Friedreich Ataxia

Subjects: Genetics & Heredity
Contributor: Nicole Yin

Friedreich ataxia is a genetic condition that affects the nervous system and causes movement problems. People with this condition develop impaired muscle coordination (ataxia) that worsens over time. Other features of this condition include the gradual loss of strength and sensation in the arms and legs; muscle stiffness (spasticity); and impaired speech, hearing, and vision. Individuals with Friedreich ataxia often have a form of heart disease called hypertrophic cardiomyopathy, which enlarges and weakens the heart muscle and can be life-threatening. Some affected individuals develop diabetes or an abnormal curvature of the spine (scoliosis).

genetic conditions

1. Introduction

Most people with Friedreich ataxia begin to experience the signs and symptoms of the disorder between ages 5 and 15. Poor coordination and balance are often the first noticeable features. Affected individuals typically require the use of a wheelchair about 10 years after signs and symptoms appear.

About 25 percent of people with Friedreich ataxia have an atypical form in which signs and symptoms begin after age 25. Affected individuals who develop Friedreich ataxia between ages 26 and 39 are considered to have late-onset Friedreich ataxia (LOFA). When the signs and symptoms begin after age 40 the condition is called very late-onset Friedreich ataxia (VLOFA). LOFA and VLOFA usually progress more slowly than typical Friedreich ataxia.

2. Frequency

Friedreich ataxia is estimated to affect 1 in 40,000 people in the United States. This condition is found in people with European, Middle Eastern, or North African ancestry. It is rarely identified in other ethnic groups.

3. Causes

Mutations in the *FXN* gene cause Friedreich ataxia. This gene provides instructions for making a protein called frataxin. Although its role is not fully understood, frataxin is important for the normal function of mitochondria, the energy-producing centers within cells. One region of the *FXN* gene contains a segment of DNA known as a GAA trinucleotide repeat. This segment is made up of a series of three DNA building blocks (one guanine and two adenines) that appear multiple times in a row. Normally, this segment is repeated 5 to 33 times within the *FXN* gene.

In people with Friedreich ataxia, the GAA segment is repeated 66 to more than 1,000 times. The length of the GAA trinucleotide repeat appears to be related to the age at which the symptoms of Friedreich ataxia appear, how severe they are, and how quickly they progress. People with GAA segments repeated fewer than 300 times tend to have a later appearance of symptoms (after age 25) than those with larger GAA trinucleotide repeats. The abnormally long GAA trinucleotide repeat disrupts the production of frataxin, which severely reduces the amount of this protein in cells. Certain nerve and muscle cells cannot function properly with a shortage of frataxin, leading to the characteristic signs and symptoms of Friedreich ataxia.

3.1. The Gene Associated with Friedreich Ataxia

- FXN

4. Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

5. Other Names for This Condition

- FA
- FRDA
- Friedreich spinocerebellar ataxia
- Friedrich's ataxia

References

1. Adinolfi S, Trifuoggi M, Politou AS, Martin S, Pastore A. A structuralapproach to understanding the iron-binding properties of phylogeneticallydifferent frataxins. Hum Mol Genet. 2002 Aug 1;11(16):1865-77.
2. Bidichandani SI, Delatycki MB. Friedreich Ataxia. 1998 Dec 18 [updated 2017Jun 1]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K,Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University ofWashington, Seattle; 1993-2020. Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK1281/
3. Castaldo I, Pinelli M, Monticelli A, Acquaviva F, Giacchetti M, Filla A,Sacchetti S, Keller S, Avvedimento VE, Chiariotti L, Cocozza S. DNA methylationin intron 1 of the frataxin gene is related to GAA repeat length and age of onsetin Friedreich ataxia patients. J Med Genet. 2008 Dec;45(12):808-12. doi:10.1136/jmg.2008.058594.

4. Chutake YK, Costello WN, Lam C, Bidichandani SI. Altered nucleosomepositioning at the transcription start site and deficient transcriptionalinitiation in Friedreich ataxia. J Biol Chem. 2014 May 30;289(22):15194-202. doi:10.1074/jbc.M114.566414.
5. Hebert MD. Targeting the gene in Friedreich ataxia. Biochimie. 2008Aug;90(8):1131-9. doi: 10.1016/j.biochi.2007.12.005.
6. Kumari D, Hayward B, Nakamura AJ, Bonner WM, Usdin K. Evidence for chromosome fragility at the frataxin locus in Friedreich ataxia. Mutat Res. 2015Nov;781:14-21. doi: 10.1016/j.mrfmmm.2015.08.007.
7. Pandolfo M, Pastore A. The pathogenesis of Friedreich ataxia and the structureand function of frataxin. J Neurol. 2009 Mar;256 Suppl 1:9-17. doi:10.1007/s00415-009-1003-2. Review.
8. Pandolfo M. Friedreich ataxia. Arch Neurol. 2008 Oct;65(10):1296-303. doi:10.1001/archneur.65.10.1296. Review.
9. Ribaï P, Pousset F, Tanguy ML, Rivaud-Pechoux S, Le Ber I, Gasparini F,Charles P, Béraud AS, Schmitt M, Koenig M, Mallet A, Brice A, Dürr A.Neurological, cardiological, and oculomotor progression in 104 patients withFriedreich ataxia during long-term follow-up. Arch Neurol. 2007 Apr;64(4):558-64.