Title

Women with Fragile X—associated Tremor/Ataxia Syndrome

Journal

Movement Disorders Clinical Practice, 7(8)

ISSN

2330-1619

Authors

Schneider, Andrea

Summers, Scott

Tassone, Flora

et al.

Publication Date

2020-11-01

DOI

10.1002/mdc3.13084

Peer reviewed

Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Women with Fragile X–associated Tremor/Ataxia Syndrome

Andrea Schneider, PhD,[1,2,*] Scott Summers, MD,[3] Flora Tassone, PhD,[4] Andreea Seritan, MD,[5] David Hessl, PhD,[1,3] Paul Hagerman, MD,[4] and Randi Hagerman, MD[1,2]

ABSTRACT: Background: Fragile X–associated tremor and ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder linked to the *FMR1* premutation.

Objectives: FXTAS in women is far less common than in men, and this study represents the largest sample reported to date.

Methods: A total of 53 female premutation carriers with FXTAS ($mean_{age}$, 66.83 years; FXTAS stages 2–5) and 55 age-matched and demographic background–matched control participants ($mean_{age}$, 61.94 years) underwent a comprehensive molecular, physiological, neuropsychological, and psychiatric assessment.

Results: The large sample of female premutation carriers showed a wide range of variability of clinical signs and symptom progression. The imaging results showed a middle cerebellar peduncles sign in only 6 patients; another symptom included high-signal intensity in the splenium of the corpus callosum, and diffuse cerebral deep white matter changes (e.g., in the pons) are more common. The rate of psychiatric disorders, especially depression, is higher than in the general population. There is a clear impairment in executive functioning and fine motor skills in connection with a higher FXTAS stage.

Conclusions: The manifestation of FXTAS symptoms in female carriers can be diverse with a milder phenotype and a lower penetrance than those observed in male premutation carriers. The middle cerebellar peduncles sign is present in only a small percentage of the sample, and we propose that the imaging criteria for FXTAS in women need to be expanded.

Fragile X–associated tremor/ataxia syndrome (FXTAS) was first described in 2001 as a late-onset neurodegenerative disorder in the grandfathers of children with full-mutation fragile X syndrome.[1] The initial symptoms of FXTAS can include intention tremor, typically beginning at age 60 years, with ataxia occurring on average 2 years later.[2–4] Some patients with FXTAS report little or no tremor. Usually, when tremor is present, memory problems and often executive function deficits can also manifest.[5,6] Once ataxia starts, a more severe decline in motor and cognitive function usually ensues.[4] Approximately 50% of males with FXTAS will develop dementia,[7] and approximately 30% to 60% will have significant parkinsonism.[8,9] In addition, neurological symptoms often associated with pain—including neuropathy—may begin before the onset of tremor.[10–12] Emotional problems including anxiety, depression, irritability, and eventually apathy are common in those with FXTAS; although anxiety or depression usually begins before the onset of FXTAS.[13–15]

Structural magnetic resonance imaging (MRI) of patients with FXTAS often shows global brain atrophy with white matter hyperintensities (WMH) in the middle cerebellar peduncles (MCP sign), the pons, the periventricular area, the splenium of the corpus callosum, and in the deep cortical and cerebellar white matter.[2,4,12,16] The neuropathology of FXTAS includes spongiosis of the area of WMH and the presence of eosinophilic intranuclear inclusions in neurons and astrocytes throughout the brain and in the peripheral nervous system in addition to many other organs.[17,18] The diagnostic criteria for FXTAS were

[1]*Medical Investigation of Neurodevelopmental Disorders Institute, Sacramento, California, USA;* [2]*Department of Pediatrics, School of Medicine, University of California–Davis, Medical Center, Sacramento, California, USA;* [3]*Department of Psychiatry and Behavioral Sciences, University of California–Davis, Medical Center, Sacramento, California, USA;* [4]*Department of Biochemistry, University of California–Davis, Medical Center, Sacramento, California, USA;* [5]*Department of Psychiatry, UCSF Weill Institute for Neurosciences, University of California, San Francisco, California, USA*

***Correspondence to:** Dr. Andrea Schneider, UC Davis MIND Institute, 2825 50th Street, Sacramento, CA 95817; E-mail: anschneider@ucdavis.edu
Keywords: FXTAS, *FMR1* female premutation.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 18 December 2019; revised 16 June 2020; accepted 3 August 2020.
Published online 23 September 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13084

initially reported in 2003[2] with the addition of inclusions added in 2004[19] to characterize definite FXTAS after death. After an international conference on the premutation, the diagnostic criteria for FXTAS were expanded to include white matter disease in the splenium of the corpus callosum and neuropathy.[20–22] The lifetime prevalence for developing FXTAS is 1:3000 to 1:6000 in men,[23] with a penetrance for male premutation carriers older than 60 years of age at 38%. This increases to 75% for male carriers 80 years of age and older.[24]

Women were originally thought to be unaffected as initial prevalence studies suggested.[24] However, women with FXTAS were subsequently reported in 2004[25] and thereafter in small cohorts; however, their phenotype is usually less severe than in men,[26–29] with a few exceptions where significant dementia has been reported.[30,31] A few studies documented the prevalence of FXTAS at 13% to 16% in older women who are premutation carriers.[32–34] Approximately 60% of men with FXTAS show the MCP sign,[27,35] but only 13% of women show this clinical radiological sign.[27] The less severe clinical symptoms in women may be caused by the activation of the second normal X chromosome, although the activation ratio between women with and without FXTAS did not differ.[26,32,36] Another study suggested that women with skewed activation ratios demonstrated no FXTAS if the skewing was in favor of the normal X, but women consistently demonstrated FXTAS if the skewing was in favor of the mutated X.[37] The correlation between the X inactivation and FXTAS was also previously reported in a few cases.[26,38]

Women with FXTAS often experience immune-mediated disorders compared with age-matched control women, and these problems include fibromyalgia and hypothyroidism.[32,39–41] Mood and anxiety disorders are prevalent in the fragile X premutation carrier population.[42] They are even more pronounced in the FXTAS population, which is perhaps due to the difficulty of coping with the diagnosis itself. Other neurodegenerative disorders (e.g., Alzheimer's disease) have been linked to neuropsychiatric syndromes, especially depression and psychosis.[43] However, the lifetime prevalence of mood and anxiety disorders is significantly higher in premutation carriers with FXTAS than in healthy controls, which could mean that FXTAS is not merely a neurological disorder but a neuropsychiatric syndrome as well.[42] Indeed, in 2019, Hagerman and colleagues described fragile X–associated neuropsychiatric disorders to summarize the most common problems associated with the *FMR1* premutation.[44]

Methods

Participants

Participants were recruited through the University of California Davis (UC Davis) Medical Investigation of Neurodevelopmental Disorders Institute's Fragile X Research and Treatment Center and local advertisements. The participants required molecular documentation of the *FMR1* premutation or normal allele. Individuals with a gray zone allele or mosaicism with the full mutation were not included (see the Molecular Analysis section). For premutation participants, only those with FXTAS stages 2 through 5[13] were recruited for this study (see the Measures section). All participants provided informed consent for a protocol approved by the UC Davis institutional review board. The final sample included 53 women with the *FMR1* premutation and a diagnosis of FXTAS (average age, 66.83; standard deviation [SD], 9.65) and 55 unaffected female control participants without the premutation (average age, 61.94; SD, 7.01).

