. Also, if a child seems to be having more infections or more serious infections than most children, the immune system should be checked. It should be remembered that if the antibody levels are only mildly low, there may not be any problems with fighting infections. However, this is still good information to know because it will be important to have an immunologist follow the antibody levels over time in case the antibody levels get lower. Also, the immunologist will be alert about infections so that the proper treatment and immune diagnosis can be given quickly.

Hypoglycemia - How it Relates to Kabuki Syndrome

By Dr. Mark Hannibal, M.D., Ph.D., FACMG, FAAP

About Author:
Dr. Mark C. Hannibal is a clinical geneticist and immunologist at the University of Washington School of Medicine. He has a research interest in Kabuki syndrome. Along with Dr. Hiroshi Kawame, Dr. Bonnie Pagon and Dr. Louanne Hudgins, he published a case series of Kabuki syndrome patients in the Journal of Pediatrics. Dr. Hannibal now follows many patients from Washington state, Idaho and Alaska

Hypoglycemia, or the presence of low blood sugar, usually measured as glucose, is most often reported as a short-lived problem in newborns with Kabuki syndrome. Glucose is the primary fuel source for the brain. If the glucose levels remain low, below an accepted "safe" level of about 60 mg/dl, it may expose a child to the risk of brain injury. Some individuals with Kabuki syndrome, however have persistent hypoglycemia throughout infancy and childhood. The underlying cause has not been found in most cases—most likely because it has not been studied well and reported in the medical literature. There are case reports suggesting some may release too much insulin—a hormone made in the pancreas that helps to lower and regulate blood sugar levels. There have also been cases reported of other hormone deficiencies that to some degree regulate blood sugar levels. These include growth hormone, adrenocorticotropic hormone (ACTH) and cortisol. There may also be other undescribed biochemical or metabolic reasons for some children with Kabuki syndrome to have hypoglycemia.

The behavioral symptoms of hypoglycemia, which overlap with nonspecific normal behaviors, can be easily overlooked. Most children experience some of the following symptoms. Infants with low blood glucose may have, low tone or floppiness (hypotonia), poor feeding, seizures, and pauses in breathing (apnea). In older children, symptoms may include sudden irritability, hunger, nervousness, shakiness, perspiration, dizziness, lightheadedness, sleepiness, confusion, difficulty speaking, or feeling anxious or weak. Suggestions that low blood sugar may occur at night, while sleeping, include crying out or having nightmares, or finding pyjamas or sheets that are damp from sweating. Children may be tired, irritable, or confused when they wake up. As you can see, these symptoms are common childhood behaviors, so there is some intuition required to feel that your child "just isn't right" and request that your physician begin to explore if low blood sugar is a possible cause. A simple test parents can do to confirm their suspicions is to see if the symptom is relieved by providing a source of simple sugars, such as a half cup of fruit juice, sugar candies (~eight lifesavers), a quarter cup of raisins, etc. The symptoms should resolve within ten to twenty minutes after eating if it is due to low blood glucose.

What is done for hypoglycemia? In most cases, a pediatric endocrinologist should help with diagnosis and management. First—how often does it occur? The amount of time that the patient's blood sugar is low is determined—often while a child is hospitalized, but it may be initiated with home blood glucose testing. At home, blood sugar may be monitored with a blood glucose meter identical to the device that an individual with diabetes mellitus would use. Treatment is tailored to the severity of hypoglycemia and its cause. Specific recommendations are impossible to recommend at this time, because no one common cause has been found for hypoglycemia in Kabuki syndrome. Minimally, simultaneous measurement of blood glucose and insulin levels should be performed. Usually, if a person has low blood glucose, insulin secretion is suppressed and measures very low. Measurement of the amount of glucose needed to keep blood sugars in the normal range should be done (determined by milligrams of glucose needed per kilogram
of patient per minute). Additional testing to assist in the diagnosis of a cause of hypoglycemia may include measuring free fatty acids, lactic acid and ketone bodies in the blood as well as ketone bodies in the urine during an episode of hypoglycemia. Beyond these tests, evaluation and interpretation of results becomes much more complex, with measurement of other hormones, organic acids or acylcarnitines. A glucagon stimulation test may be necessary. For unusual cases, the best evaluation is probably achieved by an endocrinologist working in conjunction with a biochemical genetics specialist.

