Lifetime Prevalence of Mood and Anxiety Disorders in Fragile X Premutation Carriers

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Objective: The authors studied the lifetime prevalence of *DSM-IV-TR* psychiatric disorders in a population of adults with the fragile X premutation.

Method: The Structured Clinical Interview for *DSM-IV* was conducted, from 2007–2008, in 85 individuals with the fragile X premutation, 47 with the fragile X–associated tremor/ataxia syndrome (FXTAS; 33 male, 14 female; mean age = 66 years) and 38 without FXTAS (16 male, 22 female; mean age = 52 years). Lifetime prevalence for mood and anxiety disorders among carriers with and without FXTAS was compared to available age-specific population estimates from the National Comorbidity Survey Replication (NCS-R).

Results: Among participants with FXTAS, 30 (65%) met lifetime *DSM-IV-TR* criteria for a mood disorder; 24 (52%) met lifetime *DSM-IV-TR* criteria for an anxiety disorder. Among the non-FXTAS participants, there were 15 instances of lifetime mood disorder (42%) and 18 of lifetime anxiety disorder (47%). When compared to age-specific NCS-R data, the lifetime prevalences of any mood disorder ($P < .0001$), major depressive disorder ($P < .0001$), any anxiety disorder ($P < .0001$), panic disorder ($P = .006$), specific phobia ($P = .0003$), and posttraumatic stress disorder ($P = .004$) were significantly higher in participants with FXTAS. The lifetime rates of social phobia in individuals with the premutation without FXTAS were significantly higher than NCS-R data ($P = .001$).

Conclusions: This sample of carriers of the fragile X premutation had a notably high lifetime risk of mood and anxiety disorders. Mood and anxiety disorders may be part of the clinical phenotype of the fragile X premutation conditions, especially in carriers with FXTAS. Clinicians encountering these patients are advised to consider FXTAS as a neuropsychiatric syndrome as well as a neurologic disorder.

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Fragile X syndrome (FXS) is a trinucleotide repeat disorder caused by an expansion of greater than 200 CGG repeats in the 5′ untranslated region of the fragile X mental retardation 1 gene (*FMR1*) on the X chromosome.[1] Depending on the number of CGG repeats, patients are classified as having normal alleles (5–44 repeats), premutation alleles (55–200 repeats), or full mutation alleles (> 200 repeats). Alleles between 45–54 CGG repeats are considered the *gray zone*, because the risk for expansion or clinical involvement is unclear or *gray*.[2]

The *FMR1* codes for *FMR1* protein (FMRP), which is believed to be involved in dendritic transport of messenger RNA (mRNA), regulation of translation, and synaptic plasticity.[3] It has been demonstrated that *FMR1* mRNA levels in peripheral blood leukocytes are 2- to 8-fold higher than normal in individuals with the premutation, despite a normal or slightly low level of FMRP.[4] The excess *FMR1* mRNA in premutation carriers may result in a "toxic gain of function" effect, leading to dysregulation of lamin A/C and several heat shock proteins, with subsequent accumulation, along with the *FMR1* mRNA, in intranuclear inclusions found in postmortem studies of fragile X–associated tremor/ataxia syndrome (FXTAS).[5,6]

Fragile X Premutation: Clinical Aspects

Premutation expansions are common; as common as 1 per 113–259 women and 1 per 260–810 men.[7–11] Patients with the premutation can present with a characteristic late-onset neurodegenerative disorder, FXTAS, described below. FXTAS is estimated to occur in 40% of premutation men and 8% of premutation women over 50 years of age who are identified through families of children with fragile X syndrome.[12] Primary ovarian insufficiency with early menopause affects up to 20% of premutation women.[13] Comorbid psychiatric illness is also seen in a subgroup of premutation carriers.[14–17]

