



Facts About Friedreich's Ataxia

MDA[®] Muscular
Dystrophy
Association
Fighting Muscle Disease

Dear Friends:

When I was about 14, I started having problems keeping my balance when standing or walking. After doctors did some tests, I found out I had Friedreich's ataxia.

My parents and I immediately learned all we could about FA, with MDA's help. There was no history of the disease in our family so it was a whole new world to us.

This pamphlet has been prepared to help you deal with just that situation, by giving you much of the basic knowledge about FA that you'll need as you or your child learns to live with this disease. You'll find out that FA affects each person differently, and that, while it presents challenges in daily life, there are many techniques, technological devices and medical treatments to help you meet those challenges.

You'll read here that FA doesn't affect the intellect and doesn't always take away the ability to walk. You'll also read that some exciting new research in FA may lead to the development of drugs to alleviate symptoms.

As I adjusted to being a teenager and a young woman with a disability, I learned a lot — not only about FA but about myself. I became more independent and learned to take charge of my education, my medical care and my other life experiences. Early in my years with FA, a doctor told me something that's guided me ever since: He said you can't use having a disability as an excuse for letting others make your decisions or for not pursuing your dreams.

Now, at 25, I'm studying for a master's degree in psychology and working as an assistant to two professors. When I finish my degree, I'll either get a teaching job or go on for a doctorate. I met my husband, James Smith, through MDA's magazine, *Quest*. He also has a neuromuscular disease, and together we deal with our

challenges and plan our future, just as any other couple does.

I know of many productive, successful people with FA — business leaders, outstanding students, engineers, active teens and bright kids, parents, even athletes. We've all learned to strike a balance between adapting to our limitations and surroundings, and living a fulfilling life despite them.

Besides my wonderfully supportive family and friends, I get tremendous help from the Muscular Dystrophy Association. MDA offers a great program of services, leads the world in Friedreich's ataxia research and keeps us well informed about the disease. See "MDA Is Here to Help You" on page 10 for details of the Association's program.

While MDA's research program continues making strides toward better treatments and a cure, it's good to know that people with disabilities have more opportunities than ever before to develop and use their abilities, and that the laws entitle us to equal employment opportunities and access to public places.

Whatever challenges FA presents in your life, you can be sure that MDA and all its resources are there to help you and your family. You're not alone.



Michelle Moffitt Smith
Dayton, Ohio



Michelle Moffitt Smith



Michelle and James Smith at their wedding

What Is Friedreich's Ataxia?

First described by German physician Nikolaus Friedreich in 1863, Friedreich's ataxia (FA) is a rare disease that mainly affects the nervous system and the heart.

Its major neurological symptoms include muscle weakness and, of course, *ataxia*, a loss of balance and coordination. *It doesn't affect parts of the brain involved in thinking.* Its effects on the heart range from mild, nonsymptomatic abnormalities to life-threatening problems in the heart's musculature.

FA isn't caused by anything a person does, and it's not contagious. It's a hereditary disease, caused by a defective gene that can be passed down through a family from one generation to the next. (See "Does It Run in the Family?" page 8, for more about how FA is inherited.)

Worldwide, FA affects about one in 50,000 people, making it the most common in a group of related disorders called *hereditary ataxias*. It shouldn't be confused with *spino-cerebellar ataxia*, which refers to several other distinct types of hereditary ataxia.

There's no cure for FA, but there are treatments for its cardiac symptoms and ways to manage ataxia and muscle weakness. Thanks to these treatments and the fact that FA doesn't affect mental functions, many people with FA lead active, rewarding lives. They go to college, hold careers, get married and start families.

Scientists are making rapid progress toward better treatments for FA.

In clinical trials, certain drugs have shown great promise for slowing

and even reversing the fundamental cardiac abnormalities in the disease. There's hope that the same drugs also might stave off FA's attack on the nervous system.

