



Fragile XE syndrome

Fragile XE syndrome is a genetic disorder that impairs thinking ability and cognitive functioning. Most affected individuals have mild intellectual disability. In some people with this condition, cognitive function is described as borderline, which means that it is below average but not low enough to be classified as an intellectual disability. Females are rarely diagnosed with fragile XE syndrome, likely because the signs and symptoms are so mild that the individuals function normally.

Learning disabilities are the most common sign of impaired cognitive function in people with fragile XE syndrome. The learning disabilities are likely a result of communication and behavioral problems, including delayed speech, poor writing skills, hyperactivity, and a short attention span. Some affected individuals display autistic behaviors, such as hand flapping, repetitive behaviors, and intense interest in a particular subject. Unlike some other forms of intellectual disability, cognitive functioning remains steady and does not decline with age in fragile XE syndrome.

Frequency

Fragile XE syndrome is estimated to affect 1 in 25,000 to 100,000 newborn males. Only a small number of affected females have been described in the medical literature. Because mildly affected individuals may never be diagnosed, it is thought that the condition may be more common than reported.

Causes

Fragile XE syndrome is caused by mutations in the *AFF2* gene. This gene provides instructions for making a protein whose function is not well understood. Some studies show that the *AFF2* protein can attach (bind) to DNA and help control the activity of other genes. Other studies suggest that the *AFF2* protein is involved in the process by which the blueprint for making proteins is cut and rearranged to produce different versions of the protein (alternative splicing). Researchers are working to determine which genes and proteins are affected by *AFF2*.

Nearly all cases of fragile XE syndrome occur when a region of the *AFF2* gene, known as the CCG trinucleotide repeat, is abnormally expanded. Normally, this segment of three DNA building blocks (nucleotides) is repeated approximately 4 to 40 times. However, in people with fragile XE syndrome, the CCG segment is repeated more than 200 times, which makes this region of the gene unstable. (When expanded, this region is known as the FRAXE fragile site.) As a result, the *AFF2* gene is turned off (silenced), and no *AFF2* protein is produced. It is unclear how a shortage of this protein leads to intellectual disability in people with fragile XE syndrome.

People with 50 to 200 CCG repeats are said to have an *AFF2* gene premutation. Current research suggests that people with a premutation do not have associated cognitive problems.

Inheritance Pattern

Fragile XE syndrome is inherited in an X-linked pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes in each cell. In males, who have only one X chromosome, a mutation in the only copy of the gene in each cell is sufficient to cause the condition. In females, who have two copies of the X chromosome, one altered copy of the gene in each cell can lead to less severe features of the condition or may cause no signs or symptoms at all. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

In parents with the *AFF2* gene premutation, the number of CCG repeats can expand to more than 200 in cells that develop into eggs or sperm. This means that parents with the premutation have an increased risk of having a child with fragile XE syndrome. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons; sons receive a Y chromosome from their father, which does not include the *AFF2* gene.

Other Names for This Condition

- FRAXE intellectual deficit
- FRAXE intellectual disability
- FRAXE mental retardation syndrome
- FRAXE syndrome
- mental retardation, X-linked, associated with fragile site FRAXE
- mental retardation, X-linked, FRAXE type

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
[/primer/testing/genetic-testing](#)
- Genetic Testing Registry: FRAXE
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0751157/>

Other Diagnosis and Management Resources

- Centers for Disease Control and Prevention: Developmental Screening Fact Sheet
https://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/DevelopmentalScreening.pdf

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Intellectual Disability
<https://medlineplus.gov/ency/article/001523.htm>
- Health Topic: Developmental Disabilities
<https://medlineplus.gov/developmentaldisabilities.html>

Genetic and Rare Diseases Information Center

- Fragile XE syndrome
<https://rarediseases.info.nih.gov/diseases/2378/fragile-xe-syndrome>

Additional NIH Resources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development: Intellectual and Developmental Disabilities
<https://www.nichd.nih.gov/health/topics/idds/conditioninfo/default>

Educational Resources

- Centers for Disease Control and Prevention: Intellectual Disability
<https://www.cdc.gov/ncbddd/developmentaldisabilities/facts-about-intellectual-disability.html>
- MalaCards: mental retardation, x-linked, associated with fragile site fraxe
https://www.malacards.org/card/mental_retardation_x_linked_associated_with_fragile_site_fraxe
- Orphanet: FRAXE intellectual deficit
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=100973

Patient Support and Advocacy Resources

- American Association on Intellectual and Developmental Disabilities (AAIDD)
<https://www.aaid.org/>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28fraxe+intellectual+disability%5BTIAB%5D%29+OR+%28fraxe+syndrome%5BTIAB%5D%29+OR+%28FRAXE%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

Catalog of Genes and Diseases from OMIM

- MENTAL RETARDATION, X-LINKED, ASSOCIATED WITH FRAGILE SITE
FRAXE
<http://omim.org/entry/309548>

Sources for This Summary

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