Psychopathology in Premutation Carriers Without FXTAS

Initial studies of psychiatric illness in premutation carriers focused on women, because they were more available in the evaluation of their FXS-affected children. Women may be more protected from RNA toxicity, as they have a normal X chromosome in addition to the X chromosome with the premutation.[15] Initial reports did not find significant psychopathology in female carriers compared to controls.[18] Although the stress of raising a child with FXS could certainly add to the risk for psychiatric illness, many female

Table 1. Diagnostic Criteria for Fragile X–Associated Tremor/Ataxia Syndrome (FXTAS)[a]

Diagnostic Criteria	Symptom
Molecular	CGG repeat 55–200
Clinical	
Major	Intention tremor; cerebellar gait ataxia
Minor	Parkinsonism; moderate to severe short term memory deficit; executive function deficit
Radiologic	
Major	MRI white matter lesions involving middle cerebellar peduncles
Minor	MRI lesions involving cerebral white matter; moderate to severe generalized brain atrophy
Diagnostic category	
Definite	1 major clinical and 1 major radiologic, or presence of FXTAS inclusions
Probable	2 major clinical, or 1 minor clinical and 1 major radiologic
Possible	1 major clinical and 1 minor radiologic

[a]Adapted with permission from Jacquemont et al.[32]
Abbreviation: MRI = magnetic resonance imaging.

Table 2. Fragile X–Associated Tremor/Ataxia Syndrome Stage Descriptions[a]

Stage	Description
0	Normal function
1	Subtle or questionable signs such as subtle tremor or mild balance problems, with no interference in ADLs
2	Minor, but clear, tremor and/or balance problems with minor interference with ADLs
3	Moderate tremor and/or balance problems and occasional falls with significant interference with ADLs
4	Severe tremor and/or balance problems; uses cane or walker
5	Uses wheelchair on a daily basis
6	Bedridden

[a]Based on Bacalman et al.[37]
Abbreviation: ADLs = activities of daily living.

carriers report the lifetime experience of anxiety and depression *prior* to giving birth to children who have FXS.[19]

Franke et al[16] reported a lifetime diagnosis of depressive disorders in 21.3%, major depression in 19.7%, and bipolar disorder in 11.5% of women with the premutation who were mothers of children with FXS. Thompson et al[20] studied 14 women with the premutation (and 5 with the full mutation) and found 78% to have had a lifetime history of major depression; 33% had had recurrent mood disorder. Sobesky et al[21] found lifetime prevalence in the following psychiatric disorders in women with the premutation: major depression in 42%, dysthymic disorder in 38%, social phobia in 38%, and generalized anxiety disorder in 11%. A more recent study revealed that the abnormal elevation of mRNA correlated with severity of psychiatric symptoms in men with the premutation (with and without FXTAS); this association was not observed in women with the premutation.[15]

Roberts et al[19] studied 93 women with the premutation versus 2,159 age-adjusted female controls from the National Comorbidity Survey Replication (NCS-R).[42] They completed the Structured Clinical Interview for the *DSM-IV* (SCID-I) for lifetime and current history of mood and anxiety disorders. Compared to NCS-R control prevalences, the authors found an elevated risk of lifetime major depressive disorder (43.0% vs 31.9%), lifetime panic disorder without agoraphobia (8.6% vs 2.3%), and current agoraphobia without panic disorder (3.2% vs 0.7%) in the premutation sample. The risk of mood disorders in women with the premutation was associated with *decreased* CGG repeat length and was not associated with variables pertinent to number of children with FXS or child behavioral problems, suggesting that the social stress of raising an FXS child may not account for the incidence of mood disorders. In distinction to the finding on mood disorders, the prevalence of anxiety disorders in the premutation group was correlated with number of children with FXS and problematic child behaviors.

