



# Mitochondrial Myopathies

U.S. DEPARTMENT OF HEALTH  
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## What are mitochondrial myopathies?

**M**itochondrial diseases are caused by defects in mitochondria, which are energy factories found inside almost all the cells in the body. Mitochondrial diseases that cause prominent muscular problems are called mitochondrial myopathies (*myo* means muscle and *pathos* means disease), while mitochondrial diseases that causes both prominent muscular and neurological problems are called mitochondrial encephalomyopathies (*encephalo* refers to the brain).

A typical human cell relies on hundreds of mitochondria to meet its energy needs. The symptoms of mitochondrial disease vary, because a person can have a unique mixture of healthy and defective mitochondria, with a unique distribution in the body. In most cases, mitochondrial disease is a multisystem disorder affecting more than one type of cell, tissue, or organ.

Because muscle and nerve cells have especially high energy needs, muscular and neurological problems are common features of mitochondrial disease. Other frequent complications include impaired vision, cardiac arrhythmia (abnormal heartbeat), diabetes, and stunted growth. Usually, a person with a mitochondrial disease

has two or more of these conditions, some of which occur together so regularly that they are grouped into syndromes.

## What causes mitochondrial myopathies?

**M**itochondrial diseases are caused by genetic mutations. Genes provide the instructions for making proteins, and the genes involved in mitochondrial disease normally make proteins that work inside mitochondria. Within each mitochondrion, these proteins make up part of an assembly line that uses fuel molecules (sugars and fats) derived from food combined with oxygen to manufacture the energy molecule adenosine triphosphate, or ATP.

Proteins at the beginning of the assembly line import sugars and fats into the mitochondrion and then break them down to provide energy. Proteins toward the end of the line—organized into five groups called complexes I, II, III, IV, and V—harness that energy to make ATP. This highly efficient part of the ATP manufacturing process requires oxygen, and is called the respiratory chain. Some mitochondrial diseases are named for the part of the respiratory chain that is affected, such as complex I deficiency.

A cell filled with defective mitochondria becomes deprived of ATP and can accumulate a backlog of unused fuel molecules and destructive forms of oxygen called free radicals or reactive oxygen species. These are the targets of antioxidant compounds (found in many foods and nutritional supplements) that appear to offer general defenses against aging and disease.

In such cases, excess fuel molecules are used to make ATP by inefficient means, which can generate potentially harmful byproducts such as lactic acid. (This also occurs when a cell has an inadequate oxygen supply, which can happen to muscle cells during strenuous exercise.) The buildup of lactic acid in the blood—called lactic acidosis—is associated with muscle fatigue, and might damage muscle and nerve tissue.

Muscle and nerve cells use the ATP derived from mitochondria as their main source of energy. The combined effects of energy deprivation and toxin accumulation in these cells can lead to many muscular and neurological symptoms.

## **What are the symptoms of mitochondrial myopathy?**

### **Myopathy**

The main symptoms of mitochondrial myopathy are muscle fatigue, weakness, and exercise intolerance. The severity of any of these symptoms varies greatly from one person to the next, even in the same family.

In some individuals, weakness is most prominent in muscles that control movements of the eyes and eyelids. Two common consequences are the gradual paralysis of eye movements, called progressive external ophthalmoplegia (PEO), and drooping of the upper eyelids, called ptosis. Often, people automatically compensate for PEO by moving their head to look in different directions, and might not notice any visual problems. Ptosis can impair vision and cause a listless expression, but can be corrected by surgery.

Mitochondrial myopathies also can cause weakness and wasting in other muscles of the face and neck, which can lead to difficulty with swallowing and, more rarely, slurred speech. People with mitochondrial myopathies also may experience muscle weakness in their arms and legs.

Exercise intolerance, also called exertional fatigue, refers to unusual feelings of exhaustion brought on by physical exertion. The degree of exercise intolerance varies greatly among individuals. Some people might have trouble only with athletic activities like jogging, while others might experience problems with everyday activities such as walking to the mailbox or lifting a milk carton.

Sometimes, mitochondrial disease is associated with muscle cramps. In rare instances it can lead to muscle breakdown and pain after exercise. This breakdown causes leakage of a protein called myoglobin from the muscles into the urine (myoglobinuria). Cramps or myoglobinuria usually occur when someone with exercise intolerance “overdoes it,” and can happen during the overexertion or several hours afterward.

