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Report

Fragile-X–Associated Tremor/Ataxia Syndrome (FXTAS) in Females with the *FMR1* Premutation

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We describe five female carriers of the *FMR1* premutation who presented with symptoms of tremor and ataxia and who received a diagnosis of definite or probable fragile-X–associated tremor/ataxia syndrome (FXTAS). Unlike their male counterparts with FXTAS, none of the women had dementia. Females had not been reported in previous studies of FXTAS, suggesting that they may be relatively protected from this disorder. Brain tissue was available from one of the five subjects, a women who died at age 85 years; microscopic examination revealed intranuclear neuronal and astrocytic inclusions, in accord with the findings previously reported in males with FXTAS. The work-up of families with the *FMR1* mutation should include questions regarding neurological symptoms in both older male and female carriers, with the expectation that females may also manifest the symptoms of FXTAS, although more subtly and less often than their male counterparts.

Individuals who carry premutation alleles (55–200 CGG repeats) of the fragile-X–mental retardation 1 (*FMR1* [MIM 309550]) gene are usually unaffected by the cognitive impairment associated with fragile-X syndrome (Reiss et al. 1993). However, ~20%–25% of carriers have prominent ears, mild psychiatric symptoms such as anxiety or social phobia, and/or premature ovarian failure (Sobesky 1996; Franke et al. 1998; Riddle et al. 1998; Allingham-Hawkins et al. 1999; Murray et al. 2000). Moreover, a subgroup of older adult male carriers develops a progressive neurological syndrome, fragile-X–associated tremor/ataxia syndrome (FXTAS). Onset is typically at age 50–70 years and includes progressive intention tremor and/or gait ataxia and mild parkinsonism (Hagerman et al. 2001; Berry-Kravis et al. 2003; Jacquemont et al. 2003, 2004*a*, 2004*b*; Leehey et al. 2003). More variable features include memory and executive-function deficits, with a gradual cognitive decline to dementia in some individuals; loss of vibration and tactile sensation and reflexes in the distal lower extremities; and psychiatric symptoms, including anxiety, mood lability, and depression (Hagerman et al. 2001; Jacquemont et al. 2003, 2004*a*). Associated radiological findings include global brain atrophy and white-matter disease, with a characteristic enhancement of T2 signal intensity in the middle cerebellar peduncles (MCPs) (Brunberg et al. 2002). Neuropathological examination of four males who died with FXTAS identified eosinophilic, intranuclear inclusions in 5%–40% of neurons and 30%–50% of astroglia throughout the cortex and cerebellum, with the exception of Purkinje cells, where no inclusions were observed (Greco et al. 2002). These intranuclear inclusions are ubiquitin positive but tau, synuclein, and polyglutamine negative, differentiating them from the intranuclear-inclusion disorders associated with increased CAG repeats (SCAs, HD, etc.) (Greco et al. 2002; Hagerman et al. 2003*a*). The abnormal white-matter signal seen in the MCPs on magnetic resonance imaging (MRI) corresponds to spongiform changes associated with mild axonal and myelin loss (Greco et al. 2002). The cause of

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the inclusions and the other neuropathological changes is thought to be related to a toxic effect of the elevated levels of the expanded-CGG-repeat mRNA, present in individuals with the premutation but not in those with the fully methylated full mutation (Tassone et al. 2000*a*, 2000*b*, 2001). Thus far, FXTAS has been reported only in males with the *FMR1* premutation.

Here, we present five female carriers of the *FMR1* premutation who were identified either through family studies or as patients seen at our clinic with a primary complaint related to the clinical features of FXTAS; we document the presence of inclusions in one patient for whom we performed postmortem neuropathological studies.

Cognitive testing was performed in all five patients, and results are presented in table 1. None of the women demonstrated dementia. Patient 1 has a superior IQ.

