



By Maureen A. Leehy, MD

## Understanding FXTAS: Causes, Symptoms, Diagnosis, Research

*Grandpa, now 76 years old, first fell at age 65. One knee had suddenly given out as he was walking down the street with Grammy. He had two more falls that year, and gradually his steps became uneven and lurching. After he fractured a rib at age 70 from a bad fall, he started using a cane, and by age 73 he was in a wheelchair most of the time. Starting about age 60, he had also developed shaky (tremor) hands, which progressed slowly, but gradually came to interfere with his eating. His handwriting had become large and sloppy. For a long time he could not see that anything was wrong. This frustrated Grammy, because his personality was also changing—he was easily agitated and irritable. And his memory was worsening.*

*In recent years he had lost control of his bladder function. Grammy took him to doctors, who at first said he had a common type of tremor called “essential tremor,” and that his balance problems were from strokes, which showed up on the brain MRI scan that was done. Recently, a neurologist said that his symptoms were from an inherited problem similar to the one that had caused fragile X syndrome in his grandson.*

**W**hile the story above is fictional, it accurately describes the medical problems faced by persons who develop fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS occurs in persons who carry the *premutation* form of the fragile X gene. (See page 16 for more on the fragile X gene.) Premutation carriers are not at risk for fragile X syndrome, but about 20 percent of females develop menopause before age 40 and about 40 percent of men over age 50 develop FXTAS. The occurrence of FXTAS in male premutation carriers increases with age, with about 75 percent over age 80 being affected. Women carriers develop FXTAS much less frequently than men, though its frequency among women is not yet known.

The cause of FXTAS is being actively studied by our group and others. Many researchers are interested in FXTAS. This is because it is probably caused by a type of molecular problem, called *RNA toxicity*, that has only recently been described and that likely underlies other neurological disorders of aging persons.

While FXTAS is not a common disorder, it is an important cause of balance difficulties, called *ataxia*, in aging men. FXTAS is estimated to affect about 2-5 persons per 100,000 in the general population. This is much less common than Parkinson’s disease but is similar to that of other neurological disorders such as Lou Gehrig’s disease (amyotrophic lateral sclerosis, or ALS).

### SIGNS AND SYMPTOMS

FXTAS has multiple symptoms. Some patients develop all of them, others only a few. The average age of onset is 60. A common early symptom is tremor in the arms during action; this progresses and may eventually hinder eating and handwriting. Another frequent symptom is balance difficulty and poor coordination (ataxia). The usual walk may look drunken, with staggering or leaning to one side. Some men have falls for unclear reasons or easily trip over objects they would formerly have stepped over with ease. The ability to stand on one foot or to stand with one foot straight in front of the other, touching toe to heel, is gradually lost. Some affected men look like they are developing Parkinson’s disease, with generalized slowness, stiffness and decreased facial expression.

Cognitive and psychological changes are less obvious than the motor symptoms (tremor, ataxia, parkinsonism), though for many people, they may be more problematic. The degree and type of these problems may vary considerably among affected persons. Difficulty with short-term memory is common and occurs early in the syndrome. Other symptoms include slowed thought, reduced ability to actively problem-solve or to deal with complex and new tasks. The general intellectual decline over time often results in dementia (severe thinking problems) in the late stages. These changes often affect personality. Psychological changes include

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depression and anxiety, but impatience, hostility, and moodiness may be common. It is not unusual for men with FXTAS to become impulsive, doing things that are inappropriate or irrelevant to the situation at hand. It also may become difficult for them to take initiative on and complete everyday tasks. Affected men are usually unaware they are developing these signs, and may even deny them when confronted by relatives and other people.

Nerves in the legs are often affected, such that men often have loss of sensation and reflexes in the feet when examined by their physicians. This condition is called *neuropathy*. The autonomic nervous system, which controls automatic functions, may also be affected, causing loss of bladder and bowel control and lightheadedness from a drop in blood pressure upon standing. Early on, frequent trips to the bathroom are needed; at late stage, complete loss of bladder and bowel control may occur.

#### **RISK IN MEN AND WOMEN**

Detailed studies of the motor symptoms in men and women premutation carriers show that the classic disorder described here chiefly affects men. The studies have also shown that the occurrence of FXTAS and the severity of its symptoms in men correlate with increasing CGG repeat size between 70 and 200. (See next page for discussion of CGG repeats.) FXTAS is rare in men with CGG repeat sizes under 70.

In women, increasing CGG size plus decreasing activation ratio correlate with increased ataxia. (See next page.) The lower the activation ratio, the more cells there are with an active premutation rather than normal gene. Some women carriers have been diagnosed with FXTAS, but this is uncommon. Women carriers may be prone to developing neurological problems that are different from FXTAS. Some studies suggest that women carriers are prone to symptoms that lead to diagnoses of multiple sclerosis, fibromyalgia, and, perhaps, a variety of immunological disorders. Further study of the neurological symptoms in women premutation carriers is needed (and is, fortunately, ongoing).