Measures

Each participant underwent a detailed medical history and physical/neurological examination performed by a physician with expertise in FXTAS (R.J.H.). The history included information on development; past surgeries; current and past medical issues, including pain; as well as any current and past medications. The participants self-reported their current medications and illegal substance use, which was categorized into different pharmaceutical groups and entered into the study database (eg, antidepressant, anxiolytics, etc.).

Neurological issues, including tremor, coordination, muscle tone, reflexes, strength, sensation, and gait, were covered in particular depth during both the history and physical/neurological examinations. The standardized neurological examination included an assessment of the cranial nerves, including lateral, superior, and inferior eye movements; extremity or head movement problems, including tremor and ataxia; tandem gait; frontal release signs, including snout, jaw jerk, and palmomental reflex; sensory examination of pinprick and vibration sense; and assessment of alternating movements and cranial nerves, as developed by Dr. Leehey at the University of Colorado.[3,45,46] Premutation carriers were considered to have FXTAS if they met the possible, probable, or definite criteria; see Table 1.[2] Staging of the illness was also done during these visits using previously defined criteria.[13] Briefly, stage 1 participants demonstrated subtle or unclear tremor or balance problems without a significant impact on normal daily function. These individuals were not included in this study because they did not meet the diagnostic criteria for FXTAS. Stage 2 participants (n = 14 in sample) showed minor but clearly apparent tremor and/or balance problems. These symptoms had no more than minor interference on their daily functioning. Stage 3 participants (n = 21) had a moderate tremor and/or balance problems that had a significant impact on their daily functioning. Participants at this stage must have had at least 1 fall. Stage 4 participants (n = 16) had severe tremor and/or balance problems, required assistance with many activities of daily living, and used either a cane or walker while walking. Stage 5 participants (n = 2) were incapacitated by their tremor and/or balance problems to the extent that required daily use of a wheelchair. Stage 6 participants are bedridden, and no individuals with this stage were included in the current study.

For the assessment of the neuropsychological profile, we used measures of cognitive function: Wechsler Adult Intelligence Scale, Third Edition,[47] Mini Mental State Exam, Controlled Oral Word Association Test (semantic fluency), Purdue

TABLE 1 FXTAS clinical criteria in study sample

Criteria	Description	N (Premutation Group)	N (control Group)
Molecular	*FMR1* CGG repeat size 55–200	53	0
Major signs	Intention tremor	43	3
	Other tremor:		
	•Resting	11	5
	•Intermittent	16	1
	•Postural	35	2
	•Any	47	4
	•Handwriting problems	52	4
	•Impaired finger to nose	42	2
	Gait ataxia	45	3
	Other motor problems:		
	•Wheelchair bound	5	0
	•Walker	4	0
	•Cane	17	2
	•Falling	29	2
	•Low motor tone	16	0
Minor signs	Parkinsonism:		
	Masked facies	4	0
	Increased tone	4	0
	Pill-rolling tremor	1	0
	Stiff gait	1	0
	Moderate to severe short-term memory deficits	43	8
	WMS-III Auditory Immediate Index Score	110.50 (SD 17.74)	117.66 (SD 16.92)
	WMS-III Working Memory Index Score	101.55 (SD 12.40)	111.75 (SD 13.50)
	Executive function deficits	41	1
	BDS-2 score	15.38 (SD 4.25)	22.23 (SD 2.93)
	COWAT total score	36.73 (SD 12.96)	46.97 (SD 13.82)
	Stroop Color-Word Score	45.63 (SD 9.57)	50.82 (SD 7.12)
	SDMT	46.12 (SD 11.43)	56.50 (SD 13.15)
	Processing Speed Index Score (WAIS-III)	97.02 (SD 16.49)	113.24 (SD 13.45)
Major radiological signs	MRI WM lesions in the middle cerebellar peduncles	6	0
Minor radiological signs	MRI WM lesions in cerebral white matter		
	•Pons	20	3
	•Diffuse deep WM	21	6
	•Splenium	34	2
	Moderate to severe generalized atrophy	37	6
Definite FXTAS	1 Major radiological sign + 1 major clinical symptom	6	N/A
Probable FXTAS	Either 1 major radiological + 1 minor clinical or 2 major clinical symptoms	37	N/A
Possible FXTAS	1 Minor radiological sign + 1 major clinical symptom	10	N/A

Adapted from Jacquemont et al.[2] and Hall and O'Keefe.[8]
Abbreviations: FXTAS, fragile X–associated tremor and ataxia syndrome; WMS-III, Wechsler Memory Scale, Third Edition; BDS-2, Behavioral Dyscontrol Scale, Second Edition; COWAT, Controlled Oral Word Association Test; SDMT, Symbol Digit Modalities Test; WAIS, Wechsler Adult Intelligence Scale, Third Edition; MRI, magnetic resonance imaging; WM, white matter; SD, standard deviation; N/A, not applicable.

Pegboard, Symbol Digit Modalities (processing speed), and Behavioral Dyscontrol Scale 2 (frontal-motor executive function).[48]

For the socioemotional and psychopathological profile, the structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* axis I disorders[49] was administered to all the study participants.

Neuroimaging

The structural MRIs were acquired for each study participant at the UC Davis Imagining Research Center using both a 1.5T General Electric (GE Healthcare, Chicago, IL) Signa Horizon LX Nitrogen-Vacancy/Ions (NV/I) scanner with echospeed gradients with a standard General Electric whole-head coil and a 3T Siemens (Erlangen, Germany) Trio with an 8-channel or a 32-channel head coil. A diagnostic neuroradiology specialist rated the images for symptoms of the MCP sign, white matter changes in the pons, significant diffuse cerebral deep white matter changes, atrophy, and high-signal intensity in the anterior subependymal region of the splenium of the corpus callosum.