While overexertion should be avoided, moderate exercise appears to help people with mitochondrial myopathy maintain strength.

### **Encephalomyopathy**

A mitochondrial encephalomyopathy typically includes some of the symptoms of myopathy plus one or more neurological symptoms. Again, these symptoms vary greatly among individuals in both type and severity.

In addition to affecting eye muscles, a mitochondrial encephalomyopathy can affect the eye itself and parts of the brain involved in vision. For instance, vision loss, due to optic atrophy (shrinkage of the optic nerve) or retinopathy (degeneration of some of the cells that line the back of the eye), is a common symptom of mitochondrial encephalomyopathy.

Sensorineural hearing loss is a common symptom of mitochondrial diseases. It is caused by damage to the inner ear (the cochlea) or to the auditory nerve, which connects the inner ear to the brain. Sensorineural hearing loss is permanent but it can be managed through alternative forms of communication, hearing aids, or cochlear implants. Hearing aids amplify sounds before they reach the inner ear. Cochlear implants bypass damaged parts of the inner ear and stimulate the auditory nerve.

Mitochondrial diseases can cause ataxia, which refers to trouble with balance and coordination. People with ataxia are prone to falls, and may need to use supportive aids such as railings, a walker, or a wheelchair. Physical and occupational therapy also may help.

Other common symptoms of mitochondrial encephalomyopathy include migraine headaches and seizures. There are many effective medications for treating and helping to prevent migraines and seizures, including anticonvulsants and other drugs developed to treat epilepsy.

## **Special issues in mitochondrial disease**

### **Respiratory care**

Mitochondrial diseases can affect the muscles or parts of the brain that support breathing. A person with mild respiratory problems might require occasional respiratory support, such as pressurized air. Someone with more severe problems might require permanent support from a ventilator. People should watch for signs of respiratory problems (such as shortness of breath or morning headaches) and have regular checkups with a respiratory specialist.

### **Cardiac care**

Some mitochondrial diseases can cause cardiomyopathy (heart muscle weakness) or arrhythmia (irregular heart beat). Although dangerous, cardiac arrhythmia is treatable with a pacemaker, which stimulates a normal heartbeat. People with mitochondrial disorders may need to have regular examinations by a cardiologist.

### **Other potential health issues**

People with a mitochondrial disease may experience gastrointestinal problems, diabetes, and/or kidney problems. Some of these problems are direct effects of mitochondrial defects in the digestive system, pancreas (in diabetes), or kidneys, and others are indirect effects of mitochondrial defects in other tissues. For example, myoglobinuria stresses the kidneys' ability to filter waste from the blood and can cause kidney damage.

## What issues are of special concern in children?

### **Vision**

Although gradual paralysis of eye movements (PEO) and ptosis typically cause only mild visual impairment in adults, they are potentially more harmful in children with mitochondrial myopathies.

Because the development of the brain is sensitive to childhood experiences, either PEO or ptosis during childhood can cause permanent damage to the brain's visual system. It is important for children with signs of PEO or ptosis to have their vision checked by a specialist.

### **Developmental delays**

Due to muscle weakness, brain abnormalities, or a combination of both, children with mitochondrial diseases may have difficulty developing certain skills. For example, they might take an unusually long time to reach motor milestones such as sitting, crawling, and walking. As they get older, they may be unable to get around as easily as other children their age, and may have speech problems and/or learning disabilities. Children affected by these problems may benefit from early intervention and services such as physical and speech therapy, and possibly an individualized education program at school.

## Are there specific treatments for the mitochondrial myopathies?

Instead of focusing on specific complications of mitochondrial disease, some treatments under investigation aim at fixing or bypassing the defective mitochondria. These treatments are nutritional supplements based on three natural substances involved in ATP production in our cells.

One substance, **creatine**, normally acts as a reserve for ATP by forming a compound called creatine phosphate (also called phosphocreatine). When a cell's demand for ATP exceeds the amount its mitochondria can produce, creatine can release phosphate (the "P" in ATP) to rapidly enhance the ATP supply. In fact, creatine phosphate typically provides the initial burst of ATP required for strenuous muscle activity.

Another substance, **carnitine**, generally improves the efficiency of ATP production by helping import certain fuel molecules into mitochondria and cleaning up some of the toxic byproducts of ATP production. Carnitine is available as an over-the-counter supplement called L-carnitine.

