Currently, the cause of cardiomyopathies in most children is poorly understood, but in a subset of children it is clear that the cause is an error or mistake in a gene. Genes are the blueprints or instructions that determine how the parts of our bodies will be formed and how they will function. Genes are encoded in our DNA found within each cell and passed down to our children. Mistakes in these coded instructions called mutations can cause problems with the way the body works. Many genes provide the instructions for proteins that carry out various functions within the body including making up the structures of many organs and metabolizing food substances. Errors in these instructions may fail to produce the right amount of the protein or may produce a protein that does not function properly.

In some cases, these genetic mistakes can lead to isolated cardiomyopathy without other problems. In other cases, a genetic mistake can lead to cardiomyopathy, which is associated with other medical problems such as muscle weakness, poor growth, or learning disabilities. Families in which one child has a cardiomyopathy are at increased risk for having another child or other family member with cardiomyopathy. Therefore, it is important that once a cardiomyopathy is diagnosed within the family, all of the child's brothers, sisters, and parents should also be screened with an echocardiogram. Depending on the type of cardiomyopathy diagnosed, it may be necessary to repeat the echocardiogram periodically for younger siblings throughout childhood into mid-adult life, especially if close relatives were diagnosed with cardiomyopathy at an older age.

Mistakes in many different genes can lead to cardiomyopathy in children. In teens, the most common genetic cause of isolated hypertrophic cardiomyopathy is due to mistakes in the instructions to make the proteins within the heart cell. Many of these proteins are found in the sarcomere, which allows the heart cell to contract. In many such families, the predisposition to cardiomyopathy is carried by one of the parents, either the mother or father and is autosomal dominantly inherited. Each of us has two copies of our genes. We inherit one copy of each gene from our mother and one from our father. For autosomal dominant conditions, a parent has a mistake in one copy of the gene. Since each person has two genes, there is a 50-50 chance that the parent will pass on the mistake to a child, whether it is a son or a daughter. In autosomal dominant conditions, a mistake in just one of the two copies of the gene in the child is sufficient to cause the condition. Therefore, if your family has been diagnosed with an autosomal dominant cardiomyopathy, anyone carrying the genetic mistake has a 50-50 chance of passing it on to a child. That also means that anyone in such a family that does not carry the familial mistake cannot pass the condition on to a child. For an autosomal dominant condition, multiple members of the family, generation after generation, may have the cardiomyopathy.
Cardiomyopathies in infants especially can also be caused by inborn errors of metabolism or inability of the body to break down food substances correctly to generate energy. Most of these inborn errors of metabolism are inherited in an autosomal recessive manner. These disorders include fatty acid oxidation disorders and glycogen storage disorders such as Pompe disease. In autosomal recessive conditions, an individual with a mistake in only one copy of the gene (called a carrier) does NOT have problems because the other normal copy of the gene is sufficient to allow the heart to function normally. Only when an individual has a mistake in BOTH copies of the gene are there problems. Children with autosomal recessive conditions have mistakes in both copies of their genes and usually both of their parents have a mistake in just one copy of the gene and are called carriers. A child born with an autosomal recessive cardiomyopathy, some of which are associated with inborn errors of metabolism, inherits a defective gene from each of his/her carrier parents. If both parents are carriers, the risk that their other children will have the cardiomyopathy is one in four or 25%. Usually the only individuals in the extended family at risk are brothers and sisters of the child with the cardiomyopathy.

There are other rare conditions that cause cardiomyopathies almost exclusively in male family members. This is most often the case for conditions such as Duchenne or Becker muscular dystrophy or Barth syndrome. These cardiomyopathies can occur in one of two ways. They may occur sporadically and not be inherited from the parents or they may be inherited in an X-linked manner from their mother. Mothers have two X chromosomes and usually do not have any problems with X-linked diseases because the mistake is carried on one gene on the X chromosome while the other copy of the gene on the X chromosome is fine and works normally. Boys have only one X chromosome, so if they inherit a mistake in a gene on the X chromosome, they have no second copy to rely on and, therefore, may develop the disease. If a mother carries an X-linked condition, 50% of her sons are at risk of having the condition, but her daughters generally will NOT have the condition although they may be carriers and could pass it on to their sons in the future.