Molecular Analysis

The presence of a premutation allele was determined by using a combination of Southern blot and polymerase chain reaction approach. Genotyping analyses performed as previously described.[50,51] Individuals who harbored a gray zone allele (CGG between 45 and 54 repeats) or mosaicism (some cells carry alleles in the premutation range and some in the full mutation

TABLE 2 Patient demographics

Criteria	N	Minimum	Maximum	Mean	SD	*P* (ANOVA)
FXTAS age diagnosed						
Control	N/A	N/A	N/A	N/A	N/A	N/A
Premutation	44	52.34	83.90	68.56	9.10	
Age of menopause						
Control	37	35	62	49.56	5.65	0.000
Premutation	42	27	55	42.42	7.60	
Tremor onset						
Control	4	54	70	60.50	6.81	ns
Premutation	45	30	82	59.49	12.70	
Ataxia onset						
Control	3	54	81	68.33	13.58	ns
Premutation	48	24	80	60.81	12.03	
CGG normal allele						
Control	55	14	40	27.32	4.66	ns
Premutation	53	17	42	28.53	4.74	
CGG premutation allele	N/A	N/A	N/A	N/A	N/A	N/A
Control/premutation	53	57	112	85.38	13.47	

Abbreviations: SD, standard deviation; ANOVA, analysis of variance; FXTAS, fragile X–associated tremor and ataxia syndrome; N/A, not applicable; ns, no significant differences.

range) were not included in this study. The activation ratio, indicating the percent of cells carrying the normal allele on the active X chromosome, was measured using ratios of the computer-quantified signal intensity of chosen Southern blot bands as previously described.[52]

Statistical Analysis

Data were analyzed using IBM (Armonk, NY) Statistics 26.0. Normal distribution of data was tested with the Kolmogorov–Smirnoff procedure, and descriptive statistics (mean and SD) were also calculated. The differences of variables from the physical examination and medical history, the neuropsychological and psychiatric assessments, and the imaging data compared with their occurrence depending on FXTAS stage was tested with analyses of variance, Pearson χ^2, and Kruskal–Wallis tests, and the relationship with molecular data was calculated with Pearson parametric correlations for normal distribution data and Spearman ρ coefficient correlations for nonparametric data. A Bonferroni post hoc correction for multiple comparisons was applied.

Results

FXTAS severity in women with the premutation ranged from stage 2 through stage 5 involvement, with their mean age of diagnosis at 68.56 years (range, 52.34–83.90 years; SD, 9.10).

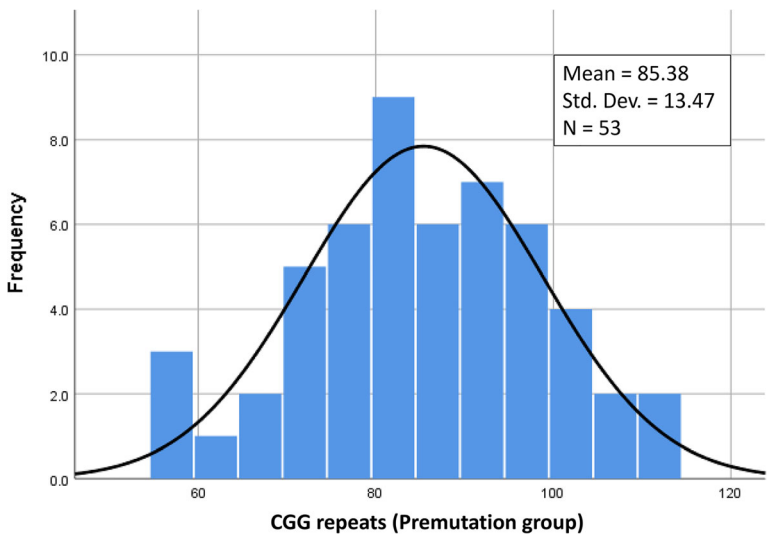

FIG 1. CGG repeat allele size distribution in the premutation subjects included in the study.

TABLE 3 Cognitive and executive functioning differences between control and premutation participants

Criteria	Control (N = 55)		Premutation (N = 53)		ANOVA
	M	SD	M	SD	*F*(Sig*)
WAIS-III Verbal IQ	112.11	12.28	107.68	13.41	2.69 ns
WAIS-III Performance IQ	115.68	15.15	102.62	14.19	18.03***
WAIS-III Full-Scale IQ	114.98	13.43	105.37	12.87	12.00***
WAIS-III Verbal Comprehension Index Score	113.77	11.93	108.70	14.06	3.41 ns
WAIS-III Perceptual Organization Index Score	113.93	15.52	104.24	14.29	9.50**
WAIS-III Working Memory Index Score	106.07	12.92	102.17	13.85	1.84 ns
WAIS-III Processing Speed Index Score	113.24	13.45	97.02	16.49	24.14***
COWAT (total score)	46.97	13.82	36.73	12.96	12.41***
Behavioral Dyscontrol Scale, Second Edition	22.23	2.93	15.38	4.25	66.31***
Mini Mental State Exam	29.46	.89	28.76	1.76	3.95*
Symbol Digit Modalities Test	56.50	13.15	46.12	11.43	15.46***

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
Abbreviations: SD, standard deviation; ANOVA, analysis of variance; IQ, intelligence quotient; ns, not significant; WAIS, Wechsler Adult Intelligence Scale, Third Edition; COWAT, Controlled Oral Word Association Test.

Table 1 provides an overview of the clinical criteria of FXTAS in the study sample, depending on major and minor signs. Table S1 provides an overview of the major and minor clinical symptoms on an individual patient level.

Table 2 provides additional sample data including information about FXTAS diagnosis, age of menopause, tremor and ataxia onset, and molecular measures.

Figure 1 shows the distribution of the premutation allele size (CGG repeats) for the 53 women with the premutation. The mean CGG repeat size was 85.38 (SD, 13.47; CGG range, 57–112), and the mean mRNA activation ratio was 0.49 (SD, 0.22; range, 0.00–1.00).

The correlation of CGG repeat size with age of menopause (R .126, p .427), tremor age of onset (R −.221, p .145), and ataxia age of onset (R −.203, p .166) did not show a significant effect, contradicting previous reports[53,54] (see Figure S1).

Table 3 shows the comparison of cognitive and executive function measures. The significant differences between women with FXTAS and the control group on the Wechsler Adult Intelligence Scale, Third Edition are apparent in the performance and processing speed scales, but not in verbal functioning or Working Memory Index score. The average full-scale intelligence quotient (IQ) for women with FXTAS was 105.37 (SD, 12.87) compared with 114.98 (SD, 13.43) in the control group ($P < 0.001$). The average nonverbal performance IQ in the FXTAS group was expectedly lower (102.62; SD, 14.19) compared with unaffected female controls (115.68; SD, 15.15; $P < 0.001$). Similarly, the Processing Speed Index score was significantly lower (FXTAS, 97.02 and SD, 16.49; control, 113.24 and SD, 13.45; $P < 0.001$). The performance IQ and Processing Speed Index scores are affected by tremor (eg, the block design, digit symbol coding, and symbol search performance are typically impaired by a hand tremor). The measures of executive function (Behavioral Dyscontrol Scale 2), the Controlled Oral Word Association Test, Symbol Digit Modalities Test, and the Mini Mental State Exam also showed significant differences between the 2 groups (see Table 3).

