



Facts About **Mitochondrial** Myopathies

MDA[®] Muscular
Dystrophy
Association
Fighting Muscle Disease

Dear Friends:

If you are reading this booklet, it's probably because you've just received a very bewildering diagnosis: mitochondrial myopathy. What is a mitochondrial myopathy, and what does the term mean? These are questions my wife, Jennifer, and I struggled with when our son, Michael, got his diagnosis in 1993.

Mitochondrial myopathies have many different faces. As you will read in this booklet, dozens of varieties of mitochondrial diseases have been identified, with a complex array of symptoms. Some symptoms can be so mild that they're hardly noticeable, while others are life-threatening.

Michael's disease causes muscle weakness, muscle cramping, fatigue, lack of endurance and poor balance. You or your family member may have similar symptoms, yet each case is unique.

When we first learned that Michael had a mitochondrial myopathy, we naturally were very frightened and uncertain about the future. As time passed, we learned that we can do things we didn't think would be possible — we can adapt to the uncertainty, control the fear, cope with changes as they occur and still have a “normal,” happy family life.

In 2004 our lives were again turned upside down, when my wife, Jennifer, learned she too had a mitochondrial disease. Jennifer's symptoms are more severe than Michael's; she experiences severe muscle weakness, fatigue, gastrointestinal problems, respiratory problems and difficulty swallowing.

This booklet has been prepared to help you understand the causes of and treatments for mitochondrial myopathies. We have found information to be a vital tool in managing Michael's and Jennifer's diseases and achieving the best possible outcome.

From this booklet you'll also learn a few encouraging things. For example, although these are very rare disorders, many of their

symptoms are common in the general population, such as heart problems, seizures and diabetes. Therefore, good medical treatments already exist to help manage many symptoms.

Always remember that researchers are continually moving toward better treatments, and ultimately, cures for mitochondrial diseases. In addition, people with disabilities have greater opportunities than ever before to make the most of their abilities, as well as legal rights to equal employment opportunity and access to public places. Children with physical and cognitive disabilities are guaranteed by law a public education with whatever supports they need.

MDA has been a very valuable ally as we continue to learn to live with mitochondrial disease. “MDA Is Here to Help You,” on page 14, will tell you more about MDA's many services.

To us, Michael is not a victim of a disease or a syndrome, but a happy, loving, young man of whom we're very proud. We've discovered that no one can predict exactly how Michael's or Jennifer's cases will progress. We've been blessed to see Michael lead a normal life, earning his Boy Scout Eagle Award and being inducted into the National Honor Society. Michael has shown that having a mitochondrial disease doesn't necessarily keep you from accomplishing anything you set your mind to.

As we struggle to adapt to the changes in our lives since Jennifer's diagnosis, it's reassuring to know that MDA is there for us, assisting us with equipment, clinics, continuing research, and just a friendly voice that understands what we are going through.

As you face the challenges ahead, we wish you the same blessing and the comfort of knowing that you are not alone.

Richard Kelly
Mansfield, Massachusetts



The Kelly family at the MDA Labor Day Telethon.

What Are Mitochondrial Diseases?

Just as some diseases are named for the part of the body they affect (like heart disease), mitochondrial diseases are so-named because they affect a specific part of the cells in the body. Specifically, mitochondrial diseases affect the mitochondria — tiny energy factories found inside almost all our cells.

