



NATIONAL **FRAGILE X** FOUNDATION
FRAGILE X CLINICAL & RESEARCH CONSORTIUM

Consensus of the FXTAS Task Force and the
Fragile X Clinical & Research Consortium

FRAGILE X-ASSOCIATED TREMOR/ATAXIA SYNDROME (FXTAS)

First Published: June 2011
Last Updated: March 2018
fragilex.org/consensus



Introduction

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).¹ FXTAS is caused by a trinucleotide CCG 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.

Approximately 1 in 150-300 women and 1 in 400-850 men in the general population are carriers of a FMR1 premutation sized repeat ^{2,3}. Among premutation carriers, about 40% of males older than 50 years and 8%-16% of women older than 40 years develop FXTAS^{4,5}. However, the risk of FXTAS in any given individual is influenced by his/her CCG 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)^{5,6}. In women, the activation ratio, or percentage of cells expressing the premutation allele, may also play a role⁷. Considering all of these factors and literature to date, we estimate that the lifetime prevalence of FXTAS in the general population is ~1 in 8000. This indicates that FXTAS is significantly less common than essential tremor or Parkinson's disease in older adults.

Diagnosis/Recognition

Onset of FXTAS is 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 specific impairments in executive functioning. Additionally, psychiatric disturbances, autonomic dysfunction, and peripheral neuropathies may be present ^{4,8}



The first neurological sign at onset is variable. Tremor appears to be the sign most likely to trigger evaluation from a health provider. Action tremor is most common, although many affected individuals may not be aware of its impact on their daily living activities. Mild, intermittent tremor may be present for years before the diagnosis. Rest tremor is less common, but can also be present, especially in patients who have more of a parkinsonism presentation. Almost all affected persons develop cerebellar gait ataxia as the disease progresses. Tandem gait is abnormal and unexplained falls occur in ~35-50% of premutation carrier men who are older than 50 years of age⁵⁹. Other impairments, including parkinsonism, sensory neuropathy, and weakness, contribute to the poor balance observed in FXTAS. However, cerebellar dysarthric “scanning” speech, oculomotor findings and appendicular ataxia are all less common in FXTAS than in other inherited cerebellar disorders. Although many affected patients have features of “classic” FXTAS, other neurological presentations, such as atypical parkinsonism, primary dementia, or neuromuscular abnormalities, can also occur as primary disease manifestations.

As the condition progresses, 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.

Individuals with FXTAS usually have abnormal MRI findings, such as white matter lesions, generalized brain atrophy, and/or increased T2 signal in the middle cerebellar peduncles (MCP sign), pons, periventricular region and/or the splenium of the corpus callosum (CCS sign).

Of note, 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.



In addition, classic FXTAS phenomenology and imaging abnormalities have been reported in fMRI gray zone carriers (41-54 CCG repeats)^{10,11} and in those with a full mutation that is unmethylated or mosaic with a premutation¹²⁻¹⁴. However, FXTAS cases with repeat sizes outside of the premutation range are rare.

Table 1 outlines the clinical diagnostic criteria on which FXTAS is based. Three levels are used to indicate the confidence of a diagnosis given symptom manifestations at the time of evaluation.

Table 1. FXTAS Diagnostic Criteria in Carriers of a fMRI Premutation	
Level of confidence	
Definite	Presence of 1 major radiological sign plus 1 major clinical symptom
Probable	Presence of either 1 major radiological sign plus 1 minor clinical symptom or has the 2 major clinical symptoms.
Possible	Presence of 1 minor radiological sign plus 1 major clinical symptom
Symptom classes	
Radiologic	
Major	MRI white matter lesions in MCPs or CCS and/or brain stem
Minor	MRI white matter lesions in cerebral white matter
Minor	Moderate to severe generalized atrophy
Minor	MRI white matter lesions in the splenium of the corpus callosum
Clinical	
Major	Intentional tremor
Major	Gait ataxia
Minor	Parkinsonism
Minor	Moderate to severe short-term memory deficiency
Minor	Executive function deficit
Minor	Neuropathy in lower extremities
Neuropathology	
Major	FXTAS intranuclear eosinophilic inclusions that are ubiquitin positive

Adapted from Berry-Kravis et al, 2007¹⁵



Testing for FXTAS

A Diagnosis of FXTAS is confirmed by testing for a premutation-sized CGG repeat expansion in FMR1 DNA in patients with a suggestive constellation of symptoms. Findings from a brain imaging study (primarily magnetic resonance imaging (MRI) can aid in the diagnosis. Table 2 outlines who should be tested for an FMR1 premutation given their presentation of neurological symptoms.

Cerebellar ataxia	If is 50 years or older and the cause is unknown
Action tremor	If is 50 years or older and the cause is unknown; AND if also has cerebellar ataxia, parkinsonism, or dementia
Dementia	If is 50 years or older and the cause is unknown; AND if also has cerebellar ataxia, parkinsonism, or action tremor
Multiple system atrophy cerebellar subtype	Especially if a prolonged course
Some FXTAS signs + family history of fragile X-associated disorders or related symptoms	Patient who has symptoms of FXTAS (e.g., action tremor, cerebellar ataxia) AND has a family history of ovarian insufficiency (including infertility) OR congenital intellectual disability or Autism Spectrum Disorder; family history of individuals diagnosed with fragile X syndrome, FXPOI, or FXTAS; family members who have been diagnosed with an FMR1 mutation.