Various clinical findings consistent with anxiety disorders, such as anxiety, social avoidance, interpersonal sensitivity, shyness, and avoidance of eye contact have been reported in carriers of the premutation, although prevalences and psychiatric diagnostic specificity are not clear at this time.[14,22,23] Franke et al[16] reported a lifetime prevalence of anxiety disorder of 41.0% in mothers of children with FXS with the premutation; this included a high lifetime risk of social phobia (18.0%) and panic disorder (11.5%). This study also demonstrated a high prevalence of social phobia that was also seen in sisters of these women with the premutation who did not have children with FXS.

FXTAS

FXTAS is a late-onset (generally > 50 years) neuropsychiatric and neurologic degenerative illness, occurring predominantly in men with the premutation; only 8% of women with the premutation are affected.[24–29] As such, FXTAS may be one of the more common late-onset, progressive neurologic diseases resulting from a single gene mutation.[30] The major motor findings in FXTAS are kinetic—intention or postural tremor, cerebellar gait and limb ataxia, and parkinsonism.[31,32] Age at onset of motor symptoms and degree of brain atrophy correlate with CGG repeat length.[33–35] The clinical features of FXTAS are shown in the diagnostic criteria in Table 1. FXTAS clinical staging is found in Table 2.

Psychopathology in FXTAS

As is common in neurodegenerative conditions, either concurrent or sequential clinical expression of psychiatric illnesses may occur in FXTAS. Indeed, the conceptualization for central nervous system–derived symptoms and signs in such illnesses is that of "neuropsychiatric" illness. Patients may experience symptoms on several psychiatric dimensions, adding further conceptual and diagnostic imprecision. In FXTAS, this dispersion of psychiatric symptoms was illustrated by Hessl et al[15] in a study of persons with the premutation both with and without FXTAS. On the Symptom Checklist-90-Revised, relative to published norms, elevated scores on somatization, obsessive compulsive, interpersonal sensitivity, psychoticism, and the global severity index were found for carriers of the premutation (both genders); increased scores on depression and phobic anxiety were found in men with the premutation relative to

published norms. These symptoms were present in carriers who did not have FXTAS, suggesting that the RNA toxicity to the limbic system may begin in early adult life or perhaps that FXTAS has a neurodevelopmental component, as suggested by Farzin et al.[17]

With the onset of FXTAS the symptoms of anxiety and depression may worsen and dementia may develop.[36–38] Dementia may present with frontal lobe features (disinhibition, inappropriate social behavior, poor executive functioning, perseveration, irritability, and mood disturbances) and subcortical features (psychomotor slowing, bradyphrenia, and attention and concentration difficulties).[31,36,37] Onset of the dementia usually follows the onset of movement disorder, and it is rare before age 50.[31] On formal assessment, patients with FXTAS are found to suffer a larger decrement in performance IQ than in verbal IQ.[31] A recent study of 15 persons with FXTAS revealed dementia in 7; 7 were also diagnosed with mood or anxiety disorders. Twelve had cognitive impairment on formal cognitive testing.[38]

The course of progression of cognitive impairment in FXTAS dementia remains obscure, although it appears likely that FXTAS dementia is insidiously progressive. Some cognitive deficits of FXTAS dementia are of severity comparable to those in Alzheimer's disease, albeit in different domains.[39] The behavioral disturbances in FXTAS dementia have been demonstrated on the Neuropsychiatric Inventory to include apathy, depression, and agitation as more common than in age-matched controls.[37]

METHOD

Patients were recruited from 3 studies, and each involved informed consent approved by the institutional review board at University of California at Davis Medical Center. The first study recruited individuals with the premutation who had neurologic symptoms including tremor and ataxia. They were assessed for the presence of FXTAS and were subsequently recruited into a study of neuroprotective agents for FXTAS. The second study evaluated young men with the premutation without any neurologic symptoms and male siblings without the premutation. The third study assessed all family members with the premutation of a proband with the full mutation.