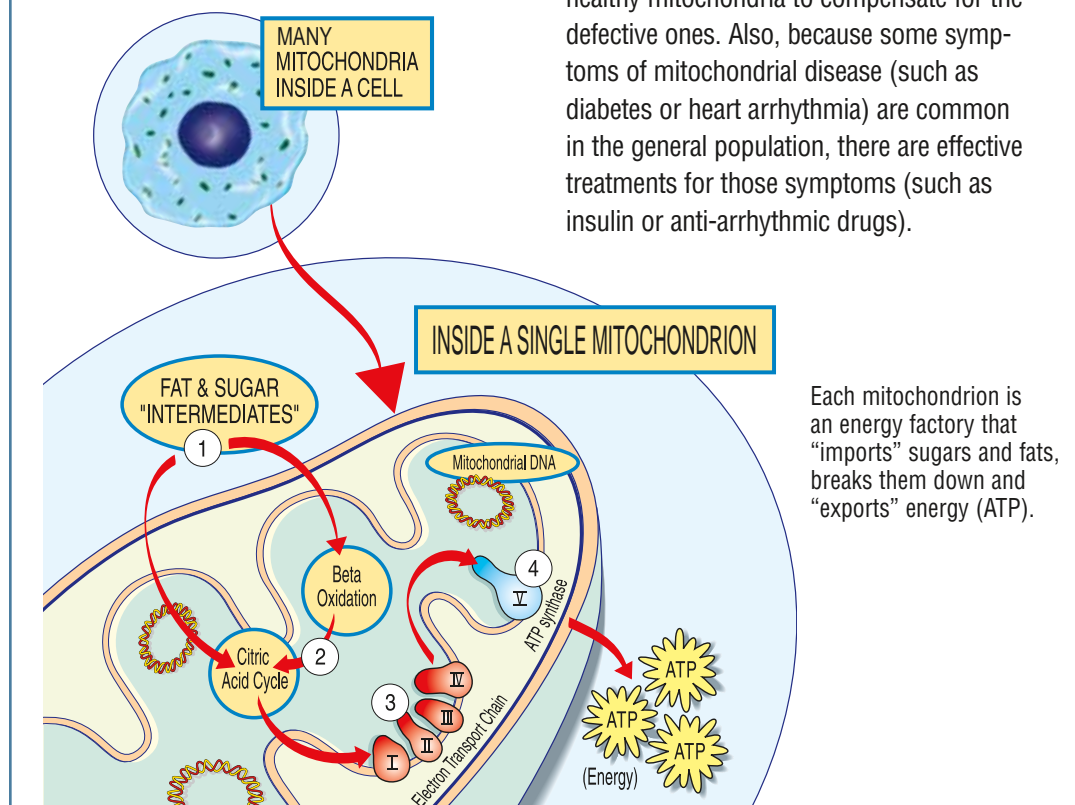
Mitochondria are responsible for producing most of the energy that's needed for our cells to function. In fact, they provide such an important source of energy that a typical human cell contains hundreds of them. A mitochondrial disease can shut down some or all the mitochondria, cutting off this essential energy supply.

Nearly all our cells rely on mitochondria for a steady energy supply, so a mitochondrial disease can be a multisystem disorder affecting more than one type of cell, tissue or organ. The exact symptoms aren't the same for everyone, because a person with mitochondrial disease can have a unique mixture of healthy and defective mitochondria, with a unique distribution in the body.

Because muscle cells and nerve cells have especially high energy needs, muscular and neurological problems — such as muscle weakness, exercise intolerance, hearing loss, trouble with balance and coordination, seizures and learning deficits — are common features of mitochondrial disease. Other frequent complications include impaired vision, heart defects, 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're grouped into syndromes.

A mitochondrial disease that causes prominent muscular problems is called a mitochondrial *myopathy* (*myo* means muscle, and *pathos* means disease), while a mitochondrial disease that causes both prominent muscular and neurological problems is called a mitochondrial *encephalomyopathy* (*encephalo* refers to the brain).

Despite their many potential effects, mitochondrial diseases sometimes cause little disability. Sometimes, a person has enough healthy mitochondria to compensate for the defective ones. Also, because some symptoms of mitochondrial disease (such as diabetes or heart arrhythmia) are common in the general population, there are effective treatments for those symptoms (such as insulin or anti-arrhythmic drugs).



Mitochondrial diseases aren't contagious, and they're not caused by anything a person does.

This booklet describes general causes, consequences and management of mitochondrial diseases, with an emphasis on myopathies and encephalomyopathies and a close look at the most common syndromes. These include:

- **Kearns-Sayre syndrome (KSS)**
- **Leigh syndrome**
- **mitochondrial DNA depletion syndrome (MDS)**
- **mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)**
- **myoclonus epilepsy with ragged red fibers (MERRF)**
- **mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)**
- **neuropathy, ataxia and retinitis pigmentosa (NARP)**
- **Pearson syndrome**
- **progressive external ophthalmoplegia (PEO)**

What causes mitochondrial diseases?

First, mitochondrial diseases aren't contagious, and they aren't caused by anything a person does. They're caused by mutations, or changes, in genes — the cells' blueprints for making proteins.

Genes are responsible for building our bodies, and are passed from parents to children, along with any mutations or defects they have. That means that mitochondrial diseases are inheritable, although they often affect members of the same family in different ways. (For more information about genetic mutations and mitochondrial disease, see "Does It Run in the Family?" on page 12.)

The genes involved in mitochondrial disease normally make proteins that work inside the

mitochondria. Within each mitochondrion (singular of mitochondria), these proteins make up part of an assembly line that uses fuel molecules derived from food to manufacture the energy molecule ATP. This highly efficient manufacturing process requires oxygen; outside the mitochondrion, there are less efficient ways of producing ATP without oxygen.