Treatment is directed at making sure sufficient food is provided to prevent low blood glucose. Frequent feedings and avoidance of prolonged fasting may be necessary, but some individuals have required continuous drip feeds through a feeding tube or modified formulas and supplements. Stressful situations, such as illnesses, even minor viral infections, may make management of

hypoglycemia difficult. In the case of prolonged inability to take food or to keep food down because of vomiting, other methods of maintaining blood sugar levels are necessary. An intravenous (IV) line, placed in a vein, can be provide glucose with IV fluid. The amount of glucose and rate of fluid provided will need to be individualized for each patient depending on the assessment of their clinical condition.

There are few reports of treatment of hypoglycemia in patients with Kabuki syndrome beyond the need for frequent feedings. Perhaps some have been treated with medications that are used for some other causes of hypoglycemia, such as producing too much insulin. One such drug, Diazoxide (trade name Hyperstat or Proglycem in the USA), may be used in combination with other drugs to keep the blood sugar in a safe range. Clearly, further reports of management of hypoglycemia in Kabuki syndrome are needed. Since it is a rare complication of a not-so-rare genetic syndrome, no one physician will have much experience. The Kabuki Syndrome Network can serve as a clearinghouse to connect family and physicians so that there is increased awareness of the potential for hypoglycemia.

I would be interested to hear about the experience of families, because this is clearly an area of management that requires more study.

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Cardiac

Approximately half the children diagnosed with Kabuki syndrome will have a cardiovascular malformation. Diverse conditions are reported, but the most common are juxtaductal coarctation of the aorta, ventricular septal defect and atrial septal defect. Often there is a combination of these defects in an infant.

Since the cardiac conditions are congenital, during the formation of the heart, no further defects should occur. Diagnosis of the cardiac conditions often occurs prior to diagnosis of Kabuki syndrome.

Cardiac Defects in Patients with Kabuki Syndrome

By Grace C. Kung, MD, FASE, FACC

About Author:
Dr. Grace Kung is a pediatric cardiologist at Children's Hospital Los Angeles and Associate Professor of Clinical Pediatrics with USC Keck School of Medicine. She specializes in non-invasive imaging and is a fellow of the America College of Cardiology and American Society of Echocardiography.

Kabuki syndrome, also known as Kabuki make-up syndrome and Niikawa-Kuroki syndrome, was initially described in 1981 by Niikawa and Kuroki [8]. Most patients have five cardinal features: distinct facial features, postnatal growth retardation, developmental delay or mental retardation, skeletal abnormalities and dermatoglyphic abnormalities which are referred to as a persistence of fetal fingerpads. At present, the diagnosis is made clinically. A prior review by the original investigators Niikawa and Kuroki reported a population of 62 patients with Kabuki syndrome and associated cardiac defects in up to 31% of patients [8]. Since then, there has been a series reported with 35 patients with an incidence of associated congenital heart disease as high as 58% [3]. Overall, associated cardiac defects have been well documented [4,6,7,9,11].

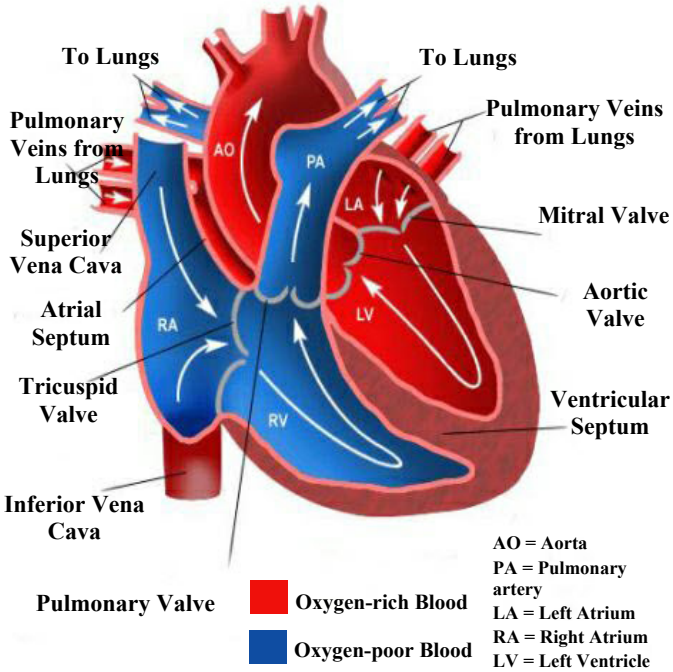

Fig 1: <u>Normal heart</u> with four chambers , two on the right and two on the left