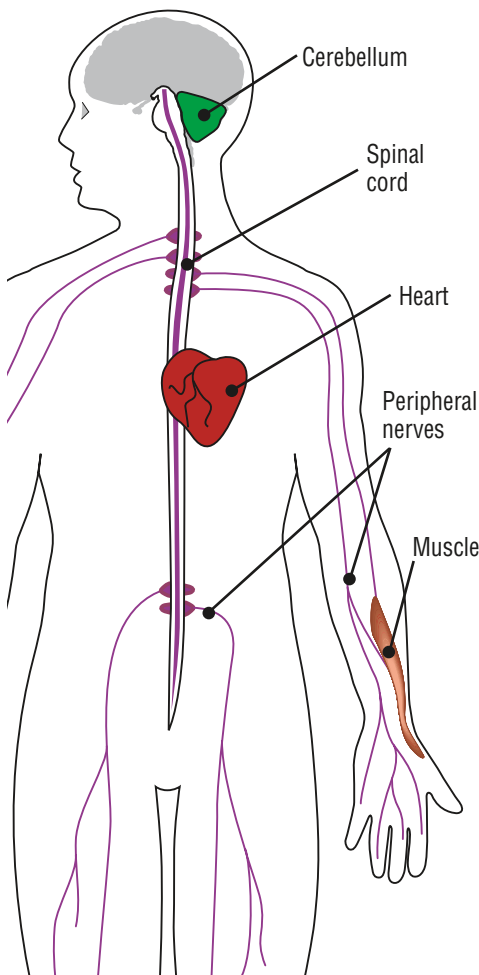
What causes FA?

FA is caused by defects, or mutations, in the *frataxin* gene. Genes are recipes for making proteins, which provide structure to our cells and drive the chemical reactions inside them. Scientists believe the frataxin protein regulates the levels of iron inside *mitochondria* — tiny cellular factories that use oxygen to produce energy. (One of these is called a *mitochondrion*.)

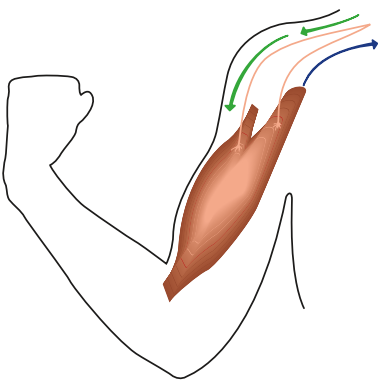
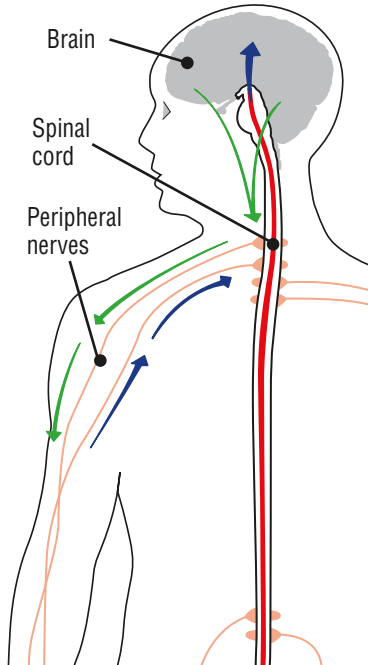
Iron is essential for this process, but if too much of it is left floating around freely inside mitochondria, it can trigger *oxidative stress* — the buildup of harmful oxygen-based free radicals. A prominent theory holds that frataxin acts like a storage depot for iron, releasing it only when it's needed. In any case, when frataxin is missing or defective, free iron accumulates in mitochondria, and oxidative stress damages the mitochondria.

Mitochondria act as an essential energy source for nearly all of the cells in our bodies, which probably explains why FA affects cells of the nervous system, heart and sometimes other tissues.

It bears repeating that FA *doesn't* affect parts of the brain involved in mental functions; it mostly affects the spinal cord and the *peripheral nerves* that connect the spinal cord to the body's muscles and sensory organs.



FA affects the heart and parts of the nervous system involved in muscle control and coordination.



The peripheral nerves carry motor signals from the spinal cord to the body's muscles. Muscle contraction creates sensations that are sent through the peripheral nerves to the spinal cord.