Patient 1 is a 67-year-old nun with a Ph.D. who experienced onset of intention tremor at age 41 years. The tremor was first noticed in her right hand when she was eating, and it gradually worsened. By age 47 years, it was hard for her to drink from a cup without spilling. By age 50 years, she found it impossible to write more than one or two words. Head tremors and ataxia developed in her 50s, resulting in frequent falling. Naldolol and clonazepam were prescribed for her tremor and were found to be helpful. At age 65 years, she began to notice leg aches, although a work-up for peripheral vascular abnormalities showed normal results. Menopause occurred at age 46 years; the patient has since begun hormone-replacement therapy (HRT).

The patient's neurological examination revealed a marked intention tremor with terminal dysmetria bilaterally, more pronounced in her left arm. She also displayed a postural tremor and an intermittent resting tremor. Deep tendon reflexes were 1+ in the upper extremities but could not be elicited in the lower extremities. She had decreased sensation to pinprick and vibration in the distal lower extremities. She was unable to tandem walk. Her plantar reflexes were flexor bilaterally. She had a mild rigidity in the upper extremities (table 1).

Axial T2–weighted images at age 67 years demonstrated mildly increased T2-signal intensity in the MCPs, right greater than left, and in the paramedian pons. The changes were most conspicuous on inversion recovery sequences (fig. 1). Also noted was a slightly increased T2-signal intensity in subependymal white matter of the frontal and parietal hemispheres (fig. 1).

Patient 2 is a 57-year-old teacher and grandmother of children who have fragile-X syndrome. She experienced onset of an intermittent tremor in her 30s and progressive balance problems beginning at age 37 years, which caused her to fall. Her gait difficulties gradually worsened over the next 15 years, requiring the use of a wheelchair by age 51 years. For the past 4 years, she has been confined to a wheelchair and can only ambulate independently for a few steps. She has been dysarthric for the past 6 years and had frequent episodes of dysphagia, with solids and liquids, over the past 3 years. She developed significant bowel and bladder incontinence in her 30s, leading to a colostomy, at age 43 years, after she had completely lost control of bowel function. Spondylosis was diagnosed at age 32 years. From her 40s onward, she experienced chronic back spasms and pain in all four extremities; more recently, she has had some complaints of mildly decreased sensation and burning paresthesias in both feet.

The patient's medical history includes bilateral carpal tunnel syndrome, fibromyalgia, cataracts, chronic daily headaches, hypertension, and type II diabetes, controlled by diet. She also has strabismus with a left-eye amblyo-

Table 1

Summary of Clinical and Molecular Findings

	Patient				
Characteristic	1	2	3	4	5
Current age (years)	67	57	85	62	74
Full-scale IQ	126	99	100	111	87
Verbal IQ	130	103	104	110	88
Performance IQ	116	94	94	111	86
Age at tremor onset (years)	41	30	82	52	71
Age at ataxia onset (years)	59	37	79	60	71
CGG repeat	18, 90	29, 93	29, 87	18, 90	30,78
FMRP level[a]	89	96	80	70	90
Activation ratio[b]	.51	.35	.53	.5	.21
mRNA level	3.25 ± .55	4.6 ± .29	1.40 ± .07	2.52 ± .27	2.6 ± .04
MRI result	+ MCP sign	No MCP sign	Pacemaker	Pacemaker	No MCP sign
FXTAS diagnosis	Definite	Probable	Definite	Probable	Probable

[a] Percentage of lymphocytes positive for FMRP by immunocytochemical staining, as described by Tassone et al. (2000*b*).

[b] Activation ratio calculated as described by Tassone et al. (1999).

