NATIONAL **FRAGILE X** FOUNDATION

FRAGILE X PREMUTATION

(Also referred to as *FMR1* Premutation)

WHAT IS A FRAGILE X PREMUTATION?

An alteration or expansion of the *FMR1* gene. In the DNA of the *FMR1* gene, there is a repeated sequence of chemical bases known by the letters **CGG**.

When this sequence repeats occurs between the **55-200 range**, the individual would be diagnosed with the Fragile X/*FMR1* premutation.

Traditionally been called "**Fragile X carriers**" because there is a risk they could pass that premutation gene copy down to a child, who could then be affected with Fragile X.

In genetics, calling someone a "carrier" often means they do not have any of the health concerns associated with that condition. However, research has discovered that both men and women may be at risk for Fragile X-associated health conditions, including Fragile X-associated tremor/ataxia syndrome (**FXTAS**) and Fragile X-associated primary ovarian insufficiency (**FXPOI**).

Additional conditions like FXPAC/FXAND and other health risks possibly associated with the *FMR1* premutation are being further researched.

FRAGILE X-ASSOCIATED TREMOR/ATAXIA SYNDROME (FXTAS)

FXTAS is an adult-onset neurodegenerative disorder, more common in males than females with the *FMR1* premutation. FXTAS progresses at different rates in different people. FXTAS symptoms may include:

- **Intention Tremor** – a shaking or trembling of the hand when using objects such as utensils and writing instruments. The tremor is not as apparent at rest.
- **Gait ataxias** – balance problems which may include falling, needing support to use the stairs, trouble stepping on/off curbs, generalized instability, or a display of wide-based gait.
- **MRI findings** – such as specific white matter lesions or generalized brain atrophy, which are strongly associated with FXTAS but may be common in other neurological conditions.
- **Neuropathy** – pain, numbness, tingling, muscle weakness, particularly in the hands and feet. Parkinsonism – tremors, slowed movements, muscle rigidity, and difficulty with balance.
- **Executive function decline** – difficulty with organizing, planning, managing tasks, decision-making, and controlling impulses.

While all individuals with FXTAS have an *FMR1* premutation, not everyone with an *FMR1* premutation will develop FXTAS. There are a few risk factors for developing FXTAS:

- **CGG repeat size** – a larger number of repeats in the premutation range increases the risk of developing FXTAS.
- **Sex** – research shows men are at greater risk than females and may experience greater severity of symptoms. About 40% of males over 50 and 8-16% of women over 40 develop FXTAS.
- **Age** – symptoms are more common at older ages.

In addition to movement disorder neurologists, specialists in psychiatry, psychology, rehabilitation, urology, and cardiology may also be needed to receive optimal care. There are FXTAS-specific clinics and research centers available. While there is currently no cure, therapies, lifestyle, and medication management may help reduce symptoms and slow the progression of FXTAS.

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FRAGILE X-ASSOCIATED PRIMARY OVARIAN INSUFFICIENCY (FXPOI)

Ovarian insufficiency is a condition where the ovaries do not function at full capacity. Some women with the *FMR1* premutation are initially identified due to fertility challenges. Not every woman with an *FMR1* premutation will develop FXPOI. Symptoms may include:

- **Irregular menstrual cycles** - ~3% of women with an *FMR1* premutation experience irregular menstrual cycles. About 1% will stop menstruating before age 18, and 7% will stop before age 29.
- **Premature Ovarian Insufficiency (POI)** – four months of unpredictable or absent menstrual periods before age 40 with FSH levels in the menopausal range.
- **Infertility or sub-fertility** – difficulty getting pregnant.
- **Early Menopause** – absent periods around ages 40-45, compared to 45-55 in the general population. May experience hot flashes and vaginal dryness.

While women with FXPOI may have symptoms similar to menopause, it differs in that some women can still become pregnant because their ovaries may occasionally release viable eggs. Additionally, they can experience a return of menstrual periods.

- **Prevalence** - ~20% of women with an *FMR1* premutation develop primary ovarian insufficiency (POI), compared to 1% of the general population.
- **Risk** - women with the *FMR1* premutation in the 80-100 CGG repeat range have a 38% risk of developing FXPOI.

If you experience sub-fertility or infertility, you can discuss various reproductive options with a reproductive endocrinologist. Because women with FXPOI have an *FMR1* premutation which may expand, you should meet with a genetic counselor to discuss reproductive considerations.

Want to know more?

- fragilex.org
- contact@fragilex.org