Fragile XE syndrome

Description

Fragile XE syndrome is a genetic disorder that impairs thinking ability and cognitive functioning. Most affected individuals have mild intellectual disabilities. 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, if present at all.

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. 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 variants (also called 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 6 to 30 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 disabilities in people with fragile XE syndrome.

Learn more about the gene associated with Fragile XE syndrome

- AFF2

Inheritance

Fragile XE syndrome is inherited in an X-linked pattern. A condition is considered X-linked if the altered 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 variant 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 rarely causes the condition and the features are often less severe than in individuals with both copies altered. Some females with only one altered copy of the gene may have no signs or symptoms at all. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

People with 61 to 200 CCG repeats are said to have an AFF2 gene premutation. In parents with a *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. In people with 31-60 CCG repeats, the number of repeats can expand in cells that develop into eggs or sperm, but it is still likely not large enough to lead to fragile XE syndrome.

Other Names for This Condition

- FRAXE intellectual deficit
- FRAXE intellectual disability
- FRAXE syndrome

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: FRAXE (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0751157/)

Genetic and Rare Diseases Information Center

- FRAXE intellectual disability (https://rarediseases.info.nih.gov/diseases/2378/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Catalog of Genes and Diseases from OMIM

- INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED 109; XLID109 (https://omim.org/entry/309548)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?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)

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