As a brief review of the anatomy of the heart and circulation, the heart consists of four chambers (Figure 1). There are two right sided chambers which receive the blood from the body after it has delivered the oxygen to the tissues and then pumps it to the lungs to receive more oxygen. Then the blood with oxygen returns to the left sided chambers to be pumped to the body to deliver the oxygen to the tissues again. In a fetus, there is a communication between the right and left upper chambers and it usually closes after birth. Otherwise in a normal heart, there is no communication between the right and left sides. A fetus also has an extra blood vessel called a patent ductus arteriosus (PDA) that it uses in the womb to divert blood away from the lungs since it is not breathing and this vessel also usually closes after birth.

The majority of the cardiac defects have been what are called 'shunt lesions', such as atrial and ventricular septal defects and patent ductus arteriosus, also known as ASD, VSD and PDA respectively [13] (Figures 2 ,3 and 4). VSDs and PDA can be detected by listening to the patient's heart and hearing a certain type of murmur. The finding is confirmed by performing and ultrasound of the heart, also known as an echocardiogram. These are called shunt lesions because there is a communication between right and left sides of the heart and allows extra' shunting' of blood flow to the lungs. This results in excess blood flow to the lungs and depending on how much there is, may result in extra fluid in the lungs and dilation of the heart. These lesions, if they occur in isolation, are

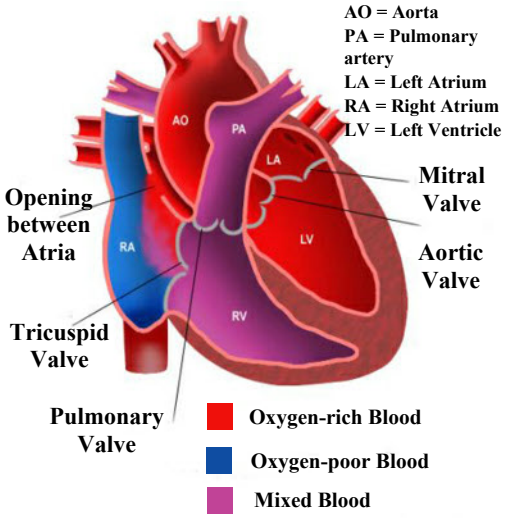

Fig 2: Heart with a communication between the two uppor chambers - atrial spetal defect or <u>ASD</u>

treatable either by cardiac catheterization device closure or with more traditional surgical closure. Device closure involves placing a catheter in the patient's leg and using that catheter to enter the heart and place a device to close the hole for an ASD or to close off an open blood vessel in the case of a PDA. Surgery involves an incision on the chest and placement on a cardiac bypass machine for the surgery.

They have also been finding problems with the left sided heart structures in up to 29% of cases. One specific lesion that is found is called Coarctation of the aorta (CoA) and is a narrowing of the aorta, or the large vessel that exits the heart to deliver blood to the body (Figure 5). This can result in diminished blood flow to the body and stress on the heart. This can be detected clinically if the patient has poor pulses or lower blood pressures in the lower body as compared to the upper body. This can also be diagnosed by echocardiography. Depending on the patient's age and severity of the narrowing, this can be addressed either by a balloon or stent in the catheterization lab or, if needed, by surgical widening of the narrowed area. The balloon or stent procedure consists of introducing a catheter from the blood vessel in the patient's leg to the area of narrowing and then inflating a balloon to dilate the narrowed area or using the balloon to place a stent to open up the narrowed area. The balloon and catheter are then removed. Surgical correction requires an incision in the chest and placement on cardiac bypass for the surgery. Coarctation of the aorta is also a common finding in patients with Turner's syndrome leading some to hypothesize an overlap between Kabuki syndrome and Turner syndrome [1,5].