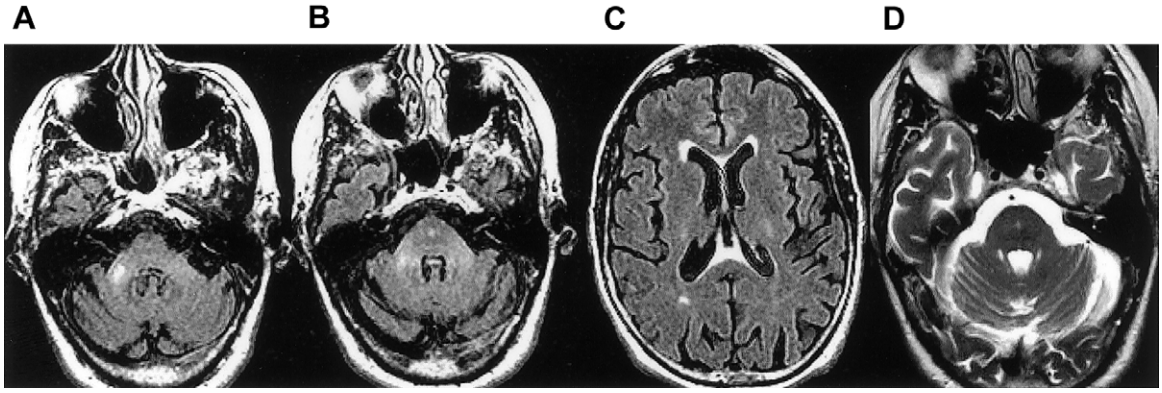

Figure 1 Axial inversion recovery images of patient 1. *A*, Increased signal intensity demonstrated in the MCPs bilaterally, right greater than left. *B* and *C*, Increased signal intensity in the paramedian pons and at the pontomesencephalic junction. *D*, Mildly increased signal intensity in subependymal white matter of the frontal lobes.

pia. Previous psychiatric diagnoses have included hyperactivity, both as a child and an adult, and postpartum depression.

The patient's neurologic examination included a mild left-sided exotropia with decreased vision in the left eye, but with no significant nystagmus. She had dysarthria, an intermittent intention tremor with decreased motor coordination, and dysmetria in all four extremities. Muscle strength and tone were normal. Deep-tendon reflexes were normal in the upper extremities and at the patellae but could not be elicited at the ankles. Plantar reflexes were flexor. She had mildly decreased sensation to pinprick and temperature in a symmetric stocking-glove distribution, with preserved vibration sense. Gait was wide-based, with an inability to tandem walk. Performance on Rhomberg testing was unsteady with eyes open.

MRI of the brain at age 57 years demonstrated no alteration in white matter–T2 signal intensity in the MCPs or cerebral hemispheres. There was mild cerebral cortical volume loss and mild prominence in size of the lateral ventricles (table 1).

Patient 3 was an 85-year-old Hispanic female who worked as a community social worker until retiring at age 65 years and raised two children and two grandchildren with fragile-X syndrome. She was diagnosed with anxiety and depression at age 75 years and was treated with fluoxetine, although she had experienced anxiety for many years prior to diagnosis. She had a mild ataxia and began using a cane at age 79 years because of gait unsteadiness. Falling episodes led to a fractured right femur at age 81 years and a fractured left hip at age 84 years. Intention tremor and extremity weakness began at age 82 years and interfered with activities of daily living. She died at age 85 years and 11 months, after complications from gastrointestinal surgery for ileus (table 1).

An MRI was not performed during the patient's life because of the presence of a pacemaker. A postmortem MRI was done on her brain, following 2 weeks of fixation in 10% formalin. There was no alteration in T2-signal intensity in the MCPs. There was mildly increased signal intensity in subependymal and deep white matter of the frontal and parietal lobes, and there was mild cerebral-cortical volume loss.