To explore this further, we calculated the individual neuropsychological differences according to FXTAS stage (see Table 4). As expected, the assessment that included a motor component (Behavioral Dyscontrol Scale 2, performance IQ, Purdue Pegboard) showed the most significant effects of FXTAS stage. In addition, the Controlled Oral Word Association Test (a verbal test with frontal executive component) showed significantly worse performance in stages 3, 4, and 5 of FXTAS.

From the medical exam, the most common symptoms in the sample were numbness (37 FXTAS, 11 controls), muscle pain (30 FXTAS, 6 controls), autonomic problems (33 FXTAS, 9 controls), severe cramps (27 FXTAS, 4 controls), osteoarthritis (27 FXTAS, 11 controls), muscle weakness (25 FXTAS,

TABLE 4 Neuropsychological differences depending on FXTAS stage

FXTAS stage	2, N = 14; M (SD)	3, N = 21; M (SD)	4, N = 16; M (SD)	5, N = 2; M (SD)	*P*	Controls, N = 55; M (SD)
WAIS-III Full Scale IQ	107.38 (11.42)	109.56 (13.90)	98.71 (10.89)	97 (0.31)	0.002	114.98 (13.43)
WAIS-III Verbal IQ	108.69 (13.25)	110.33 (11.29)	103.40 (15.98)	111.00 (0.41)	ns	112.11 (12.28)
WAIS-III Performance IQ	105.15 (11.76)	106.74 (15.68)	96.36 (11.31)	79 (2.31)	0.000	115.68 (15.15)
WAIS-III Working Memory	103.31 (14.32)	104.44 (11.62)	99.67 (15.88)	84.00 (9.01)	ns	106.07 (12.92)
BDS-2	16.77 (3.76)	16.47 (4.70)	13.14 (3.11)	10 (1.23)	0.000	22.23 (2.93)
COWAT total score	40.77 (16.48)	39.25 (10.89)	30.31 (10.19)	11 (3.21)	0.001	46.97 (13.82)
MMSE	28.45 (1.50)	29.23 (1.14)	28.00 (2.92)	29.50 (0.70)	ns	29. 46 (0.89)
Purdue Pegboard	31.54 (6.61)	30.32 (4.49)	25.14 (8.61)	Missing	0.000	38.46 (5.31)

Abbreviations: FXTAS, fragile X–associated tremor and ataxia syndrome; SD, standard deviation; WAIS-III, Wechsler Adult Intelligence Scale, Third Edition; BDS-2, Behavioral Dyscontrol Scale, Second Edition; COWAT, Controlled Oral Word Association Test; MMSE, Mini Mental State Exam; ns, not significant.

TABLE 5 Psychiatric differences (Structured Clinical Interview for *DSM-IV* Axis I Disorders, *DSM-IV* criteria)

Criteria	Premutation (N = 53)	% of N	Control (N = 55)	% of N	*P* (Fisher Exact Test)	Lifetime prevalence in US adult population[a]
MDD	29	54.71	11	20	0.049	16.5
Dysthymia	3	5.66	4	7.27	ns	2.5
Bipolar I d/o	1	1.88	0	0	ns	3.9
Panic disorder	9	16.98	1	1.81	0.010	4.7
Social phobia	20	37.7	6	10.90	0.000	12.1
Specific phobia	17	32.07	10	18.18	0.001	12.5
Generalized anxiety	9	16.98	3	5.45	0.028	5.7
PTSD	3	5.66	2	3.63	ns	6.8
OCD	1	1.88	1	1.81	ns	1.6

[a]Data from Kessler et al.[51] Sex differences not reported for individual psychiatric disorders.
Abbreviations: *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; MDD, major depressive disorder; Bipolar I d/o, Bipolar I disorder; PTSD, posttraumatic stress disorder; OCD, obsessive compulsive disorder; ns, not significant.

1 control), peripheral neuropathy (37 FXTAS, 6 controls), migraines (21 FXTAS, 4 controls), bladder incontinence (25 premutation, 8 controls), thyroid problems (20 FXTAS, 7 controls), restless leg syndrome (18 FXTAS, 6 controls), hearing loss (19 FTXAS, 6 controls), fibromyalgia (11 FXTAS, 3 controls), and osteoporosis (14 FXTAS, 7 controls).

The Structured Clinical Interview for DSM-IV Axis I Disorders interview showed elevated rates for depression, panic disorder, social phobia, specific phobia, and generalized anxiety disorder (Table 5) in the female FXTAS group compared to both the female control group and the prevalence rates published by the National Institute of Mental Health[55] for the general US adult population (men and women). Data for substance abuse, alcohol (0 FXTAS, 2 controls) and cannabis (0 FXTAS, 0 controls) was also obtained, although the prevalence rates were decreased compared with previous reports in male premutation carriers.[14,56]

Table 6 shows that women with FXTAS take a much higher rate of prescription medications, especially for neuropsychiatric conditions, and over-the-counter medications than unaffected, age-matched female controls. There are no significant differences in stimulants, osteoporosis treatments, or substance abuse, including illegal substances.

Neuropathology/Neuroimaging Findings

The patients were scanned on a 3T Siemens Magnetom TrioTim syngo MR B15 MRI system with either an 8-channel or a 32-channel head coil. The structural observations were done with the T2 fluid-attenuated inversion recovery images sagittal plane, T2 turbo spin echo acquisition in the oblique axial plane. After recording, the images were evaluated for the presence of increased T2 signal intensity in the cerebrum, pons, cerebellum, and corpus callosum. Figure 2A–D provides examples for the most common findings, with Figure 2A showing a severe form of WMH. The most common MRI findings in the women with FXTAS was a general atrophy in different areas of the cortex (37 of 53 women, 69.81%); only 6 control participants showed this finding (10.90%). A high-signal intensity in the anterior subependymal region of the splenium of the corpus callosum was found in 34 women with FXTAS (64.15%) compared with only 2 controls (3.63%). The MCP sign occurred in only 6 women (11.32%) with FXTAS. A total of 20 women with FXTAS had WMH in the pons (37.73%) compared with only 3 (5.45%) female controls. Of the patients, 21 showed diffuse cerebral deep

TABLE 6 Self-reported medications in the study sample

Criteria	Premutation, N = 53; n (%)	Controls, N = 55; n (%)	*P* (ANOVA)
Neuropsychiatric medications			
Antidepressants	30 (56.6)	14 (25.45)	0.005
Anxiolytics	104 (18.86)	11 (20)	0.000
Stimulants	4 (7.54)	1 (1.81)	ns
Antipsychotic/mood stabilizer/anticonvulsants	15 (28.3)	4 (7.27)	0.002
Medications for treatments of somatic complaints			
Anti-inflammatory	32 (60.37.7)	14 (25.45)	0.009
ChEIs/NMDA antagonists	18 (33.96)	1 (1.81)	0.000
Hormonal supplements[a]/Immunomodulators	28 (52.83)	18 (32.72)	0.001
Dietary[b]/diabetic	34 (64.15)	14 (25.45)	0.000
Osteoporosis medication	9 (16.98)	5 (9.09)	ns
OTC supplements/omega3/vitamins	24 (12.7)	13 (7.15)	0.006
Drugs of abuse[c]	14 (26.41)	9 (16.36)	ns

[a]Levothyroxine, estrogen, anti-estrogens, progestin, bronchodilators, and neurohormones.
[b]Statins, laxatives, diuretics, antidiarrheal, probiotics, gastroesophageal reflux disease medication.
[c]Opioids, cocaine, alcohol abuse, and polydrug dependency.
Abbreviations: ANOVA, analysis of variance; ChEIs, cholinesterase inhibitors; NMDA, *N*-methyl-D-aspartate; OTC, over the counter; ns, not significant.

