

Prevalence

We report agreed-upon prevalence numbers where possible from trusted sources, but it is important to remember that many are estimated ranges and not exact numbers. Here, we cover the prevalence of the *FMR1* premutation, Fragile X syndrome (including FXS with autism), and the FX-associated disorders FXPOI and FXTAS.

The Four Forms of the *FMR1* Gene:

1. **Typical** <45 CGG repeats
2. **Intermediate (Gray Zone)** 45-54 CGG repeats
3. **Premutation** 55-200 CGG repeats
4. **Full Mutation (Fragile X syndrome)** >200 CGG repeats

See Genetics & Inheritance for more about CGG repeats.

Prevalence of the *FMR1* Premutation

Premutation: 55 and 200 CGG repeats

The exact number of people who have a fragile X premutation is unknown. However, according to a 2012 study by the CDC, the frequency of the Fragile X premutation in the U.S. is:

- ~ 1 in 151 females, or about 1 million females.
- ~ 1 in 468 males, or about 320,000 males.

Available research estimates that between 1 in 148 and 1 in 291 females and between 1 in 290 and 1 in 855 males in the United States may have a Fragile X premutation. This prevalence translates into well over 1 million individuals with the Fragile X premutation in the United States. Additional prevalence studies worldwide note considerable ethnic variability, with some places showing higher or lower estimates of the Fragile X premutation prevalence. All of these estimates are based on a limited number of studies.[1, 2, 3, 4, 5, 6]

These statistics are important because both men and women are at risk for having symptoms linked to Fragile X-associated disorders.

Premutation Facts:

- Women with a premutation reported their last menstrual cycle at an earlier age vs. people without — age 48 vs. 51.
- Men and women with a premutation are 4x as likely to report dizziness or fainting vs. people without — 18% vs. 4%.
- Men and women with a premutation are 2x as likely to report numbness vs. people without — 29% vs. 13%.
- Both males and females can be carriers or have the Fragile X premutation, and both can be affected by the condition. This differs from other X-linked conditions.
- The most significant issue for males with the Fragile X premutation is the risk for FXTAS. The vast majority of males with the Fragile X premutation are clinically unaffected.

Learn more about the premutation

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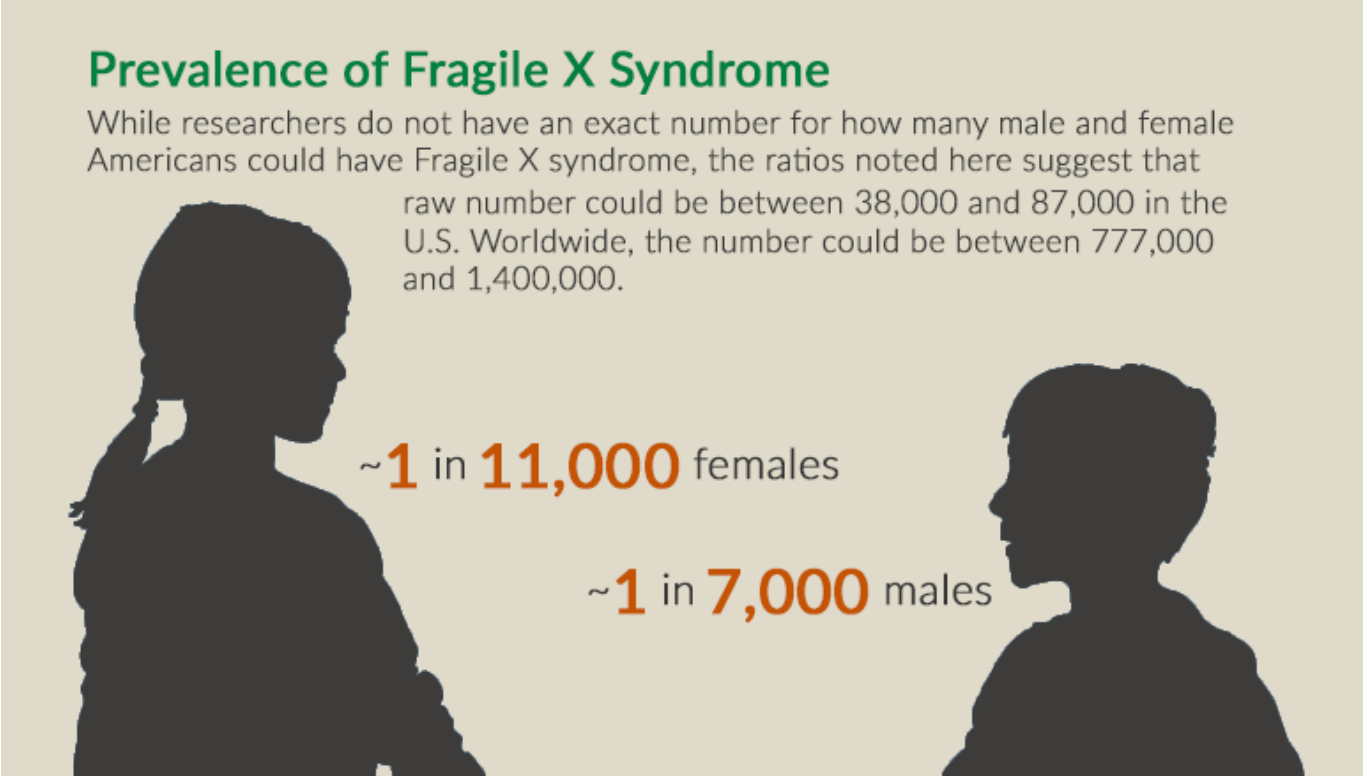
Prevalence of Fragile X Syndrome

