



Fragile X syndrome

Fragile X syndrome is a genetic condition that causes a range of developmental problems including learning disabilities and cognitive impairment. Usually, males are more severely affected by this disorder than females.

Affected individuals usually have delayed development of speech and language by age 2. Most males with fragile X syndrome have mild to moderate intellectual disability, while about one-third of affected females are intellectually disabled. Children with fragile X syndrome may also have anxiety and hyperactive behavior such as fidgeting or impulsive actions. They may have attention deficit disorder (ADD), which includes an impaired ability to maintain attention and difficulty focusing on specific tasks. About one-third of individuals with fragile X syndrome have features of autism spectrum disorders that affect communication and social interaction. Seizures occur in about 15 percent of males and about 5 percent of females with fragile X syndrome.

Most males and about half of females with fragile X syndrome have characteristic physical features that become more apparent with age. These features include a long and narrow face, large ears, a prominent jaw and forehead, unusually flexible fingers, flat feet, and in males, enlarged testicles (macroorchidism) after puberty.

Frequency

Fragile X syndrome occurs in approximately 1 in 4,000 males and 1 in 8,000 females.

Genetic Changes

Mutations in the *FMR1* gene cause fragile X syndrome. The *FMR1* gene provides instructions for making a protein called FMRP. This protein helps regulate the production of other proteins and plays a role in the development of synapses, which are specialized connections between nerve cells. Synapses are critical for relaying nerve impulses.

Nearly all cases of fragile X syndrome are caused by a mutation in which a DNA segment, known as the CGG triplet repeat, is expanded within the *FMR1* gene. Normally, this DNA segment is repeated from 5 to about 40 times. In people with fragile X syndrome, however, the CGG segment is repeated more than 200 times. The abnormally expanded CGG segment turns off (silences) the *FMR1* gene, which prevents the gene from producing FMRP. Loss or a shortage (deficiency) of this protein disrupts nervous system functions and leads to the signs and symptoms of fragile X syndrome.

Males and females with 55 to 200 repeats of the CGG segment are said to have an *FMR1* gene premutation. Most people with a premutation are intellectually normal.

In some cases, however, individuals with a premutation have lower than normal amounts of FMRP. As a result, they may have mild versions of the physical features seen in fragile X syndrome (such as prominent ears) and may experience emotional problems such as anxiety or depression. Some children with a premutation may have learning disabilities or autistic-like behavior. The premutation is also associated with an increased risk of disorders called fragile X-associated primary ovarian insufficiency (FXPOI) and fragile X-associated tremor/ataxia syndrome (FXTAS).

Inheritance Pattern

Fragile X syndrome is inherited in an X-linked dominant 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. (The Y chromosome is the other sex chromosome.) The inheritance is dominant if one copy of the altered gene in each cell is sufficient to cause the condition. X-linked dominant means that in females (who have two X chromosomes), a mutation in one of the two copies of a gene in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), a mutation in the only copy of a gene in each cell causes the disorder. In most cases, males experience more severe symptoms of the disorder than females.

In women, the *FMR1* gene premutation on the X chromosome can expand to more than 200 CGG repeats in cells that develop into eggs. This means that women with the premutation have an increased risk of having a child with fragile X syndrome. By contrast, the premutation in men does not expand to more than 200 repeats as it is passed to the next generation. Men pass the premutation only to their daughters. Their sons receive a Y chromosome, which does not include the *FMR1* gene.

Other Names for This Condition

- fra(X) syndrome
- FRAXA syndrome
- FXS
- marker X syndrome
- Martin-Bell syndrome
- X-linked mental retardation and macroorchidism

Diagnosis & Management

Formal Treatment/Management Guidelines

- American College of Medical Genetics and Genomics Practice Guideline <http://www.acmg.net/PDFLibrary/Fragile-X-Carrier-Testing.pdf>

Genetic Testing

- Genetic Testing Registry: Fragile X syndrome
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0016667/>

Other Diagnosis and Management Resources

- GeneReview: FMR1-Related Disorders
<https://www.ncbi.nlm.nih.gov/books/NBK1384>
- MedlinePlus Encyclopedia: Fragile X syndrome
<https://medlineplus.gov/ency/article/001668.htm>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Fragile X syndrome
<https://medlineplus.gov/ency/article/001668.htm>
- Health Topic: Fragile X Syndrome
<https://medlineplus.gov/fragilexsyndrome.html>

Genetic and Rare Diseases Information Center

- Fragile X syndrome
<https://rarediseases.info.nih.gov/diseases/6464/fragile-x-syndrome>

Additional NIH Resources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development
<https://www.nichd.nih.gov/health/topics/fragilex>
- Eunice Kennedy Shriver National Institute of Child Health and Human Development: Primary Ovarian Insufficiency
<https://www.nichd.nih.gov/health/topics/poi>

Educational Resources

- American College of Medical Genetics and Genomics Practice Guideline
<http://www.acmg.net/PDFLibrary/Fragile-X-Carrier-Testing.pdf>
- Boston Children's Hospital
<http://www.childrenshospital.org/conditions-and-treatments/conditions/f/fragile-x-syndrome>
- Centre for Genetics Education (Australia)
<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-54-fragile-x-syndrome>
- Disease InfoSearch: Fragile X Syndrome
<http://www.diseaseinfosearch.org/Fragile+X+Syndrome/2906>
- Emory University School of Medicine: Fragile X Premutation--a Cause of Premature Ovarian Failure
<http://genetics.emory.edu/documents/resources/factsheet46.pdf>
- Emory University School of Medicine: Fragile X Syndrome
<http://genetics.emory.edu/documents/resources/factsheet47.pdf>
- Kennedy Krieger Institute
<https://www.kennedykrieger.org/patient-care/diagnoses-disorders/fragile-x-syndrome>
- MalaCards: fragile x syndrome
http://www.malacards.org/card/fragile_x_syndrome
- Orphanet: Fragile X syndrome
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=908
- Your Genes Your Health from Cold Spring Harbor Laboratory
<http://www.ygyh.org/fragx/whatisit.htm>

Patient Support and Advocacy Resources

- FRAXA Research Foundation
<https://www.fraxa.org/>
- March of Dimes
<https://www.marchofdimes.org/baby/fragile-x-syndrome.aspx>
- National Fragile X Foundation
<https://fragilex.org/>
- National Organization for Rare Disorders (NORD)
<https://rarediseases.org/rare-diseases/fragile-x-syndrome/>

GeneReviews

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

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22fragile+x+syndrome%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Fragile+X+Syndrome%5BMAJR%5D%29+AND+%28fragile+X+syndrome%5BTI%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D>

OMIM

- FMR1 GENE
<http://omim.org/entry/309550>

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