Proteins at the beginning of the mitochondrial assembly line act like cargo handlers, importing the fuel molecules — sugars and fats — into the mitochondrion. Next, other proteins break down the sugars and fats, extracting energy in the form of charged particles called electrons.

Proteins toward the end of the line — organized into five groups called complexes I, II, III, IV and V — harness the energy from those electrons to make ATP. Complexes I through IV shuttle the electrons down the line and are therefore called the electron transport chain, and complex V actually churns out ATP, so it's also called ATP synthase.

A deficiency in one or more of these complexes is the typical cause of a mitochondrial disease. (In fact, mitochondrial diseases are sometimes named for a specific deficiency, such as complex I deficiency.)

When a cell is filled with defective mitochondria, it not only becomes deprived of ATP — it can accumulate a backlog of unused fuel molecules and oxygen, with potentially disastrous effects.

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 actually damage muscle and nerve tissue.

Meanwhile, unused oxygen in the cell can be converted into destructive compounds called reactive oxygen species, including so-called free radicals. (These are the targets of so-called antioxidant drugs and vitamins.)

ATP derived from mitochondria provides the main source of power for muscle cell contraction and nerve cell firing. So, muscle cells and nerve cells are especially sensitive to mitochondrial defects. The combined effects of energy deprivation and toxin accumulation in these cells probably give rise to the main symptoms of mitochondrial myopathies and encephalomyopathies.

What happens to someone with a mitochondrial disease?

Myopathy

The main symptoms of mitochondrial myopathy are muscle weakness and wasting, and exercise intolerance. It's important to remember that 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 heads to look in different directions, and might not even notice any visual problems. Ptosis is potentially more frustrating because it can impair vision and also cause a listless expression, but it can be corrected by surgery, or by using glasses that have a "ptosis crutch" to lift the upper eyelids.

Mitochondrial myopathies also can cause weakness and wasting in other muscles of the face and neck, which can lead to slurred speech and difficulty with swallowing. In these instances, speech therapy or changing the diet to easier-to-swallow foods can be

useful. Sometimes, people with mitochondrial myopathies experience loss of muscle strength in the arms or legs, and might need braces or a wheelchair to get around.

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 only have trouble with athletic activities like jogging, while others might experience problems with everyday activities like walking to the mailbox or lifting a milk carton.

Sometimes, exercise intolerance is associated with painful muscle cramps and/or injury-induced pain. The cramps are actually sharp contractions that may seem to temporarily lock the muscles, while the injury-induced pain is caused by a process of acute muscle breakdown called *rhabdomyolysis*, leading to leakage of 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.

Encephalomyopathy

A mitochondrial encephalomyopathy typically includes some of the above-mentioned symptoms of myopathy plus one or more neurological symptoms. Again, these symptoms show a great deal of individual variability in both type and severity.

Hearing impairment, migraine-like headaches and seizures are among the most common symptoms of mitochondrial encephalomyopathy. In at least one syndrome, headaches and seizures often are accompanied by stroke-like episodes.

Fortunately, there are good treatments for some of these conditions. Hearing impairment can be managed using hearing aids and alternate forms of communication. Often, headaches can be alleviated with medications, and seizures can be prevented with drugs used for epilepsy (anti-epileptics).



Mitochondrial myopathies can affect entire families.



Some people with mitochondrial myopathies lose strength in their legs and need a wheelchair to get around.

In addition to affecting the musculature of the eye, 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. Compared to muscle problems, these effects are more likely to cause serious visual impairment.

Often, mitochondrial encephalomyopathy causes ataxia, or trouble with balance and coordination. People with ataxia are usually prone to falls. One can partly avoid these problems through physical and occupational therapy, and the use of supportive aids such as railings, a walker or — in severe cases — a wheelchair.



Occupational therapy is important for children with mitochondrial myopathies.



Mitochondrial myopathy can lead to respiratory problems that require support from a ventilator.

Special issues in mitochondrial myopathies and encephalomyopathies

Respiratory care

Sometimes, these diseases can cause significant weakness in the muscles that support breathing.

Also, mitochondrial encephalomyopathies sometimes cause brain abnormalities that alter the brain's control over breathing.

A person with mild respiratory problems might require occasional respiratory support, such as pressurized air, while someone with more severe problems might require permanent support from a ventilator. Those with mitochondrial disorders should watch for signs of respiratory insufficiency (such as shortness of breath or morning headaches), and have their breathing checked regularly by a specialist.