Adapted from Berry-Kravis et al, 2007¹⁵

Current Treatment Guidelines

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. It is also important to evaluate other potential causes of dementia such as vitamin B12 deficiency, folate deficiency and depression. Treatable causes of cerebellar ataxia should be considered in cases with significant gait symptoms.



This typically includes testing liver and renal function, Vitamin E, Copper, thyroid function, autoimmune (SSA/SSB, ANA, Gad-65, Celiac) and paraneoplastic disorders¹⁶. Reversible causes of neuropathy should also be considered, including diabetes, monoclonal proteins, and vitamin B12 deficiency. Additionally, individualized care regarding possible adverse events from medications is essential. Referral to physical therapy and/or rehabilitative medicine, urology, genetic counseling and social work should be considered.

Currently, intervention is limited to symptomatic therapy as there have been no effective medications based on controlled clinical trials. Treatment recommendations are based on anecdotal reports and knowledge of other disorders that are similar to FXTAS^{4,9}. For example, action tremor and parkinsonism in FXTAS may respond to medications used for essential tremor and Parkinson disease, respectively. Action tremor may respond to B-blockers, primidone and topiramate. Deep brain stimulator surgery can be considered for tremor. Unilateral surgery with non-traditional targets may be less likely to worsen ataxia or cognition after surgery. Medications for cerebellar dysfunction can be considered, such as amantadine, buspirone, varenicline, riluzole, or ampyra, although none have proven efficacy in FXTAS or other inherited ataxias. Treatment of psychiatric symptoms with selective serotonin inhibitors may be effective, although patients need to be monitored for worsening of balance.

It is important to note that 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. Specialty fields helpful in the care of individuals with FXTAS include neurology, psychiatry, psychology, rehabilitation, urology, cardiology and movement disorders neurology.

Genetic counseling for individuals with FXTAS and their family members is recommended, due to the inheritance of the X-linked FMR1 expansion mutation. .



All daughters of men diagnosed with FXTAS (i.e., confirmed to have a premutation sized CGG repeat) are obligate FMR1 premutation carriers. For women with FXTAS (again, with confirmed premutation sized CGG repeat expansions), each child will have a 50% chance of receiving the FMR1 mutation, with the potential of their premutation expanding to a full mutation (<200 repeats). The full mutation leads to fragile X syndrome, the most common inherited form of intellectual and developmental disabilities and the most common known single gene cause of Autism Spectrum Disorder (ASD). The expansion to the full mutation depends on the size and number of AGG interruptions in the premutation allele carried by the mother¹⁷.

How can I find a physician who is knowledgeable about FXTAS?

Fragile X Clinical and Research Consortium clinics can provide information or referral to a Neurologist or other physician with experience in caring for patients with FXTAS. (<https://fragilex.org/research/>). The National Fragile X Foundation can also provide information (**800-688-8765** or **fragilex.org**).

Additional Resources

<https://fragilex.org/learn/fxtas/>

Author note: This guideline document was written and reviewed by members of the Fragile X Clinical & Research Consortium (FXCRC) and by members of the International FXTAS consortium. It has been approved by and represents the current consensus of this group of clinical and research experts.



The **Fragile X Clinical & Research Consortium** was founded in 2006 and exists to improve the delivery of clinical services to families impacted by fragile X syndrome and to develop a research infrastructure for advancing the development and implementation of new and improved treatments. Members of the International FXTAS consortium (IFA) also contributed to this report. Please contact the **National Fragile X Foundation** for more information. (**800-688-8765** or **fragilex.org**)



References:

