

## Friedreich's Ataxia (FA)

### What is Friedreich's ataxia?

Friedreich's ataxia is a slowly progressive degenerative disorder of the nervous system and heart. The disorder, named for the physician who first identified it in 1863, results in an inability to coordinate voluntary muscle movements (ataxia). This condition is caused by the premature death of nerve cells that are responsible for the control of balance and coordination.

### What are the neurological symptoms?

In this disorder, the ataxia affects upper and lower limbs and the head and neck. There is also a loss of position sense in the legs.

Unsteadiness in standing and an uneven gait are usually the first symptoms. Other symptoms appear as the disorder progresses. They include poor coordination in the upper limbs, often making writing difficult, weakness, especially in the lower limbs; and difficulty speaking and enunciating words (dysarthria). Irregularities in voice pitch and loudness develop with the loss of muscle control in relation to speech. In most cases, eye movements also become irregular as a consequence of loss of coordination of eye muscles. Some people experience a decrease in visual or hearing acuity because of optic or auditory nerve involvement.

Friedreich's ataxia usually results in an inability to walk within eight to ten years following the onset of symptoms. Occasionally the disorder has a slower course, with prolonged periods when symptoms remain relatively stable. Friedreich's ataxia does not affect mental acuity.

### What is the age of onset?

Symptoms of Friedreich's ataxia can appear anywhere between five and twenty years of age, but are usually seen before puberty. There are, however, people who are first affected by FA as adults.

### What non-neurological problems are associated with Friedreich's ataxia?

Friedreich's ataxia causes several problems in addition to those that result from the degeneration of nerves. Almost all people with FA have signs of heart disease when investigated with an electrocardiogram or heart ultrasound, although many may not have cardiac symptoms. The heart becomes bigger than normal (hypertrophic cardiomyopathy), but weaker. Heart disease may be severe and cause abnormalities in heartbeat rhythm and insufficient strength of the heart muscle (heart failure). People with cardiac symptoms usually experience palpitations, chest pain and shortness of breath (dyspnea). An increased incidence of diabetes mellitus due to abnormal insulin secretion in the pancreas has been noted in some people with Friedreich's ataxia. Scoliosis (curvature of the spine)

is also found in some people with this disorder. It is thought to be a result of poor posture and lack of coordination. As occurs in many diseases of nerves, many individuals with Friedreich's ataxia have clubfeet.

## What causes Friedreich's ataxia?

After many years of research, the gene responsible for Friedreich's ataxia was found on Chromosome 9. This gene is known as Frataxin. Genes are segments of DNA that contain information necessary to make proteins. Proteins are molecules that determine how we are made, what we look like and how we will function. The protein normally made (encoded) by gene Frataxin is known as frataxin.

Friedreich's ataxia occurs because this protein, frataxin, is not made in sufficient amounts. An explanation of why this happens is described below.

DNA is a very long chain of nucleotides, smaller chemical units that contain one of four different bases: Guanine (G), Cytosine (C), Adenine (A) and Thymine (T). Nucleotides are like the letters of a simple, four-letter alphabet. Within a gene, hundreds to thousands of nucleotides are arranged in a specific sequence, providing the "code" to make a specific protein. Very often, this "code" is broken up into several pieces, called exons, that are separated by silent, noncoding DNA sequences called introns. The most common DNA abnormality causing FA is located in an intron of the frataxin gene. It consists of the expansion of a trinucleotide repeat. Scientists have known for a number of years that our DNA contains sequences of nucleotides in threes, called trinucleotides ("tri"=three), which repeat themselves. Trinucleotide repeats are sometimes found within genes, in exons as well as in introns, and they may be of different lengths in different "normal" individuals. However, when a trinucleotide repeat becomes too long, it may adversely affect the function of the gene in which it is located. Trinucleotide repeats have been shown to be associated with a number of genetic diseases including myotonic dystrophy and more recently, Friedreich's ataxia. The trinucleotide repeat in FA is a repetition of the trinucleotide GAA in the first intron of the FA gene. In a person who has Friedreich's ataxia, the number of repeats is higher than what would be considered normal. A person with FA has more than 100 and up to almost 2,000 GAA triplets, whereas non-affected individuals have less than 40. It is this high number of repeats in the intron that reduces the expression of the protein frataxin. The longer the repeat, the less frataxin is made, explaining why the higher the number of repeats, the earlier the onset of symptoms in a person with FA.