Fragile X Syndrome: 200 or more CGG repeats

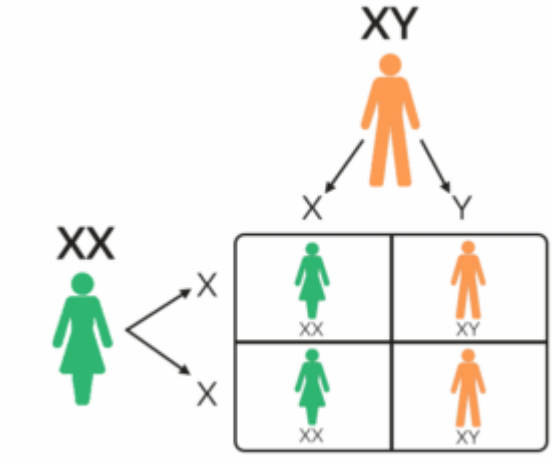
FXS has been detected in all populations and ethnic groups. As a result, efforts have been made to determine the overall prevalence of FXS and the difference in prevalence between males and females. Studies have been undertaken in the "special needs" and general populations.

The exact number of people who have FXS is unknown, but a review of research studies on the prevalence of FXS diagnoses estimated:

- ~ 1 in 7,000 males have been diagnosed with FXS.
- ~ 1 in 11,000 females have been diagnosed with FXS.



Why are there fewer females than males with Fragile X syndrome?



The reason there are fewer females with FXS than males is that the gene for FXS is located on the X chromosome. Males, having only one X chromosome (XY), will develop FXS because of a mutation of their single X chromosome. Females, who have two X chromosomes (XX), can have the unaffected X reduce the effects of the affected X. This typically leads to no or milder symptoms of FXS. (This is an important distinction, as many females with the full mutation do not consider themselves, nor are they considered by others, to have “Fragile X syndrome.”)

How many Americans have full-mutation Fragile X syndrome?

While researchers do not have an exact number for how many Americans (males and females) could have full-mutation Fragile X syndrome, the ratios noted above suggest that the raw number of individuals could be as high as 87,000 or as low as 38,000. (Worldwide, the number could be between 1,400,000 and 777,000.)

However, it is important to note that some published papers suggest a greater prevalence and some a lower prevalence than the numbers cited above.