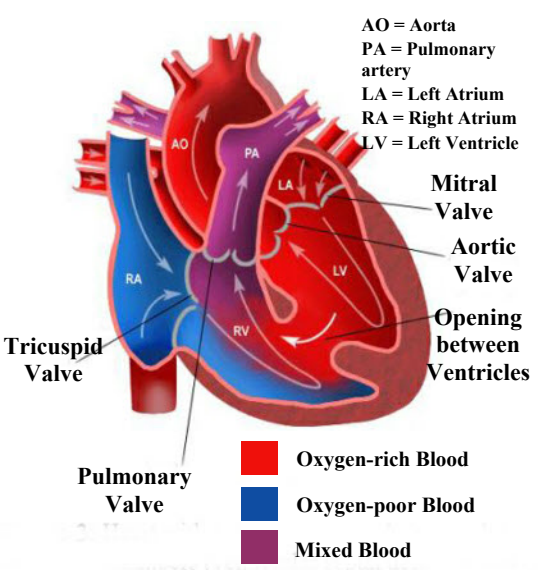

Fig 3: Heart with a communication between the two lower chambers - ventricular septal defect or <u>VSD</u>

There are also more severe types of heart defects that can be found in patients with Kabuki syndrome including Tetralogy of Fallot (TOF) and Transposition of the Great Arteries (TGA). The most significant type of defect is referred to as a 'single ventricle physiology' meaning that there is only one functioning ventricle instead of two. We did a case report of such a finding in three patients specifically with what is called Hypoplastic Left Heart Syndrome (HLHS) where the left side of the heart is significantly smaller and cannot function properly [14]. These patients cannot simply have a hole closed or a narrowing made bigger, they need multiple surgeries to eventually separate out the unoxygenated blood from the oxygenated blood. Fortunately, this finding is very rare, as only 5 such cases have been reported in the literature.

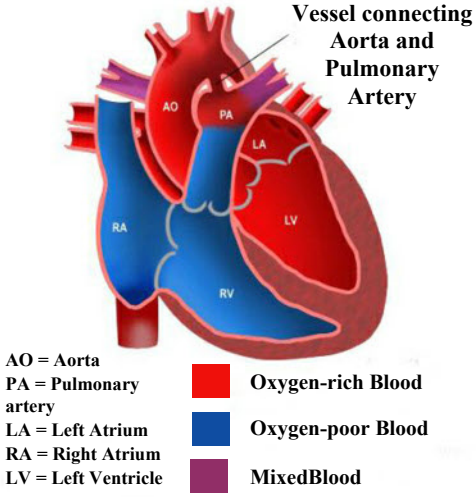

Fig 4: Heart with a persistent blood vessel between the aorta and pulmonary artery - patent ductus arteriosis or <u>PDA</u>

These are all considered congenital heart defects and occur when there is a problem with how the heart is formed very early on at about 6-8 weeks gestational age. Most of these defects can even be detected pre-natally by a specialized ultrasound focusing on the baby's heart called a fetal echocardiogram after 20 weeks gestation age. Some lesions such as an ASD, PDA and CoA are harder to see pre-natally but can be diagnosed after the baby is born by ultrasound as well. Once the heart has finished forming, it is unlikely that further defect will occur. After the baby is born, another echocardiogram is performed to confirm any abnormal finding on the fetal echocardiogram. Since these are abnormalities of formation of the heart, no further defects should occur. How the baby does will depend on the specific cardiac

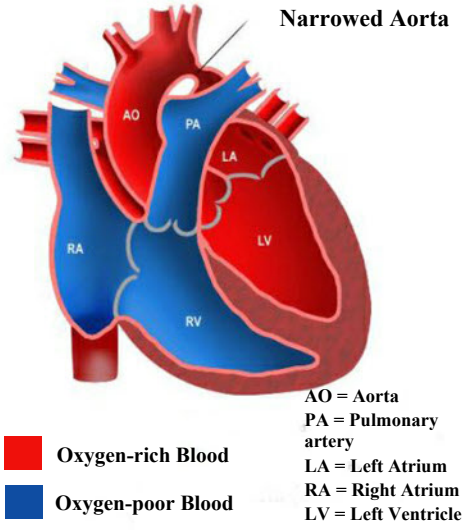

Fig 5: Narrowing of the aorta - coarctation of the aorta or <u>CoA</u>

defect and how they respond to any intervention that may be needed.

The main difficulty with Kabuki syndrome is that it can be hard to diagnose as an infant whereas most of these cardiac defects are diagnosed either pre-natally or within the first month or so of life, often in the neonatal period. In fact, the features typical of Kabuki syndrome may be under-recognized and underappreciated in the neonatal period, only to become more pronounced with time and patient growth [12]. The cardiac disease often occurs before the diagnosis of the syndrome, thus we also propose that patients with left-sided heart defects, including HLHS, who have normal chromosomes, developmental delay and growth failure may benefit from periodic genetic evaluations during the first few years of life to assess for Kabuki syndrome and to assist parents in counselling and prognosis.