It is important to understand how this genetic disorder is transmitted within a family. There are thousands of genes in each one of us that prescribe how each of us will look and how our bodies will function. Each gene comes in pairs: half from our mother and half from our father. They are packaged on chromosomes. We have 23 pairs of

## How is Friedreich's ataxia diagnosed?

Diagnosis is made through a complete physical examination and history that may include tests for reflex and sensory responses. Laboratory tests such as an electromyogram (EMG), that measures the electrical activity of muscle and nerve cells may be used to confirm the diagnosis. In addition, the physician may do an electrocardiogram (EKG) to determine if there are abnormalities in the heartbeat. Blood and urine tests may be done to check for problems related to diabetes. X-rays are used as a diagnostic tool if scoliosis is suspected. As a result of finding the gene Frataxin, accurate diagnostic testing is available for people with FA and their families.

## Is there any cure or treatment?

Although there is no known cure for Friedreich's ataxia, many problems associated with the disorder can be treated. Orthopedic intervention that may include surgery or bracing can alleviate scoliosis. Physiotherapy and occupational therapy can help people with FA to achieve their optimum level of health and mobility. Heart problems may be treated with diet, medication and an appropriate health regimen. Diet or insulin therapy may be necessary to control diabetes mellitus or high levels of blood sugar.

chromosomes. 22 pairs are known as autosomes, meaning they are the same in males and females. The 23rd pair is known as the sex chromosomes (XX in females, XY in males). The FA gene is found on Chromosome 9. It is one of the autosomal chromosomes. This gene, when faulty, is known to be inherited in an autosomal recessive pattern. This means that the disorder affects male and female children equally (autosomal) and will develop in a child only when both mother and father carry a copy of the faulty gene (recessive) and both parents transmit that copy to the child. When both parents are carriers, there is a 25% chance with each pregnancy that the child will be affected. A child who receives a faulty copy of the gene from one parent and a normal copy from the other (50% chance) becomes a "carrier" like his/her parents and never develops symptoms of the disease. A child who receives a normal copy of the gene from each parent (25% chance) is unaffected by the disease and is not a carrier.

Persons with FA, therefore, have an expanded GAA repeat on both copies of the Frataxin gene. Rarely, a person with FA may have only one larger than normal GAA repeat, and a different type of abnormality in the other copy of the Frataxin gene.

### What research is being done?

Research continues into many aspects of Friedreich's ataxia. The genetic fault in FA is associated with GAA expansion and research is looking to determine the mechanism(s) by which this expansion suppresses frataxin expression and how the number of repeats affects both the severity of the disorder and the age of onset. Other research is attempting to further understand the classification of FA to help explain the wide variations in the way that it presents. Mechanisms causing such a wide

difference in the number of repeats found in different people with FA are not yet fully understood. In addition, in-depth studies of diabetes and heart disease are being conducted to help explain their relationship to FA. Research is looking at increased understanding of the action of frataxin. Scientists have determined that frataxin is localized in mitochondria. Mitochondria are small structures (organelles) within cells that function as power plants, producing energy by carrying out the oxidation of food-derived molecules. By studying a simple model organism, baker's yeast, that makes a protein very similar to human frataxin, it was discovered that lack of frataxin leads to the accumulation of iron in the mitochondria. Excess iron is very toxic because it may react with oxygen-derived molecules and produce free radicals, highly reactive substances that damage all cellular structures. This kind of cell damage is called oxidative damage and is suspected to have a role in many neurodegenerative disorders. If iron-derived oxidative damage is confirmed by further studies to cause FA, this may lead to new treatments aimed at removing the excess iron and free radicals. (Individuals should not alter their diets in any attempt to remove excess iron). An increase in our understanding of the role of frataxin is essential to design new treatments and hopefully, to find a cure for Friedreich's ataxia.

Other scientists are conducting research into the biochemistry, neurobiology and biophysics of central and peripheral nerves, heart and skeletal muscle and the interactions between muscle and nerve. Not only will these studies be useful in uncovering the pathological process in Friedreich's ataxia, they may also provide essential knowledge that will enable us to intervene in the degenerative process and to promote regeneration and repair of the damaged nerve cells.

### How can I help?

Muscular Dystrophy Canada conducts year-round fund raising campaigns to support our diverse programs. Your gift will help the Association provide the dollars necessary to assist individuals living with neuromuscular disorders, and fund much needed medical research and educational information. Please make a gift through our National office or any Regional or Community Muscular Dystrophy Canada office.

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