European Reference Network
for rare or low prevalence complex diseases

Network
Neurological Diseases
(ERN-RND)

Coordinator
Universitätsklinikum
Tübingen — Deutschland

FRIEDREICH'S ATAXIA

INFORMATION LEAFLET ON FRIEDREICH'S ATAXIA FOR 13 -17 YEAR OLD ADOLOSCENTS

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Adopted for use by the ERN-RND by Dr Mary Kearney, European Patient Advocate in 2022.

Introduction

Friedreich's Ataxia (FA) is a debilitating, life shortening, degenerative, rare, neuro-muscular, genetic, disorder. Onset of symptoms can vary from childhood to adulthood. They initially include clumsiness of movement, weakness and muscle loss which causes an unsteadiness in standing and walking which can be mistaken for drunkenness. It was first described in 1863 by a German neurologist and pathologist called Nicholas Friedreich.

The word ataxia comes from the Greek word "ataxis" which means "without order" or "unco-ordinated". The disease usually starts with the person being clumsy, things fall out of one's hands, the affected individual like to walk by a wall. Ataxia can affect the fingers and hands, the arms and legs, the body, speech, swallowing or eye movement. There are many types of ataxia (see ERN patient leaflet on ataxia).

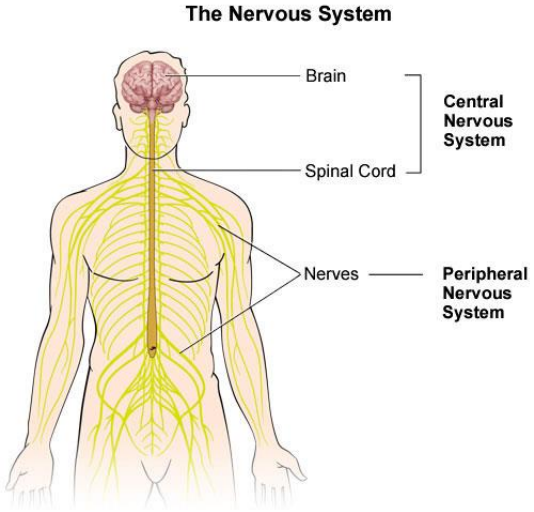


Figure 1: Details of the nervous system Courtesy of UC San Diego Health

FA is caused because of the deterioration of:

- a particular part of the brain – the cerebellum,
- spinal cord and
- nerves (known as peripheral nerves) in the body.

Even though the disease is related to the brain it does not affect intelligence. FA is a progressive disorder and slowly worsens to the point that patients need a wheelchair. There is no cure yet but research is on-going. The genetic test for FA was discovered in 1996. Friedreich's ataxia (FA) is inherited from both parents and it known as a recessive ataxia.

What is a recessive ataxia?

A recessive ataxia is where a condition is passed on by receiving the faulty gene from both parents. The parents, themselves, rarely have symptoms but each carries a recessive gene.

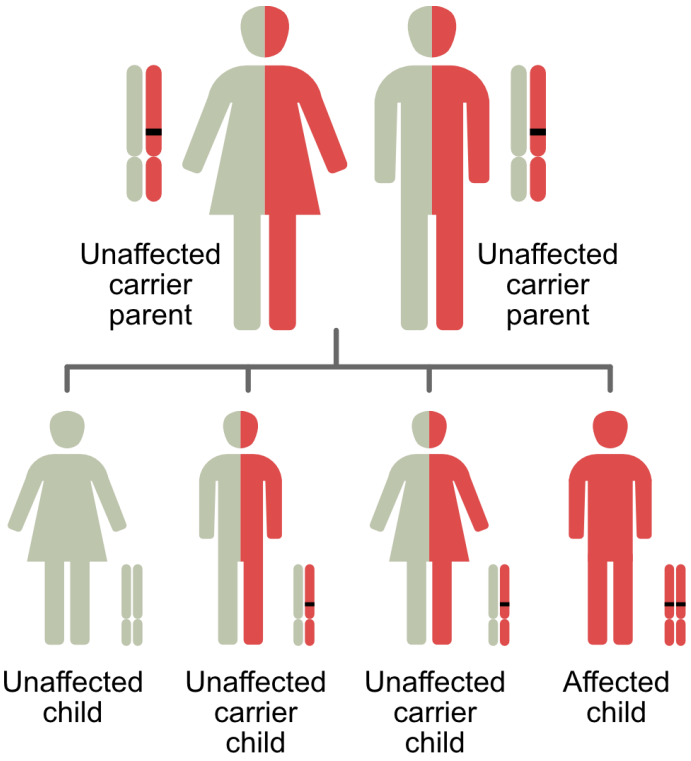


Figure 2: How a recessive ataxia is inherited;
Courtesy of European Research Network,
Rare Neurological Disease group

A recessive gene may be passed down for generations and the family would not be aware that they had the faulty gene until people with the same abnormal gene have children together.