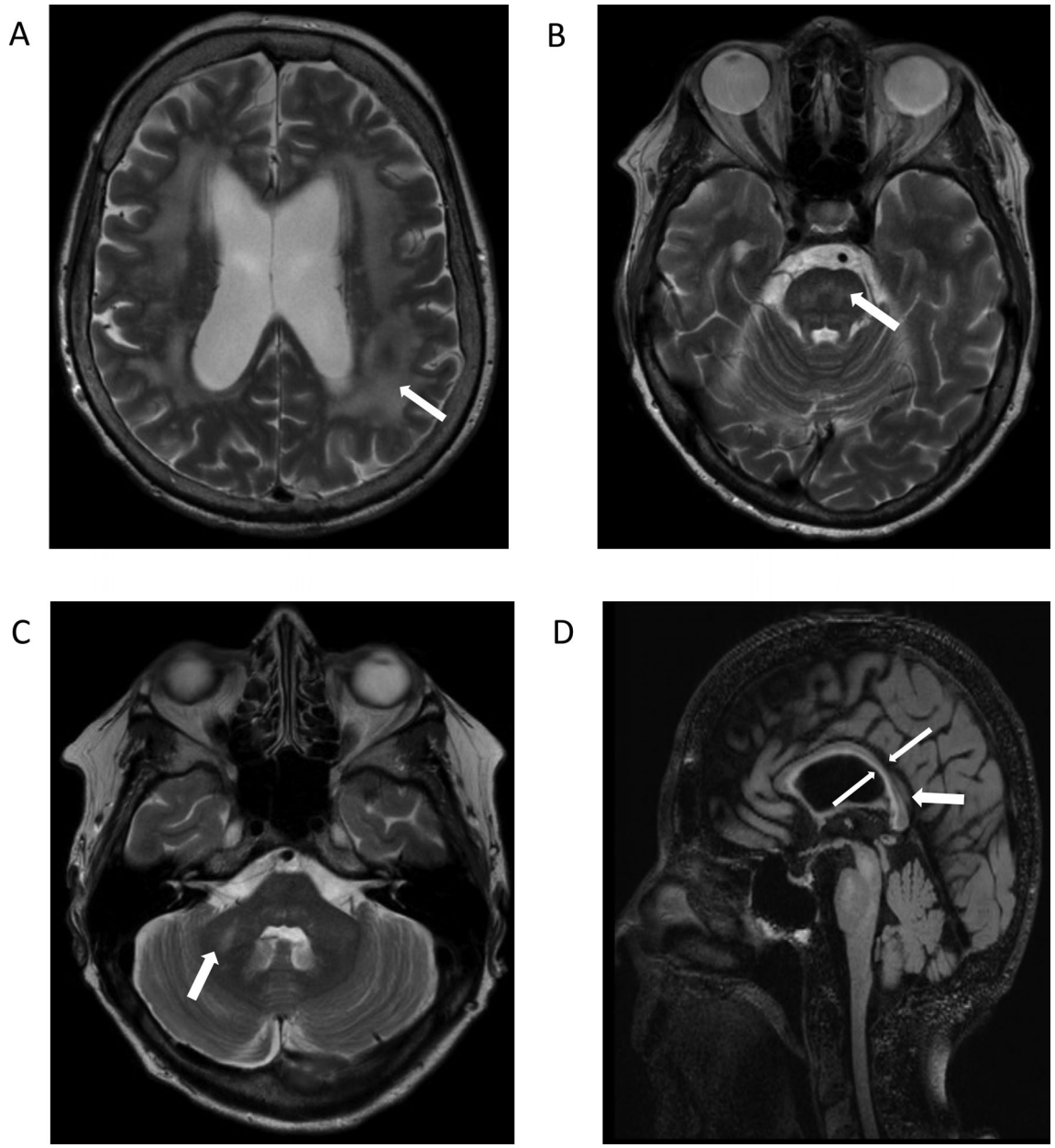

FIG 2. Overview of magnetic resonance imaging findings in selected women with fragile X–associated tremor and ataxia syndrome, white arrows pointing to region of interest. (**A**) Severely increased T2 signal intensity in the deep white matter of the cerebrum, especially in the periventricular regions. (**B**) Increased T2 signal intensity in the pons. (**C**) Increased T2 signal intensity in the middle cerebellar peduncles (sign). (**D**) Increased T2 signal intensity in the splenium of the corpus callosum and a general thinning of the corpus callosum.

white matter changes (39.62%) compared with only 6 (10.90%) controls.

Discussion

FXTAS in women with the *FMR1* premutation is far less common than in men, and this study represents the largest group of women with FXTAS reported to date. The mean age of FXTAS diagnosis for these participants was 68.56 years, which is slightly older than the average age of diagnosis in men.[3] Women with FXTAS also had a broad spectrum of phenotypic variability; however, studies reported that female premutation carriers do not always report medical issues consistent with their doctor's diagnosis.[57]

From a neuropsychological perspective, the most remarkable finding is the lack of decline in cognitive verbal ability (up to

stage 4), working memory, and in Mini Mental State Exam score through the stages of FXTAS, which differs from previous reports regarding cognitive deficits in men with FXTAS.[7,58,59] On the other hand, there was a decline in executive function, and cognitive/motor performance abilities throughout the stages of FXTAS in these women. The executive function and performance abilities are known cognitive problems associated with FXTAS in both men and women, and in some individuals, these problems begin even before the onset of tremor and ataxia.[5,59] It is likely that the tremor interferes with performance during performance IQ testing.

Another remarkable difference compared with men with FXTAS is the degree of MRI involvement. A previous small report demonstrated the MCP sign in up to 13% of women with FXTAS,[27] and this study provides further evidence of the lower rate in this particular finding. Moreover, this is significantly different from the 60% prevalence in men with FXTAS.[60] The MCP sign is a major radiological criterion for the diagnosis of FXTAS, but this finding is less common in women and thus less sensitive for detecting those women with FXTAS. Conversely, WMH in the splenium of the corpus callosum was the most common pathological MRI finding in this study. Apartis and colleagues[12] first recognized the higher frequency of WMH in the splenium of the corpus callosum, subsequently suggesting its addition as a major criterion for diagnosis in FXTAS.[12] The current data suggest that this sign may serve as a more reliable metric in the diagnosis of FXTAS in women with the premutation. Longitudinal studies are warranted to see if disease progression on MRI is significantly different in female participants with FXTAS compared with males.

