

The Fragile X Premutation

What is the Fragile X Premutation?

Typically, a “carrier” of a genetic mutation is defined as a person who inherits an altered form of a gene but shows no effects of that mutation. A carrier has an altered form of a gene that can lead to having a child or grandchild with a genetic disorder. We are all carriers of gene mutations, many of which are “silent” (which means we can pass the gene on but suffer no ill effects from it ourselves). However, **this is not the case with** Fragile X. Carriers of the Fragile X premutation are also at risk to develop Fragile X-associated conditions including Fragile X-associated tremor/ataxia syndrome (FXTAS) and Fragile X-associated primary ovarian insufficiency (FXPOI).

The gene for Fragile X (the *FMR1* gene) is on the X chromosome, which is why Fragile X syndrome is called an X-linked condition. Often in X-linked conditions, only females are carriers and only their male children are affected. However, in Fragile X, both males and females can be carriers (have the Fragile X premutation), and both can be affected (have the full mutation of the *FMR1* gene, Fragile X syndrome) the Fragile X premutation.

This occurs because the changes in the *FMR1* gene go through stages as it is passed down in a family. These stages start with the typical gene and then proceed to the premutation and then the full mutation. The differences in the stages are determined by the number of “CGG repeats” (repeats of a DNA pattern). In most other X-linked conditions, there is no middle “premutation” state, so males with the mutation are either affected or non-carriers.

Check out this 90-second video asking, What is the Fragile X premutation?

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Understanding the Fragile X Premutation Range of Symptoms

Having a Fragile X premutation does not mean an individual will develop any associated conditions, but it may increase the risk of certain associated conditions. Many individuals lead healthy lives with no symptoms.

The best way to obtain care for any symptom experienced by someone with the Fragile X premutation is to share and focus on the symptoms. While disclosing your Fragile X status may be helpful, obtaining treatment for symptoms you are experiencing may or may not be impacted due to your Fragile X carrier status.

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CGG Repeat Ranges

An individual with the Fragile X premutation is a male or female with 55 to 200 CGG repeats in the *FMR1* gene. The full mutation (Fragile X syndrome) is defined as over 200 CGG repeats. (A typical *FMR1* gene has 6-54 CGG repeats, individuals with CGG repeats in this range do not have Fragile X.)

Intermediate or “Gray Area” Alleles

An allele is a term for a gene variant. Some individuals have what is called an

“intermediate” or “gray area” sized allele, with 45-54 CGG repeats. They are not considered to have Fragile X and do not appear to be associated with any clinical or medical issues, developmental disabilities, or social/emotional difficulties. These alleles are considered to be “intermediate” because there is a small chance that they are mildly unstable and may expand to a premutation in future generations. Individuals with an intermediate-sized allele are not at risk for having a child with a full mutation. Generally, we don’t use the term “carrier” for those with an intermediate allele.

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Issues for Females

Females with the Fragile X premutation are at risk to have a child, male or female, with Fragile X syndrome. The levelof risk is related to the number of CGG repeats identified in her *FMR1* gene. The larger the number, the higher the risk for expansion from a premutation to a full mutation if it is passed on.

Physical Effects

About 20% of women with the Fragile X premutation develop primary ovarian insufficiency (FXPOI) over their reproductive life span. One well-documented risk factor for FXPOI is the premutation repeat size: the highest risk for ovarian dysfunction is for women carrying premutation alleles in the 80–100 CGG repeat range. Primary ovarian insufficiency can be experienced in females without the Fragile X premutation; this occurs in approximately 1%-2% of females under 40.[1]

On average, women with the Fragile X premutation experience natural menopause at an earlier age compared to those without the Fragile X premutation. On average, females with the Fragile X premutation may experience menopause about 5 years earlier than those in the general population, who experience menopause between 45 and 55 years old.[2, 3]

A very small percentage (about 3%) of women with the Fragile X premutation will have menstrual cycle irregularities in their teens or 20s due to Fragile X-associated primary ovarian insufficiency (FXPOI). An even smaller number (1%) of women with the Fragile X premutation will stop having periods prior to age 18, and about one-third (7% of women with the Fragile X premutation — stop having periods at or

before age 29.[2, 3]

Social-Emotional Effects

Though many women with a premutation show no significant mental health issues, some have reported increased general anxiety, shyness, and social anxiety. There is also evidence that women with the Fragile X premutation are at increased risk for depression. Any individual with the Fragile X premutation who is concerned about depression should seek the services of a mental health professional.

Given the stresses and emotional aspects of parenting a child with disabilities, along with stresses that can accompany the various reproductive issues associated with having the Fragile X premutation, researchers have found it difficult to establish emotional effects that are a direct biological result of the Fragile X premutation. Research regarding these possible associations and incidences is ongoing.

Women's Health & the Fragile X Premutation

We have an ebook available from the Emory University School of Medicine. It includes information on inheritance, FXPOI, FXTAS, family planning, resources, a health worksheet, and more.

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Issues for Males

A male with the Fragile X premutation will pass his premutation (as a premutation, not a full mutation) on to all of his daughters and none of his sons. A male with the Fragile X premutation is not at risk of having a daughter with Fragile X syndrome.

The most significant issue for males with the Fragile X premutation is the risk for FXTAS.

Other than the FXTAS risk in older males, many males with the Fragile X premutation are clinically unaffected. There have been reports of a small subset of boys with a premutation who have an additional diagnosis of autism, ADHD, or

other learning or behavioral disorders. In a small subset of boys, these developmental disorders may be caused by an interaction of various genetic and non-genetic factors, one of which may be the *FMR1* premutation. Research regarding this possible association is ongoing.

TIP: Speak with your healthcare provider about any concerns with anesthesia. You could also consider sharing this article: General Anesthetic Use in Fragile X Spectrum Disorders from the NIH.

Men's Health & the Fragile X Premutation

We have an ebook available from the Emory University School of Medicine. It includes information on what the premutation is, how it works, the symptoms you can expect, who should be tested (and how), and more.

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Prevalence

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.[4, 5, 6, 7, 8, 9]

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Join the Int'l Fragile X Premutation Registry

If you have the premutation or are related to someone who is, you can contribute to future discoveries that will help our and the world's understanding of how the Fragile X premutation affects health by joining the International Fragile X Premutation Registry.

It's easy to join!

If you are considering enrolling, here's a summary of what you need to know:

1. **Who can join:** Fragile X premutation carriers and non-carriers related to someone affected by Fragile X are invited to enroll. Learn more about who can join.
2. **Enrolling:** No data is given to researchers or pharmaceutical companies. Data entered by registrants is only used to understand opportunities that are relevant to the registrant. Learn more about enrolling.
3. **Participation:** You will not be directly contacted by researchers. Instead, you will be sent the approved materials from the governance committee about the potential project, and it is your choice whether or not to contact the researcher. Learn more about your participation.
4. **Your rights**: You can request your data be removed from the Premutation Registry at any time. You can email Glenda M. Espinal at gmespinal@ucdavis.edu for details or learn more about your rights.
5. **Security:** Data is managed and stored within the REDCap system and housed in a cloud data center at Amazon Web Services. All web-based information transmission is encrypted. Learn more about security.
6. **Results**: You'll be sent updates on new discoveries as a result of the registry.

The International Fragile X Premutation Registry was created in partnership with an international advisory committee of dedicated Fragile X professionals from some of

the world’s most respected institutions and patient advocacy organizations.

If you have questions, we can help. Please contact Anna De Sonia at anna@fragilex.org, she’d love to hear from you!

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