Cardiac care

Sometimes, mitochondrial diseases directly affect the heart. In these cases, the usual cause is an interruption in the rhythmic beating of the heart, called a *conduction block*.

Though dangerous, this condition is treatable with a pacemaker, which stimulates normal beating of the heart. Cardiac muscle damage also may occur. People with mitochondrial disorders may need to have regular examinations by a cardiologist.

Other potential health issues

Some people with mitochondrial disease experience serious kidney problems, gastrointestinal problems and/or diabetes. Some of these problems are direct effects of mitochondrial defects in the kidneys, digestive system or pancreas (in diabetes), and others are indirect effects of mitochondrial defects in other tissues.

For example, rhabdomyolysis can lead to kidney problems by causing a protein called myoglobin to leak from ruptured muscle cells into the urine. This condition, myoglobinuria, stresses the kidneys' ability to filter waste from the blood, and can cause kidney damage.

Special issues in children

Vision: Though PEO and ptosis typically cause only mild visual impairment in adults, they're potentially more harmful in children with mitochondrial myopathies.

Because the development of the brain is sensitive to childhood experiences, PEO or ptosis during childhood can sometimes cause permanent damage to the brain's visual system. For this reason, it's 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 who are severely affected by these problems may benefit from services

such as physical therapy, speech therapy and possibly an individualized education program (IEP) at school.

How are mitochondrial diseases treated?

While mitochondrial myopathies and encephalomyopathies are relatively rare, some of their potential manifestations are common in the general population. Consequently, those complications (including heart problems, stroke, seizures, migraines, deafness and diabetes) have highly effective treatments (including medications, dietary modifications and lifestyle changes). (See “Special issues in children,” page 6.)

It’s fortunate that these treatable symptoms are often the most life-threatening complications of mitochondrial disease. With that in mind, people affected by mitochondrial diseases can do a great deal to take care of themselves by monitoring their health and scheduling regular medical exams.

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

Although they don’t work for everyone, they do help some people. (Always check with your physician to see what’s best for your condition.)

One substance, *creatine*, normally acts as a reserve for ATP by forming a compound called *creatine phosphate*. 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 (also called *phosphocreatine*) 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*, or *coQ10*, is a component of the electron transport chain, which uses oxygen to manufacture ATP. Some mitochondrial diseases are caused by coQ10 deficiency, and there’s good evidence that coQ10 supplementation is beneficial in these cases. Some doctors think that coQ10 supplementation also might alleviate other mitochondrial diseases.

Creatine, L-carnitine and coQ10 supplements often are combined into a “cocktail” for treating mitochondrial disease. Although there’s little scientific evidence that this treatment works, many people with mitochondrial disease have reported modest benefits. You should consult your doctor or MDA clinic director before taking any medication or supplement.

What syndromes occur with mitochondrial disease?

Note: Typically, these syndromes are inherited in either a maternal pattern or a so-called Mendelian pattern, and/or they’re sporadic, which means occurring with no family history. For more information about inheritance, see “Does It Run in the Family?” page 12.

KSS: Kearns-Sayre syndrome

Inheritance pattern:

sporadic

Onset:

before age 20

Features:

This disorder is defined by PEO (usually as the initial symptom) and *pigmentary retinopathy*, a “salt-and-pepper” pigmentation in the retina that can affect vision, but often leaves it intact. Other common symptoms include conduction block (in the heart) and



The brain’s visual system can be affected in children with mitochondrial myopathy.



Some children with mitochondrial myopathies experience developmental delays.

ataxia. Less typical symptoms are mental retardation or deterioration, delayed sexual maturation and short stature.

Leigh syndrome: subacute necrotizing encephalomyopathy (MILS = maternally inherited Leigh syndrome)

Inheritance pattern:
maternal, Mendelian

Onset:
infancy

Features:
Leigh syndrome causes brain abnormalities that can result in ataxia, seizures, impaired vision and hearing, developmental delays and altered control over breathing.

It also causes muscle weakness, with prominent effects on swallowing, speech and eye movements.

MDS: mitochondrial DNA depletion syndrome

Inheritance pattern:
Mendelian

Onset:
infancy

Features:
This disorder typically causes muscle weakness and/or liver failure, and more rarely, brain abnormalities. “Floppiness,” feeding difficulties, and developmental delays are common symptoms; PEO and seizures are less common.