#### **FXTAS NATURAL HISTORY**

Research on the motor signs of FXTAS has shown that tremor usually occurs first, with 50 percent of men having onset at about age 60. After onset of a motor sign, 50 percent of men develop ataxia within two years, falls within six years, become dependent on a walking aid within 15 years, and die within 21

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years. Information on life expectancy is sketchy and variable; affected men have lived from five to 25 years after onset of a motor sign. In the last months of their lives, some men have difficulty with speaking, swallowing and other basic functions. Note that in these studies the onset of disease was defined as the onset of a motor sign (tremor or ataxia), but onset of thinking and

psychological problems may occur months or years earlier.

#### **DIAGNOSIS**

Since the first description of FXTAS by our group was published only recently (2001), most persons with the condition had been given other diagnoses. Many were told they had essential tremor, Parkinson's disease, or some form of ataxia. Others were told their symptoms were from strokes, a car accident, arthritic spine changes, or a variety of other conditions. Even now, many primary care physicians are unaware of the disorder, and most doctors, including neurologists, have not seen a person with FXTAS. Persons with FXTAS are usually cared for by neurologists, sometimes primary care physicians, and rarely by neurologists who specialize in movement disorders.

A FXTAS diagnosis is usually made because a family member (usually a grandson) has FXS, and another family member learns about FXTAS through lay literature (such as this article). The person then approaches the affected man's physician. A conclusive diagnosis requires (1) the presence of the signs described above in a person (usually male) over age 50, and (2) that the fragile X gene test reveals the premutation. The diagnosis is supported by the finding of an "MCP sign" on the brain MRI. An MCP sign is a brightness on the MRI image in specific brain regions called the middle cerebellar peduncles (MCPs). While an MCP sign is not always present in affected persons, it is very rarely seen in any disorders other than FXTAS. Brain imaging usually also shows the overall brain size is smaller than expected, or *atrophied*.

The diagnosis of FXTAS is confirmed by autopsy, which shows

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## The ABCs—and Xs—of FXTAS Genetics

By Liane Abrams, M.S., C.G.C.

Fragile X-associated tremor/ataxia syndrome (FXTAS) was first described in grandfathers of children with fragile X syndrome (FXS) in 2001 by Dr. Randi Hagerman and her group at the UC Davis M.I.N.D. Institute. These grandfathers, all over 50 years of age and carriers of the FMRI premutation, were generally healthy until the onset of FXTAS symptoms. We now know that FXTAS can also occur in females (also over 50 years of age), though the incidence is much lower and is usually accompanied by milder symptoms. Initially, most cases of FXTAS were identified in families with FXS, but now cases are often diagnosed in adult neurology clinics. That means some newly diagnosed families have never heard of Fragile X.

The symptoms and course of FXTAS are described in the adjoining article by Dr. Maureen Leehy. Here we review the genetics of FXS and FXTAS, and who is at risk for the latter.

### FXTAS GENETICS

FXTAS is due to a change in the Fragile X gene (called the FMRI gene) on the X chromosome. Genes are the units of heredity that are responsible for making or regulating proteins in our bodies. They are found on chromosomes, of which most individuals have 46. Two of these chromosomes are sex chromosomes—two Xs in females and an X and Y in males. The gene is like a factory with different parts—the part involved in Fragile X is called the promoter. The promoter of the FMRI gene contains a specific pattern of DNA (the molecule that makes up your genes) called a CGG repeat. A normal FMRI gene contains about 5-45 CGG repeats. Individuals who have a Fragile X premutation (often called carriers) have about 55-200 CGG repeats, and those with a full mutation have over 200 CGG repeats, causing fragile X syndrome.

Individuals with 45-54 repeats are said to have a gene in the “intermediate” or “grey zone” range. These genes are stable in most families, though some families show instability (changes of one or more CGG repeats). There are no reports of grey zone genes leading to the birth of a child with FXS or to any of the symptoms associated with being a carrier such as FXTAS or ovarian dysfunction.

At this time it is estimated that symptoms of FXTAS occur in about 30-40 percent of males with a premutation and less than 5 percent of females with a premutation. Early studies suggest that the risk for FXTAS increases in men as they get older (this is called age-related penetrance). The risk in males from 50-59 years old with a premutation is approximately 17 percent; ages 60-70 approximately 38 percent; ages 70-80 years approximately 47 percent; and over 80, about 74 percent.

### FEMALES AND THE FMRI GENE

In females with the premutation, the lower incidence and milder symptoms of FXTAS occur for a number of reasons. Since females have two X chromosomes, their other, presumably normal X chromosome provides some protection from the effects of the X with the premutation. Also, in each cell of the female body, one of the Xs is randomly activated (turned on) while the other is turned off. The activation ratio is the ratio of cells with the premutation X turned on to those with the normal X turned on. If you have a low activation ratio that means you have more of the premutation Xs turned on (and thus fewer of the normal Xs activated). This may account for those women who do get FXTAS, as they have less protection from their normal X chromosome.

