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Facts about Myopathies

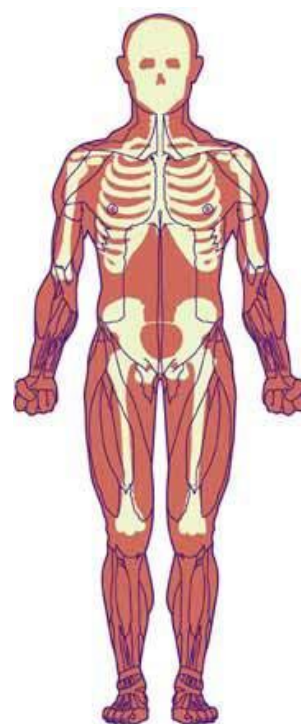
What are Myopathies?

The word myopathy means "disease of muscle." More specifically, myopathies are diseases that cause problems with the tone and contraction of skeletal muscles (muscles that control voluntary movements.) These problems range from stiffness (called *myotonia*) to weakness, with different degrees of severity.

Some myopathies, especially when they're present from birth, have life-threatening complications. But, with time and physical therapy, some people born with myopathies can gain muscle strength. Others often can manage their symptoms through medication, lifestyle modifications, or use of orthopaedic and respiratory equipment.

This fact sheet focuses on six *inheritable* myopathies (myopathies that can be passed from parent to child).

- **myotonia congenita** (Thomsen's disease and Becker type)
- **paramyotonia congenita** (Eulenberg's disease)
- **periodic paralysis** (hyperkalaemic, hypokalaemic, normokalaemic)
- **central core disease**
- **nemaline myopathy** (rod body disease)
- **myotubular myopathy** (centronuclear myopathy)



Myopathies can cause weakness or stiffness in all of the body's voluntary muscles. Because muscles support the body's posture, severe muscle weakness can lead to skeletal deformities.

What causes the Inheritable Myopathies?

These inheritable myopathies are caused by *mutations*, or changes, in genes — the blueprints for making proteins that are necessary for our bodies to function correctly. Genes are responsible for building our bodies; we inherit them — along with any mutations or defects they have — from our parents, and pass them on to our children. (For more information on how myopathies are inherited, see "Does It Run in the Family?")

In the inheritable myopathies, genetic mutations cause defects in various proteins necessary for muscle tone and contraction.

What are muscle tone and contraction, and what controls them?

Contraction is the forceful shortening or tightening of muscle, which pulls on the joints to cause movement. In other words, when your brain "tells" a muscle to move, you cause it to contract, and it's then able to do what you're asking.

Muscle tone refers to a readiness for contraction that makes resting muscle resistant to stretching. Or, a toned muscle holds its shape and its elasticity and is able to respond

by contracting when you want it to move. Bodies with poor muscle tone appear "floppy." Good muscle tone is important for posture and coordination.

A skeletal muscle's tone and contraction depend on its ability to respond to stimulation from nerve cells, which are responding to signals sent from the brain, such as your decision to move your hand or leg. A muscle is actually a bundle of individual muscle cells, each one stimulated by a single nerve cell.

The process of muscle contraction begins when the nerve cells release chemical signals onto the muscle cells. These signals cause the opening of *ion channels*, pores in each muscle cell's outer surface that open and close to regulate ion movement. Ion channels allow certain ions — charged molecules of sodium, calcium, potassium or chloride — to pass into and out of the muscle cell, creating electrical currents. Opening of sodium and calcium channels causes an electrical excitation that will lead to contraction, while opening of potassium and chloride channels keeps the excitation from occurring.

The purpose of the electrical *excitation* is to stimulate the opening of still more channels that release calcium from internal compartments in the muscle cell. Finally, the freed calcium ions trigger muscle contraction by stimulating the sliding action of *filament proteins*.

These rod-like proteins run lengthwise within the muscle cell and are anchored at opposite ends by scaffolds called *z-discs*. When the filament proteins slide past each other — by an energy-dependent, ratchet-like mechanism — they cause shortening of the muscle cell and shortening (contraction) of the whole muscle.

If this process is disrupted at any stage between the nerve's signalling the muscle and the filament proteins' action, the muscle loses its normal capacity for tone and contraction. At one extreme, the muscle might be limp and weak, and at the other extreme, the muscle may be unable to relax.