All participants underwent a neurologic examination to clarify the presence or absence of the motor signs of FXTAS, utilizing diagnostic criteria as reported by Jacquemont et al.[31] All participants completed psychometric testing, including IQ, Mini-Mental State Examination (MMSE),[69] Behavioral Dyscontrol Scale,[70] and Stroop.[71] The participants also completed a psychiatric evaluation, which included the Structured Clinical Interview for *DSM-IV* (SCID).[72] The SCID is a structured clinical interview for *DSM-IV* psychiatric disorders. The format of the SCID begins with a general medical and psychiatric history, and then proceeds with diagnostic criteria for mood, psychotic, substance use, anxiety, somatoform, and adjustment disorders. The interviewer asks a prescribed series of questions that correspond to the *DSM-IV* diagnostic criteria for the various psychiatric disorders. The format of the SCID includes breakdown for current and past psychiatric disorders, duration of each episode, age at onset of first episode, severity of functional impairment, and other details. To render a formal diagnosis of a psychiatric illness based on SCID-derived data requires the validation of *DSM-IV* criteria for each illness. Current and lifetime illness experience may be tabulated separately. Interview data are then gleaned from the interview document for analysis. The SCID interviews were completed from 2007 to 2008 by 3 of the authors (J.A.B., A.L.S., and A.S.), all of whom are experienced at conducting this interview for research programs. As this is a detailed structured clinical interview, test-retest reliability is high, and this instrument is considered a "gold standard" for psychiatric epidemiology.[40,41] One of its major benefits, as the interviewer is required to progress throughout major categories of psychiatric disorders in the conduct of the interview, is its utility in helping the interviewer to document psychiatric comorbidity. Of relevance in our cohort are psychiatric comorbidity, both *across* psychiatric disorder boundaries (eg, a patient with independent history of mood and anxiety disorders) and *within* psychiatric disorder boundaries (eg, a patient with 2 or more distinct anxiety disorders).

In interpretation of SCID interview data, the examiner seeks to describe patients' illness in terms of *caseness* (eg, a patient with a history of major depression and panic disorder is considered a *case* of each illness), so that multiple diagnoses (*cases*) in a single patient are allowed. Weaknesses of the SCID include the failure to include criteria for cognitive, personality, and childhood-onset disorders. An additional weakness of the SCID paradigm, particularly in the analysis of older patients with risk of cognitive impairment, is the requirement of intact memory to recall prior illness experiences.

Our primary analyses focused on mood and anxiety disorders. All other analyses are considered secondary and exploratory. We compared the lifetime prevalence of mood

Table 3. Characteristics of Patients With Premutation With and Without FXTAS[a]

	FXTAS (n = 47)			Non-FXTAS (n = 38)			
Variable	n	Mean	SD	n	Mean	SD	*P* Value
Age, y	47	66.40	7.88	38	51.61	11.67	< .0001
Male sex, n (%)	33	70%	…	16	43%	…	.0154
Education, y	46	14.98	2.89	31	15.42	1.82	.4528
CGG repeats	43	90.26	20.45	25	101.28	63.90	.2987
FMR1 mRNA	37	3.00	0.99	23	2.91	1.55	.7848
Verbal IQ	40	108.00	21.42	37	114.30	13.91	.1336
Performance IQ	39	103.59	16.91	37	112.38	16.21	.0236
Full scale IQ	38	107.29	14.00	37	111.89	22.58	.2908
MMSE score	46	28.57	2.46	19	29.79	0.42	.0353
BDS2 score	42	15.60	4.83	35	21.23	3.54	< .0001
Stroop score	41	43.98	9.27	14	45.93	4.12	.4508

[a]Data are presented as mean and SD except where noted.
Abbreviations: BDS2 = Behavioral Dyscontrol Scale, 2nd version; *FMR1* = fragile X mental retardation 1 gene; FXTAS = fragile X–associated tremor/ataxia syndrome; MMSE = Mini-Mental State Examination; mRNA = messenger RNA.