MELAS: mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes

Inheritance pattern:
maternal

Onset:
childhood to early adulthood

Features:
MELAS causes recurrent stroke-like episodes in the brain, migraine-like headaches, vomiting and seizures, and can lead to permanent brain damage. Other common symptoms include PEO, general muscle weakness, exer-

cise intolerance, hearing loss, diabetes and short stature.

MERRF: myoclonus epilepsy with ragged red fibers

Inheritance pattern:
maternal

Onset:
late childhood to adolescence

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

MNGIE: mitochondrial neurogastrointestinal encephalomyopathy

Inheritance pattern:
Mendelian

Onset:
usually before age 20

Features:
This disorder causes PEO, ptosis, limb weakness and gastrointestinal (digestive) problems, including 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).

NARP: neuropathy, ataxia and retinitis pigmentosa

Inheritance pattern:
maternal

Onset:
infancy to adulthood

Features:
NARP causes neuropathy (see above), ataxia and retinitis pigmentosa (degeneration of the retina in the eye, with resulting loss of vision). It also can cause developmental delay, seizures and dementia.

Pearson syndrome

Inheritance pattern:
sporadic

Onset:
infancy



Mitochondrial myopathies can be inherited, and severity can vary within a family.

Features:

This syndrome causes severe anemia and malfunction of the pancreas. Children who survive the disease usually go on to develop KSS.

PEO: progressive external ophthalmoplegia**Inheritance pattern:**

maternal, Mendelian, sporadic

Onset:

Usually in adolescence or early adulthood

Features:

As noted above, PEO is often a symptom of mitochondrial disease, but sometimes it stands out as a distinct syndrome. Often, it's associated with exercise intolerance.

How are mitochondrial diseases diagnosed?

None of the hallmark symptoms of mitochondrial disease — muscle weakness, exercise intolerance, hearing impairment, ataxia, seizures, learning disabilities, cataracts, heart defects, diabetes and stunted growth — 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 patient's personal medical history, and then proceeds with physical and neurological exams.

Diagnostic tests in mitochondrial diseases

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

Depending on information found during the medical history and exams, the physician

might proceed with more specialized tests that can detect abnormalities in muscles, brain and other organs.

The most important of these tests is the muscle biopsy, which involves removing a small sample of muscle tissue to examine. 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's also possible to extract mitochondrial proteins from the muscle and measure their activity.

In addition to the muscle biopsy, noninvasive techniques can be used to examine muscle without taking a tissue sample. For instance, a technique called muscle phosphorus magnetic resonance spectroscopy (MRS) can measure levels of phosphocreatine and ATP (which are often depleted in muscles affected by mitochondrial disease).

CT scans and MRI scans can be used to visually inspect the brain for signs of damage, and surface electrodes placed on the scalp can be used to produce a record of the brain's activity called an electroencephalogram (EEG).

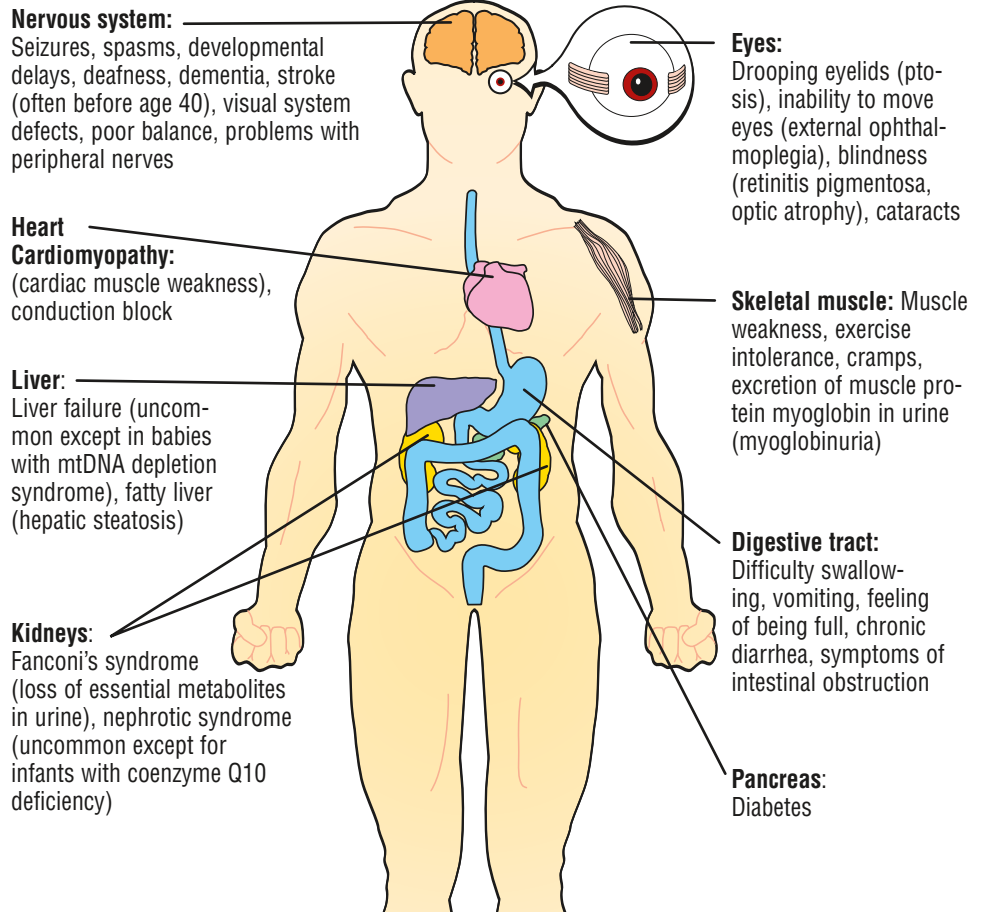
Similar techniques might be used to examine the functions of other organs and tissues in the body. For example, an electrocardiogram (EKG) can monitor the heart's activity, and a blood test can detect signs of kidney malfunction.