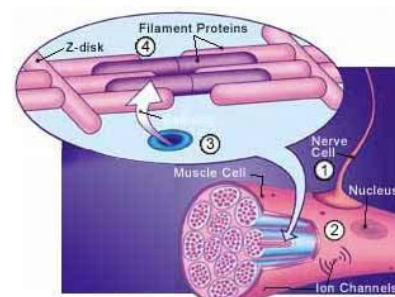
Many of the inheritable myopathies are caused by mutations that interfere with ion channels, preventing necessary ions from flowing through the muscle cells. These disorders (myotonia congenita, paramyotonia congenita, periodic paralysis and central core disease) are sometimes called *channelopathies*.

Central core disease seems to damage, and thus weaken, muscles by causing an excess release of internal calcium. The other channelopathies interfere with normal muscle tone and contraction by causing over- or underexcitation.

A fifth myopathy, nemaline myopathy, is caused by mutations that affect filament proteins. When the filament proteins fail to do their jobs, muscles can't contract properly, causing a loss of tone and strength.

At least one myopathy (a type of myotubular myopathy) is caused by mutations in a muscle protein required for normal muscle development. When this protein is absent or inactive, the muscles don't form properly.

Some of the inheritable myopathies are congenital, meaning they cause problems from the time of birth. Others have a later onset, with symptoms appearing in childhood or adulthood.



A muscle cell is stimulated to contract by chemical signals sent from an adjoining nerve cell (1). Those signals open ion channels at the muscle cell's surface, causing an inward/outward flow of ions that acts as an electrical current (2). Inside the muscle cell, the current spreads and causes opening of ion channels that line calcium storage compartments, releasing the calcium ions trapped within (3). The freed calcium ions trigger nearby filament proteins to slide past each other, pulling the Z-discs closer together and shortening the muscle cell (4).

What happens to someone with an Inheritable Myopathy?

Some of the congenital inheritable myopathies cause severe, general muscle weakness that creates problems with basic activities like swallowing and breathing. These problems can be fatal if not dealt with, but they can be treated with assistive medical devices like feeding tubes and mechanical ventilators.

Other inheritable myopathies cause episodes of muscle weakness or stiffness that are milder and more localized and temporary in nature. These episodes often can be managed through medication, or by careful control of exercise and diet.

Unlike muscular dystrophies, myopathies usually don't cause muscles to die but just keep them from working properly. Also, myopathies are usually non-progressive — that is, a myopathy usually doesn't grow significantly worse over a person's lifetime. In fact, some children with myopathies gain strength as they grow older.

Finally, some myopathies can give people a listless facial expression, caused by weakness of muscles in the face. Myopathies have no effect on intelligence.

Special issues in Inheritable Myopathies

Anaesthesia: People with myopathies can experience adverse reactions to certain anaesthetic drugs used during surgery. Although these drugs sometimes just aggravate the myopathy, they also can produce a potentially fatal reaction called *malignant hyperthermia*, which refers to a dangerously high increase in body temperature. People with central core disease are especially at risk for malignant hyperthermia because the two conditions are sometimes caused by the same ion channel defects.

Malignant hyperthermia is triggered by certain inhaled anaesthetics (like halothane) and certain muscle relaxants (like succinylcholine). These drugs can intensify ion channel defects and boost muscle metabolism — the set of chemical reactions that provides energy to muscle. The increased metabolism raises body temperature, and causes excessive contraction and rhabdomyolysis — a process of acute muscle breakdown. The resulting leakage of ions and muscle proteins into the circulatory system can cause life-threatening damage to the heart, lungs and kidneys.

People with central core disease aren't always susceptible to malignant hyperthermia. Those who are susceptible won't experience malignant hyperthermia unless they're exposed to triggering anaesthetics.

Before having surgery, people who have a personal or family history of central core disease — or any other myopathy — should consult their doctors about the risks of anaesthesia and about the availability of "nontriggering" anaesthetics.

Respiratory care: Nemaline myopathy and congenital (X-linked) myotubular myopathy cause weakening of the respiratory muscles (those that control the lungs). Therefore, people with either of these diseases probably may need to use mechanical ventilation to support breathing, and should have their breathing monitored regularly by a specialist. Also, weak lungs are susceptible to infection, so signs of respiratory illness should be taken seriously.



