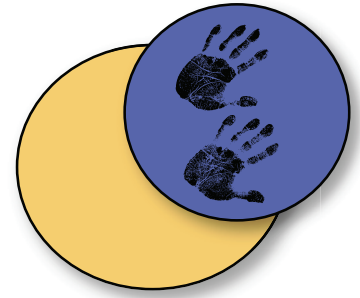


## Immunity and Blood Disorders



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.

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# 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.

*Correspondence to:*

*Dr. Mark Hannibal*

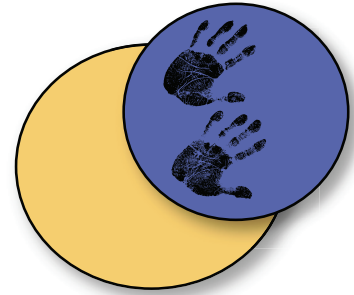
*Tel: 206-987-2056*

*E-mail: [mhanni@u.washington.edu](mailto:mhanni@u.washington.edu)*

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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:*

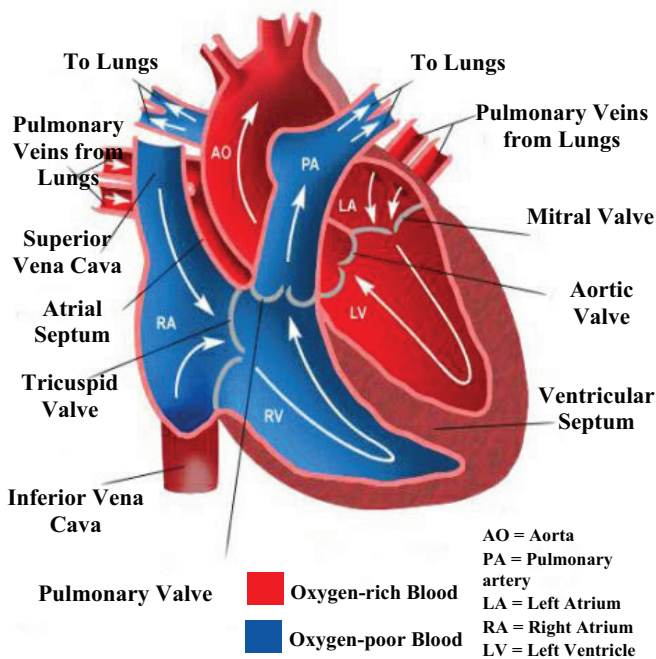
*Dr. Grace Kung is a pediatric cardiologist at Children’s Hospital Los Angeles and Associate Professor of Clinical Pediatrics with USC Keck School of Medicine. She specializes in non-invasive imaging and is a fellow of the America College of Cardiology and American Society of Echocardiography.*

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

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 an 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

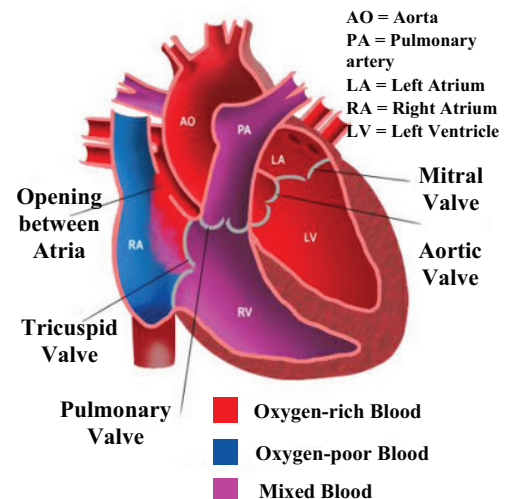
there is, may result in extra fluid in the lungs and dilation of the heart. These lesions, if they occur in isolation, are



**Fig 1: Normal heart with four chambers , two on the right and two on the left**

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].