Finally, a genetic test can determine whether someone has a genetic mutation that causes mitochondrial disease. Ideally, the test is done using genetic material extracted from blood or from a muscle biopsy. It's important to realize that, although a positive test result can confirm diagnosis, a negative test result isn't necessarily meaningful.

Diagnostic Tests in Mitochondrial Diseases

Type	Test	What it shows
Family history	Clinical exam or oral history of family members	Can sometimes indicate inheritance pattern by noting “soft signs” in unaffected relatives. These include deafness, short stature, migraine headaches and PEO.
Muscle biopsy	<ol style="list-style-type: none"> 1. Histochemistry 2. Immunohistochemistry 3. Biochemistry 4. Electron microscopy 	<ol style="list-style-type: none"> 1. Detects abnormal proliferation of mitochondria and deficiencies in cytochrome c oxidase (COX, which is complex IV in the electron transport chain). 2. Detects presence or absence of specific proteins. Can rule out other diseases or confirm loss of electron transport chain proteins. 3. Measures activities of specific enzymes. A special test called <i>polarography</i> measures oxygen consumption in mitochondria. 4. May confirm abnormal appearance of mitochondria. Not used much today.
Blood enzyme test	<ol style="list-style-type: none"> 1. Lactate and pyruvate levels 2. Serum creatine kinase 	<ol style="list-style-type: none"> 1. If elevated, may indicate deficiency in electron transport chain; abnormal ratios of the two may help identify the part of the chain that is blocked. 2. May be slightly elevated in mitochondrial disease but usually only high in cases of mitochondrial DNA depletion.
Genetic test	<ol style="list-style-type: none"> 1. Known mutations 2. Rare or unknown mutations 	<ol style="list-style-type: none"> 1. Uses blood sample or muscle sample to screen for known mutations, looking for common mutations first. 2. Also can look for rare or unknown mutations but may require samples from family members; this is more expensive and time-consuming.

Mitochondrial Disease: An Inside Look



The main problems associated with mitochondrial disease — low energy, free radical production and lactic acidosis — can result in a variety of symptoms in many different organs of the body.

This diagram depicts common symptoms of mitochondrial disease, of which most affected people have a specific subset. Many of these symptoms are treatable.

Does It Run in the Family?

Mitochondrial genetics are complex, and often, a mitochondrial disease can be difficult to trace through a family tree. But since they're caused by defective genes, mitochondrial diseases do run in families.

To understand how mitochondrial diseases are passed on through families, it's important to know that there are two types of genes essential to mitochondria. The first type is housed within the nucleus — the part of our cells that contains most of our genetic material, or DNA. The second type resides exclusively within DNA contained inside the mitochondria themselves.

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

Most nDNA (along with any mutations it has) is inherited in a Mendelian pattern, loosely meaning that one copy of each gene comes from each parent. Also, most mitochondrial diseases caused by nDNA mutations (including Leigh syndrome, MNGIE and even MDS) are *autosomal recessive*, meaning that it takes mutations in both copies of a gene to cause disease.

Unlike nDNA, mtDNA passes only from mother to child. That's because during conception, when the sperm fuses with the egg, the sperm's mitochondria — and its mtDNA — are destroyed. Thus, mitochondrial diseases caused by mtDNA mutations are unique because they're inherited in a maternal pattern (see illustration).