Finally, **coenzyme Q10**, also called CoQ10 or ubiquinone, is a component of the mitochondrial respiratory chain (which uses oxygen to manufacture ATP). CoQ10 is also an antioxidant. Some mitochondrial diseases are caused by CoQ10 deficiency, and CoQ10 supplementation is clearly beneficial in these cases. It might provide some relief from other mitochondrial diseases.

Creatine, L-carnitine, and CoQ10 supplements often are combined into a “cocktail” for treating mitochondrial disease. Although there is a need for careful studies to confirm the value of this treatment, some people with mitochondrial disease have reported modest benefits.

## **How are mitochondrial myopathies inherited?**

**T**he inheritance of mitochondrial diseases is complex, and often a mitochondrial myopathy can be difficult to trace through a family tree. In fact, many cases of mitochondrial disease are sporadic, meaning that they occur without any family history.

To understand how mitochondrial diseases are inherited, it is important to know that there are two types of genes essential to mitochondria. The first type is housed within the nucleus—a compartment within our cells that contains most of our genetic material, or DNA. The second type resides exclusively within DNA contained inside the mitochondria.

Mutations in either nuclear DNA (nDNA) or mitochondrial DNA (mtDNA) can cause mitochondrial disease.

Nuclear DNA is packaged into structures called chromosomes—22 pairs of non-sex related chromosomes (called autosomes) and a single pair of sex chromosomes (XX in females and XY in males). This means that except for genes on the X chromosome, everyone has two copies of the genes in nDNA, with one

copy inherited from each parent. There are three inheritance patterns seen for diseases caused by nDNA mutations:

- Autosomal recessive means that it takes two mutant copies of a gene—one inherited from each parent—to cause the disease.
- Autosomal dominant means it takes just one mutant copy of a gene—inherited from one parent—to cause the disease.
- Usually, X-linked diseases appear only in males. An affected male's mother and any daughters he has will carry the gene for the disease but typically will not have symptoms.

Unlike nDNA, mtDNA passes only from mother to child. This is because during conception, when the sperm fuses with the egg, the sperm's mitochondria and its mtDNA are destroyed. Mitochondrial diseases caused by mtDNA mutations are unique because they are inherited in a maternal pattern. A mother can pass defective mtDNA to any of her children, but only her daughters—and not her sons—will pass it to the next generation.

Another unique feature of mtDNA diseases arises from the fact that a typical human cell contains only one nucleus but hundreds of mitochondria. A single cell can contain both mutant and normal mitochondria, and the balance between the two will determine the cell's health, which can also explain the range of symptoms in mtDNA diseases.

The risk of passing on a mitochondrial disease to a child depends on many factors, including whether the disease is caused by mutations in nDNA or mtDNA. To find out more about these risks, talk with a doctor or genetic counselor.

## **What syndromes occur with mitochondrial disease?**

**S**ome syndromes associated with mitochondrial disease are:

### **Barth syndrome**

Onset: infancy

Features: Typical symptoms include cardiomyopathy, general muscle weakness, and a low white blood cell count, which leads to an increased risk of infection. This syndrome was once considered uniformly fatal in infancy, but some individuals are now living much longer.

Inheritance pattern: X-linked

### **Chronic progressive external ophthalmoplegia (cPEO)**

Onset: usually in adolescence or early adulthood

Features: PEO is often a symptom of mitochondrial disease. In some people, it is a chronic, slowly progressive condition associated with instability to move the eyes and general weakness and exercise intolerance.

Inheritance pattern: autosomal, but may occur sporadically

## **Kearns-Sayre syndrome (KSS)**

Onset: before age 20

Features: PEO (usually as the initial symptom) and pigmentary retinopathy, a “salt-and-pepper” pigmentation in the retina that can affect vision. Other common symptoms include cardiomyopathy, conduction block (a type of cardiac arrhythmia) ataxia, short stature, neuropathy, and deafness.

Inheritance pattern: autosomal (mostly sporadic)

## **Leigh syndrome (MILS, or maternally inherited Leigh syndrome)**

Onset: infancy or early childhood

Features: Brain abnormalities that can result in abnormal muscle tone, ataxia, seizures, impaired vision and hearing, developmental delays, and respiratory problems. Infants with the disease have a poor prognosis.