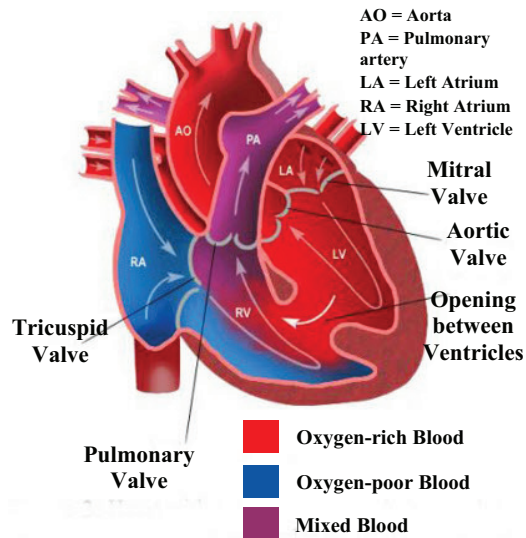
As a brief review of the anatomy of the heart and circulation, the heart consists of four chambers (Figure 1).



**Fig 2: Heart with a communication between the two upper chambers - atrial septal defect or ASD**

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



**Fig 3: Heart with a communication between the two lower chambers - ventricular septal defect or VSD**

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].

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

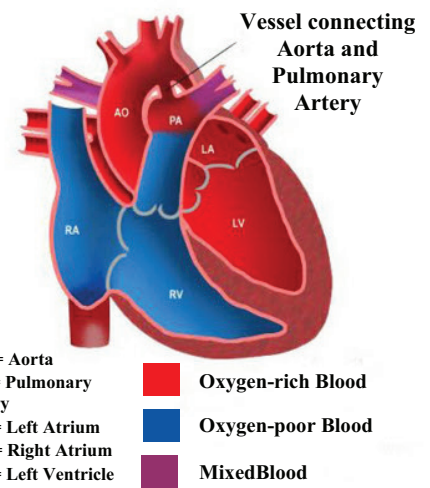
that is found is called Coarctation of the aorta (CoA) and is a narrowing of the aorta, or the large vessel that exits the heart to deliver blood to the body (Figure 5). This can result in diminished blood flow to the body

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.

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.

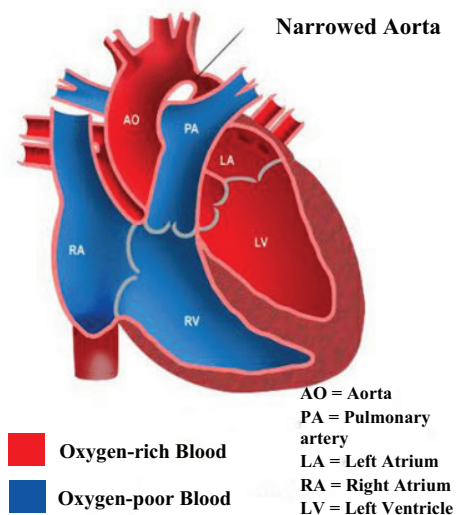
Once the heart has finished forming, it is unlikely that further defect will occur. After the baby is born, another echocardiogram is performed to confirm any abnormal finding on

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 4: Heart with a persistent blood vessel between the aorta and pulmonary artery - patent ductus arteriosus or PDA**

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 5: Narrowing of the aorta - coarctation of the aorta or CoA**



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,

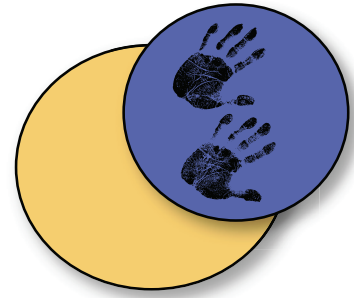
only to become more pronounced with time and patient growth [12]. The cardiac disease often occurs before the diagnosis of the syndrome, thus we also propose that patients with left-sided heart defects, including HLHS, who have normal chromosomes, developmental delay and growth failure may benefit from 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.



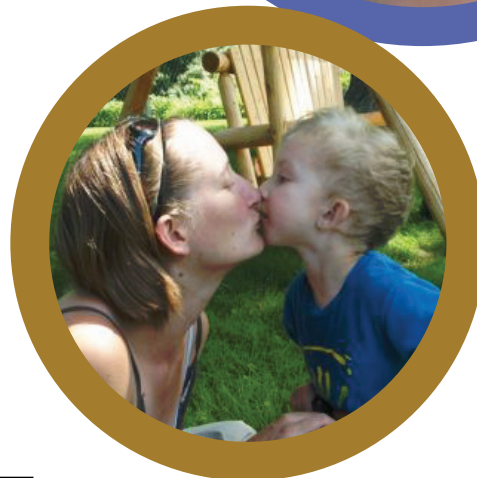
## Endocrine and GenitalUrinary Disorders



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.