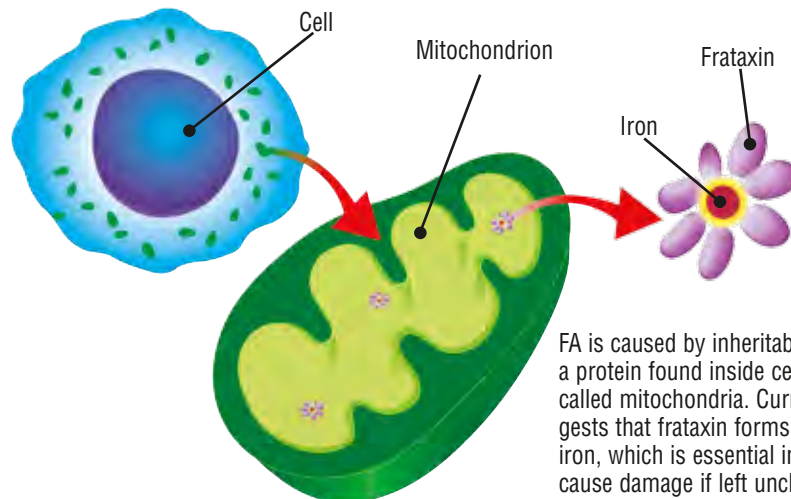
FA also affects the function of the cerebellum, a structure at the back of the brain that helps plan and coordinate movements.

When you decide to move your arm, nerve cells in your brain send an electrical signal to your spinal cord, and your peripheral nerves pass the signal on to your arm muscles. And as your arm moves, you feel it moving because nerve cells there send an electrical signal back through your peripheral nerves, up to your brain.

In FA, this flow of sensory information through the peripheral nerves and the spinal cord is most severely affected. There's also some impairment of muscle-controlling signals from the cerebellum and spinal cord. Combined, these problems lead to the progressive losses of balance, coordination and muscle strength that characterize FA.

What happens to someone with FA?

FA typically has its onset in childhood, between 10 and 15 years of age, but has been diagnosed in people from ages 2 to 50. An earlier onset is usually associated with a more severe course.



For most people, ataxia is the first symptom, and other symptoms — including cardiac problems — may appear later. As you read about these symptoms, keep in mind that their sequence and severity vary greatly from person to person.

Ataxia, weakness and spasticity

Usually, ataxia first affects the legs and torso, and comes to light when the affected person — or perhaps a parent or teacher — notices frequent tripping, poor performance in sports or just an unsteady walk. Balance and coordination continue to decline over time, and muscles in the legs become weak and easily fatigued, making it increasingly difficult to walk. Someone with the “typical” form of FA might begin using a wheelchair anytime between five and 15 years after disease onset.

Several years later, people with FA may have difficulty with speech, and their words might come out in a slow, jerky pattern. This problem, known as *dysarthria*, is caused by incoordination and weakness of the tongue and other facial muscles, not by an impairment of language skills or intellect. Some people with FA also develop swallowing difficulties, or *dysphagia*, which can allow food to enter the airway and cause choking or respiratory infections.

FA is caused by inheritable defects in frataxin, a protein found inside cellular energy factories called mitochondria. Current research suggests that frataxin forms a storage depot for iron, which is essential in mitochondria but can cause damage if left unchecked.



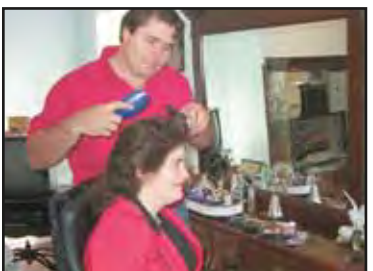
The muscle weakness caused by FA may eventually require use of a wheelchair.



FA doesn't impair the intellect.



The effects of FA vary greatly from one person to another. For example, the man above has a strong upper body, while the woman below needs help with daily grooming.



Later in the disease, ataxia and weakness of the arms and hands can interfere with the performance of fine manual tasks like writing or manipulating buttons and zippers. Many people with FA who've lost the ability to walk maintain their upper-body strength and coordination for several years afterward.

Spasticity (muscle spasm) is a common complaint of people with FA, and may be especially prominent in late-onset cases.

Sensory impairment

Loss of tactile (touch) sensation is a cardinal symptom of FA, but is often detectable only through laboratory testing. Vibration sense and position sense ("knowing" where your body is positioned in space) are impaired early in the disease, and perception of light touch, pain and temperature may be affected later. Most people with FA also have reduced or absent leg reflexes, such as the knee-jerk reflex.

In a small fraction of people, FA leads to hearing loss or visual impairment.