Children of parents with the recessive ataxia genes have the following genetic odds for each child that they might have:

1) a 25% chance of not having the disease,
2) a 50% chance of being a carrier without showing symptoms and
3) a 25% chance of having the disease.

Symptoms

Friedreich's ataxia may present in several ways. The most usual presentation is clumsiness in carrying out small tasks, such as carrying drinks, falling when going up a

stairs, tripping in the dark etc. Occasionally, curvature of the spine (scoliosis) or heart difficulties may be a presenting sign. Symptoms usually present between 5-15 years of age but it can present at a younger or older age.

Other early symptoms would include weakness in legs, unsteadiness in standing, difficulties in walking, Typically, people with FA may over or under extend their leg when walking, in addition, the feet may be higher than necessary when walking and brought down too hard on the ground.

Usually, FA results in the individual using a wheel-chair within 8-10 years after diagnosis. However, with increasing use of different walking aids, it may be possible not to require a wheel-chair for a longer period.

Figure 3: Posterior walker

FA is a slowly progressive condition with no remissions. Scientists describe the progression in two stages the ambulatory stage, where the person is able to walk and the non-ambulatory stage where the patient is not able to walk.

The ambulatory stage is characterized by a decrease in or absence of muscle reflexes in addition to unsteady paces when moving. Patients generally have an elevated heel and flexed toes which produce a foot deformity known as Friedreich's foot. Loss of touch sensation may occur in the arms and legs.

In the non-ambulatory stage patients have so much difficulty walking that they need to use a wheelchair or other orthopaedic aid. This normally happens in second or third decade of life. The hands and arms become affected, making writing and other tasks difficult. Breakdowns in the person's voice, irregularities in pitch and loudness, and other changes in voice quality such as speech muscle control. It can become increasingly difficult to sit upright.

Diagnosis

When a patient presents with symptoms resembling those of ataxia it is important to be checked out by a neurologist. Generally, an evaluation will involve:

1. Medical examination
2. Blood test
3. Xray to search for abnormalities in the brain and spinal cord.

X-rays that might be included:

a) Brain CT scan (a sophisticated x-ray technique for imaging the brain and/or spinal cord),

b) Brain MRI scan (Magnetic resonance imaging of body tissue including the brain and/or spinal cord)

In Friedreich's Ataxia there are minor changes in the cerebellum on MRI scan. The major impact for ataxia in FA is as a result from spinal cord atrophy.

Figure 4: MRI scanner

Conditions associated with FA

There are several conditions associated with FA. Some people may have none of them and some may have quite a few of the. They include

- Heart condition- there are many heart conditions associated with FA. Abnormalities in heartbeat rhythm and diminished strength of the heart muscle have been noted in large percentage of Friedreich's Ataxia patients; with palpitations and dyspnea (shortness of breath) the most common found symptoms.

- Scoliosis - which is a curvature of the spine? It develops during the early stage of life. If it severe it may cause breathing problems.

- Foot abnormality - pes cavus, this is where the arch of the foot is pronounced

- Diabetes - Abnormally high blood and urinary sugar levels

In 2014, guidelines were published on the management of Friedreich's Ataxia. It is available on www.ern-end.eu and www.curefa.org. These guidelines are currently being updated and a new version is due to be published in the next few months (May 2022).

The science behind abnormal FA Gene

We all start life as one cell. It contains 46 chromosomes which are often referred to as 23 pairs. One gets 23 chromosomes from each parent. During growth, the cells in our body divide to make new cells. What starts as a single cell grows into billions of cells. The chromosomes are located in the nucleus of the every cell in the body. Genes are located in chromosomes.
These chromosomes are present at the start of a person's life. Chromosomes are thread like structures located inside the nucleus of animal and plant cells Therefore, the faulty gene is in every cell in the body.