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

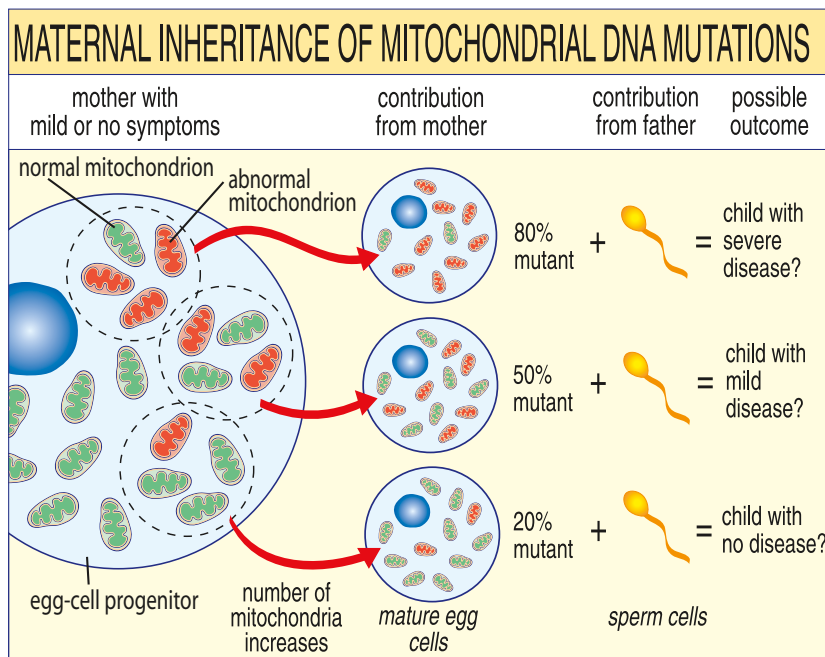
This helps explain why the symptoms of mitochondrial disease can vary so much from person to person, even within the same family.

Imagine that a woman's egg cells (and other cells in her body) contain both normal and mutant mitochondria, and that some have just a few mutant mitochondria, while others have many. A child conceived from a "mostly healthy" egg cell probably won't develop disease, and a child conceived from a "mostly mutant" egg cell probably will.

Also, the woman may or may not have symptoms of mitochondrial disease herself.

The risk of passing on a mitochondrial disease to your children depends on many factors, including whether the disease is caused by mutations in nDNA or mtDNA.

A good way to find out more about these risks is to talk to a doctor or genetic counselor at your local MDA clinic. Also, see MDA's booklet "Facts About Genetics and Neuromuscular Diseases."



The severity of a mitochondrial disease in a child depends on the percentage of abnormal (mutant) mitochondria in the egg cell that formed him or her.

MDA's Search for Treatments and Cures

The MDA website is constantly updated with the latest information about the neuromuscular diseases in its program. See the latest research news at www.mda.org.

With MDA's support, scientists continue to make significant progress in their quest to fully understand and treat mitochondrial diseases.

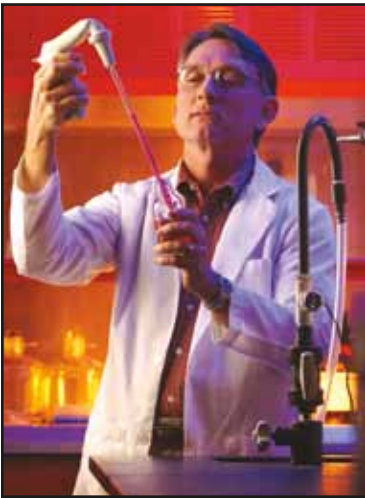
Unique progress has been made in MNGIE, a disease in which a flaw in a gene in the nucleus indirectly causes a mitochondrial problem. MDA-funded researchers are experimenting with infusing donor stem cells into patients with MNGIE to restore normal metabolic conditions and halt damage to the mitochondria.

In addition, MDA-funded scientists have identified many of the genetic defects that cause mitochondrial diseases. They've used knowledge of those genetic defects to create animal models of mitochondrial disease, which can be used to investigate potential treatments. They've also designed genetic tests that allow accurate diagnosis of mitochondrial defects and provide valuable information for family planning.

Perhaps most important, knowing the genetic defects that cause mitochondrial disease opens up the possibility of developing treatments that target them.

