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Facts about Friedreich's Ataxia (FA) (FRDA)

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, non-symptomatic 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?" 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 *spinocerebellar 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.

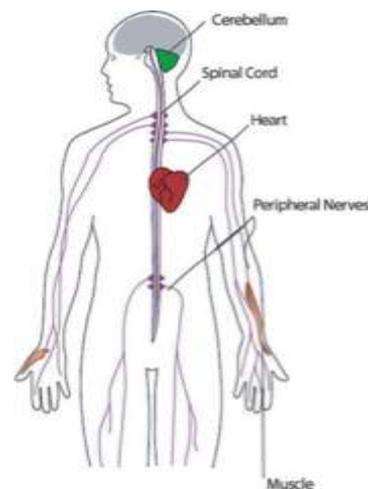
In clinical trials, certain drugs have shown great promise for slowing and even reversing the fundamental cardiac abnormalities in the disease. There's hope that the same drugs also might stave off FA's attack on the nervous system.

What causes FA?

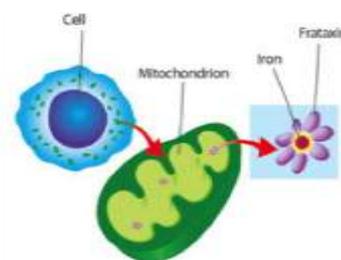
FA is caused by defects, or mutations, in the *frataxin* gene. Genes are recipes for making proteins, which provide structure to our cells and drive the chemical reactions inside them. Scientists believe the frataxin protein regulates the levels of iron inside *mitochondria* — tiny cellular factories 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.



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



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.



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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 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 characterise 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.

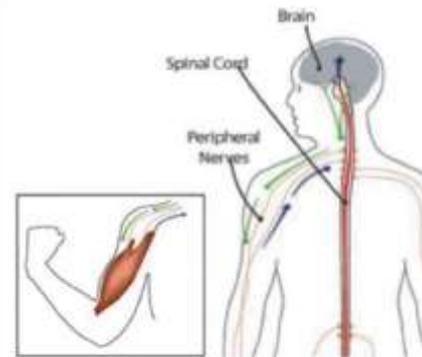
For most people, ataxia is the first symptom, and other symptoms — including cardiac problems – may appear later. As you read about these symptoms, keep in mind that their sequence and severity vary greatly from person to person.

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 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.

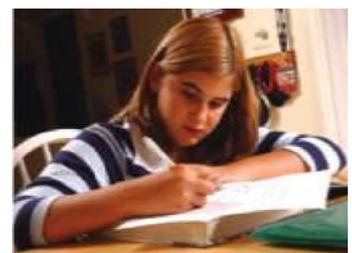
Later in the disease, ataxia and weakness of the arms and hands can interfere with the performance of fine manual tasks like writing or manipulating buttons and zippers. Many people with FA who've lost the ability to walk maintain their upper-body strength and coordination for several years afterward.



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.



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



FA doesn't impair the intellect.



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Spasticity (muscle spasm) is a common complaint of people with FA onset cases, 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 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 specialised 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



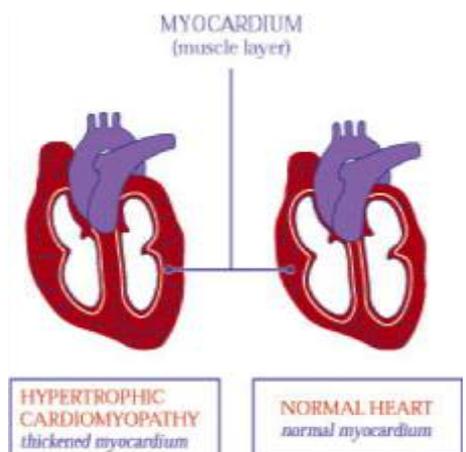
The effects of FA vary greatly from one person to another. For example, the man on the left has a strong upper body, while the woman to the right needs help with daily grooming.



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



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



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



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decreases its production of insulin, which helps the body store and utilise 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 causing the greatest risk of fatality. Recent medical advances have improved the treatment of these conditions.

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 stabilise 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 doctor 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.



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 stabilise the spine.



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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 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 specialised tests for evaluating the function of your (or your child's) muscles and nerves. The doctor begins with a physical *Electromyography (EMG)* is done by inserting a needlelike electrode into exam to determine a neuromuscular 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.

Computerised 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?").



The doctor begins with a physical exam to determine a neuromuscular disease diagnosis.

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.



Two of this family's three children have FA.

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 people worldwide are FA carriers, but in some ethnic groups the frequency is higher.

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 doctor or genetic counsellor can give you more information about the risks of inheriting or passing on FA. Also, see MDA's fact sheet, "Genetics and Neuromuscular Diseases."



Search for treatments and cures

In 1988 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 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, scientists are also investigating the possibility of treating FA with iron chelators — drugs that capture iron and carry it through the body to be excreted.

Meanwhile, 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 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