Fragile X-associated tremor/ataxia syndrome

Fragile X-associated tremor/ataxia syndrome (FXTAS) is characterized by problems with movement and thinking ability (cognition). FXTAS is a late-onset disorder, usually occurring after age 50, and its signs and symptoms worsen with age. This condition affects males more frequently and severely than females. Affected individuals have areas of damage in the part of the brain that controls movement (the cerebellum) and in a type of brain tissue known as white matter, which can be seen with magnetic resonance imaging (MRI). This damage leads to the movement problems and other impairments associated with FXTAS.

The characteristic features of FXTAS are intention tremor, which is trembling or shaking of a limb when trying to perform a voluntary movement such as reaching for an object, and problems with coordination and balance (ataxia). Typically intention tremors will develop first, followed a few years later by ataxia, although not everyone with FXTAS has both features. Many affected individuals develop other movement problems, such as a pattern of movement abnormalities known as parkinsonism, which includes tremors when not moving (resting tremor), rigidity, and unusually slow movement (bradykinesia). In addition, affected individuals may have reduced sensation, numbness or tingling, pain, or muscle weakness in the lower limbs. Some people with FXTAS experience problems with the autonomic nervous system, which controls involuntary body functions, leading to the inability to control the bladder or bowel.

People with FXTAS commonly have cognitive disabilities. They may develop short-term memory loss and loss of executive function, which is the ability to plan and implement actions and develop problem-solving strategies. Loss of this function impairs skills such as impulse control, self-monitoring, focusing attention appropriately, and cognitive flexibility. Many people with FXTAS experience anxiety, depression, moodiness, or irritability.

Some women develop immune system disorders, such as hypothyroidism or fibromyalgia, before the signs and symptoms of FXTAS appear.

Frequency

Studies show that approximately 1 in 450 males has the genetic change that leads to FXTAS, although the condition occurs in only about 40 percent of them. It is estimated that 1 in 3,000 men over age 50 is affected. Similarly, 1 in 200 females has the genetic change, but only an estimated 16 percent of them develop signs and symptoms of FXTAS.

Causes

Mutations in the *FMR1* gene increase the risk of developing FXTAS. The *FMR1* gene provides instructions for making a protein called FMRP, which helps regulate the production of other proteins. FMRP plays a role in the development of synapses, which are specialized connections between nerve cells. Synapses are critical for relaying nerve impulses.

Individuals with FXTAS have a mutation in which a DNA segment, known as a CGG triplet repeat, is expanded within the *FMR1* gene. Normally, this DNA segment is repeated from 5 to about 40 times. In people with FXTAS, however, the CGG segment is repeated 55 to 200 times. This mutation is known as an *FMR1* gene premutation. An expansion of more than 200 repeats, a full mutation, causes a more serious condition called fragile X syndrome, which is characterized by intellectual disability, learning problems, and certain physical features.

For unknown reasons, the premutation leads to the overproduction of abnormal *FMR1* mRNA that contains the expanded repeat region. The *FMR1*mRNA is the genetic blueprint for the production of FMRP. Researchers believe that the high levels of mRNA cause the signs and symptoms of FXTAS. The mRNA has been found in clumps of proteins and mRNA (intranuclear inclusions) in brain and nerve cells in people with FXTAS. It is thought that attaching to *FMR1* mRNA and forming clumps keeps the other proteins from performing their functions, although the effect of the intranuclear inclusions is unclear. In addition, the repeat expansion makes producing FMRP from the mRNA blueprint more difficult, and as a result, people with the *FMR1* gene premutation can have less FMRP than normal. A reduction in the protein is not thought to be involved in FXTAS. However, it may cause mild versions of the features seen in fragile X syndrome, such as prominent ears, anxiety, and mood swings.

Inheritance Pattern

An increased risk of developing FXTAS is inherited in an X-linked dominant pattern. The *FMR1* gene is located on the X chromosome, one of the two sex chromosomes. (The Y chromosome is the other sex chromosome.) The inheritance is dominant because one copy of the altered gene in each cell is sufficient to elevate the risk of developing FXTAS. In females (who have two X chromosomes), a mutation in one of the two copies of the *FMR1* gene in each cell can lead to the disorder. In males (who have only one X chromosome), a mutation in the only copy of the gene in each cell can result in the disorder. However, not all people who inherit an *FMR1* premutation will develop FXTAS. In X-linked dominant disorders, males typically experience more severe symptoms than females.

Fewer females than males develop FXTAS because the X chromosome that contains the premutation may be turned off (inactive) due to a process called X-inactivation. Early in embryonic development in females, one of the two X chromosomes is permanently inactivated in somatic cells (cells other than egg and sperm cells). X-inactivation ensures that females, like males, have only one active copy of the X

chromosome in each body cell. Usually X-inactivation occurs randomly, so that each X chromosome is active in about half the body's cells. Sometimes X-inactivation is not random, and one X chromosome is active in more than half of cells. When X-inactivation does not occur randomly, it is called skewed X-inactivation. Researchers suspect that the distribution of active and inactive X chromosomes may help determine the severity of FXTAS in females or whether they develop signs and symptoms of the condition.

Other Names for This Condition

- fragile X tremor/ataxia syndrome
- FXTAS

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Fragile X tremor/ataxia syndrome
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1839780/

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22fragile+X-associated+tremor+ataxia+syndrome%22

Other Diagnosis and Management Resources

- Fragile X Research Foundation of Canada: FXTAS
  http://www.fragilexcanada.ca/index.php?id=103,0,0,1,0,0
- GeneReview: FMR1-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK1384
- Merck Manual Consumer Version
  https://www.merckmanuals.com/home/brain,-spinal-cord,-and-nerve-disorders/movement-disorders/fragile-x%E2%80%93associated-tremor-ataxia-syndrome

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Tremor
  https://medlineplus.gov/ency/article/003192.htm
- Health Topic: Genetic Brain Disorders
  https://medlineplus.gov/geneticbraindisorders.html

- Health Topic: Movement Disorders
  https://medlineplus.gov/movementdisorders.html
- Health Topic: Neurologic Diseases
  https://medlineplus.gov/neurologicdiseases.html
- Health Topic: Tremor
  https://medlineplus.gov/tremor.html

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Tremor Fact Sheet
  https://www.ninds.nih.gov/Disorders/All-Disorders/Tremor-Information-Page

Educational Resources

- MalaCards: fragile x-associated tremor/ataxia syndrome
  https://www.malacards.org/card/fragile_x_associated_tremor_ataxia_syndrome
- Merck Manual Consumer Version
  https://www.merckmanuals.com/home/brain,-spinal-cord,-and-nerve-disorders/movement-disorders/fragile-x%E2%80%93associated-tremor-ataxia-syndrome
- National Fragile X Foundation: FXTAS
  https://fragilex.org/understanding-fragile-x/tremor-ataxia-syndrome-fxtas/
- Orphanet: Fragile X-associated tremor/ataxia syndrome
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=93256
- University of Colorado, Colorado Fragile X Consortium
  http://www.ucdenver.edu/academics/colleges/medicalschool/programs/fragilex/Pages/FXTAS_basic.aspx

Patient Support and Advocacy Resources

- National Fragile X Foundation
  https://fragilex.org/

Clinical Information from GeneReviews

- FMR1-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK1384

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28fragile+x-associated+tremor/ataxia+syndrome%5BTIAB%5D%29+OR+%28fragile+x+tremor/ataxia+syndrome%5BTIAB%5D%29+OR+%28fxtas%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- FRAGILE X TREMOR/ATAXIA SYNDROME
  http://omim.org/entry/300623

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