

FRAGILE X INFO:

FRAGILE X-ASSOCIATED TREMOR/ATAXIA SYNDROME

Overview

Fragile X is a group of conditions associated with changes in the Fragile X gene – called FMR1 and located on the X chromosome. The FMR1 gene can undergo changes, when inherited, which affects a pattern of DNA called CGG repeats. Typically, the FMR1 gene has up to 54 CGG repeats, though the range between 45 – 54 repeats, is called the intermediate or gray zone. A premutation carrier has 55–200 CGG repeats, and someone with a full mutation has more than 200 CGG repeats.

When a premutation or full mutation is present, it can result in a Fragile X-associated Disorder (FXD). These include:

- Fragile X syndrome (FXS): A condition affecting intellectual, behavioral, and social development. It occurs in both males and females who have a *full mutation* of the FMR1 gene.
- Fragile X-associated tremor/ataxia syndrome (FXTAS): An adult onset (over 50 years of age) neurological condition, seen in males and females, but more common and more severe in some male *premutation carriers*. It can cause tremors, memory, and balance issues.
- Fragile X-associated primary ovarian insufficiency (FXPOI): A condition affecting ovarian function that can lead to infertility and early menopause in some female *premutation carriers*.
- Other issues may be present in *premutation carriers*, and this is an ongoing area of study for researchers.

General

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that was discovered in 2001 after clinicians noted a pattern of neurological symptoms present in older (primarily male) grandparents and parents of persons with fragile X syndrome (FXS).

- FXTAS is caused by a trinucleotide CGG repeat expansion in the premutation range (55-200) in the FMR1 gene.
- It is an inherited neurodegenerative disorder that typically affects adults over 50 years old and is associated with a spectrum of neurological and medical symptoms.
- FXTAS affects men with more frequently than women because of the protective effect of the second X chromosome in women.

FXTAS Statistics

- The number of individuals in the U.S. who have or *are at risk* for a premutation-associated condition ranges from 1 in 151 females, or about 1 million women, to 1 in 468 males, or about 350,000 men.
- Among premutation carriers, about 40% of males older than 50 years and 8%-16% of women older than 40 years develop FXTAS.
- The risk of FXTAS in any given individual is influenced by his/her CGG repeat size (a larger number of repeats increases the risk), sex (men are at greater risk), and age (symptoms are more common at older ages).
- In women, the activation ratio, or percentage of cells expressing the premutation allele, may also play a role.
- The lifetime prevalence of FXTAS in the general population is estimated to be 1 in 8000. This indicates that FXTAS is significantly less common than essential tremor or Parkinson's disease in older adults.

Onset of FXTAS

- Typically, in the early seventh decade, with mean age of onset of tremor and/or ataxia in men at approximately 61 years.
- Symptoms of FXTAS vary among individuals. Typically, they include progressive signs of tremor, cerebellar ataxia, parkinsonism, and cognitive decline, with impairments in executive functioning.
- Tremor appears to be the sign most likely to trigger evaluation from a health provider.

Progression

- Cognitive dysfunction such as executive impairment, memory deficits and eventually dementia may occur.
- These symptoms may influence intelligence, working memory, remote recall, information-processing speed, and temporal sequencing.
- Impaired executive function may lead to psychiatric and behavioral disorders as noted by increased anxiety, irritability, agitation, hostility, obsessive-compulsiveness, apathy, and depression.

Diagnosis of FXTAS

- FXTAS only occurs in individuals who have a Fragile X (FMR1) premutation. Therefore, it is essential that anyone being considered for this diagnosis is tested for and confirmed as a premutation carrier.
- Neurological exam.
- Magnetic resonance imaging (MRI) findings consistent with FXTAS, such as specific white matter lesions in the brain or generalized brain atrophy.

Interventions and Treatments

The goal of therapy for FXTAS is to reduce symptoms and eventually to slow the progression of disease. Management of FXTAS is complex and involves appropriate follow-up by an adult neurologist.

- Treatments for FXTAS should be individualized as symptoms vary in every individual.
- Treatments should also be approached globally utilizing medications, psychological counseling, rehabilitative interventions such as speech, occupational and physical therapy, and gait training.
- Consideration should also be given to supportive services and counseling for the family.
- Genetic counseling for individuals with FXTAS and their family members is recommended.

Notes:

- All daughters of men diagnosed with FXTAS (those confirmed to be premutation carriers) will also be premutation carriers.
- For women with FXTAS (again, those confirmed to be premutation carriers), each child will have a 50% chance of receiving the FMR1 mutation, with the potential of their premutation expanding to a full mutation (>200 CGG repeats).
- About 20% of women with the FMR1 premutation develop fragile X-associated primary ovarian insufficiency (FXPOI). Women with FXPOI **do not** have an increased risk of FXTAS compared with women who carry premutations and have normal ovarian function.

Find a FXTAS Doctor

- Visit the NFXF Website: <https://fragilex.org/our-research/fragile-x-clinics/fxtas/>
- Call the National Fragile X Foundation 800-688-8765.

International Fragile X Premutation Registry. For individuals with the premutation and their families. The registry will help advance research into the premutation condition. Learn more at fragilex.org/ifxpr.

About the NFXF

The National Fragile X Foundation (NFXF) was founded in 1984 to support individuals with Fragile X syndrome (FXS), their families, and the professionals who work with them. Today, it is a comprehensive resource not only for FXS, but also for the conditions of Fragile X-associated tremor/ataxia syndrome (FXTAS), Fragile X-associated primary ovarian insufficiency (FXPOI), and other premutation carrier issues. The organization offers help for today and hope for tomorrow with personalized support, community, education, awareness, advocacy, and research. Get your free Fragile X 101 e-book, Welcome Packet, connect with your local chapter, learn about the upcoming conference, and more at <https://fragilex.org/welcome-packet>

If you have specific questions about what to expect, treatments, clinics, well, just about anything, please email treatment@fragilex.org or call (800) 688-8765.

Resource:

Consensus of the FXTAS Task Force and the Fragile X Clinical & Research Consortium - Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

https://fragilex.org/wp-content/uploads/2018/04/Fragile-X-associated-tremor-ataxia-syndrome_2018.pdf