Gross examination of the brain, which weighed 980 g, showed mild parietal gyral atrophy and a marked decrease in ventricular size, suggesting agonal brain edema. Histological studies of hematoxylin and eosin stain demonstrated eosinophilic intranuclear inclusions in neurons and astroglia throughout the cerebrum and cerebellum, with the exception of Purkinje cells (fig. 2). Ependymal and

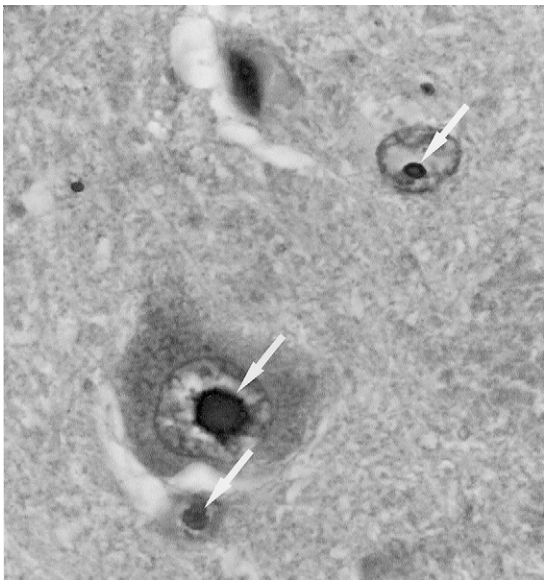

Figure 2 Ubiquitin-positive intranuclear inclusions from the hippocampus of patient 3.

subependymal cells and epithelial cells of the choroid plexus showed the intranuclear inclusions. Immunocytochemical staining of the inclusions was positive for ubiquitin and negative for tau- and α-synuclein. The inclusions were negative for silver and PAS staining.

Patient 4 is the 62-year-old sister of patient 1. She has raised nine children, and all but one are affected with fragile-X syndrome.

Patient 4 developed an intermittent intention tremor at age 52 years that gradually worsened and began interfering with eating at age 60 years. Intermittent head tremor began at age 57 years, but it is usually subtle and not noticed by others. Over the past year, she developed a tremor at rest in her hands, and her handwriting became illegible.

Numbness in her right foot began at age 52 years, after ankle surgery, and appeared in her left foot at age 59 years. Patient 4 complained of muscle pain in her legs approximately four times per week for the past 5 years and weakness in her arms for the past 2–3 years. More frequent falling began 1.5 years ago, and she now requires handrail support when using stairs. Memory deficits have occurred for the past 2–3 years, but she felt this to be consistent with her age.

Medical history includes hyperthyroidism treated with surgery, bradycardia and arrhythmias consistent with sick-sinus syndrome (pacemaker implanted at age 56 years), pericarditis, glaucoma, status post surgery for carpal tunnel syndrome, and hypertension treated for the past 10 years with hydrochlorothiazide.

On examination, she had tremor at rest, when posturing, and with action; tremor in the left hand was worse than the right. Head tremor was also visible. Deep-tendon reflexes were 1+ in the upper extremities and could not be elicited in the lower extremities. In the lower extremities, she had decreased sensation to pin prick and vibration (table 1).

Patient 5 is a 74-year-old woman who first developed light-headedness and unsteady gait at age 71 years, resulting in frequent falls. At about the same time, she noticed tremor in her hands when carrying food on a plate and, later, when writing, embroidering, and doing puzzles. These symptoms were accompanied by numbness in her lower extremities. Her symptoms gradually worsened, leading to her first evaluation at age 74 years. At that time, she reported some improvement of her tremor while taking inderol and significant improvement while taking primidone.

On examination, she had a mild intention tremor, which was worse on the right side. She also had mild parkinsonism, characterized by mild bradykinesia, positive retropulsion, upper-extremity rigidity that was worse on the right side, and mild dystonia involving her neck muscles. Lower extremities had symmetrical reflexes but decreased sensation to pin prick and vibration. Tandem walking demonstrated ataxia, and gait was mildly broad based.