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Neurological Disorders

Most individuals with Kabuki Syndrome have mild to moderate intellectual disability, with a small percentage falling in the severe range. Hypotonia is characteristic of Kabuki, hampering motor development and feeding.

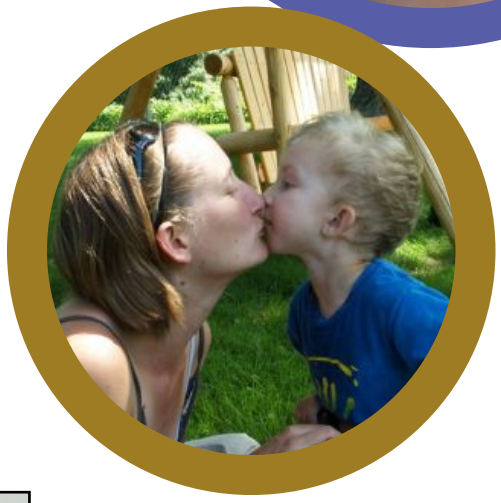
To date, there is very limited information available on the developmental outcome of individuals with Kabuki Syndrome. One such study dedicated specifically to intellectual and adaptive behaviors, identified a clear pattern of weakness in visuospatial construction and relative strength in verbal and non-verbal reasoning. One published article, describing the long-term follow-up of three individuals, found that although they were able to achieve independent daily living skills and hold part-time jobs, they required sheltered living environments. Appropriate long-term planning will be essential.

Hypotonia is a very common characteristic, although studies show an improvement with age. Other neurological abnormalities include microcephaly and seizures. There does not appear to be any one type of seizure associated with KS, although the majority have localization-related epilepsy. The age of onset can range from infancy to middle childhood.

Endocrine and GenitalUrinary Disorders

Hypoglycemia is usually a short-lived problem in infants, but it has also been reported in older children. Vigilant monitoring during fasting periods for surgeries is essential.

Renal tract infections can occur, sometimes due to structural abnormalities and/or immune dysfunction. Common renal anomalies include renal dysplasia, renal agenesis, horseshoe kidney, and ectopic kidney. Ureter abnormalities include obstruction, reflux, and duplication.



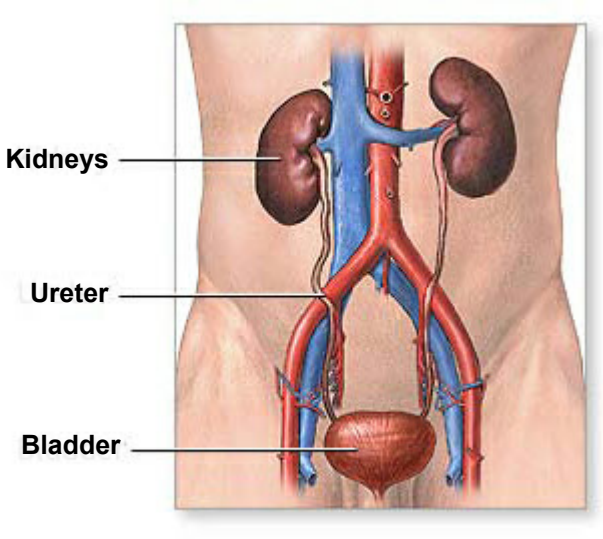
Undescended testes, hypospadias, and small penis have all been reported. A significant amount of girls have premature breast development and, rarely, premature onset of puberty. Growth hormone deficiency, congenital hypothyroidism, and insulin-dependent diabetes mellitus are all rare findings in KS.