People with central core disease are at risk for malignant hyperthermia during surgery.

Cardiac care: The myopathies almost never affect heart muscle directly, but sometimes they can cause indirect damage to the heart. In nemaline myopathy and congenital myotubular myopathy, an inadequate oxygen supply to the body during severe bouts of respiratory weakness can lead to heart problems. In hyperkalaemic periodic paralysis, certain conditions can trigger potassium elevation in the blood, which can interfere with contraction of the heart.

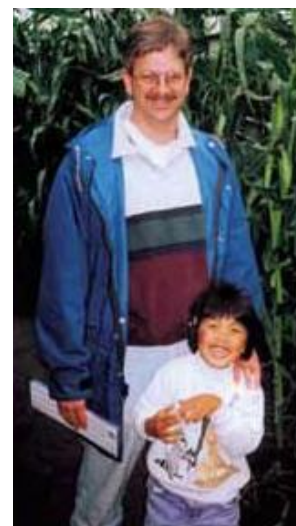
People with these diseases should be wary of potential heart problems and have their cardiac function checked by a specialist.

What are the symptoms and treatments for each Inheritable Myopathy?

Myotonia congenita	
Cause:	This disease is caused by mutations in the gene for a chloride channel that's necessary for shutting off the electrical excitation that causes muscle contraction.
Inheritance:	autosomal recessive (Becker-type), autosomal dominant (Thomsen's)
Onset:	early to late childhood
Symptoms:	The main problems faced by people with this disease are delayed muscle relaxation and muscle stiffness, typically provoked by sudden movements after rest. The stiffness can interfere with simple activities like walking, grasping and chewing, but is usually manageable by doing warm-up movements. The disease doesn't cause any muscle wasting; instead, it can sometimes cause muscle enlargement and increased muscle strength. Becker-type myotonia is the most common form of myotonia congenita, while Thomsen's disease is a very rare, relatively mild form.
Treatment:	Someone who has myotonia congenita can lead a long, productive life, and can even excel at sports where strength is more important than agility. Your neuromuscular clinic doctor can tell you about appropriate exercises, and if necessary, appropriate medications for dealing with muscle stiffness.
Paramyotonia congenita	
Also called:	Eulenberg's disease. (Some researchers regard paramyotonia congenita as a form of periodic paralysis.)
Cause:	Sodium channels normally open to cause muscle excitation, and then close to end the excitation. In paramyotonia congenita, mutations in the muscle sodium channel gene prolong the channel's opening, causing higher-than-normal muscle excitation.
Inheritance:	autosomal dominant
Onset:	congenital symptoms: Paramyotonia congenita causes episodes of muscle stiffness and weakness — mostly in the face, neck, and upper extremities — that can last from minutes to hours. The stiffness is sensitive to exercise and cold. During brief exercise, over-excitation of muscles can cause

	stiffness, and with prolonged exercise, the over-excitation can occasionally lead to a fatigue-like weakness or even complete paralysis. Cold exposure can have similar effects, but some people experience muscle stiffness, weakness or, sometimes, temporary paralysis even when they're warm.
Treatment:	By avoiding strenuous exercise and cold, most people with this condition can largely escape disability. But medications can be beneficial, especially for those who experience symptoms independent of exercise and cold. Your neuromuscular clinic doctor can give you more information about these medications.
PERIODIC PARALYSES	
<p>In these diseases, faulty ion channels cause "attacks" of temporary muscle weakness that can result in temporary paralysis when severe.</p> <p>There are different types of periodic paralysis, distinguished by what happens to potassium levels in the blood (specifically the fluid portion of the blood, or serum). In the hyperkalaemic type (hyperKPP), high serum potassium levels can cause attacks. In the hypokalaemic type (hypoKPP), low serum potassium levels can trigger attacks. ('kalaemic' refers to potassium; hyper means too much and hypo too little.)</p> <p>Unlike the case for most myopathies, many people with hypoKPP and some people with hyperKPP experience progressive, permanent muscle damage that occurs independently of the attacks.</p>	
Hyperkalaemic periodic paralysis	
Cause:	This disease is caused by distinct mutations in the muscle sodium channel gene. These mutations cause very slow closing of the sodium channel, leading to episodes of prolonged muscle excitation and weakness, and myotonia (muscle stiffness) in some people. It's not fully understood just how high levels of potassium interact with the defective sodium channels to trigger attacks.
Inheritance:	autosomal dominant
Onset:	childhood
Symptoms:	Attacks of weakness usually last 15 minutes to an hour, but can last for a day or more. They can recur daily in severe cases. The attacks commonly occur after rest preceded by vigorous exercise, and can be aggravated by stress, pregnancy, or foods high in potassium. During attacks not caused by excess potassium intake, a person can become hyperkalaemic or remain normokalemic (with no change in serum potassium levels). The frequency of attacks usually declines after middle age.
Treatment:	<p>To keep hyperKPP attacks to a minimum, stick to a diet rich in carbohydrates and low in potassium, and avoid strenuous exercise. When you do exercise, be sure to "cool down" with mild activity before resting.</p> <p>During an attack, certain prescription drugs can be used to alleviate symptoms. Your MDA clinic director can give you more specific information on how to manage hyperKPP through appropriate exercise, diet and medication.</p>

