

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.

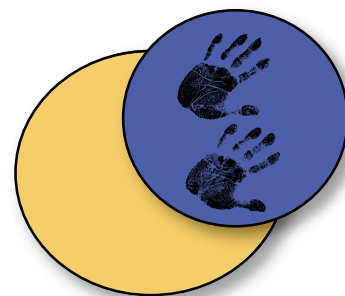
After all, a delayed flight does eventually arrive! We are not suggesting that we get hung-up on the terms we use, just that they are respectful and accurate for the situation.

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. Please contact Peta Colton - petal@sakks.org - at SAKKS for updated information on testing within Australia.

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

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.

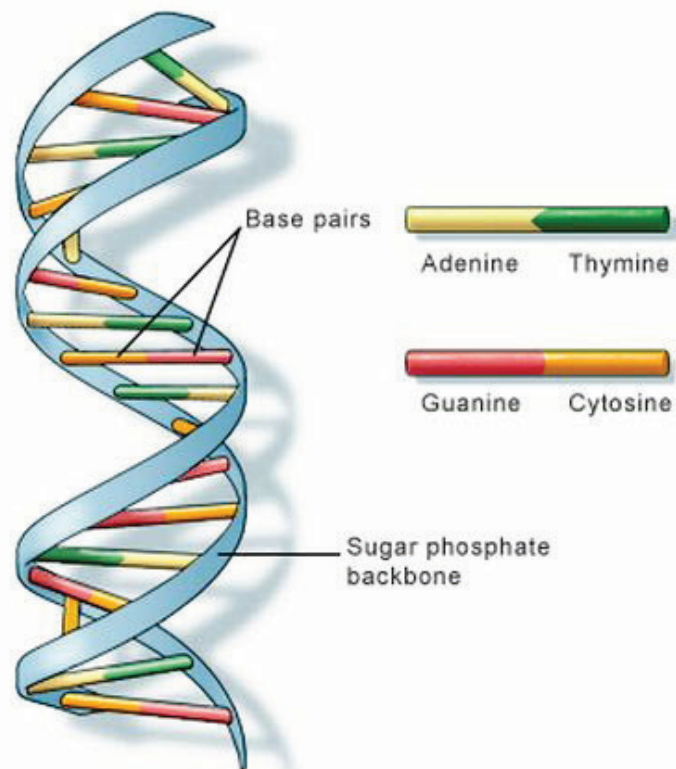


Figure 1

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.

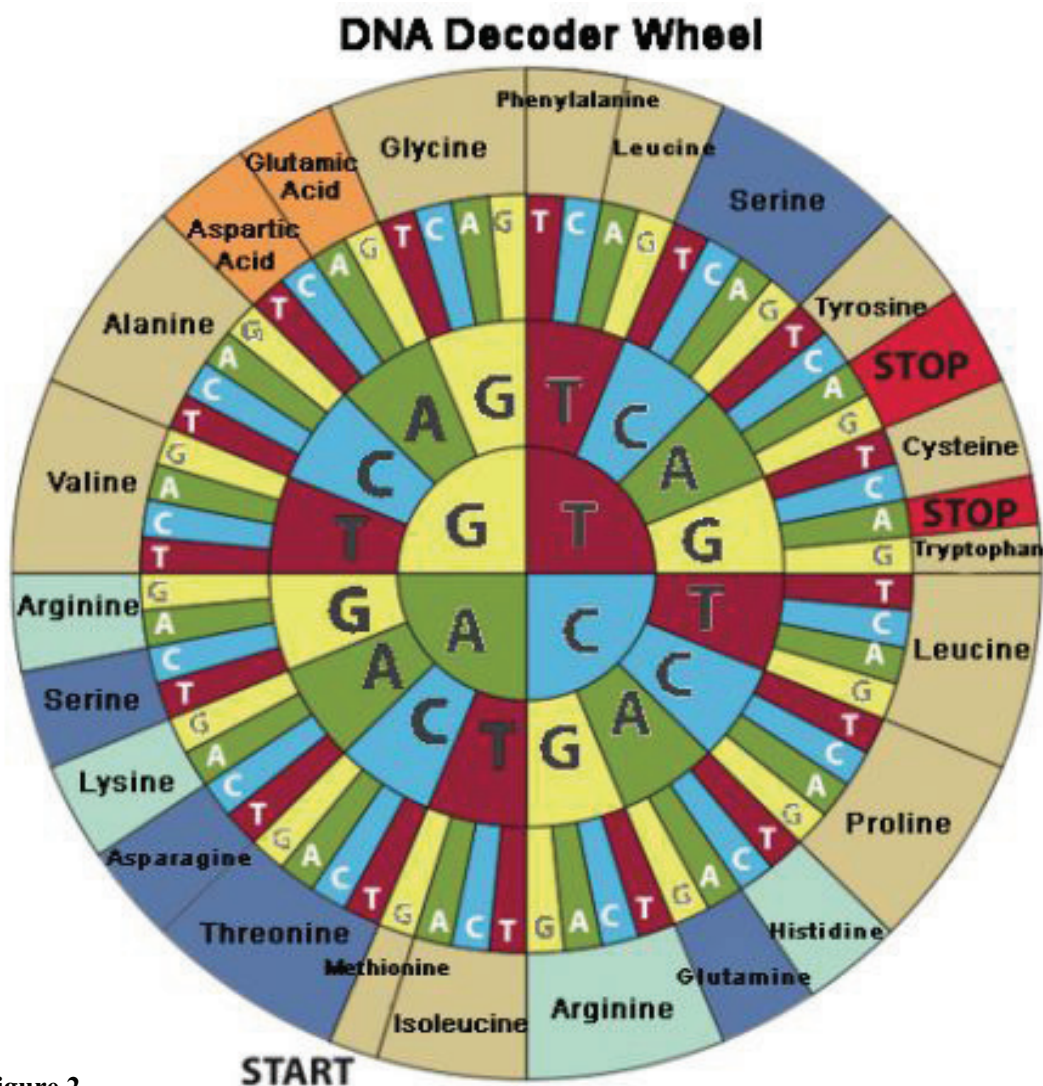


Figure 2

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.