Rarely, cardiomyopathies can be associated with neurological problems such as muscle weakness, seizures, neuropathy, deafness, and other medical problems. In these rare families, the cardiomyopathy may be inherited through the maternal lineage due to the inheritance of a small number of genes within specialized parts of the cell called mitochondria. In such families, the disease cannot be passed through males. Only a mother carrying a mitochondrial mutation can pass on the disease to her children. Potentially all of her children could be affected, although the severity of the symptoms often differs between the children.

**Genetic Diagnosis**

In addition to cardiologists, some children with cardiomyopathies should be evaluated by geneticists in order to determine the cause of the cardiomyopathy so therapy can be optimized for them. Genetic evaluation is also useful in determining if any other members of the family are at risk for cardiomyopathy so they can also receive the best medical care. Part of this evaluation should include examination of your family tree to see if other members of the family have had cardiomyopathy, a heart condition, a related medical condition or died at a young age of unknown cause.

In rare circumstances a particular cardiomyopathy may be caused by an inborn error of metabolism. In these cases, the cardiomyopathy is caused by a deficiency of an enzyme or protein that breaks down food substances to generate energy for the heart. In certain circumstances, these inborn errors of metabolism can be treated with vitamins, dietary modification or enzyme replacement that can actually reverse and potentially cure the cardiomyopathy. Although these cases are rare, they should be considered in appropriate children since therapy must be based not only on the heart condition but also on the underlying metabolic condition. A battery of blood tests, urine tests, and occasionally skin or muscle biopsies may be necessary to make these diagnoses. Often the diagnosis can be confirmed with a specific DNA-based genetic test that may also be helpful in testing other family members and offer the option of prenatal diagnosis in a future pregnancy.
For families in which there appears to be generation after generation of individuals affected with cardiomyopathy, there is now a genetic blood test available that can test for mistakes in many but not all of the sarcomeric genes. If a mutation is identified in one family member, other members of the family can be tested for the same mutation using a blood sample. Testing is expensive and insurance coverage for the testing varies by plan, so consultation with your individual carrier is advisable before ordering the test.

For children in whom the cardiomyopathy is not isolated but associated with problems with growth, development or other medical problems, it may be helpful to consult with a clinical geneticist experienced in pediatric cardiomyopathy. There are many genetic disorders associated with cardiomyopathy and other medical problems, but they are generally rare and difficult to recognize. Genetic testing is available for many of these disorders, but it takes a physician familiar with genetic disorders to know which one of these tests is most appropriate for your child.

If a genetic basis can be identified for your child’s cardiomyopathy, various means of prenatal diagnosis are available that rely on a DNA-based genetic test. If a genetic mutation is identified in the child, the parents should be tested to determine if they also carry the mutation to accurately assess the risk that a future child will have the cardiomyopathy. Parents should consult a geneticist to review all of their options for planning their family prior to trying to get pregnant.

If no genetic basis has been identified in your child, it is unlikely that any prenatal testing will prove helpful in determining the risk of cardiomyopathy in a future child. Prenatal echocardiograms rarely demonstrate evidence of cardiomyopathy prior to birth, and a normal prenatal echo will not ensure that a child will not later develop cardiomyopathy.

GENETICS OF CARDIOMYOPATHIES

The genetic basis of each of the functional types of cardiomyopathy has been studied since the late 1980s and progress has been made in each category. This section provides details on the specific genetic mutations responsible for different forms of cardiomyopathy and highlights how this information can be used for clinical care. The search for the remaining genes, as well as for improved diagnostic and therapeutic approaches, is ongoing.
Dilated Cardiomyopathy (DCM) Including X-Linked and Mitochondrial Myopathies