Hypokalaemic periodic paralysis	
Causes:	This disease seems to be caused by a reduced availability of the sodium channels necessary for muscle excitation. That condition can be brought about by certain genetic defects in the sodium channels themselves, or strangely, by genetic defects in a channel that acts like a key to the muscle's calcium stores.
Inheritance:	autosomal dominant
Onset:	early childhood to adulthood
Symptoms:	Attacks of weakness can occur daily and usually happen in the morning (during waking) or at night. Some people with the disease might experience only a few mild attacks in their lifetime. But the most severe attacks cause nearly full-blown paralysis.
Treatment:	As in hyperKPP, attacks of hypoKPP can be prevented by avoiding strenuous activity and alleviated by medications. The dietary precautions, however, are nearly opposite. High-carbohydrate foods can trigger hypokalaemia and contribute to an attack, while potassium intake can restore serum potassium levels and stem an oncoming attack. Ask your MDA clinic director for specific recommendations about diet, exercise and medications.
Central core disease	
Causes:	This rare disease appears to have multiple origins. But it's commonly caused by defects in a channel that acts like a gate to internal calcium stores. The defect causes leakage of calcium from the stores, which appears to damage muscle cells.
Inheritance:	autosomal dominant, autosomal recessive in rare cases
Onset:	congenital
Symptoms:	<p>The disease is named for damaged areas within muscle cells (the cores), where the filament proteins are disorganized, and mitochondria (the tiny energy-producing factories that power muscle contraction) are missing.</p> <p>This disease causes poor muscle tone (hypotonia) and persistent muscle weakness in infants. In rare cases, toddlers with the disease fail to walk at all, but usually they just reach motor milestones late. Older children and adults typically experience mild disabilities that worsen slowly with time, if at all. Due to chronic muscle weakness, many people develop skeletal deformities, including joint dislocations and scoliosis, or curvature of the spine that can compress vital internal organs.</p> <p>People with this disease should be cautious about surgery because they face an especially high risk of malignant hyperthermia, a potentially fatal reaction to certain anesthetic drugs (see "Anaesthesia").</p>
Treatment:	Someone with a severe form of central core disease might need a walker or other support devices for mobility, but many people require none. Unlike the case for other myopathies, people with this disease can benefit from