Many of the medical problems associated with the premutation, including fibromyalgia, autonomic problems (eg, bowel and bladder incontinence), and peripheral neuropathy, are reported here. Although pain was seen in >40% of the women with FXTAS, there was no significant increase in the use of opioids (11%) compared with age-matched controls (6.3%). Previous reports have shown increased use of alcohol or other drugs of abuse in men with the premutation,[14,56,61] which we did not find in this study on women with the *FMR1* premutation. Neurons with the premutation have increased stress markers with premature loss of viability compared with controls[62] and thus may be at higher risk for cell death from exposure to toxic substances. It is possible there was not a large enough sample size or perhaps a sampling bias (discussed later) that contributed to this. Future research should be directed in this area as case reports have theorized substance abuse accelerates the disease progression of FXTAS.[63–66]

In general, tremors are often diagnosed as an essential or familial tremor early on. Nevertheless, the significant worsening of these symptoms within the FXTAS pathology spectrum begins later in life. This usually occurs in the patient's 60s, but may occur earlier after deleterious events such as a prolonged surgery, general anesthesia, significant psychiatric distress or medical illness, or drug use.[41,64–66]

This study demonstrated significantly higher rates of multiple psychiatric disorders in women with FXTAS compared with age-matched controls, including major depressive disorder, panic disorder, social phobia, and generalized anxiety disorder. There was no significant correlation with FXTAS stage and onset of psychiatric disorders; the majority of women who were carriers reported a higher rate of depression and anxiety at earlier stages of FXTAS (stages 2 and 3). The medications used demonstrated that these problems are being treated, and antidepressants, anxiolytics, and antipsychotics/mood stabilizers were used at increased rates compared with controls.

The limitations of our study include a sample bias because women with FXTAS will often self-refer, and they may represent a more severely affected sample compared to one obtained in a screening study or with an unbiased selection. Also, the majority of our sample consisted of participants with a higher socioeconomic status and White ethnicity. Furthermore, we did not control for having a child with neurodevelopmental disorders, including fragile X syndrome, autism, or other significant medical issues in either the premutation or the control group. This could have caused a bias toward a higher rate of depression and anxiety.

This study is the most extensive report to date characterizing the phenotypic profile of women with the *FMR1* premutation and FXTAS. The results showed increased rates of major depressive disorder, panic disorder, social and specific phobias, and generalized anxiety disorder compared with women without the premutation. This study also provided new insights that cognitive performance and working memory may be less impaired compared with men with FXTAS and that WMH in the corpus callosum may be a better sign of FXTAS in women compared with the MCP sign, which is more common in men. Further studies should be conducted analyzing longitudinal MRI changes and whether FXTAS progresses more slowly in women compared with men.

Acknowledgments

We thank Patrick Adams for administering the magnetic resonance imaging scans, Dr. Zukhrofi Muzar and Lindsey Partington for data support, Kylee Cook for help with data retrieval, Dan Thu Nguyen and Andrew Ligsay for critically reviewing the manuscript, and Jennifer Cogswell for the majority of the neuropsychological testing. We would also like to thank Louise Gane for her genetic counseling and patient support. Also, we thank all the participants and their families.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

A.Schneider: 1C, 2A, 2B, 3A

S.S.: 1C, 3B

F.T.: 1C, 3B
A.Seritan: 1C, 3B
D.H.: 1A, 2C, 3B
P.H.: 1A, 1B, 3B
R.H.: 1A, 1B, 1C, 3B

Disclosures

Ethical Compliance Statement: This study was approved by the institutional review board of the University of California at Davis, Protocol-ID 240410-7, study "Characterization and Treatment of CNS Abnormalities in Carriers of Fragile X" and institutional review board ID 254134-23, study "Genotype-Phenotype Relationships in Fragile X Families," Federal-Wide-Assurance no. 00004557; expiration date, December 22, 2020; IRB Organization Number, 0000251. Informed consent was obtained from all patients and control participants, who signed an informed consent document before the beginning of study participation. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflict of Interest: This work was supported by Grants HD036071 (Eunice Kennedy Shriver National Institute of Child Health and Human Development), UL1DE019583 (National Institute of Dental and Craniofacial Research), RL1AG032115 (National Institute on Aging), AG18442 (National Institute on Aging), and UL1 TR000002; linked award TL1 TR000133, Health and Human Administration of Developmental Disabilities 90DD0596; and the National Institutes of Health–funded Medical Investigation of Neurodevelopmental Disorders Intellectual and Developmental Disabilities Research Center (U54 HD079125).

Financial Disclosures for the Previous 12 Months: Andrea Schneider, PhD, reports UC Davis employment and grant funding. Scott Summers, MD, reports Veterans Affairs and UC Davis employment. Flora Tassone, PhD, reports UC Davis employment and grant funding. Andreea Seritan, MD, reports UC San Francisco employment and grant funding. David Hessl, PhD, reports UC Davis employment, grant funding, honoraria, and consultancy and advisory boards: Novartis, Roche, Seaside Therapeutics, and Marinus. Paul Hagerman, MD, reports UC Davis employment and grant funding. Randi Hagerman, MD, reports UC Davis employment, grant funding, honoraria, and consultancy and advisory boards: Zynerba, Ovid, and Fulcrum Therapeutics. The authors have no conflicts of interest to report related to this work. ■