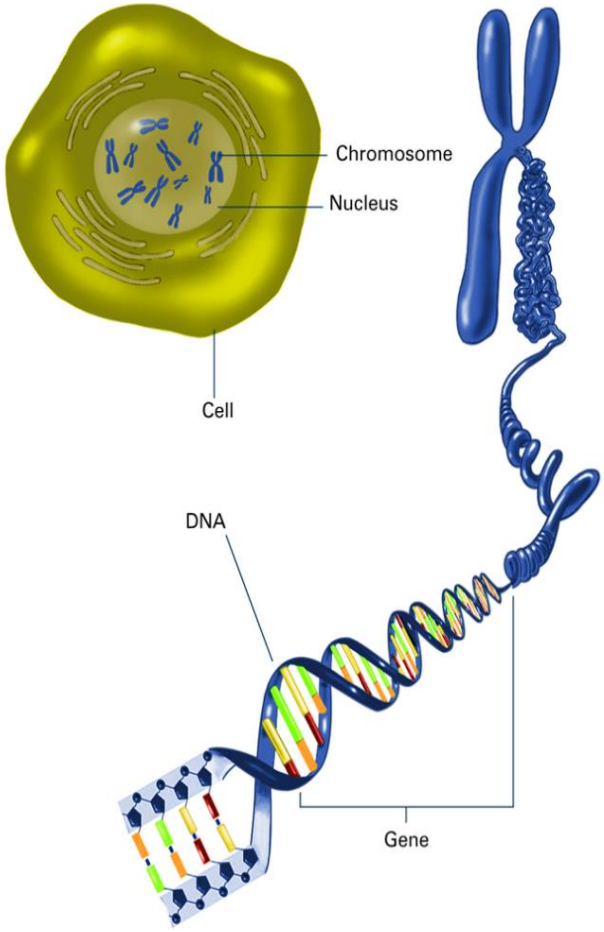
There are roughly 4000 genes on each chromosome. We have about 100,000 genes in total. We all have up to 20 defective genes in our body.

Most of the time we are unaware of the defective genes. A person with FA has a defective gene on each of his 9th chromosome which causes the person to develop Friedreich's Ataxia.

Genes are made up of desoxyribonucleic acid (DNA) which is referred to as DNA that make each person unique (i.e. DNA dictates the colour of our eyes, hair etc).

Several sections of DNA form a gene. Friedreich's ataxia (and other inherited ataxias) is caused by a defect in the DNA.

Genes are too small to be seen even with the most powerful microscope. As tiny as they are, genes play a powerful role.



Source: National Institute of General Medical Sciences (CC BY-NC-SA3.0)

Figure 5: Cell nucleus showing where the chromosomes are kept and details of a gene

Scientific detail of the DNA abnormality in Friedreich's Ataxia:

The 46 chromosomes (23 pairs) are tightly coiled chains of DNA containing millions of chemicals called bases. These bases are adenine, thymine, cytosine, and guanine, abbreviated they are *A,* T, *C* and *G.* Certain bases always pair together such as *"A* with T; C with *G".* The base pairs, in sets of three join together to form coded messages. These coded messages are like "recipes" for making amino acids. The paired bases tell the body how to assemble different proteins. Proteins make up cells, tissues and specialized enzymes that our bodies need to function normally.

The code which is altered in FA is called *GAA.* It is normally repeated 7 to 22 times for a normal person but for a person with FA it can be repeated 300 to 1000 times. As a result of this expanded gene, the frataxin protein is significantly reduced.

The role of frataxin in FA

Frataxin works in the mitochondria in the cells. Mitochondria are one of the small, but very important tiny elements in the cytoplasm of the cells. Mitochondria may be rod shaped, spherical, branched or ring shaped. They contain gene and ribosome. Ribosomes are principally involved in protein making.

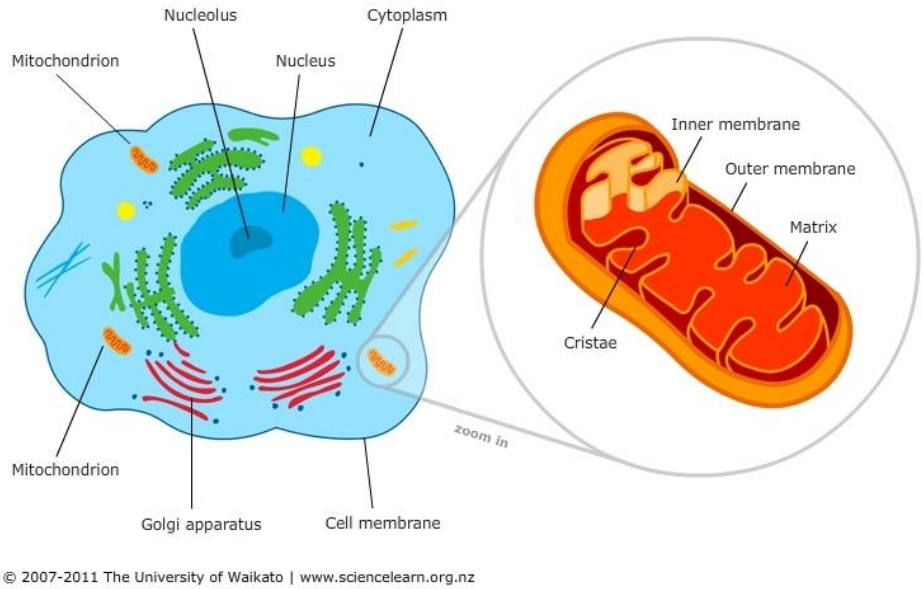


Figure 6: picture of cell showing mitochondria and detail of mitochondria

The mitochondria are the energy-producing power plants of cells. It was found that the shortage of frataxin in the mitochondria led to a toxic build up of iron there. When this toxic iron reacted with oxygen it produced free radicals. Free radicals destroy cells. In Friedreich's ataxia these free radicals are produced and so cause damage to

the nervous system. Once the free radicals destroy the nerve cells they cannot be replaced.

