Friedreich Ataxia
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What is Friedreich ataxia?

Friedreich ataxia (also called FA) is a rare inherited disease that causes progressive nervous system damage and movement problems. It usually begins in childhood and leads to impaired muscle coordination (ataxia) that worsens over time.

In Friedreich ataxia nerve fibers in the spinal cord and peripheral nerves degenerate, becoming thinner. Peripheral nerves carry information from the brain to the body and from the body back to the brain, such as a message that the feet are cold or a signal to the muscles to generate movement. The cerebellum, part of the brain that coordinates balance and movement, also degenerates to a lesser extent. This damage results in awkward, unsteady movements and impaired sensory functions. The disorder also causes problems in the heart (in as many as one-third of affected individuals) and spine, and some people with the condition will also develop diabetes. The disorder does not affect thinking and reasoning abilities (cognitive functions).
Friedreich ataxia is caused by a defect (mutation) in a gene labeled FXN, which carries the genetic code for a protein called frataxin. Individuals who inherit two defective copies of the gene, one from each parent, will develop the disease. Although rare, Friedreich ataxia is the most common form of hereditary ataxia in the United States, affecting about 1 in every 50,000 people. Both male and female children can inherit the disorder.

The rate of progression varies from person to person. Generally, within 10 to 20 years after the appearance of the first symptoms the person is confined to a wheelchair. Individuals may become completely incapacitated in later stages of the disease. Friedreich ataxia can shorten life expectancy, and heart disease is the most common cause of death. However, some people with less severe features of FA live into their sixties or older.

The disorder is named after Nikolaus Friedreich, a German doctor who described the condition in the 1860s.

What are the signs and symptoms?

Symptoms typically begin between the ages of 5 and 15 years, although they sometimes appear in adulthood. Approximately 15 percent of people with Friedreich ataxia have onset after age 25. The first neurological symptom to appear is usually difficulty walking and poor balance (gait ataxia, often described as appearing dizzy or even drunk). Another early sign of the disease is slowness and slurring of speech (dysarthria).
With time speech becomes hesitant and jerky (often referred to as “scanning of speech”). The difficulty coordinating movement (ataxia) can affect all of the muscles. It gradually worsens and slowly spreads to the arms and the trunk (torso). As the muscle weakness progresses most affected individuals develop increased muscle tone (spasticity). Up to two-thirds of people with Friedreich ataxia also develop scoliosis (a curving of the spine to one side) that often requires surgical intervention for treatment. Most affected individuals also develop difficulty swallowing, due to difficulty coordinating the muscles of the tongue and throat.

In addition to the movement impairments, there is often a loss of sensation in the arms and legs, which may spread to other parts of the body. Other features include loss of normal reflexes, especially in the knees and ankles, and muscle weakness. Many individuals with later stages of Friedreich ataxia also develop hearing and vision loss.

Other symptoms that may occur include heart palpitations and shortness of breath. These symptoms are the result of various forms of heart disease that often accompany Friedreich ataxia, such as enlargement of the heart (hypertrophic cardiomyopathy), formation of fiber-like material in the muscles of the heart (myocardial fibrosis), and heart failure. Heart rhythm abnormalities such as a fast heart rate (tachycardia) and impaired conduction of cardiac impulses within the heart (heart block) are also common.
About 50 percent of people with FA develop carbohydrate intolerance and 30 percent develop diabetes. Most individuals with the disease tire very easily and find that they require more rest and take a longer time to recover from common illnesses such as colds and flu.

**How is Friedreich ataxia diagnosed?**

A diagnosis of Friedreich ataxia requires a careful clinical examination, which includes a medical history and a thorough physical exam, in particular looking for balance difficulty, loss of joint sensation (proprioception), absence of reflexes, and signs of neurological problems. Genetic testing now provides a conclusive diagnosis. Other tests that may aid in the diagnosis or management of the disorder include:

- electromyogram (EMG), which measures the electrical activity of muscle cells,
- nerve conduction studies, which measure the speed with which nerves transmit impulses,
- electrocardiogram (also called EKG or ECG), which gives a graphic presentation of the electrical activity or beat pattern of the heart,
- echocardiogram, which records the position and motion of the heart muscle,
- blood tests to check for elevated glucose levels and vitamin E levels, and
- magnetic resonance imaging (MRI) or computed tomography (CT) scans, tests which provide brain and spinal cord images that are useful for ruling out other neurological conditions.
How is Friedreich ataxia inherited?

People have two copies of every gene, with one copy being inherited from each parent. In Friedreich ataxia, a person needs to inherit two copies of the defective FXN gene to develop the disease. A person who inherits only one abnormal copy of the gene is called a carrier. A carrier will not develop the disease but could pass the gene mutation on to his or her children. About one in 90 Americans of European ancestry carries an abnormal FXN gene.

How is the protein frataxin affected?

The FXN gene provides instructions for the production of a protein called frataxin. In the normal version of the gene, a triplet sequence of DNA (labeled guanine-adenine-adenine, or GAA) is repeated between 7 and 22 times. In the defective FXN gene, the GAA repeat occurs over and over again—hundreds, even up to a thousand times. The GAA repeat sequence greatly reduces the amount of frataxin produced by the cell. Earlier disease onset and severity of progression may be related to the number of GAA copies in the individual genetic code.

This abnormal pattern, called a triplet repeat expansion, has been implicated as the cause of several diseases in which the individual needs to inherit only one abnormal gene. Friedreich ataxia is the only known genetic disorder that requires inheriting two copies of the abnormal gene to cause the disease. Almost all people with FA (98 percent) have two copies of this mutant form of FXN, but it is not found in all cases of the disease.
About two percent of affected individuals have other defects in the FXN gene that are responsible for causing the disease.