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Table 4. Lifetime Prevalence of Mood Disorders, Non-FXTAS and FXTAS vs Age-Adjusted National Comorbidity Survey (NCS) Data[a]

	Any Mood Disorder			Major Depressive Disorder			Dysthymic Disorder			Bipolar Disorders		
Subject Characteristic	%	n/n	*P* Value	%	n/n	*P* Value	%	n/n	*P* Value	%	n/n	*P* Value
Non-FXTAS	41.7	15/36	.031	22.2	8/36	.88	11.1	4/36	.094	8.3	3/36	.295
NCS (age category 45–59 y)	24.2			20.1			3.8			3.7		
FXTAS, male	62.5	20/32	<.0001*	31.3	10/32	.013*	0	0/32	…	6.3	2/32	.805
FXTAS, all	65.2	30/46	<.0001*	43.5	20/46	<.0001*	2.2	1/46	.905	4.4	2/46	.241
NCS (age category 60+ y)	12.2			10.7			1.3			1.3		

[a]*P* values were adjusted for multiple testing using the false discovery rate (FDR) criterion; a significant *P* value after FDR adjustment is indicated by an asterisk.
Abbreviation: FXTAS = fragile X–associated tremor/ataxia syndrome.

Table 5. Lifetime Prevalence of Anxiety Disorders, Non-FXTAS and FXTAS vs Age-Adjusted National Comorbidity Survey (NCS) Data[a]

	Any Anxiety Disorder			Panic Disorder			Specific Phobia			Social Phobia			Generalized Anxiety Disorder			PTSD			Obsessive-Compulsive Disorder		
Subject Characteristic	%	n/n	*P* Value	%	n/n	*P* Value	%	n/n	*P* Value	%	n/n	*P* Value	%	n/n	*P* Value	%	n/n	*P* Value	%	n/n	*P* Value
Non-FXTAS	47.4	18/38	.128	13.2	5/38	.142	23.7	9/38	.173	34.2	13/38	.001*	2.6	1/38	.409	2.6	1/38	.248	0	0/38	…
NCS (age category 45–59 y)	34.2			5.9			14.4			12.6			7.6			9.2			2.4		
FXTAS, male	50.0	16/32	.005*	3.1	1/32	1	21.9	7/32	<.0001*	15.6	5/32	.558	12.5	4/32	.088	9.4	3/32	.214	0	0/32	…
FXTAS, all	52.2	24/46	<.0001*	10.9	5/46	.006*	26.1	12/46	.0003*	17.4	8/46	.023	10.9	5/46	.072	13.0	6/46	.004*	0	0/46	…
NCS (age category 60+ y)	17.8			2.1			7.7			6.8			4.0			2.8			0.6		

[a]*P* values were adjusted for multiple testing using the false discovery rate (FDR) criterion; a significant *P* value after FDR adjustment is indicated by an asterisk.
Abbreviations: FXTAS = fragile X–associated tremor/ataxia syndrome, PTSD = posttraumatic stress disorder.

and anxiety disorders to available age-specific population estimates from the NCS-R,[42] a nationally representative sample that used both the Composite International Diagnostic Interview (CIDI) and the SCID. For the NCS-R, 9,282 adult interviews were completed, with statistical weighting models applied to demographic variables. Lifetime prevalence of psychiatric illness was reported stratified by age and gender.

The CIDI is mostly used by the World Health Organization in World Mental Health surveys, and it is based on the *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision. This classification system is comparable to the *DSM-IV-TR*, and it focuses on the coding of diseases, social circumstances, and external causes of injury or illnesses. Several studies have been published so far about the comparison between the diagnostic specificity of the CIDI and SCID.[43–45] Especially for the diagnoses of mood and anxiety disorders, Kessler et al[46,47] described an excellent concordance of both instruments.