As of late 2009, some MDA-supported researchers are working on ways to add therapeutic genes to mitochondria. Others are concentrating on understanding the

biochemical processes that go on inside mitochondria, with the goal of correcting or working around these to treat mitochondrial abnormalities, whether or not new genes are added. Still others are studying the behavior of mitochondria as they exist inside cells as miniature organs ("organelles"), interacting with each other and with other cellular components.



MDA Is Here to Help You

The Muscular Dystrophy Association offers a vast array of services to help you and your family deal with mitochondrial myopathy. The staff at your local MDA office is there to assist you in many ways. The Association's services include:

- nationwide network of clinics staffed by top neuromuscular disease specialists
- MDA summer camps for kids with neuromuscular diseases
- help with locating durable medical equipment through its national equipment program
- financial assistance with repairs or modifications to all types of durable medical equipment
- annual occupational, physical, respiratory or speech therapy consultations
- annual flu shots
- support groups for those affected, spouses, parents or other caregivers
- online support services through the e-community *myMDA* and through *myMuscleTeam*, a program that helps recruit and coordinate in-home help

MDA's public health education program helps you stay abreast of research news, medical findings and disability information through magazines, publications, educational speakers, seminars, videos and newsletters.

MDA's website at www.mda.org contains thousands of pages of valuable information, including disease specifics, research findings, clinical trials and past magazine articles.

Everyone registered with MDA automatically receives *Quest*, MDA's award-winning quarterly magazine. *Quest* publishes detailed articles about research findings, medical and day-to-day care, helpful products and devices, social and family issues, and much more. Other MDA publications can be found at www.mda.org/publications; many booklets are available in Spanish. Ask your local office for "MDA Services for the Individual, Family and Community" and for help with obtaining copies of other publications.

If you have any questions about mitochondrial myopathy, someone at MDA will help you find the answer. To reach your local MDA office, call (800) 572-1717.



On the cover:
Mattie was MDA's National Goodwill Ambassador from 2002 through 2004, and became a best-selling poet who touched millions of lives with his messages of peace and hope. Mattie had mitochondrial myopathy and lost his life just before turning 14. His siblings also had the disease, and his mother, Jeni, has an adult form of the disease.

MDA's Purpose and Programs

The Muscular Dystrophy Association fights neuromuscular diseases through an unparalleled worldwide research effort. The following diseases are included in MDA's program:

Muscular Dystrophies

Myotonic dystrophy (*Steinert disease*)
Duchenne muscular dystrophy
Becker muscular dystrophy
Limb-girdle muscular dystrophy
Facioscapulohumeral muscular dystrophy
Congenital muscular dystrophy
Oculopharyngeal muscular dystrophy
Distal muscular dystrophy
Emery-Dreifuss muscular dystrophy

Motor Neuron Diseases

Amyotrophic lateral sclerosis (*ALS*)
Infantile progressive spinal muscular atrophy
(*Type 1, Werdnig-Hoffmann disease*)
Intermediate spinal muscular atrophy
(*Type 2*)
Juvenile spinal muscular atrophy
(*Type 3, Kugelberg-Welander disease*)
Adult spinal muscular atrophy (*Type 4*)
Spinal-bulbar muscular atrophy
(*Kennedy disease*)

Inflammatory Myopathies

Polymyositis
Dermatomyositis
Inclusion-body myositis

Diseases of Neuromuscular Junction

Myasthenia gravis
Lambert-Eaton (myasthenic) syndrome
Congenital myasthenic syndromes

Diseases of Peripheral Nerve

Charcot-Marie-Tooth disease
Friedreich's ataxia
Dejerine-Sottas disease

Metabolic Diseases of Muscle

Phosphorylase deficiency (*McArdle disease*)
Acid maltase deficiency (*Pompe disease*)
Phosphofructokinase deficiency
(*Tarui disease*)
Debrancher enzyme deficiency
(*Cori or Forbes disease*)
Mitochondrial myopathy
Carnitine deficiency
Carnitine palmityl transferase deficiency
Phosphoglycerate kinase deficiency
Phosphoglycerate mutase deficiency
Lactate dehydrogenase deficiency
Myoadenylate deaminase deficiency

Myopathies Due to Endocrine Abnormalities

Hyperthyroid myopathy
Hypothyroid myopathy

Other Myopathies

Myotonia congenita
Paramyotonia congenita
Central core disease
Nemaline myopathy
Myotubular myopathy
Periodic paralysis



MDA's website, mda.org, is constantly updated with the latest research news and information about the diseases in its program. Follow MDA on Facebook, Twitter and YouTube.



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