1. Hagerman, R. J. et al. Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X. *Neurology* 57, 127-130 (2001).
2. Hunter, J. et al. Epidemiology of fragile X syndrome: a systematic review and meta-analysis. *American journal of medical genetics. Part A* 164A, 1648-1658, doi:10.1002/ajmg.a.36511 (2014).
3. Tassone, F. et al. FMR1 CGG allele size and prevalence ascertained through newborn screening in the United States. *Genome medicine* 4, 100, doi:10.1186/gm401 (2012).
4. Hagerman, R. J. & Hagerman, P. Fragile X-associated tremor/ataxia syndrome - features, mechanisms and management. *Nature reviews. Neurology* 12, 403-412, doi:10.1038/nrneurol.2016.82 (2016).
5. Jacquemont, S. et al. Penetrance of the fragile X-associated tremor/ataxia syndrome in a premutation carrier population. *Jama* 291, 460-469, doi:10.1001/jama.291.4.460 (2004).
6. Jacquemont, S., Leehey, M. A., Hagerman, R. J., Beckett, L. A. & Hagerman, P. J. Size bias of fragile X premutation alleles in late-onset movement disorders. *Journal of medical genetics* 43, 804-809, doi:10.1136/jmg.2006.042374 (2006).
7. Plenge, R. M., Stevenson, R. A., Lubs, H. A., Schwartz, C. E. & Willard, H. F. Skewed X-chromosome inactivation is a common feature of X-linked mental retardation disorders. *American journal of human genetics* 71, 168-173, doi:10.1086/341123 (2002).
8. Hall, D. A. et al. Update on the Clinical, Radiographic, and Neurobehavioral Manifestations in FXTAS and FMR1 Premutation Carriers. *Cerebellum* 15, 578-586, doi:10.1007/s12311-016-0799-4 (2016).
9. Leehey, M. A. Fragile X-associated tremor/ataxia syndrome: clinical phenotype, diagnosis, and treatment. *Journal of investigative medicine : the official publication of the American Federation for Clinical Research* 57, 830-836, doi:10.2310/JIM.0b013e3181af59c4 (2009).
10. Hall, D., Tassone, F., Klepitskaya, O. & Leehey, M. Fragile X-associated tremor ataxia syndrome in FMR1 gray zone allele carriers. *Movement disorders : official journal of the Movement Disorder Society* 27, 296-300, doi:10.1002/mds.24021 (2012).
11. Liu, Y., Winarni, T. I., Zhang, L., Tassone, F. & Hagerman, R. J. Fragile X-associated tremor/ataxia syndrome (FXTAS) in grey zone carriers. *Clinical genetics* 84, 74-77, doi:10.1111/cge.12026 (2013).
12. Pretto, D. I. et al. Intranuclear inclusions in a fragile X mosaic male. *Translational neurodegeneration* 2, 10, doi:10.1186/2047-9158-2-10 (2013).
13. Loesch, D. Z. et al. Fragile X-associated tremor/ataxia phenotype in a male carrier of unmethylated full mutation in the FMR1 gene. *Clinical genetics* 82, 88-92, doi:10.1111/j.1399-0004.2011.01675.x (2012).
14. Santa Maria, L. et al. FXTAS in an unmethylated mosaic male with fragile X syndrome from Chile. *Clinical genetics* 86, 378-382, doi:10.1111/cge.12278 (2014).
15. Berry-Kravis, E. et al. Fragile X-associated tremor/ataxia syndrome: clinical features, genetics, and testing guidelines. *Movement disorders : official journal of the Movement Disorder Society* 22, 2018-2030, quiz 2140, doi:10.1002/mds.21493 (2007).
16. Shakkottai, V. G. & Fogel, B. L. Clinical neurogenetics: autosomal dominant spinocerebellar ataxia. *Neurologic clinics* 31, 987-1007, doi:10.1016/j.ncl.2013.04.006 (2013).
17. Nolin, S. L. et al. Fragile X full mutation expansions are inhibited by one or more AGG interruptions in premutation carriers. *Genetics in medicine : official journal of the American College of Medical Genetics* 17, 358-364, doi:10.1038/gim.2014.106 (2015).



FXTAS Glossary

- **Tremor** – A quivering or shaking movement that happens when you are not trying to do it (involuntary). Action tremor occurs when you're actively trying to do something. Rest tremor occurs when the muscles are at rest, and you are not trying to move.
- **Ataxia** – Loss of control or incoordination of body movements
 - **Cerebellar ataxia** – A loss of body control caused by differences in the cerebellum, the part of the brain that coordinates movement. The first signs that someone has cerebellar ataxia might be bad balance and walking, and uncoordinated eye movements. It can cause poor articulation when speaking or slurred speech, which is called dysarthria.
- **Parkinsonism** – A combination of symptoms including tremor, slow movements, rigidity or muscles being tensed, and unsteadiness
- **Autonomic dysfunction** – Changes to the autonomic nervous system. The autonomic nervous system controls things like heart rate, body temperature, breathing rate, and sensation or feeling. Dysfunction or changes in the autonomic nervous system can lead to very high or low heart rates, sweating too much or too little, weakness, and other symptoms.
- **Peripheral neuropathy** – Caused by damage to the peripheral nerves, which are the nerves that send information from your brain and spinal cord to the rest of your body. This often feels like stabbing, burning, or tingling, especially in the hands and feet.
 - **Sensory neuropathy** – Caused by damage to the sensory nerves (these are the nerves that sense pain or temperature). It may feel similar to peripheral neuropathy, and people may also have reduced ability to sense pain or very hot or cold temperatures.
- **Tandem gait** – Often done as part of a neurologic examination, or during an exam with a Neurologist. Walking so that with each step, the toes of the back foot touch the heels of the front foot.
- **Cerebellar dysarthric “scanning” speech** – Words are broken into separate syllables, often with a pause between the syllables, and with each syllable spoken at different volumes.
- **Oculomotor** – Having to do with eye movement
- **Executive functioning** – Executive functioning is an umbrella term for the skills requiring mental control and self-regulation. Executive functioning skills include inhibition (the ability to stop your behavior at the appropriate time), the ability to shift easily from one situation to another, the ability to regulate your emotional responses, and others. Impairment in executive function occurs when a person has difficulties with one or more of the executive function skills.
- **Temporal sequencing** – A sequence of events happening in a period of time. Remembering the order of events is important to our everyday lives