The triplet repeat expansion greatly disrupts the normal production of frataxin. Frataxin is found in the energy-producing parts of the cell called mitochondria. Research suggests that without a normal level of frataxin, certain cells in the body (especially peripheral nerve, spinal cord, brain, and heart muscle cells) produce energy less effectively and have been hypothesized to have a buildup of toxic byproducts leading to what is called “oxidative stress.” Lack of normal levels of frataxin also may lead to increased levels of iron in the mitochondria. When the excess iron reacts with oxygen, free radicals can be produced. Although free radicals are essential molecules in the body metabolism, they can also destroy cells and harm the body.

Can Friedreich ataxia be cured or treated?

As with many degenerative diseases of the nervous system, there is currently no cure or effective treatment for Friedreich ataxia. However, many of the symptoms and accompanying complications can be treated to help individuals maintain optimal functioning as long as possible. A multi-specialty team approach is essential to the treatment of the individual with Friedreich ataxia. Doctors can prescribe treatments for diabetes, if present; some of the heart problems can be treated with medication as well. Orthopedic problems such as foot deformities and scoliosis can be corrected with braces or surgery. Rehabilitative therapy
(physical, occupational, and vocational) can help individuals become as functionally independent as possible. Swallowing and speech issues should be followed closely. Hearing impairment can be helped with hearing aids.

**What services are useful to people with Friedreich ataxia and their families?**

Genetic testing is essential for proper clinical diagnosis, and can aid in prenatal diagnosis and determining a person carrier status. Genetic counselors can help explain how Friedreich ataxia is inherited.

A primary care physician can screen people for complications such as heart disease, diabetes, and scoliosis, and can refer individuals to specialists such as cardiologists, physical therapists, and speech therapists to help deal with some of the other associated problems.

Support and information for families is also available through a number of private organizations. These groups can offer ways to network and communicate with others affected by FA. They can also provide access to patient registries, clinical trials information, and other useful resources.

**What research is being done?**

The 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.

The range of NIH-funded research on Friedreich ataxia (FA) includes determining what causes the gene mutation and how it functions, gaining a better understanding of frataxin, and investigating ways to override the genetic mutation and to develop treatments for the disease. In addition to the NINDS, several other Institutes and Centers of the NIH support research on Friedreich ataxia.

In Friedreich ataxia the expanded GAA triplet-repeat reduces the production of frataxin but the exact mechanism of how the gene is “silenced” (turned off) is unknown. Among current NINDS-funded projects, researchers hope to define the mechanisms involved in the silencing of the FXN gene, which could reveal potential ways to restore normal gene function. One such project uses induced pluripotent stem cell (iPSC) lines that have been turned into (an action called derived) neuronal cells as a model system to study the mechanisms of FXN gene silencing. (iPSCs are a type of stem cell that can be derived from skin or blood cells and be activated to become other types of cells of the body.) This work will hopefully reveal new therapeutic strategies for Friedreich ataxia and potentially also related repeat expansion diseases. Another project is using iPSC-derived cell models to identify gene expression changes in Friedreich ataxia to better understand the mitochondrial defects associated with the disease and develop biomarkers (signs that can indicate the diagnosis or progression of a disease) for future clinical trials.
Other NINDS–supported researchers are working to develop new animal models of Friedreich ataxia that closely mimic the gene mutations found in people affected by the disease. These new models, along with already existing models, are needed as critical research tools to define the cellular defects of the disease in more detail and to enhance the search for novel therapies.

NIH-funded researchers are also studying the metabolic defects of mitochondria (the energy-producing “power plants” in cells) in people with Friedreich ataxia. For example, one project is analyzing the role of frataxin in iron-sulfur cluster biosynthesis in mitochondria. In addition, a project of the Therapeutics for Rare and Neglected Diseases program of the National Center for Advancing Translational Sciences (NCATS) is seeking to develop a protein replacement therapy for Friedreich ataxia that uses a new technology to deliver functional frataxin protein to mitochondria.

More information about Friedreich ataxia research supported by NINDS and other NIH Institutes and Centers can be found using NIH RePORTER (www.projectreporter.nih.gov), a searchable database of current and past research projects supported by NIH and other federal agencies. RePORTER also includes links to publications and resources from these projects. Another useful resource is ClinicalTrials.gov (https://clinicaltrials.gov/), an NIH registry of all registered clinical trials for human diseases.
Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
800-352-9424
www.ninds.nih.gov

Information also is available from the following organizations:

Friedreich’s Ataxia Research Alliance (FARA)
533 W. Uwchlan Avenue
Downington, PA 19335
484-879-6160
www.CureFA.org

Genetic Alliance
4301 Connecticut Avenue, N.W.
Suite 404
Washington, DC 2008-2369
202-966-5557
800-336-GENE (4362)
www.geneticalliance.org

Muscular Dystrophy Association
222 S. Riverside Plaza, Suite 1000
Chicago, IL 60606
800-572-1717
www.mda.org
National Ataxia Foundation
600 Highway 169 South
Suite 1725
Minneapolis, MN 55426
763-553-0020
https://ataxia.org

National Organization for Rare Disorders (NORD)
55 Kenosia Avenue
Danbury, CT 06810
203-744-0100
Voice Mail 800-999-NORD (6673)
www.rarediseases.org

U.S. National Library of Medicine
National Institutes of Health, DHHS
8600 Rockville Pike
Bethesda, MD 20892
888-346-3656
www.nlm.nih.gov