Skeletal abnormalities

Certain skeletal abnormalities are common in FA. Many people experience inversion (inward turning) of the feet, and a little over half have *pes cavus* — a shortened foot with a high arch. For people who are still walking, these conditions can cause painful blisters and calluses.

About two-thirds of people with FA develop curvature of the spine, or *scoliosis*, which can cause pain and impair the ability to breathe by distorting the chest cavity and interfering with the lungs' functioning.

These skeletal abnormalities often occur in neuromuscular diseases because as some muscles around bones weaken, others remain strong, pulling the bones into abnormal positions. However, because *pes cavus* and scoliosis can

occur early in FA (in some people, scoliosis is even the first symptom), there's speculation that frataxin deficiency might have direct effects on bone development.

Cardiac problems

Cardiac abnormalities occur in about 75 percent of people with FA, but they vary widely in severity. Some people with FA have abnormalities so mild that they're noticeable only through specialized laboratory testing. However, others have life-threatening cardiac problems, making heart failure a leading cause of death in FA.

The cardiac abnormality most often seen in FA is *hypertrophic cardiomyopathy*, an enlargement of cardiac muscle that shrinks the blood-filled chambers in the heart, decreasing its pumping capacity. Enlargement of the heart can also lead to arrhythmia — a heartbeat that's too fast or too slow, and doesn't adjust efficiently to the body's demands.

Extreme fatigue, chest pain, shortness of breath, lightheadedness, palpitations and/or pooling of blood in the ankles could be symptoms of declining cardiac function. If these symptoms occur regularly, it's a good idea to visit a cardiologist and to return for regular checkups.

Diabetes

About 10 percent of people with FA have diabetes, and another 20 percent have a mild form of diabetes called *glucose intolerance*. Both occur when the pancreas decreases its production of insulin, which helps the body store and utilize sugar (glucose). In FA, these conditions appear to be a direct result of frataxin deficiency in the pancreas.

Life span

Studies in the 1980s and 1990s found that the average life span of people with FA was around 30 to 40 years after diagnosis, with cardiac disease and diabetes

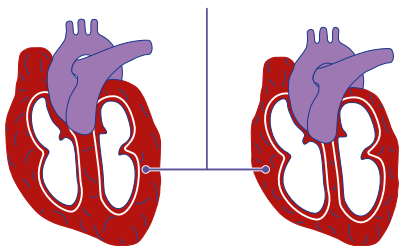


Curvature of the spine affects about two-thirds of those with FA.



People with FA often have pes cavus or other skeletal abnormalities.

MYOCARDIUM
(muscle layer)



**HYPERTROPHIC
CARDIOMYOPATHY**
thickened myocardium

NORMAL HEART
normal myocardium

FA may lead to enlargement of the myocardium, the muscle layer on the outside of the heart.

causing the greatest risk of fatality. Recent medical advances have made these conditions less deadly than in the past.

How is FA treated?

Historically, treatments for FA have targeted specific symptoms rather than the disease itself, and to a large degree, those treatments still make up the standard of care for FA.

Fortunately, FA's most life-threatening symptom — heart disease — can be controlled with treatments developed for use in the general population. For example, certain drugs (ACE inhibitors, diuretics and beta blockers) can decrease the workload of the heart, and pacemakers or medications can stabilize an arrhythmic heartbeat. Likewise, diabetes can be managed with insulin.

There are surgical procedures for correcting foot deformities and scoliosis, and though they're not trivial, they usually are effective. (One type of scoliosis surgery is called *spinal fusion* because it involves straightening the spine and then placing small pieces of bone over it, which grow together with the spinal bones and fuse them in place.)

Although there's no way to stop the progression of ataxia or muscle weakness in FA, several types of rehabilitation therapy can make it easier to cope with these problems. For example, a physical therapist can help you stretch tight muscles and enhance flexibility, and a speech therapist can help you retrain your tongue and facial muscles to improve speech and swallowing. Your MDA clinic can provide you with referrals to these specialists.

Until recently, these were the only treatments considered worth trying in FA, but the discovery of frataxin and its roles in iron regulation and oxidative

stress have opened the door to treatments that might attack the underlying disease process.

Antioxidants — chemicals that naturally scavenge free radicals and thus defend against oxidative stress — have shown great promise against FA. Some have been tested only in laboratory studies, but others, such as coenzyme Q10, vitamin E and idebenone, have been tested in clinical trials.