Inheritance pattern: maternal, autosomal recessive, X-linked

## **Mitochondrial DNA depletion syndromes (MDDS)**

Onset: infancy

Features: A myopathic form of MDDS is characterized by weakness that eventually affects the respiratory muscles. Some forms of MDDS, such as Alpers syndrome, are marked by brain abnormalities and progressive liver disease. The anticonvulsant sodium valproate should be used with caution in children with Alpers syndrome because it can increase the risk of liver failure.

Inheritance pattern: autosomal

## **Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)**

Onset: childhood to early adulthood

Features: The hallmarks of MELAS are encephalomyopathy with seizures and/or dementia, lactic acidosis, and recurrent stroke-like episodes. These episodes are not typical strokes, which are interruptions in the brain's blood supply that cause sudden neurological symptoms. However, the episodes can produce stroke-like symptoms in the short term (such as temporary vision loss, difficulty speaking, or difficulty understanding speech) and lead to progressive brain injury. The cause of the stroke-like episodes is unclear.

Inheritance pattern: maternal

## **Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)**

Onset: usually before age 20

Features: This disorder is characterized by PEO, ptosis, limb weakness, and gastrointestinal (digestive) problems, including vomiting, chronic diarrhea, and abdominal pain. Another common symptom is peripheral neuropathy (a malfunction of the nerves that can lead to sensory impairment and muscle weakness).

Inheritance pattern: autosomal recessive

## **Myoclonus epilepsy with ragged red fibers (MERRF)**

Onset: late childhood to adolescence

Features: The most prominent symptoms of MERRF are myoclonus (muscle jerks), seizures, ataxia, and muscle weakness. The disease also can cause hearing impairment and short stature.

Inheritance pattern: maternal

## **Neuropathy, ataxia, and retinitis pigmentosa (NARP)**

Onset: infancy to adulthood

Features: NARP is caused by an mtDNA mutation that is also linked to MILS, and the two syndromes can occur in the same family. In addition to the core symptoms for which it is named, NARP can involve developmental delay, seizures, and dementia. (Retinitis pigmentosa refers to a degeneration of the retina in the eye, with resulting loss of vision).

Inheritance pattern: maternal

## **Pearson syndrome**

Onset: infancy

Features: This syndrome involves severe anemia and malfunction of the pancreas. Children who have the disease usually go on to develop Kearns-Sayre syndrome.

Inheritance pattern: autosomal (often sporadic)

## How are mitochondrial diseases diagnosed?

**T**he hallmark symptoms of mitochondrial myopathy include muscle weakness, exercise intolerance, impaired hearing and vision, ataxia, seizures, learning disabilities, heart defects, diabetes, and poor growth—none of which are unique to mitochondrial disease. However, a combination of three or more of these symptoms in one person strongly points to mitochondrial disease, especially when the symptoms involve more than one organ system.

To evaluate the extent of these symptoms, a physician usually begins by taking the individual's medical history. Because mitochondrial diseases are genetic, a family history also is an important part of the diagnosis. Physical and neurological exams also will be part of the evaluation.

The physical exam typically includes tests of strength and endurance, such as an exercise test (which can involve activities like repeatedly making a fist). The neurological exam can include tests of reflexes, vision, speech, and basic cognitive (thinking) skills.

Typically, the doctor will order laboratory tests to look for diabetes and liver and kidney problems. The doctor is likely to order an electrocardiogram (EKG) to check the heart for signs of arrhythmia and cardiomyopathy.

Tests may be ordered to look for abnormalities in the brain and muscles. Diagnostic imaging that produce detailed pictures of organs, bones, and tissues, such as computed tomography (CT) or magnetic resonance imaging (MRI), might

be used to inspect the brain for developmental abnormalities or signs of damage. In an individual who has seizures, the doctor might order an electroencephalogram (EEG), which involves placing electrodes on the scalp to record brain activity.

Since lactic acidosis is a common feature of mitochondrial disease, it is routine to test for elevated lactic acid in the blood and urine. Some cases might warrant measuring lactic acid in the cerebral spinal fluid (CSF) that fills spaces within the brain and spinal cord. The measurement can be made by collecting CSF through a spinal tap, or estimated by MR spectroscopy—a technique that uses an MRI signal to detect changes in the level of lactic acid and other chemicals in the brain.

One of the most important tests for mitochondrial disease is the muscle biopsy, which involves removing and examining a small sample of muscle tissue. When treated with a dye that stains mitochondria red, muscles affected by mitochondrial disease often show ragged red fibers—muscle cells (fibers) that have excessive mitochondria. Other stains can detect the absence of essential mitochondrial enzymes in the muscle. It also is possible to extract mitochondrial proteins from the muscle and measure their activity.