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.

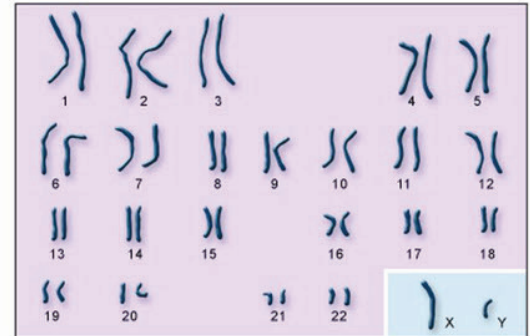


Figure 3

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.

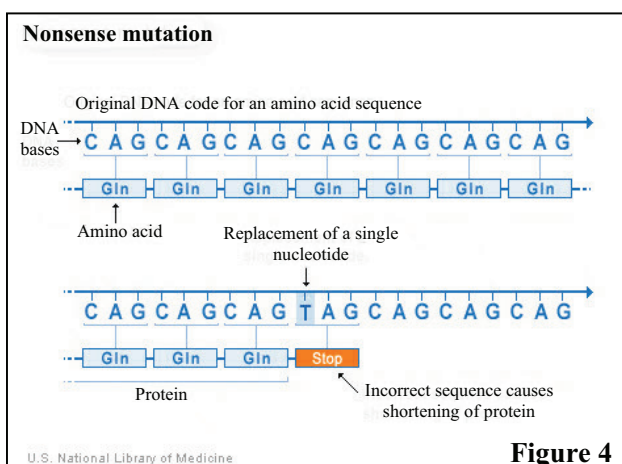


Figure 4

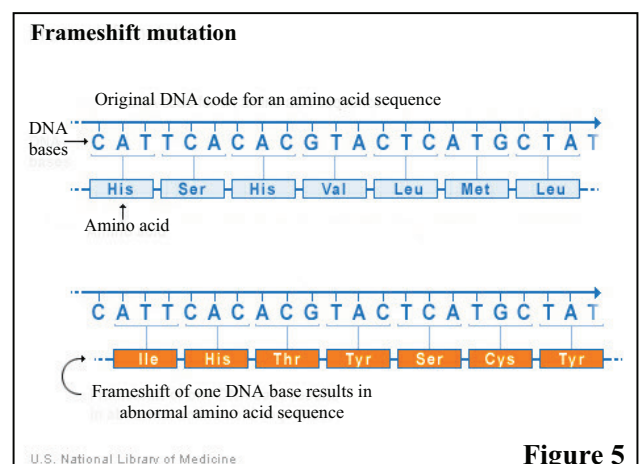


Figure 5

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.

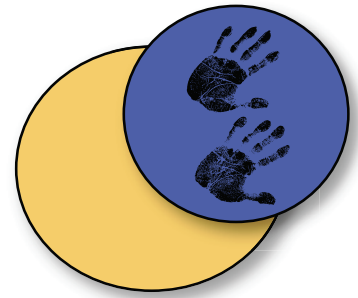
It's not yet known how the changes to the gene change the function of protein or why it causes the features of Kabuki syndrome. It's also not known if different changes within the gene can lead to more or less severe clinical features. But now that the gene has been identified, scientists have the next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

* Inserted following Aug 15, 2010 publication release.

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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



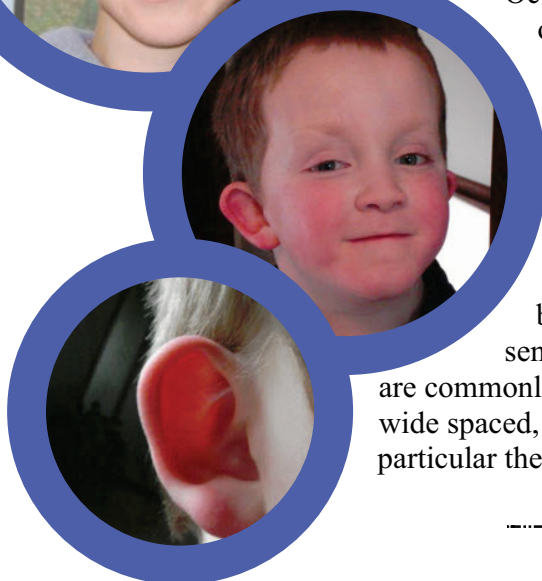
Facial characteristics typically include:

- 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 multidisciplinary 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.

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.



Figure 2

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.

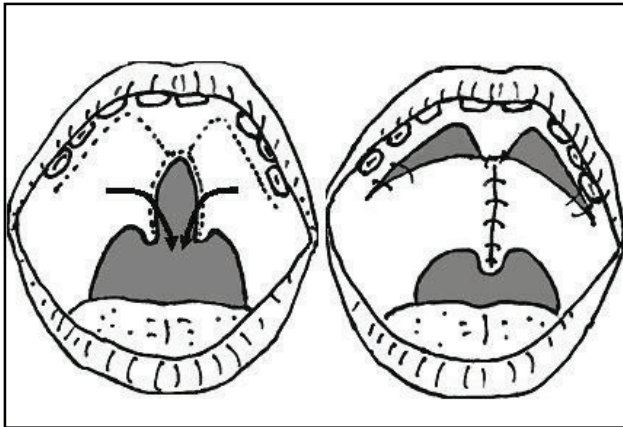


Figure 3

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 a 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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