Because the FMRI gene is on the X chromosome, it is inherited in a specific genetic pattern, called X-linked inheritance. The premutation can occur in both males and females, as they both have at least one X chromosome. (As mentioned above, females usually have two X chromosomes.) The premutation can potentially expand to a full mutation when passed from a mother to her offspring—both boys and girls. In boys the full mutation will cause fragile X syndrome. Because of their second, presumably normal X chromosome, girls with a full mutation can have anywhere from subtle or mild to significant features of FXS.

All women with a premutation (as well as those with a full mutation) are at some risk to have a child with FXS. A woman has a 50/50 chance of passing on her X with the premutation (which can expand to a full mutation) and a 50/50 chance of passing on her X with the normal FMRI gene. The risk for a premutation to expand to a full mutation is dependent on her number of CGG repeats—the higher the number, the greater the risk of expansion to a full mutation in her children. Females with a premutation also have increased incidence of early menopause, infertility and ovarian dysfunction, also known as premature ovarian failure (POF). Finally, as mentioned above, a small number of females with the premutation have developed FXTAS.

### MALES AND THE FMRI GENE

A man with a premutation will pass it on to all of his daughters and none of his sons (he passes his Y chromosome on to his sons). The premutation tends to stay stable in sperm, therefore daughters of men with a premutation usually have repeat sizes somewhat similar to their fathers. All daughters of male premutation carriers are premutation

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very specific abnormalities, including deposits, called *inclusions*, within specific cells of the brain and other body parts.

### TREATMENT OPTIONS

There is as yet no conclusive research regarding treatment that slows the progression or reduces the symptoms of FXTAS. Our group of researchers has applied for funding to study whether lithium, a medication usually used to treat manic-depressive disorder, and memantine (Namenda) slows FXTAS progression. The following is a brief discussion on our experience in treating FXTAS symptoms.

**Tremor**—Beta-blocker medications, such as propranolol (Inderal), and primidone (Mysoline) have reduced tremor in some FXTAS patients. Beta-blockers have to be used with caution, if at all, in persons with diabetes, asthma, and a slow heart rate. Other medications being considered as possible treatments include alprazolam, clonazepam and lorazepam, because they reduce anxiety as well as tremor. Topiramate is useful in essential tremor, but there are no data yet regarding its use in FXTAS, and it may worsen cognition.

It has been reported that two men with FXTAS underwent deep brain stimulation, a surgery in which electrodes are placed in the brain and connected via a wire under the skin to an electrical generator implanted under the skin of the chest. One had temporary improvement in tremor but worsening of ataxia; the other had marked reduction in tremor with persistence of ataxia.


**Ataxia**—Ataxia is usually non-responsive to medication. Amantadine briefly helped a few persons with FXTAS. Some

persons with FXTAS have been previously misdiagnosed with normopressure hydrocephalus, a disorder that improves with placement of a shunt in the brain. However, patients with FXTAS did poorly after shunting.

**Parkinsonism**—A few patients had mild, short-lived improvement with carbidopa/levodopa (Sinemet). In the rare instance when a person had both FXTAS and primary Parkinson's disease, the carbidopa/levodopa was helpful.

**Other FXTAS symptoms**—Donepezil (Aricept) appears to be transiently useful in treating the dementia associated with FXTAS in some patients. Anxiety and depression are effectively treated with selective serotonin reuptake inhibitors (SSRIs) such as sertraline (Zoloft), fluoxetine (Prozac) or citalopram (Celexa). Venlafaxine (Effexor) may be particularly useful for agitation and disinhibited behavior. Gabapentin (Neurontin) reduces leg pain in FXTAS.

### CONCLUSION


FXTAS is a recently described disorder that, at present, is under-recognized. Families need to understand how the premutation can affect aging family members, especially men. More research on the neurological and medical effects of the premutation on women is needed, as is further definition of the cause, course, and treatment of FXTAS. 

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carriers themselves, and are thus at risk for ovarian and reproductive difficulties and for having offspring with FXS. As mentioned above, a large number of men diagnosed with FXTAS are maternal grandfathers to children with FXS (though any man with an FMR1 premutation, regardless of whether he has had children, is at risk for FXTAS). Because males have only one X chromosome, those with a full mutation generally have FXS, as their FMR1 gene is usually either poorly- or non-functioning.

Though FXTAS and FXS are due to different CGG repeat ranges within the FMR1 gene, the test for FXTAS is the same as that used to diagnose FXS. The test, called the FMR1-DNA test, measures the number of CGG repeats, and should include both PCR and southern blot analysis.

Anyone with symptoms as described in the accompanying article may be a carrier of the FMR1 premutation. If appropriate, a physician can order the FMR1-DNA test. It should be noted, however, that neurologists may not be aware of this newly described disorder. If not, patients or family members can encourage them to visit the NFXF website for more information and a short video.

Finally, it is very important for any newly diagnosed individuals or families to meet with a genetic counselor to better understand the genetics of FMR1-associated disorders. 

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