Coenzyme Q10 (coQ10) is a small molecule present in mitochondria, where it helps combine oxygen with "fuel" from carbohydrates and fat to produce energy. Also known as *ubiquinone*, it's available over the counter as a dietary supplement.

A clinical trial showed that coQ10 combined with vitamin E could increase energy production in the cardiac and voluntary muscles of people with FA. Idebenone, a synthetic analogue of coQ10, has generated even more excitement because it's been shown to shrink the enlarged hearts of people with FA.

In ongoing trials, these substances are being tested for their potential effects on cardiac function and ataxia. In the meantime, they remain unregulated by the U.S. Food and Drug Administration, and thus, there are no guarantees regarding their quality or safety, and they aren't covered by insurance.

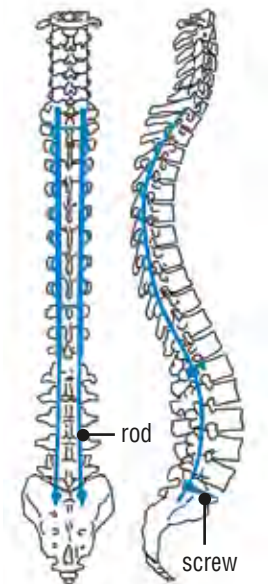
How is FA diagnosed?

If you or your child has symptoms of FA, you'll probably be referred to a neurologist, who will use several tests to determine whether you have FA or a different disease with similar symptoms.

Typically, the neurologist will begin by conducting a basic physical exam and a



Physical therapy can help people with FA maintain mobility, and massage can help alleviate muscle tightness.



Scoliosis surgery often involves using rods and screws to straighten and stabilize the spine.

careful assessment of your personal and family history. During the physical exam, the neurologist is likely to devote special time and attention to *testing reflexes*, including the knee-jerk reflex. Loss of reflexes is an early and almost universal feature of FA.

At some point, the neurologist might need to use specialized tests for evaluating the function of your (or your child's) muscles and nerves. *Electromyography (EMG)* is done by inserting a needlelike electrode into a muscle and recording the electrical signals it generates during contraction.

A *nerve conduction velocity test (NCV)* is done by placing surface electrodes on the skin at various points over a nerve. One electrode delivers small shocks to the nerve and the others record the nerve's responses. Because FA damages the nerves, those responses are typically smaller than normal in people with FA.

Computerized tomography (CT scan) or *magnetic resonance imaging (MRI)* might be performed to look for extensive changes in the cerebellum, which are more common in spinocerebellar ataxias than in FA.

Finally, the neurologist is likely to take samples of *blood and urine*. Both will be used to check for chemical imbalances that occur in diseases other than FA.

Perhaps most importantly, cells in the blood provide DNA (genetic material) that can be used for *genetic testing*. Although recent studies describe a rare variant of FA not linked to the frataxin gene, tests for frataxin mutations are highly reliable and can be used to confirm or exclude a diagnosis of FA in almost all cases. The tests also can be used prenatally and to determine carrier status (see "Does It Run in the Family?" page 8).

Does It Run in the Family?

On being told their child has a genetic disease like FA, bewildered parents often ask, “But it doesn’t run in the family, so how could it be genetic?”

The answer is that the mutations underlying FA can run silently through a family, because the disease is inherited in an *autosomal recessive* pattern.

Autosomal refers to the fact that the frataxin gene is on chromosome 9, one of the 22 pairs of autosomes (chromosomes other than the X or Y). *Recessive* means it takes two defective copies of the frataxin gene to cause FA, with one copy inherited from each parent, neither of whom would normally have FA symptoms.

Thus, FA might seem to occur “out of the blue.” But in reality, both parents are FA *carriers*, each silently harboring a mutation in frataxin. Many parents have no idea that they’re carriers of FA until they have a child who has the disease.

About 1 in 100 Americans are FA carriers, but in some ethnic groups the frequency is higher. For example, about one in 70 people of Acadian (Cajun) ancestry are carriers.

The most common type of mutation in the frataxin gene is called a *trinucleotide repeat expansion*. Spelled out in the four chemical “letters” that make up DNA, it looks like a stutter in the frataxin gene.