Comparisons of the current study's prevalence estimates to NCS-R's age-specific prevalence figures were based on the exact binomial method (2-sided test at level .05). (*P* values were adjusted for multiple testing using the false discovery rate (FDR) criterion, and a significant *P* value after FDR adjustment is indicated by an asterisk in Tables 4 and 5.) There was 1 missing data point for mood disorders and anxiety in the FXTAS group and 2 missing data points in the group without FXTAS. This is a 1-sample comparison of the proportion to published prevalence figures for age groups similar to the age of our study premutation cohort with and without FXTAS. Patient characteristics (see Table 3), including molecular measures (CGG repeat number, *FMR1* mRNA), were based on *t* tests for continuous variables and Fisher exact test for categorical variables.

RESULTS

Patient characteristics, including demographics, CGG, *FMR1* mRNA, and cognitive testing results are summarized by FXTAS status in Table 3. Mean age of carriers with FXTAS (n = 47) was 66.4 years (SD = 7.9; range, 54–87) and for carriers without FXTAS (non-FXTAS; n = 38), the mean age was 51.6 years (SD = 11.7; range, 35–76; see Table 3 for details). Participants with the premutation with no neurologic signs and stage 1 FXTAS (n = 11) were combined as 1 group, since stage 1 FXTAS has no definite tremor or ataxia, and it does not include a definitive diagnosis of FXTAS (Table 2), while stages 2–5 FXTAS participants were combined as the FXTAS group. The relationship between FXTAS stage and SCID anxiety and mood disorders was not significant. In addition, we did not find a significant association between mRNA levels and number of CGG repeats to the presence of a SCID-diagnosed disorder.

To compare age-specific lifetime prevalences of mood and anxiety disorders, we selected NCS-R data for the age categories of 45–59 and 60+ years to compare with those from our samples of non-FXTAS and FXTAS participants, respectively. These NCS-R age-specific categories include the mean age of our study groups. When we examined lifetime prevalence of any mood disorder, both carriers with and without FXTAS had higher prevalences compared to NCS-R

general population estimates. However, this prevalence in carriers without FXTAS was not significant after *P* value adjustment. Observed lifetime prevalence of major depressive disorder in premutation carriers without FXTAS was similar to that in the NCS-R general population. However, among patients with FXTAS, lifetime prevalence of major depressive disorder was significantly higher than in the NCS-R. There was no difference with NCS-R figures with respect to the lifetime prevalence of dysthymic disorder and bipolar disorders. The higher prevalence estimates for major depressive disorder and any mood disorder in FXTAS remained unchanged for men with FXTAS (n = 32, after excluding women with FXTAS). Details are provided in Table 4.

With respect to anxiety disorders, the participants with FXTAS had higher lifetime prevalence of any anxiety disorder, panic disorder, specific phobia, social phobia, and posttraumatic stress disorder (PTSD) than were found in the NCS-R. However, the increased prevalence of social phobia was not significantly higher after *P* value adjustment. Premutation carriers without FXTAS also had higher lifetime prevalence of social phobia, although lifetime prevalence of other anxiety disorders and the aggregate of any anxiety disorder were not different from NCS-R general population estimates. The higher prevalence estimates for any anxiety disorder and specific phobia in FXTAS remained significant for men with FXTAS (n = 32, after excluding women with FXTAS). However, panic disorder and PTSD prevalences were not significant among men with FXTAS after excluding women. Details are provided in Table 5.

DISCUSSION

This project examined the lifetime prevalences of *DSM-IV* psychiatric disorders in a cohort of 85 carriers of the fragile X premutation. To examine psychiatric disorders in the premutation cohort with and without FXTAS, the analysis was accordingly stratified by these groups. These lifetime prevalences were compared to corresponding age-specific general population estimates (NCS-R). Because of our low numbers of female participants, analysis controlling for gender was not done. When compared to age-specific NCS-R data, the lifetime prevalence of any mood disorder, major depressive disorder, any anxiety disorder, panic disorder, specific phobia, and PTSD was significantly higher in the participants with FXTAS.