References

1. Hagerman RJ, Leehey M, Heinrichs W, et al. Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X. *Neurology* 2001;57(1):127–130.
2. Jacquemont S, Hagerman RJ, Leehey M, et al. Fragile X premutation tremor/ataxia syndrome: molecular, clinical, and neuroimaging correlates. *Am J Hum Genet* 2003;72(4):869–878.
3. Leehey MA, Berry-Kravis E, Min SJ, et al. Progression of tremor and ataxia in male carriers of the FMR1 premutation. *Mov Disord* 2007;22(2):203–206.
4. Juncos JL, Lazarus JT, Graves-Allen E, et al. New clinical findings in the fragile X-associated tremor ataxia syndrome (FXTAS). *Neurogenetics* 2011;12(2):123–135.
5. Brega AG, Goodrich G, Bennett RE, et al. The primary cognitive deficit among males with fragile X-associated tremor/ataxia syndrome (FXTAS) is a dysexecutive syndrome. *J Clin Exp Neuropsychol* 2008;30(8):853–869.
6. Grigsby J, Brega AG, Engle K, et al. Cognitive profile of fragile X premutation carriers with and without fragile X-associated tremor/ataxia syndrome. *Neuropsychology* 2008;22(1):48–60.
7. Seritan AL, Nguyen DV, Farias ST, et al. Dementia in fragile X-associated tremor/ataxia syndrome (FXTAS): comparison with Alzheimer's disease. *Am J Med Genet B Neuropsychiatr Genet* 2008;147B(7):1138–1144.
8. Hall DA, O'Keefe A. Fragile x-associated tremor ataxia syndrome: the expanding clinical picture, pathophysiology, epidemiology, and update on treatment. *Tremor Other Hyperkinet Mov (N Y)* 2012;2:tre-02-56-352-1.https://doi.org/10.7916/D8HD7TDS.
9. Niu YQ, Yang JC, Hall DA, et al. Parkinsonism in fragile X-associated tremor/ataxia syndrome (FXTAS): revisited. *Parkinsonism Relat Disord* 2014;20(4):456–459.
10. Hagerman PJ, Hagerman RJ. Fragile X-associated tremor/ataxia syndrome-an older face of the fragile X gene. *Nat Clin Pract Neurol* 2007;3(2):107–112.
11. Soontarapornchai K, Maselli R, Fenton-Farrell G, et al. Abnormal nerve conduction features in fragile X premutation carriers. *Arch Neurol* 2008;65(4):495–498.
12. Apartis E, Blancher A, Meissner WG, et al. FXTAS: new insights and the need for revised diagnostic criteria. *Neurology* 2012;79(18):1898–1907.
13. Bacalman S, Farzin F, Bourgeois JA, et al. Psychiatric phenotype of the fragile X-associated tremor/ataxia syndrome (FXTAS) in males: newly described fronto-subcortical dementia. *J Clin Psychiatry* 2006;67(1):87–94.
14. Seritan AL, Bourgeois JA, Schneider A, Mu Y, Hagerman RJ, Nguyen DV. Ages of onset of mood and anxiety disorders in fragile X premutation carriers. *Curr Psychiatry Rev* 2013;9(1):65–71.
15. Bourgeois JA, Coffey SM, Rivera SM, et al. A review of fragile X premutation disorders: expanding the psychiatric perspective. *J Clin Psychiatry* 2009;70(6):852–862.
16. Brunberg JA, Jacquemont S, Hagerman RJ, et al. Fragile X premutation carriers: characteristic MR imaging findings of adult male patients with progressive cerebellar and cognitive dysfunction. *AJNR Am J Neuroradiol* 2002;23(10):1757–1766.
17. Greco CM, Hagerman RJ, Tassone F, et al. Neuronal intranuclear inclusions in a new cerebellar tremor/ataxia syndrome among fragile X carriers. *Brain* 2002;125(Pt 8):1760–1771.
18. Hunsaker MR, Greco CM, Spath MA, et al. Widespread non-central nervous system organ pathology in fragile X premutation carriers with fragile X-associated tremor/ataxia syndrome and CGG knock-in mice. *Acta Neuropathol* 2011;122(4):467–479.
19. Hagerman PJ, Hagerman RJ. The fragile-X premutation: a maturing perspective. *Am J Hum Genet* 2004;74(5):805–816.
20. Hagerman PJ, Hagerman RJ. Fragile X-associated tremor/ataxia syndrome. *Ann N Y Acad Sci* 2015;1338:58–70.
21. Hall DA, Birch RC, Anheim M, et al. Emerging topics in FXTAS. *J Neurodev Disord* 2014;6(1):31.
22. Leehey M, Hall DA, Liu Y, Hagerman RJ. Clinical neurological phenotype of FXTAS. In: Tassone F, Hall D., eds. *The Fragile X-Associated Tremor Ataxia Syndrome (FXTAS).* New York, NY: Springer Science & Business Media. LLD; 2010. pp. 1-16.
23. Jacquemont S, Leehey MA, Hagerman RJ, Beckett LA, Hagerman PJ. Size bias of fragile X premutation alleles in late-onset movement disorders. *J Med Genet* 2006;43(10):804–809.
24. Jacquemont S, Hagerman RJ, Leehey MA, et al. Penetrance of the fragile X-associated tremor/ataxia syndrome in a premutation carrier population. *JAMA* 2004;291(4):460–469.
25. Hagerman RJ, Leavitt BR, Farzin F, et al. Fragile-X-associated tremor/ataxia syndrome (FXTAS) in females with the FMR1 premutation. *Am J Hum Genet* 2004;74(5):1051–1056.
26. Berry-Kravis E, Potanos K, Weinberg D, Zhou L, Goetz CG. Fragile X-associated tremor/ataxia syndrome in sisters related to X-inactivation. *Ann Neurol* 2005;57(1):144–147.
27. Adams JS, Adams PE, Nguyen D, et al. Volumetric brain changes in females with fragile X-associated tremor/ataxia syndrome (FXTAS). *Neurology* 2007;69(9):851–859.

28. Rodriguez-Revenga L, Pagonabarraga J, Gomez-Anson B, et al. Motor and mental dysfunction in mother-daughter transmitted FXTAS. *Neurology* 2010;75(15):1370–1376.

29. Adams PE, Adams JS, Nguyen DV, et al. Psychological symptoms correlate with reduced hippocampal volume in fragile X premutation carriers. *Am J Med Genet B Neuropsychiatr Genet* 2010;153B(3):775–785.

30. Tassone F, Greco CM, Hunsaker MR, et al. Neuropathological, clinical and molecular pathology in female fragile X premutation carriers with and without FXTAS. *Genes Brain Behav* 2012;11(5):577–585.

31. Hagerman R, Hagerman P. Advances in clinical and molecular understanding of the FMR1 premutation and fragile X-associated tremor/ataxia syndrome. *Lancet Neurol* 2013;12(8):786–798.

32. Coffey SM, Cook K, Tartaglia N, et al. Expanded clinical phenotype of women with the FMR1 premutation. *Am J Med Genet A* 2008;146A(8):1009–1016.

33. Rodriguez-Revenga L, Madrigal I, Blanch-Rubió J, et al. Screening for the presence of FMR1 premutation alleles in women with fibromyalgia. *Gene* 2013;512(2):305–308.

34. Chonchaiya W, Nguyen DV, Au J, et al. Clinical involvement in daughters of men with fragile X-associated tremor ataxia syndrome. *Clin Genet* 2010;78(1):38–46.

35. Cohen S, Masyn K, Adams J, et al. Molecular and imaging correlates of the fragile X-associated tremor/ataxia syndrome. *Neurology* 2006;67(8):1426–1431.

36. Hall DA, Robertson-Dick EE, O'Keefe JA, Hadd AG, Zhou L, Berry-Kravis E. X-inactivation in the clinical phenotype of fragile X premutation carrier sisters. *Neurol Genet* 2016;2(1):e45.