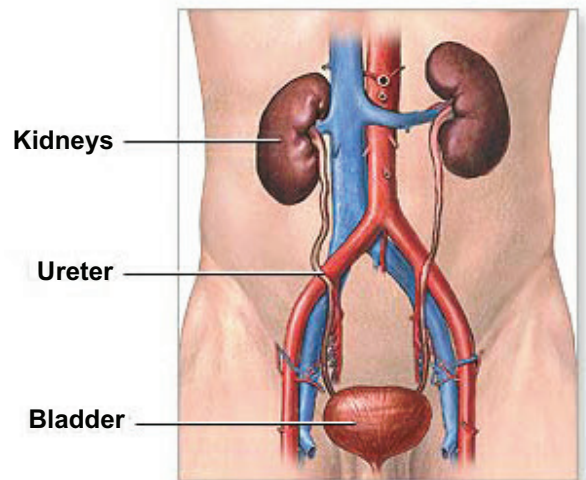


## Kidney Anomalies in a Person with Kabuki Syndrome

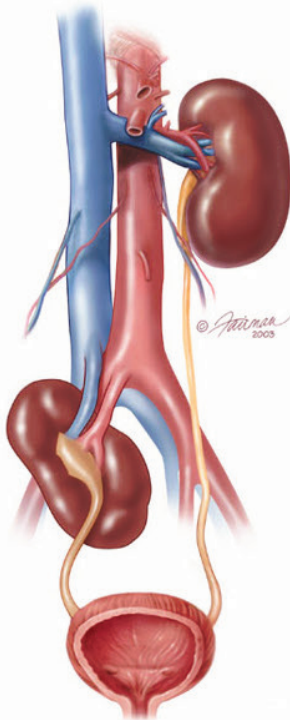
By Doctor Paul Henning, Pediatric Nephrologist

*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-teretic reflux), ectopic kidneys, horseshoe kidney (fusion abnormalities), renal dysplasia (and probably renal agenesis) and ureteric duplication.



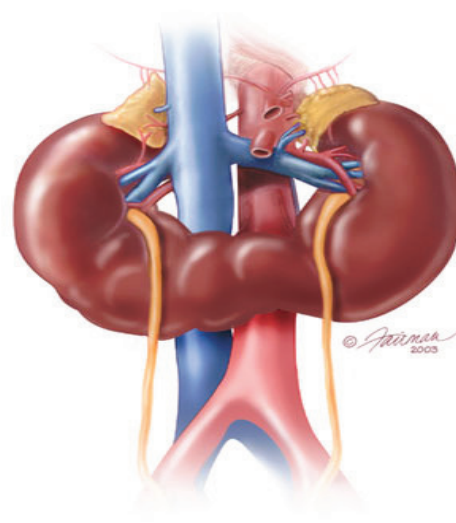
**Normal Kidneys**



**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.

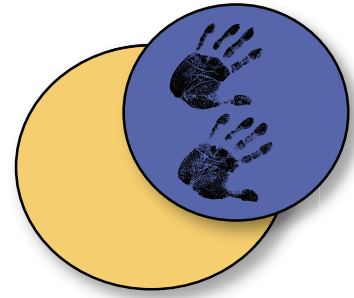
Although less common, structural and functional abnormalities of the abdominal organs can be serious. These may include diaphragm hernias or eventration, malrotation of the intestines, and abnormalities with the anus or rectum in the form of anal atresia, anovestibular fistula or anteriorly placed anus.

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## Ectodermal

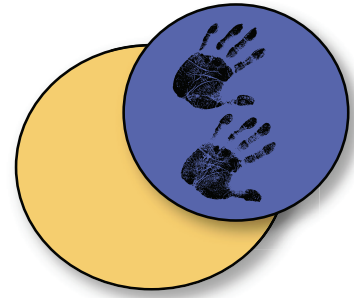


Individuals with Kabuki syndrome can have hyperelastic skin, suggestive of a connective tissue disorder. The hands feel soft and are short with short fingers, in particular the fifth fingers. Persistent fetal fingertip pads is highly characteristic of Kabuki syndrome. Mild cutaneous syndactyly is common,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