The analysis of these lifetime prevalences did not include assessment of associated and antecedent events, which may be of importance, in particular in the increased prevalence of PTSD in FXTAS. It may be postulated that patients with FXTAS, by virtue of their increased experience of anxiety symptoms in general, may be somewhat more disposed to develop PTSD when exposed to traumatic experiences than their counterparts in the NCS-R. This phenomenon could be a productive area of future study. The lifetime prevalence of social phobia in premutation participants without FXTAS was significantly higher than in NCS-R data. The lifetime prevalences of mood and anxiety disorder diagnoses for both the premutation group without FXTAS and the group with FXTAS are both high compared to general population studies using similar structured interviews.

In addition to the NCS-R study, several other studies using *DSM*-referenced diagnostic interviews to assess the lifetime prevalence of mood and anxiety disorders in adult population-based cohorts have been conducted.[44,48–58] While employing different diagnostic instruments, these comparable studies reported lifetime prevalences of mood (8%–21%) and anxiety (15%–29%) disorders at rates similar to those in the NCS-R study.

Previous studies of psychopathology in premutation carriers had included only female participants and found significant lifetime prevalences of mood and/or anxiety disorders.[16,19–21] Our study is the first large study of psychopathology in premutation carriers to include a large percentage of male premutation patients (70% of the FXTAS group, 43% of the non-FXTAS group). As men in the general population tend to have a lower prevalence of psychiatric illness (particularly major depression) than women, our findings are all the more striking.

It is important to emphasize that the current study examined the lifetime (not necessarily current) prevalence of mood and anxiety disorders in individuals with the fragile X premutation. As we did not, in this study, assess the age at onset of psychiatric disorders, the temporal sequencing of "psychiatric illness first, motor symptoms second" is suggested because we saw a higher prevalence of certain psychiatric problems in premutation carriers in those without FXTAS compared to the general population. Further studies of the age at onset of psychiatric syndromes are underway to address this issue specifically.

It is hypothesized that vulnerability to lifetime mood and anxiety disorders may be a condition of the fragile X premutation itself, rather than purely a consequence of social stressors, such as the experience of a degenerative neuropsychiatric condition or the responsibility of caring for a child with FXS. While responsibility for the care of a neurodevelopmentally impaired child with FXS can clearly represent a profound chronic social stressor, many of our participants were diagnosed with premutation carrier status as the result of pedigree analysis of an affected grandchild and had not been primarily responsible for care for an impaired child. Further studies examining age at onset of the first episode of psychiatric disorders and social stressors (such as raising a FXS child) in premutation carriers are now underway to address these potential contributing factors.

We note here that recent brain imaging studies document that men with the premutation without FXTAS who are not raising affected children have abnormal reductions in amygdala and hippocampal activation related to both abnormal elevation of *FMR1* mRNA and psychiatric symptoms.[59,60] Additional reports of progressive decline in executive function, such as working memory and attention in men with the premutation beginning in the third decade of life, may point toward a neurophysiological basis of psychiatric disorder in this population.[61] Evidence of psychopathology and

neurophysiological deficits before the onset of FXTAS is not surprising, because evidence of RNA toxicity, including inclusions, develop in the premutation mouse throughout the limbic system, including the amygdala and hippocampus, earlier than expected and before the onset of FXTAS in the mouse.[62]

There is an apt comparison available between the psychopathology in fragile X premutation conditions and Parkinson's disease. Indeed, it has been the experience of our research group that many patients with FXTAS, by virtue of their progressive motor symptoms, are often initially diagnosed with variants of Parkinson's disease. While the research methodologies differ, the literature to date assessing lifetime mood and anxiety disorders prevalence in Parkinson's disease are similar to our findings, especially in patients with FXTAS. The lifetime prevalence of mood disorder is as high as 60% and of anxiety disorders (including simple phobia and panic disorder) is as high as 40% in Parkinson's disease.[63–68] As such, the possibility exists that Parkinson's disease with mood and anxiety disorder comorbidity may share a common neuroanatomic pathway (at least in functional terms) with fragile X premutation conditions. Further research studies enrolling fragile X premutation patients and Parkinson's disease patients in the same research protocol would be desirable to further examine this comparison.