Kidney Anomalies in a Person with Kabuki Syndrome

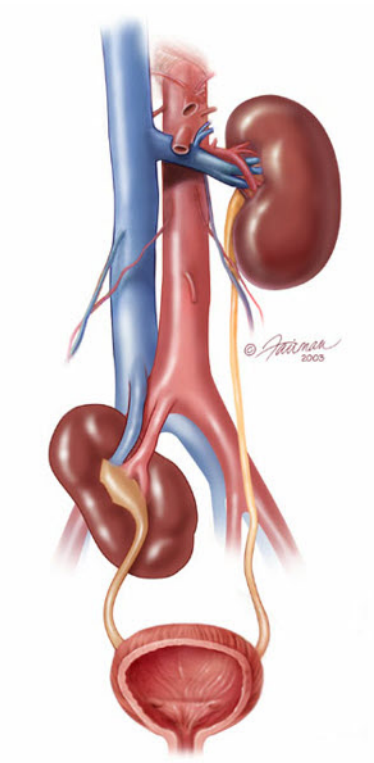
By Doctor Paul Henning, Pediatric Nephrologist

Note: Not all persons with Kabuki Syndrome are affected by kidney anomalies

Approximately 25% of persons with Kabuki Syndrome can present with renal anomalies. They represent anatomical abnormalities in foetal development and may cause clinical problems over a wide range of severity. Anomalies that have been reported include hydronephrosis (associated with obstruction of the urinary tract or vesico-reteric reflux), ectopic kidneys, horseshoe kidney (fusion abnormalities), renal dysplasia (and probably renal agenesis) and ureteric duplication.



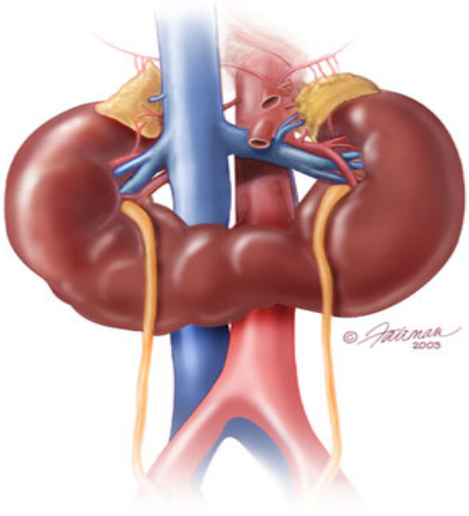
Normal Kidneys



Ectopic Kidney

Many of these anomalies may be asymptomatic but they do carry an increased risk for urinary tract infection and less frequently renal calculi. Kidney damage may arise from these problems and occasionally surgery is indicated. Renal tract ultrasound to detect anomalies is justified and appropriate screening for urine infection should be undertaken if anomalies are identified. Referral to a urologist or nephrologist may be needed where severe or complex abnormalities are present.

Significant loss of renal function is uncommon in Kabuki Syndrome patients but when present has usually been associated with congenital renal dysplasia (sometimes in a single kidney). A very small number of individuals have been reported to reach end-stage kidney failure. Dialysis and kidney transplantation have been successfully performed.



Horseshoe Kidney

GastroIntestinal System

Gastroesophageal reflux is prevalent in young children with Kabuki Syndrome, hindering the child's health, appetite and growth. Undiagnosed diarrhea and/or constipation is commonly reported. It is suspected that hypotonia may be a contributing factor.

Although less common, structural and functional abnormalities of the abdominal organs can be serious. These may include diaphragm hernias or eventration, malrotation of the intestines, and abnormalities with the anus or rectum in the form of anal atresia, anovestibular fistula or anteriorly placed anus.

Ectodermal

Individuals with Kabuki syndrome can have hyperelastic skin, suggestive of a connective tissue disorder. The hands feel soft and are short with short fingers, in particular the fifth fingers. Persistent fetal fingertip pads is highly characteristic of Kabuki syndrome. Mild cutaneous syndactyly is common, usually between fingers II/III or III/IV.

Individuals can have abnormalities with the nails, hair and skin. Nails can be absent, incompletely formed and fragile. Brittle hair, irregular diameter and twisting of shafts, and increased body hair have been rarely reported. Many parents report a rosy, dry appearance to their children's cheeks for no apparent reason. A significant number of individuals have a sacral sinus or dimple.

Anesthesia Concerns

Hypoglycemia is usually a short-lived problem in infants, but it has also been reported in older children. Vigilant monitoring during fasting periods for surgeries is essential.

Certain physical (structural) features associated with Kabuki syndrome could complicate the effects of anesthesia. These may include:

- Micrognathia
- Obstructive sleep apnea
- Stenosis of central airways
- Renal abnormalities
- Diaphragmatic eventration
- Cleft or high arched palate
- Hypotonia
- Cardiac anomalies
- Seizures
- Scoliosis