37. Mila M, Ramos FMI, Grupo AEGH/CIBERER. Clinical guideline of gene FMR1-associated diseases: fragile X syndrome, primary ovarian insufficiency and tremor-ataxia syndrome. *Med Clin (Barc)* 2014;142(5):219–225.

38. Jacquemont S, Orrico A, Galli L, et al. Spastic paraparesis, cerebellar ataxia, and intention tremor: a severe variant of FXTAS? *J Med Genet* 2005;42(2):e14.

39. Winarni TI, Chonchaiya W, Sumekar TA, et al. Immune-mediated disorders among women carriers of fragile X premutation alleles. *Am J Med Genet A* 2012;158A(10):2473–2481.

40. Leehey MA, Legg W, Tassone F, Hagerman R. Fibromyalgia in fragile X mental retardation 1 gene premutation carriers. *Rheumatology (Oxford)* 2011;50(12):2233–2236.

41. Jalnapurkar I, Rafika N, Tassone F, Hagerman R. Immune mediated disorders in women with a fragile X expansion and FXTAS. *Am J Med Genet A* 2015;167A(1):190–197.

42. Bourgeois JA, Seritan AL, Casillas EM, et al. Lifetime prevalence of mood and anxiety disorders in fragile X premutation carriers. *J Clin Psychiatry* 2011;72(2):175–182.

43. Cummings J, Ritter A, Rothenberg K. Advances in management of neuropsychiatric syndromes in neurodegenerative diseases. *Curr Psychiatry Rep* 2019;21(8):79.

44. Hagerman RJ, Protic D, Rajaratnam A, Salcedo-Arellano MJ, Aydin EY, Schneider A. Fragile X-associated neuropsychiatric disorders (FXAND). *Front Psychiatry* 2018;9:564. https://doi.org/10.3389/fpsyt.2018.00564.

45. Leehey MA, Berry-Kravis E, Goetz CG, Hagerman RJ. Clinical neurological phenotype of FXTAS. In: Tassone F, Berry-Kravis E, eds. *The Fragile X-Associated Tremor Ataxia Syndrome (FXTAS)*. New York: Springer; 2011:1–16.

46. Leehey MA. Fragile X-associated tremor/ataxia syndrome: clinical phenotype, diagnosis, and treatment. *J Invest Med* 2009;57(8):830–836.

47. Wechsler D. *Wechsler Adult Intelligence Scale-Third Edition: Administration and Scoring Manual*. San Antonio, TX: Harcourt Assessment, Inc.; 1997.

48. Grigsby J, Kaye K. *Behavioral Dyscontrol Scale: Manual*. (2nd Ed.). Ward, CO: BDS; 1996.

49. First MB, Williams Janet BW, Spitzer RL, Gibbon M. *Structured Clinical Interview for DSM-IV Axis I Personality Disorders (SCID-I), Clinician Version*. Arlington, TX: American Psychiatric Publishing, Inc.; 1997.

50. Tassone F, Pan R, Amiri K, Taylor AK, Hagerman PJ. A rapid polymerase chain reaction-based screening method for identification of all expanded alleles of the fragile X (FMR1) gene in newborn and high-risk populations. *J Mol Diagn* 2008;10(1):43–49.

51. Tassone F, Hagerman RJ, Taylor AK, Gane LW, Godfrey TE, Hagerman PJ. Elevated levels of FMR1 mRNA in carrier males: a new mechanism of involvement in the fragile-X syndrome. *Am J Hum Genet* 2000;66(1):6–15.

52. Tassone F, Hagerman RJ, Iklé DN, et al. FMRP expression as a potential prognostic indicator in fragile X syndrome. *Am J Med Genet* 1999;84(3):250–261.

53. Tassone F, Adams J, Berry-Kravis EM, et al. CGG repeat length correlates with age of onset of motor signs of the fragile X-associated tremor/ataxia syndrome (FXTAS). *Am J Med Genet B Neuropsychiatr Genet* 2007;144(4):566–569.

54. Leehey MA, Berry-Kravis E, Goetz CG, et al. FMR1 CGG repeat length predicts motor dysfunction in premutation carriers. *Neurology* 2008;70(16 Pt 2):1397–1402.

55. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62(6):593–602.

56. Kogan CS, Turk J, Hagerman RJ, Cornish KM. Impact of the Fragile X mental retardation 1 (FMR1) gene premutation on neuropsychiatric functioning in adult males without fragile X-associated Tremor/Ataxia syndrome: a controlled study. *Am J Med Genet B Neuropsychiatr Genet* 2008;147B(6):859–872.

57. Hall D, Todorova-Koteva K, Pandya S, et al. Neurological and endocrine phenotypes of fragile X carrier women. *Clin Genet* 2016;89(1):60–67.

58. Cornish KM, Kogan CS, Li L, Turk J, Jacquemont S, Hagerman RJ. Lifespan changes in working memory in fragile X premutation males. *Brain Cogn* 2009;69(3):551–558.

59. Grigsby J, Cornish K, Hocking D, et al. The cognitive neuropsychological phenotype of carriers of the FMR1 premutation. *J Neurodev Disord* 2014;6(1):28.

60. Brown SS, Stanfield AC. Fragile X premutation carriers: a systematic review of neuroimaging findings. *J Neurol Sci* 2015;352(1–2):19–28.

61. Dorn MB, Mazzocco MM, Hagerman RJ. Behavioral and psychiatric disorders in adult male carriers of fragile X. *J Am Acad Child Adolesc Psychiatry* 1994;33(2):256–264.

62. Chen Y, Tassone F, Berman RF, et al. Murine hippocampal neurons expressing Fmr1 gene premutations show early developmental deficits and late degeneration. *Hum Mol Genet* 2010;19(1):196–208.

63. Muzar Z, Lozano R. Current research, diagnosis, and treatment of fragile X-associated tremor/ataxia syndrome. *Intractable Rare Dis Res* 2014;3(4):101–109.

64. Muzar Z, Adams PE, Schneider A, Hagerman RJ, Lozano R. Addictive substances may induce a rapid neurological deterioration in fragile X-associated tremor ataxia syndrome: a report of two cases. *Intractable Rare Dis Res* 2014;3(4):162–165.

65. Martinez-Cerdeno V, Lechpammer M, Lott A, Schneider A, Hagerman R. Fragile X-associated tremor/ataxia syndrome in a man in His 30s. *JAMA Neurol* 2015;72(9):1070–1073.

66. Muzar Z, Lozano R, Schneider A, et al. Methadone use in a male with the FMRI premutation and FXTAS. *Am J Med Genet A* 2015;167(6):1354–1359.

Supporting Information

Supporting information may be found in the online version of this article.

Figure S1 (**a**) Relation of CGG repeat size and tremor age of onset. (**b**) Relation of CGG repeat size and ataxia age of onset.

Table S1 FXTAS criteria in *FMR1* premutation sample, individual level.