A potential confounder in the analysis of lifetime history of mood and anxiety disorders in patients with the premutation may be related to the comorbidity of dementing illness in patients with FXTAS. Mood and anxiety disorders are common comorbidities in dementing illnesses; thus, primary FXTAS dementia may eventually lead to dementia-associated mood and anxiety disorders, instead of mood and/or anxiety disorders' antedating dementing illness. Secondly, patients with clinical dementia may, by dint of retrograde amnesia, have difficulty in accurately describing previously experienced psychiatric illness in sufficient detail to render an accurate *DSM-IV* diagnosis in the SCID interview. In our cohort, however, the mean MMSE score was 28.6 for the FXTAS group and 29.8 for non-FXTAS, scores consistent with intact cognitive function. Our participants' intact cognitive status is reinforced by IQ results, with mean full-scale IQ scores of 107 in the FXTAS group and 112 in the non-FXTAS group. Despite high mean MMSE and IQ scores, 2 of the participants met criteria for dementia, and 1 had mild cognitive impairment. When performing SCID interviews with these participants, we obtained collateral information from their spouses in completing the SCIDs. Therefore, it is unlikely that cognitive function introduced bias in the vast majority of our participants' recall of their psychiatric histories. Similarly, due to the small number of patients with cognitive impairment, the possible number of dementia-associated mood and anxiety disorders in our cohort is quite low.

Although the majority of patients with FXTAS were clinic-referred for their movement disorder, none were referred due to psychiatric concerns. In addition, younger individuals with the premutation without FXTAS seen in the study were not clinically referred but were recruited from pedigrees of families affected by FXS, also unrelated to psychiatric concerns. Despite these efforts to minimize selection bias, we recognize that potential selection bias may still exist and, therefore, may affect the prevalence estimates of psychiatric disorders observed in our sample. Future studies examining psychiatric conditions in carriers of the premutation should attempt to control for various sources of bias and confounding factors and employ well-matched control groups. In addition, further study of the sequencing of the experience of psychiatric disorders in this population by examination of the age at onset of the first episode of the various SCID-diagnosed psychiatric illness compared to the age at onset of motor symptoms is planned to elucidate the issue of primary versus secondary illness episodes.

Despite the imprecision of attribution of the genesis of mood and anxiety disorders in this population, clinicians encountering patients with a family history of FXS (or any autism-spectrum disorder) and/or dementing illness or movement disorder should consider *FMR1* DNA testing as part of the clinical evaluation. In many cases, positive identification of the premutation in an older adult with the aforementioned motor or cognitive signs has led to first diagnosis of FXS in grandchildren or other family members, and as such genetic counseling is strongly recommended in these cases. Prompt clinical intervention with medication and/or psychotherapy for mood and anxiety disorders should be offered for these patients. Vigilance for cognitive and motor status is also highly recommended.

CONCLUSION

Lifetime prevalences of mood and anxiety disorders were found to be high in individuals with the fragile X premutation with FXTAS. Participants with the premutation without FXTAS had a high prevalence of lifetime mood disorders overall (although the lifetime prevalences of major depression, dysthymic disorder, and bipolar disorder were not individually significantly more common than in the NCS-R) and social phobia. This study is consistent with an emerging neuropsychiatric phenotype in fragile X carriers in which genetically-determined mood and anxiety disorders appear to be substantial clinical components of this disorder. This illness may well represent a relatively common neuropsychiatric disorder that is attributable to a single gene mutation. Clinicians encountering mood and anxiety disorders in patients with a family history of intellectual disability apparent in childhood and/or dementia, particularly dementia with a movement disorder, may wish to obtain confirmatory DNA testing for the fragile X premutation in these patients.

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