Noninvasive techniques can be used to examine muscle without taking a tissue sample. For instance, MR spectroscopy can be used to measure levels of the organic molecule phosphocreatine and ATP (which are often depleted in muscles affected by mitochondrial disease).

Finally, genetic testing can determine whether someone has a genetic mutation that causes mitochondrial disease. These tests use genetic material extracted from blood or from a muscle biopsy. Although a positive test result can confirm diagnosis of a mitochondrial disorder, a negative test result can be harder to interpret. It could mean a person has a genetic mutation that the test was not able to detect.

## What research is being done?

**T**he mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. The NINDS is a component of the National Institutes of Health (NIH), the leading supporter of biomedical research in the world.

In conjunction with other NIH Institutes, private organizations, and industry, NINDS supports research focused on effective treatments and cures for mitochondrial myopathies and other mitochondrial diseases.

Scientists are investigating the possible benefits of exercise programs and nutritional supplements, primarily natural and synthetic versions of CoQ10. While CoQ10 has proven benefit for primary CoQ10 deficiency, it is unclear whether other nutritional supplements are useful for treating mitochondrial diseases.

Scientists have identified many of the genetic mutations that cause mitochondrial diseases. They have used that knowledge to create animal models of mitochondrial disease, which can be used to investigate potential treatments.

Scientists also have designed genetic tests that allow accurate diagnosis of mitochondrial defects and provide valuable information for family planning.

Most importantly, knowing the genetic mutations that cause mitochondrial disease opens up the possibility of developing treatments that are specifically targeted. One remarkable example where knowledge about mitochondrial disease genetics has led to a potential therapy is MNGIE. This syndrome is caused by genetic defects in an enzyme called thymidine phosphorylase (TP). Loss of the TP enzyme causes the body to accumulate metabolites called nucleosides. Some of these are the building blocks for DNA, and their accumulation appears to destabilize mtDNA. Researchers have shown that they can restore the enzyme and reduce nucleoside levels in the blood by giving individuals with MNGIE an infusion of blood-forming stem cells from a donor. Further study is needed to establish whether this treatment affects the clinical course of MNGIE.

Scientists hope to develop unique approaches to treating mitochondrial diseases through a better understanding of mitochondrial biology. The mitochondria in a single cell are not static; new mitochondria are born, old or damaged ones die, and two or more mitochondria can even fuse to become one. Because people affected by mitochondrial disease often have a mixture of healthy and mutant mitochondria in their cells, effective therapy could involve getting the healthy mitochondria to take over. It might be possible to rescue mutant mitochondria

by stimulating them to fuse with healthy mitochondria. Another approach might be to stimulate the birth of new mitochondria, encouraging the healthy ones to multiply and outnumber the mutants. Some diabetes drugs are known to stimulate new mitochondria, and are being eyed as potential treatments for mitochondrial disorders.

Finally, scientists have developed a potential way to prevent the passage of mutant mitochondria from mother to child. The approach would involve transferring the nDNA from a woman with mtDNA disease into another woman's egg cell that has healthy mitochondria and has had its own nDNA removed. Then, standard assisted reproduction techniques could be used to fertilize this egg cell and implant it into the woman who donated the nDNA. Researchers have tested the approach in monkeys and shown that it can produce healthy offspring of an nDNA donor, with no signs of the donor's mtDNA.

## Where can I get more information?

**F**or more information about mitochondrial diseases, other neurological disorders, or research programs funded by the NINDS, contact the Institute's Brain Resources and Information Network (BRAIN) at:

### **BRAIN**

P.O. Box 5801

Bethesda, MD 20824

301- 496-5751

800-352-9424

*www.ninds.nih.gov*

Information about mitochondrial diseases is available from the following organizations:

**Muscular Dystrophy Association**

3300 East Sunrise Drive  
Tucson, AZ 85718-3208  
520-529-2000  
800-572-1717  
*www.mda.org*

**National Organization for Rare Disorders (NORD)**

55 Kenosia Avenue  
Danbury, CT 06813-1968  
203-744-0100 (voice mail)  
800- 999-6673  
*www.rarediseases.org*

**United Mitochondrial Disease Foundation**

8085 Saltsburg Road, Suite 201  
Pittsburgh, PA 15239  
412-793-8077  
888-317-8633  
*www.umdff.org*





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