Treatment

There is no proven treatment for FA at present. However, there is a significant amount of research and clinical trials going on in an effort to find a cure FA (see next section). Below are listed, important things to do when you have FA.

Keep active

It is recommended to keep as active as you can helps, particularly at the early stages of diagnosis slow down the progression of FA. They believe that keeping active keeps your muscles going for longer. In particular swimming and horse-riding are particular good activities as the repeated action involved stimulate the nervous system, prevents loss of strength in the hope the individual can preserve their ability to walk.

As the illness progresses, it is more difficult to keep exercising but it is very important to remain as active as possible. While attendance at physio therapy can be recommended, no country has the resources to finance weekly physiotherapy for those with FA. Exercise needs to be incorporated into the lifestyle of the person with FA.

Special emphasis on keeping the achilles tendon mobile so that the individual can move their ankle 'up and down'. The ability to move the ankle is important as it plays an important part in helping the person with FA transfer from their chair, to the toilet, bed etc.

Eat a Healthy diet

A good healthy diet low in "fast sugars" is important to try and keep energy levels up and prevent diabetes mellitus.

Organize regular review of FA and the associated conditions

Many of the associated conditions can be treated as there is cures for them. Back and foot problems can be helped by injections or surgery. Heart problems can be reviewed by your doctor.

Look after your mental health

A diagnosis of FA is life changing for a person and their family. It is bound to affect one's mood and ability to cope with the significant challenges FA poses. Mental health concerns can affect physical, emotional, and social wellbeing. Strategies that may help a person with Friedreich ataxia experiencing mental health issues:

a) Medication is often effective for treating depression, anxiety the benefit to the individual would be large, so it may be worth trying. Ways to limit undesirable side effects (such as dizziness or worsening balance), which would likely have a greater impact on individuals with Friedreich ataxia than other people, should be considered.
b) Counselling unlike medication would not have any undesirable effects If counselling is effective, the benefit would be large.
c) Lifestyle changes: keep active, keep in touch with friends, consider joining an internet or other such patient organization for those with Friedreich's Ataxia. Try and do as much as you can for yourself. Consider going to college, partime work, learning to drive.

Encourage your extended family to get checked for the FA gene or seek genetic counselling

If a person has a genetic ataxia, it is helpful for patients are their families to undergo genetic counselling. Brothers and sisters of individuals with FA worry about having FA. It is important that siblings have someone to talk to confidentially about this. As there is no treatment yet for FA, there is no particular rush to do the genetic test to see if the brothers or sister have FA.

Carrier risk and risk of affected offspring for individuals with FRDA and their relatives

Relationship to individual with Friedreich's Ataxia (FA)	Risk of being a carrier	risk of having an affected child
Parents	1 in 1	1 in 4
Sibling	1 in 2	1 in 680
Aunt/Uncle	1 in 2	1 in 680
First cousin of person with FA	1 in 4	1 in 1360
First cousin once removed	1 in 8	1 in 2720
Second cousin	1 in 16	1 in 5440

Table 1: Risk of developing FA

Table 1 helps answer the questions that families might have about the chances of other family members getting FA. Carrier testing should be first undertaken on the closest relative as a negative result means that genetic testing of more distant relatives may not be necessary.

RESEARCH

FA is a slowly progressing condition so it is difficult to judge how responsive it is to a drug in a few weeks. Therefore, such trials could even take more than 2 years. Designing the trial is very difficult. Most scientists agree that clinical trial should be "double blind". A double-blind trial means that patients are al given pills which look similar but are in fact different dosages. Some of the pills with actually not contain the active drug being tested at all.

Internationally, there are several organisations, laboratories, universities and hospitals involved in research in FA (see figure 7 - FARA pipeline). In fact, it is difficult to keep up to date on all developments. The American patient organisation Friedreich's Ataxia research Alliance (known as FARA) website gives up to date information of international clinical trials on FA. On their site, they have a research pipeline which shows all the different trials taking place at present see www.curefa.org

As of August 2022, the drug omaveloxolone (OMAV) has shown some good results in FA. These were initially made available in October 2020 in the early days of the COVID pandemic. Omav is still not approved in the USA (August 2022) by the Food and Drugs Administration (FDA). Europe understand that talks are at an early stage with the European Medicines Agency (EMA) re getting approval in Europe but it may be necessary to have randomized double-blind trial, which might include some children before the EMA or the FDA will consider reviewing Omav as a treatment for FA.

References

www.ern-rnd.eu

www.curefa.org