Normally, the gene contains five to 30 repeats of the three-letter chemical phrase “GAA,” but in people with FA, the gene can contain hundreds to thousands of GAA repeats. Longer repeat expansions tend to cause an earlier onset and faster progression, but the association isn’t strong enough to predict the course of FA in individual cases.

In more than 95 percent of people with FA, both copies of the frataxin gene contain expanded repeats. In the rest, just one copy of the frataxin gene is expanded and the other contains a single-letter change in the DNA code, called a *point mutation*.

In FA carriers, the frataxin gene can contain a repeat expansion, a point mutation or a *premutation* — a number of expanded repeats that’s just below the disease-causing range. In the germ line (ova and sperm), premutations might or might not expand into the disease-causing range, which makes it complicated for some carriers to determine their risks of passing on FA.

As a general rule, a child with a biological sibling affected by FA has a 25 percent chance of inheriting the disease.

Your MDA clinic physician or genetic counselor can give you more information about the risks of inheriting or passing on FA. Also, see MDA’s pamphlet, “Facts About Genetics and Neuromuscular Diseases.”



People of Acadian ancestry, like this teen, may be at higher risk for FA.



Two of this family’s three children have FA.

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.

In 1988, MDA-funded scientists linked Friedreich's ataxia to chromosome 9, and in 1996 they identified FA-causing mutations in the frataxin gene. By the next year, they'd devised a genetic test for FA.

Besides this important advance in diagnosis and carrier testing, the discovery of frataxin mutations has opened doors to several potential treatments for FA.

The frataxin gene was unknown until it was tagged as the culprit behind FA. Since then, much research has focused on determining the normal functions of the frataxin protein in an effort to find ways of compensating for its shortage in FA.

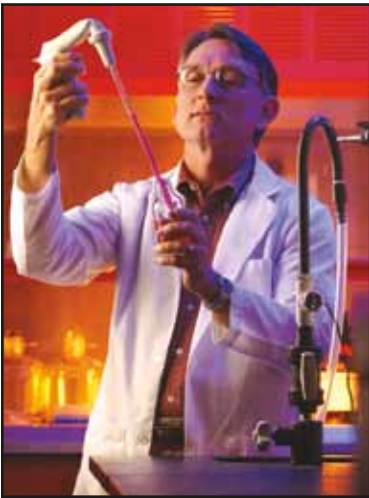
An important breakthrough came when MDA-funded scientists discovered that a single-celled organism, baker's yeast, has its own version of frataxin. Baker's yeast has a long history in genetic research, and when the scientists eliminated the frataxin gene in yeast cells, they found that the cells' mitochondria accumulated iron and were damaged by oxidative stress. Cells from people with FA proved to have similar defects.

These studies laid the groundwork for testing antioxidants — like idebenone, coQ10 and vitamin E — first in laboratory experiments on frataxin-deficient cells, and then in clinical trials involving people with FA.

Given that iron buildup occurs in FA, MDA-funded scientists also are investigating the possibility of treating FA with iron chelators — drugs that capture iron and carry it through the body to be excreted.

Meanwhile, MDA-funded research is leading to more efficient tests of these potential treatments. In 2001, scientists reported that they'd developed a mouse model of FA that can be used to determine which treatments should be fast-tracked into clinical trials. And researchers are developing better ways to monitor oxidative stress, as well as heart and muscle function in people with FA, which will make it easier to interpret clinical trial results.

While MDA-funded scientists are hopeful that antioxidants and iron chelators will slow the course of FA, they're also striving to achieve long-term correction of FA using gene therapy. In a step toward that goal, they've found that the expanded repeats underlying FA cause frataxin DNA to fold into an abnormal shape that inhibits production of the frataxin protein. Although it will be many years before gene therapy can be tested in humans, laboratory experiments have shown that it's possible to design short fragments of DNA that prevent abnormal folding of frataxin DNA and increase its conversion into frataxin protein.



MDA Is Here to Help You

The Muscular Dystrophy Association offers a vast array of services to help you and your family deal with Friedreich's ataxia. 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 Friedreich's ataxia, someone at MDA will help you find the answer. To reach your local MDA office, call (800) 572-1717.



On the cover:
Erin, who has Friedreich's ataxia, monitors her cardiac function closely and gets help from several specialists.

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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