A father with hypokalaemic periodic paralysis



A boy with central core disease

	exercise. Scoliosis and other skeletal problems can usually be corrected by use of orthopaedic devices or by surgery. Your doctor can tell you more about the risks of surgery, and about anaesthetic drugs that are safe.
Nemaline myopathy (also called 'rod body' disease)	
Causes:	This disease is caused by a variety of genetic defects, each one affecting one of the filament proteins required for muscle tone and contraction.
Inheritance:	autosomal recessive, autosomal dominant
Onset:	congenital to adulthood
Symptoms:	<p>The disease gets its name from the fact that the muscle cells contain abnormal clumps of threadlike material — probably disorganized filament proteins — called <i>nemaline</i> bodies (<i>nema</i> is Greek for "thread"). It causes weakness and poor tone (<i>hypotonia</i>) in the muscles of the face, neck and upper limbs, and often affects the respiratory muscles (those that control breathing).</p> <p>The infantile-onset cases tend to be the most severe. Usually, infants with the disease lack the muscle strength and tone required for simple postures and movements. They also have serious difficulties with feeding and respiration. Although many infants with the disease die from respiratory failure or lung infections, some survive to adulthood. Affected children usually attain motor milestones slowly, and at puberty they might experience further weakening, necessitating use of a wheelchair.</p> <p>For adults, even non-congenital forms of the disease can cause life-threatening respiratory problems. Adults also might experience swallowing and speech problems, and those with restricted mobility might develop scoliosis. However, even people who have had the disease since birth can lead active lives.</p>
Treatment:	An infant with nemaline myopathy usually requires a feeding tube to deliver nutrition and mechanical ventilation to support respiration. Children and adults also can benefit from respiratory support, since respiratory failure during sleep can be a persistent danger. Mobility and strength can be improved significantly by physical and orthopaedic therapies. If you or your child has nemaline myopathy, your neuromuscular clinic doctor can provide further information about treatments.
Myotubular myopathy (also called Centronuclear myopathy)	
Causes:	The most common form (X-linked) is caused by defects or deficiencies of myotubularin, a protein thought to promote normal muscle development.
Inheritance:	X-linked, autosomal recessive, autosomal dominant
Onset:	congenital (X-linked); infancy to early adulthood (autosomal recessive); childhood to adulthood (autosomal dominant)
Symptoms:	X-linked myotubular myopathy usually affects only boys, and causes severe muscle weakness and hypotonia noticeable at birth and sometimes before. The weakness and hypotonia interfere with posture and movement, and cause life-threatening difficulties with feeding and respiration.



A baby with nemaline myopathy



A boy with myotubular myopathy

	<p>Sometimes, failure or infection of the lungs causes death in early infancy, but about two-thirds of boys survive to at least 1 year of age. Usually, these boys require a feeding tube and a mechanical ventilator. Most attain motor milestones slowly, and some might not walk at all. However, most boys gradually gain muscle strength, and a few grow up with little disability.</p> <p>Independent of skeletal muscle problems, some boys with X-linked myotubular myopathy experience problems in other organ systems. These include anaemia, gallstones, accelerated growth and serious liver abnormalities.</p> <p>The autosomal forms affect boys and girls equally. They cause muscle problems similar in quality to those of the X-linked form, but the autosomal dominant form is considered mild and the recessive form intermediate. In these forms muscle problems grow worse with age. Problems with other organs haven't been reported.</p>
<p>Treatment:</p>	<p>Until recently, nearly all infants with X-linked myotubular myopathy were expected to die within their first few months of life. However, intensive support of feeding and ventilation may significantly improve their life expectancy and allow a high quality of life. Respiratory support and monitoring also might be necessary for children and adults diagnosed with autosomal forms of myotubular myopathy. Also, most people with this disease benefit from physical and orthopaedic therapies. Your neuromuscular clinic doctor can give you more information about treatment.</p>

How are these six Inheritable Myopathies diagnosed?

Usually, diagnosis begins with evaluation of the patient's *personal and family history*, and proceeds with physical and neurological *examinations* that test reflexes and strength. The exams can detect problems with muscle tone and contraction, and the histories can bring to light patterns of inheritance and conditions that might have aggravated the muscle problems in the past.

Given this information, a doctor can sometimes distinguish an inheritable myopathy from other diseases that affect muscle function, such as muscular dystrophies and neurological disorders. But to accurately identify the myopathy and plan an appropriate course of treatment, the doctor can use several specialized tests:

A *muscle biopsy*, the removal of a small piece of muscle tissue, is used to look for physical signs of muscle disease. Under the microscope, muscles affected by central core disease, nemaline myopathy or myotubular myopathy have fairly distinctive appearances.

Also, muscle biopsy can be used to see how isolated muscles respond to different potentially harmful conditions. For example, to determine a patient's susceptibility to malignant hyperthermia, a biopsied muscle can be tested for its reaction to potentially dangerous anaesthetic drugs.

