



## FMR1 gene

fragile X mental retardation 1

### Normal Function

The *FMR1* gene provides instructions for making a protein called FMRP. This protein is present in many tissues, including the brain, testes, and ovaries. In the brain, it may play a role in the development of connections between nerve cells (synapses), where cell-to-cell communication occurs. The synapses can change and adapt over time in response to experience (a characteristic called synaptic plasticity). FMRP may help regulate synaptic plasticity, which is important for learning and memory. The protein's role in the testes and ovaries is not well understood.

Researchers believe that FMRP acts as a shuttle within cells by transporting molecules called messenger RNA (mRNA), which serve as the genetic blueprint for making proteins. FMRP likely carries mRNA molecules from the nucleus to areas of the cell where proteins are assembled. FMRP also helps control when the instructions in these mRNA molecules are used to build proteins, some of which may be important for functioning of the nerves, testes, or ovaries.

One region of the *FMR1* gene contains a particular DNA segment known as a CGG trinucleotide repeat, so called because this segment of three DNA building blocks (nucleotides) is repeated multiple times within the gene. In most people, the number of CGG repeats ranges from fewer than 10 to about 40. This CGG repeat segment is typically interrupted several times by a different three-base sequence, AGG. Having AGG scattered among the CGG triplets appears to help stabilize the long repeated segment.

### Health Conditions Related to Genetic Changes

#### Fragile X syndrome

Almost all cases of fragile X syndrome are caused by an expansion of the CGG trinucleotide repeat in the *FMR1* gene. In these cases, CGG is abnormally repeated from 200 to more than 1,000 times, which makes this region of the gene unstable. As a result, the *FMR1* gene is turned off (silenced) and makes very little or no protein. A loss or shortage of FMRP disrupts normal functions of nerve cells and, consequently, the nervous system, causing severe learning problems, intellectual disability, and the other features of fragile X syndrome. About one-third of males with an *FMR1* gene mutation and the characteristic signs of fragile X syndrome also have features of autism spectrum disorders that affect communication and social interaction.

Fewer than 1 percent of all cases of fragile X syndrome are caused by other changes in the *FMR1* gene. Mutations may delete part or all of the gene or change one of the

building blocks (amino acids) used to make FMRP. These genetic changes alter the 3-dimensional shape of the protein or prevent any protein from being produced. The abnormal or missing protein disrupts nervous system functions, leading to the signs and symptoms of fragile X syndrome.

### Fragile X-associated primary ovarian insufficiency

A trinucleotide repeat expansion in the *FMR1* gene increases a woman's risk of developing a condition called fragile X-associated primary ovarian insufficiency (FXPOI). In this condition, the CGG trinucleotide repeat in the *FMR1* gene is repeated about 55 to 200 times, which is referred to as a premutation. Women who develop FXPOI may experience irregular menstrual cycles, an inability to have children (infertility), early menopause, and elevated levels of a hormone known as follicle stimulating hormone (FSH). About 20 percent of women with a premutation have the most serious form of the condition, called overt POI, which leads to abnormal menstrual cycles and elevated FSH levels before age 40 and often causes infertility. Other women with the premutation have occult POI, a milder form of the condition that causes reduced fertility, although the women have normal menstrual cycles.

For unknown reasons, the premutation leads to the overproduction of abnormal *FMR1* mRNA that contains the repeat expansion. Researchers believe that the abnormal mRNA causes the signs and symptoms of FXPOI. It is thought that the mRNA attaches (binds) to other proteins and keeps them from performing their functions. In addition, the repeats make producing protein from the blueprint more difficult, and consequently, some people with the *FMR1* gene 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 (described above), such as prominent ears, and may experience emotional problems such as anxiety or depression.

### Fragile X-associated tremor/ataxia syndrome

Men, and some women, with an *FMR1* gene premutation are at increased risk of developing a disorder known as fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS is characterized by progressive problems with movement (ataxia), tremor, memory loss, reduced sensation in the lower extremities (peripheral neuropathy), and mental and behavioral changes. The disorder usually develops late in life and worsens over time.

As in FXPOI (described above), the premutation causes overproduction of abnormal *FMR1* mRNA containing the expanded repeat region, and researchers believe that this abnormal mRNA causes FXTAS. The abnormal mRNA has been found in clumps of proteins and mRNA (intranuclear inclusions) that are found in brain and nerve cells in people with FXTAS. Some researchers speculate that the proteins found in the inclusions cannot perform their normal functions, which could lead to the signs and symptoms of FXTAS. Another hypothesis is that the inclusions could cause the death

of nerve cells important for movement and mental function. However, the exact role the inclusions play in the development of the disorder is unknown.

People with FXTAS may have a reduced amount of FMRP. While a reduction in this protein is not thought to be involved in FXTAS, it may lead to mild versions of features seen in fragile X syndrome (described above), such as prominent ears, anxiety, and mood swings.

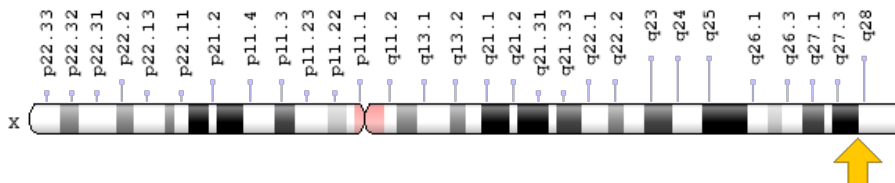
### Other disorders

Researchers have shown that some children with a premutation (55 to 200 CGG repeats) in the *FMR1* gene have learning disabilities, attention-deficit/hyperactivity disorder (ADHD), intellectual disability, or developmental disorders that affect communication and social interaction (such as autism spectrum disorder).

### **Chromosomal Location**

Cytogenetic Location: Xq27.3, which is the long (q) arm of the X chromosome at position 27.3

Molecular Location: base pairs 147,911,919 to 147,951,127 on the X chromosome (Homo sapiens Updated Annotation Release 109.20190905, GRCh38.p13) (NCBI)



Credit: Genome Decoration Page/NCBI

### **Other Names for This Gene**

- FMR1\_HUMAN
- FMRP
- FRAXA
- Protein FMR-1

## **Additional Information & Resources**

### Educational Resources

- National Fragile X Foundation: FXPOI  
<https://fragilex.org/understanding-fragile-x/fxpoi-primary-ovarian-insufficiency/>
- National Fragile X Foundation: FXTAS Information  
<https://fragilex.org/understanding-fragile-x/tremor-ataxia-syndrome-fxtas/>

### 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%28FMR1%5BTIAB%5D%29+OR+%28fragile+X+mental+retardation+1%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5BIa%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D>

### Catalog of Genes and Diseases from OMIM

- FMRP TRANSLATIONAL REGULATOR 1  
<http://omim.org/entry/309550>

### Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology  
[http://atlasgeneticsoncology.org/Genes/GC\\_FMR1.html](http://atlasgeneticsoncology.org/Genes/GC_FMR1.html)
- ClinVar  
<https://www.ncbi.nlm.nih.gov/clinvar?term=FMR1%5Bgene%5D>
- HGNC Gene Symbol Report  
[https://www.genenames.org/data/gene-symbol-report/#!/hgnc\\_id/HGNC:3775](https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:3775)
- Monarch Initiative  
<https://monarchinitiative.org/gene/NCBIGene:2332>
- NCBI Gene  
<https://www.ncbi.nlm.nih.gov/gene/2332>
- UniProt  
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