Learn more about FXS

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Prevalence of the FXS-Autism Link

Many studies have evaluated the FXS-autism link over the past decade. Since many children with Fragile X syndrome are interested in social interactions, they may not meet the diagnostic criteria for autism, even though they exhibit some features such as poor eye contact, shyness, social anxiety, hand flapping, and sensory issues.

FXS-Autism Facts:

- Autism is much more common in boys than in girls with Fragile X syndrome. According to the CDC, a national parent survey found that 46% of males and 16% of females with FXS have been diagnosed or treated for autism.
- 40% of individuals with Fragile X syndrome are diagnosed with autism by their doctor in a Fragile X clinic.
- Studies show that individuals with Fragile X syndrome who have autism can have a more significant intellectual disability (lower IQ) than those with Fragile X syndrome who do not have autism.
- About 10% of children with autism are identified as having another genetic and chromosomal disorder, such as Fragile X syndrome.

Given the possibility of a link, it is recommended that all children with autism, both male and female, be referred for genetic evaluation and testing for Fragile X syndrome and any other genetic cause of autism.

Learn more about FXS + Autism

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Prevalence of FXTAS

Among premutation carriers, the chance of developing FXTAS is:

- ~ 40% of males over 50
- ~ 8%–16% of women over 40

Among the general population, considering all of the factors and literature to date, it is estimated that the lifetime prevalence of FXTAS is

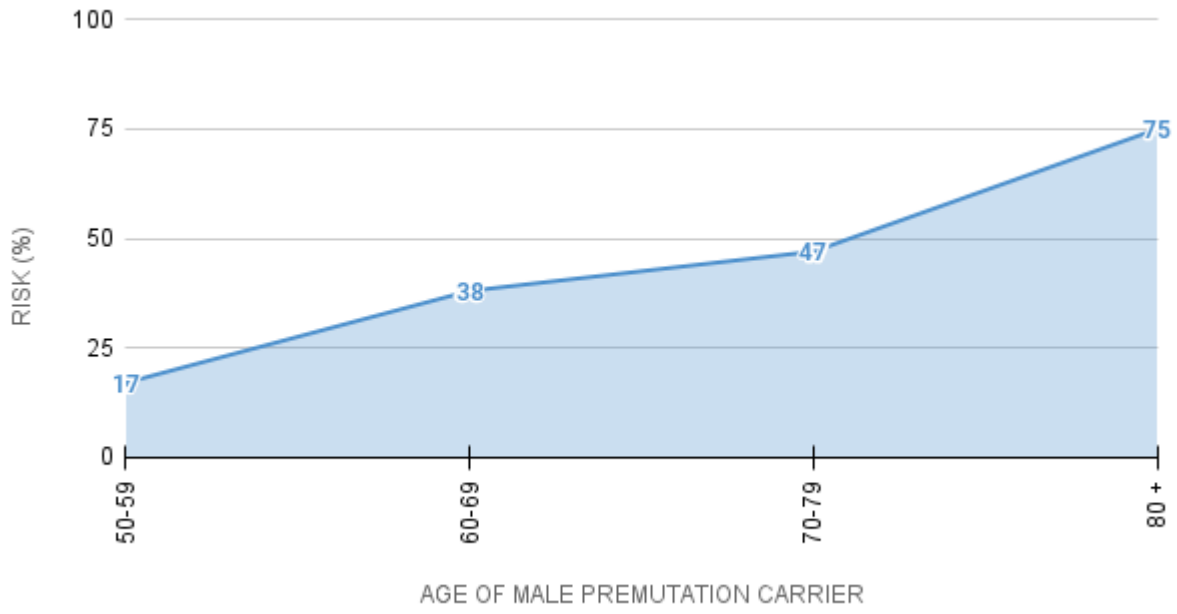
- ~ 1 in 8,000

This indicates that FXTAS is significantly less common than essential tremor or Parkinson's disease in older adults.

FXTAS Facts:

- The number of CGG repeats influences the risk of FXTAS in any given individual. The larger the number, the higher the risk.
- Males are at greater risk than females.
- Symptoms are more common in older age.
- In women, the activation ratio, or percentage of cells expressing the premutation allele, may also play a role.