A muscle's activity can be measured by *electromyography* (EMG), which involves observing the electrical signals that a muscle produces during contraction. A needle-

like electrode inserted into the muscle "reads" the electrical signals and sends them to a monitor called an oscilloscope. The technique usually causes some discomfort, but is useful for diagnosing channelopathies, which can show telltale abnormal signals on the oscilloscope.

Because the channelopathies sometimes just cause temporary muscle problems induced by changes in exercise, diet or temperature, the affected muscles might appear normal during a visit to the doctor's office. Therefore, the doctor might use a *provocative* test to elicit and evaluate a mild occurrence of the muscle problem.

An *exercise test*, which can involve anything from repeatedly making a fist to riding a stationary bicycle, usually can reveal symptoms of a channelopathy. Also, a doctor might test for periodic paralysis by having the patient consume safe doses of carbohydrate or potassium, or for *paramyotonia congenita* by immersing the patient's arm in cold water.

Finally, with just a blood sample, *genetic tests* can check for specific genetic defects that give rise to some of the inheritable myopathies.

These tests are safe, relatively painless and very accurate. However, because some of the genetic defects that cause inheritable myopathies remain to be discovered, a negative test result doesn't necessarily mean a person doesn't have a myopathy.

Does it run in the family?

On being told they have a genetic disorder such as an inheritable myopathy, patients often ask, "But it doesn't run in the family, so how could it be genetic?" Inheritable myopathies can run in a family, even if only one person in the biological family has it.

This is because genetic diseases can be inherited in three different ways: X-linked, autosomal dominant and autosomal recessive. Inheritable myopathies are inherited in all three ways.

X-linked means that the genetic mutation (*or defect*) is located on the X chromosome. For many X-linked diseases, a normal copy of the gene can compensate for the defective copy. Because males have only one X chromosome while females have two, X-linked diseases almost always affect males.

Autosomal means the mutation occurs on a chromosome other than the X or Y. Therefore, autosomal diseases affect males and females equally.

Autosomal recessive means that two copies of a defective gene are required for the full-blown disease. One copy is inherited from each parent, neither of whom would normally have the disease. Autosomal dominant means that one copy of a defective gene is enough to cause disease. So, a person who inherits the defective gene from a parent will have the disease, as will the parent.

Inheritable myopathies passed on in an autosomal dominant pattern can be easy to trace through the family tree. In contrast, X-linked or autosomal recessive disorders might seem to occur "out of the blue." But in reality, one or both parents might be carriers who silently harbor a genetic mutation. Many parents have no idea they're carriers of a disease until they have a child with the disease.

Inheritable myopathies actually can occur "out of the blue," when a new mutation occurs during the child's conception. These are called spontaneous mutations, and after they occur, they can be passed on to the next generation.

A good way to find out more about your risk of inheriting or passing on an inheritable myopathy is to talk to your neuromuscular clinic physician or genetic counsellor.

Also, see our pamphlet "Genetics and Neuromuscular Diseases" or visit the Centre for Genetics Education website (www.genetics.com.au).

Search for treatments and cures

Scientists have made significant progress toward understanding the genetic defects that cause inheritable myopathies, and treating them.

In the early 1990s, researchers discovered that ion channel defects were at the root of several myopathies. In the mid-1990s, they found that defective filament proteins give rise to nemaline myopathy. They've established that X-linked myotubular myopathy is caused by defects in a previously unknown protein called myotubularin.

These discoveries have enabled the design of genetic tests that facilitate accurate diagnosis and prognosis, and they're paving the way for treatments that attack the myopathies at their source.

The discovery of ion channel defects underlying myotonia congenita, paramyotonia congenita and the periodic paralyses has led to the development and use of drugs that bind to ion channels and modify their activities to restore normal muscle function.

In the future, drug treatments might become available for central core disease and nemaline and myotubular myopathies. To this end, scientists are rapidly deciphering the functions of myotubularin.

Researchers are also working on several different strategies to replace or repair defective genes, and these gene therapy techniques hold great promise for treating the inheritable myopathies.

Along the same lines, scientists are investigating the possible therapeutic uses of stem cells — primitive cells that generate all of the cells in the body. Scientists hope to use stem cells to produce healthy muscle cells that could replace myopathic muscle cells.