Many different genes have been identified that cause DCM. Over the past decade, mutations in the cytoskeletal/sarcolemmal genes (delta-sarcoglycan, metavinculin, desmin), Z-disk genes (ZASP, alpha-actinin-2, MLP, titin), sarcomeric genes (beta-myosin, alpha-tropomyosin, myosin binding protein-C, troponin-T) and lamin A/C genes have all been shown to cause dilated cardiomyopathy. Some are X-linked, related to mutations in the dystrophin gene, which cause Duchenne and Becker muscular dystrophies. In these disorders boys usually have weakness in their leg muscles before the cardiomyopathy becomes symptomatic. Barth syndrome is another X-linked cardiomyopathy, caused by mutations in the G4.5/tafazzin gene. Barth Syndrome is associated with muscle weakness and multiple infections due to low white blood cell counts. These three muscle-related disorders can be diagnosed by a genetic blood test or muscle biopsy. Like HCM, mutations in many of the sarcomeric genes (beta-myosin, alpha-tropomyosin, myosin binding protein-C, troponin T) can also cause DCM and are autosomally dominantly inherited from one parent. Genetic testing for autosomal dominantly inherited DCM genes is not nearly as extensive as the testing available for HCM genes.

Additional causes of DCM have been identified as well. Abnormalities of mitochondrial function related to mutations in the mitochondrial DNA and inborn errors of metabolism related to the acyldehydrogenase genes can be causes of DCM in infants. Most inborn errors of metabolism are autosomally recessively inherited and associated with problems with the way the body breaks down fats. These fatty acid oxidation disorders can be readily diagnosed initially by a blood test followed by an enzymatic test performed from a skin biopsy. It is important to diagnose these fatty acid oxidation disorders since the heart function can be greatly improved by dietary manipulation and giving a vitamin called carnitine.

Non-genetic causes of DCM are also relatively common in children with cardiomyopathy. Inflammation of the heart or myocarditis, which can progress to DCM, is often due to a viral infection and can affect both young as well as older children and adolescents. The more common viral infections include adenovirus, parvovirus, and the enteroviruses, particularly the Coxsackie B3 and B4 viruses. There are specialized diagnostic tests that in many cases can identify the viral cause of myocarditis.

Hypertrophic Cardiomyopathy (HCM)

In some children, especially teenagers, hypertrophic cardiomyopathy is inherited in an autosomal dominant manner from one parent due to a mistake in one of the many genes encoding proteins in the sarcomere, necessary for heart muscle contraction. The identified genetic mutations include beta-myosin, cardiac actin, cardiac troponin T, cardiac troponin I, alpha-tropomyosin, myosin binding protein-C, titin, muscle LIM protein and the essential and regulatory myosin light chains. Genetic testing from a blood sample is now available for many of these sarcomeric genes. To inquire about whether specific testing is appropriate for you/your child, ask you cardiologist and/or geneticist.

Recently, non-sarcomere related genes have been identified, and these include AMP kinase and the alpha-iduronidase gene casing Fabry’s disease. In other cases, the heart becomes hypertrophied because material accumulates in the heart due to a missing protein that normally metabolizes or breaks down the material. One such example that can cause hypertrophic cardiomyopathy in infants is Pompe disease, which can be associated with weak muscles in the arms and legs as well. It is important to evaluate infants for Pompe disease since the protein that is missing can be replaced through an intravenous infusion every two weeks and can reverse the cardiomyopathy, although muscle weakness may persist.

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

ARVD/C is inherited as an autosomal dominant disorder. Multiple genes have been identified, including ryanodine receptor 2, desmoplakin and plakophilin-2. ARVD/C can also be associated with Naxos syndrome, an autosomal recessive disorder caused by mutations in the plakoglobin protein and characterized by severe problems with the skin, teeth, hair and nails in addition to the heart. A similar autosomal recessive disorder is Carvajal syndrome and is caused by mutations in the protein desmoplakin. Limited clinical testing is available.

Left Ventricular Noncompaction (LVNC)

The inheritance pattern in LVNC can be autosomal dominant, X-linked or maternally transmitted due to mitochondrial mutations. LVNC can be caused by mutations in the X-linked gene (G4.5) that causes Barth syndrome and mitochondrial disorders, or it can be autosomally dominantly inherited through the alpha-dystrobrevin and ZASP proteins. Genetic testing is available for Barth syndrome and many of the mitochondrial disorders.