Percent Chance of Male Premutation Carriers Developing Core Symptoms of FXTAS



For men who are premutation carriers, the chance of developing core symptoms of FXTAS (tremor, problems with walking or balance) increases with age

Within families already known to have someone with a Fragile X condition, studies have found that about 8%-16% of females with the premutation develop some FXTAS symptoms. The symptoms in females tend to be milder.

FXTAS may be one of the most common adult-onset single-gene neurological diseases, similar in prevalence to other neurodegenerative diseases such as ALS (Lou Gehrig's disease). However, more studies within the general population are necessary before the true incidence is known.

Learn more about FXTAS

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Prevalence of FXPOI

About 20% of women who carry a Fragile X premutation over their reproductive lifespan develop POI (primary ovarian insufficiency) compared with only 1% in the general population.

Not all women with a premutation experience FXPOI. One well-documented risk factor is the premutation repeat size. The usual premutation repeat size is 55-200, and although these group ranges are not exact, women with premutation alleles in the 80–100 CGG repeat range are at the highest risk for ovarian dysfunction. One study estimated the risk of FXPOI to be 38% in this high-risk group, although more studies are needed to understand why and to better define high-risk alleles.

Menstrual Cycle Irregularities:

- Evidence shows women with a premutation vs. people without a premutation reported their last menstrual cycle at an earlier age — age 48 vs. 51.
- About one-third of women with FXPOI, equivalent to 7% of women with the premutation, stop having periods at or before age 29.
- Approximately 3% of women with the premutation will have menstrual cycle irregularities in their teens or 20s due to FXPOI.
- 1% of women who carry the premutation will stop having periods before the age of 18.

Related Studies:

- Predictors and Risk Model Development for Menopausal Age in Fragile X Premutation Carriers (*Genetics in Medicine)*
- Refining the Risk for Fragile X–Associated Primary Ovarian Insufficiency (FXPOI) by FMR1 CGG Repeat Size (*Genetics in Medicine)*

- Identifying Susceptibility Genes for Primary Ovarian Insufficiency on the High-Risk Genetic Background of a Fragile X Premutation (*Fertility and Sterility*)

Learn more about FXPOI

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Prevalence of Intermediate or Gray Zone Alleles

Approximately 1 in 20 — or 5% — of individuals have an intermediate allele.

There appear to be no clinical associations with intermediate alleles. Most intermediate alleles are stable and do not change over generations.

Individuals with an intermediate allele are not at risk for any Fragile X-associated disorders or for having children with Fragile X syndrome. However, in a small number of families, intermediate alleles show some slight instability and can lead to a premutation in future generations.

Learn more about intermediate or “gray zone” alleles

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Fragile X Prevalence Studies

Readers interested in reviewing the scientifically based prevalence studies may wish to access the following:

Data and Statistics on Fragile X Syndrome (*CDC*)

Fragile X Gray Zone Alleles Are Associated With Signs of Parkinsonism and Earlier Death (*Movement Disorders*)

Epidemiology of Fragile X Syndrome (*Chapter 4, Fragile X Syndrome: From Genetics to Targeted Treatment*)

The Future of Fragile X Syndrome: CDC Stakeholder Meeting Summary (*Pediatrics*)

Fragile X Syndrome: Prevalence, Treatment, and Prevention in China (*Frontiers in*

Neurology)

Incidence of Fragile X Syndrome By Newborn Screening for Methylated FMR1 DNA (*The American Journal of Human Genetics*)

Prevalence of the Fragile X Syndrome in African-Americans (*American Journal of Medical Genetics*)

FMR1 and the Fragile X Syndrome: Human Genome Epidemiology Review (*Genetics in Medicine*)

Screening for Fragile X Syndrome in Women of Reproductive Age (*Prenatal Diagnosis*)

Population Studies of the Fragile X: A Molecular Approach (*American Journal of Medical Genetics*)