This report describes five women, two of them sisters, with definite or probable FXTAS without dementia. Previous published reports of FXTAS have not found involvement in women, suggesting that they are far less frequently affected than males (Hagerman et al. 2001; Brunberg et al. 2002; Leehey et al. 2002; Berry-Kravis et al. 2003; Jacquemont et al. 2003, 2004*a*). In the study by Jacquemont et al. (2004*b*), a direct comparison of 59 females with the premutation with 34 control individuals did not demonstrate significant symptoms of FXTAS, either by questionnaire responses or by standardized neurological examination. In addition to the presence of the *FMR1* premutation, criteria for a "definite" diagnosis of FXTAS include intention tremor and/or ataxia and increased T2-signal intensity in the MCPs (Jacquemont et al. 2003). Patient 1 met these criteria.

Neurohistological studies of patient 3 demonstrated eosinophilic inclusions in neurons and astrocytes that were identical to those previously reported in males with FXTAS. These inclusions have been seen in all (9/9) cases examined to date of males who have died with FXTAS, but they have not been found in controls. One female with the premutation, who died at age 67 years but without any clinical or radiological features of FXTAS, did not have inclusions (Hagerman et al. 2003*a*). The inclusions appear to be pathognomonic of FXTAS; when seen with clinical findings of tremor and/or ataxia, this meets diagnostic criteria for definite FXTAS (Hagerman and Hagerman 2004 [in this issue]). Therefore, patient 3 meets the criteria for definite FXTAS.

The diagnosis of "probable" FXTAS does not require MCP involvement but does require the presence of tremor and ataxia. In the study by Jacquemont et al. (2003), nearly one-half of the cases did not have the MCP involvement. Patients 2, 4, and 5 met the criteria for probable FXTAS, each having both tremor and ataxia.

In controlled studies, females with the premutation have not had significant neurological symptoms, compared with controls (Berry-Kravis et al. 2003; Jacquemont et al. 2004*b*). The relative lack of symptomatology in females may be related to the presence of the second X chromosome and random X inactivation, so that a portion of the cells in the brain have the active, normal *FMR1* gene. Alternatively, a sex-specific effect, perhaps related to estrogen, may be protective in females. Patients 1, 2, and 4 received postmenopausal HRT, whereas patients 3 and 5 did not.

We have hypothesized that FXTAS—as well as the inclusions themselves—is caused by a toxic gain of function of the elevated *FMR1* mRNA (Hagerman et al. 2001, 2003*b*; Greco et al. 2002; Hagerman and Hagerman 2004 [in this issue]). Further support for the toxic gain-of-function model comes from animal studies, wherein CGG

repeats, placed either in the mouse *FMR1* homologue (*Fmr1*) or in a heterologous gene in *Drosophila,* give rise to neural-cell inclusions (Jin et al. 2003; Willemsen et al. 2003).

Positively skewed X inactivation, with the normal allele preferentially carried on the active X chromosome, could mitigate the toxic effects of elevated mRNA; however, none of the patients in the current study were skewed toward the normal, active allele. Skewing toward activation of the premutation X has been seen in two sisters with spastic paraparesis and extensive white-matter disease, including the MCP involvement. This presentation may be a severe variant of FXTAS (Tassone et al. 2002).

These five females with FXTAS demonstrate a broad spectrum of symptomatology, ranging from relatively severe disease that is slowly progressive from mid-adulthood (patient 1) to a mild case (patient 3) beginning late in life (age 79 years). The five women all demonstrated a clinical course that was typical of males with FXTAS and included intention tremor, ataxia, parkinsonism, and peripheral neuropathy. However, none of these female patients had dementia (which is seen in ~20% of males with FXTAS [Jacquemont et al. 2004*a*]), and all IQs were either normal or high, although mild executive-function deficits were seen in patients 2 and 3.

We recommend that families with the *FMR1* mutation be studied for the presence of FXTAS in both male and female grandparents and in mothers who are carriers of the *FMR1* premutation. The expectation is that female carriers (1/260 in the general population) will probably manifest these symptoms more subtly and less often than their male counterparts.

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Electronic-Database Information

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *FMR1*)

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