

Expanded Clinical Phenotype of Women With the *FMR1* Premutation

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Fragile X-associated tremor/ataxia syndrome (FXTAS) is generally considered to be uncommon in older female carriers of premutation alleles (55–200 CGG repeats) of the fragile X mental retardation 1 (*FMR1*) gene; however, neither prevalence, nor the nature of the clinical phenotype, has been well characterized in female carriers. In this study, we evaluated 146 female carriers (mean, 42.3 years; range, 20–75 years) with and without core features of FXTAS (tremor; gait ataxia), and 69 age-matched controls (mean, 45.8 years; range, 21–78 years). Compared with controls, carriers with definite or probable FXTAS had greater medical co-morbidity, with increased prevalence of thyroid disease ($P=0.0096$), hypertension ($P=0.0020$), seizures ($P=0.0077$), peripheral neuropathy ($P=0.0040$), and fibromyalgia ($P=0.0097$), in addition to the typical symptoms of FXTAS—tremor ($P<0.0001$) and ataxia ($P<0.0001$). The non-FXTAS pre-

mutation group had more complaints of chronic muscle pain ($P=0.0097$), persistent paraesthesias in extremities ($P<0.0001$), and history of tremor ($P<0.0123$) than controls. The spectrum of clinical involvement in female carriers with FXTAS is quite broad, encompassing a number of medical co-morbidities as well as the core movement disorder. The remarkable degree of thyroid dysfunction (17% in the non-FXTAS group and 50% in the FXTAS group) warrants consideration of thyroid function studies in all female premutation carriers, particularly those with core features of FXTAS. © 2008 Wiley-Liss, Inc.

Key words: FXTAS; fragile X premutation; neuropathy; hypothyroidism

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INTRODUCTION

Until 1991, women who harbored a premutation allele (55–200 CGG repeats) of the fragile X mental retardation 1 (*FMR1*) gene were thought to be unaffected by the expanded allele. Cronister et al. (1991) reported a higher rate of premature ovarian failure (POF) in carrier females than in those with either full mutation expansions (>200 CGG repeats) or normal alleles; an association that has been confirmed by multiple subsequent studies [Allingham-Hawkins et al., 1999; Murray et al., 2000; Sullivan et al., 2005]. More recently, fragile X-associated tremor/ataxia syndrome (FXTAS), a neurodegenerative movement disorder, has been reported in females with the premutation [Hagerman et al., 2004; Zuhlke et al., 2004; Berry-Kravis et al., 2005; Jacquemont

et al., 2005; O'Dwyer et al., 2005], although its penetrance and expression appear to be much lower than in male carriers [Jacquemont et al., 2004b]. Furthermore, females with FXTAS generally have milder involvement both neuroradiologically [Adams

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et al., in press] and cognitively, compared to males with FXTAS [Hagerman et al., 2004], due in part to the protective influence of the second X chromosome [Hagerman et al., 2004; Berry-Kravis et al., 2005; Jacquemont et al., 2005].

FXTAS typically occurs in carriers over 50 years of age, and has core features of intention tremor and gait ataxia. Associated signs of FXTAS include autonomic dysfunction, peripheral neuropathy, executive cognitive function deficits, and general cognitive decline [Hagerman et al., 2001; Leehey et al., 2002; Jacquemont et al., 2003; Loesch et al., 2005a,b; Bacalman et al., 2006]. Individuals with FXTAS have global CNS atrophy, white matter disease in the middle cerebellar peduncles (MCP) and subcortical and periventricular regions [Brunberg et al., 2002; Jacquemont et al., 2003] and astrocytic and neuronal intranuclear inclusions throughout the CNS [Greco et al., 2002, 2006; Louis et al., 2006].

The neurodegenerative changes in FXTAS are thought to be due to a toxic gain of function of the expanded-repeat *FMR1* mRNA in carriers, [Jin et al., 2002; Allen et al., 2004; Hagerman and Hagerman, 2004; Iwahashi et al., 2006; Tassone et al., 2000b], with the expanded-repeat *FMR1* mRNA itself present within the inclusion bodies [Tassone et al., 2004]. More than 20 proteins have been identified within the inclusions, including the small stress-response protein, α B-crystallin, the nuclear intermediate filament protein, lamin A/C, the RNA binding protein, hnRNP A2, and myelin basic protein [Greco et al., 2002, 2006; Iwahashi et al., 2006]. Dysregulation of at least two of these proteins, α B-crystallin and lamin A/C, is clearly related to disease pathogenesis [Arocena et al., 2005].

Medical comorbidities frequently affecting women with the premutation include increased incidence of osteoporosis [Hundscheid et al., 2003], and endocrine issues such as elevated FSH and POF [Welt et al., 2004; Sullivan et al., 2005]. POF has also been reported in females with a gray zone allele (45–54 CGG repeats) with a frequency that is twice that in the females without a CGG expansion [Bodega et al., 2006]. Furthermore, Loesch et al. [2005a] have noted that a spectrum of neurological problems may exist in those with the premutation. Some of these problems may be related to FXTAS pathogenesis, but clinical features often do not meet the diagnostic criteria for FXTAS as described in Jacquemont et al. [2003] and Hagerman and Hagerman [2004].

To address the possibility of a broad phenotype in adult female carriers, the current study has documented medical and neurological problems present in female carriers of the fragile X premutation, who were ascertained through families with known fragile X syndrome probands. We document important medical comorbidities that should lead to more systematic evaluation for their presence in women who harbor premutation alleles.

MATERIALS AND METHODS

Subjects

Study subjects included 146 females with a premutation allele and 69 female controls, all recruited through a study of genotype–phenotype relationships in families affected by fragile X syndrome. This research took place at the M.I.N.D. Institute at University of California at Davis, between 2002 and 2006. Most of the women with a premutation allele were mothers of children with fragile X syndrome, although other participants included sisters, aunts, and grandmothers of children with fragile X syndrome who were identified by cascade testing. Fifteen women referred themselves for participation in our study because they were concerned about neurological symptoms, and we subsequently diagnosed 12 of these with definite or probable FXTAS. The control subjects were wives of males with the premutation, female family members with normal alleles who were identified by cascade testing, females recruited from staff and faculty at the M.I.N.D. Institute, and females from the general population. Demographic information can be found in Table I.

Following the clinical evaluation, which included a neurological examination as described below, the 146 carriers were divided into two groups: non-FXTAS ($n = 128$) and FXTAS ($n = 18$). Women were assigned to the FXTAS group if they currently met the neurological criteria for definite FXTAS or probable FXTAS, as defined by the classification system described in Jacquemont et al. [2003]. By definition, these patients had a combination of major and minor radiological signs (MCP hyperintensities, cerebral white matter lesions, moderate-to-severe generalized atrophy) and clinical symptoms (intention tremor, gait ataxia, parkinsonism, moderate-to-severe working memory deficiency, executive cognitive function deficits). Thus, the non-FXTAS group could have included individuals with some neurological features and other symptoms that did not meet criteria for probable or definite FXTAS [Jacquemont et al., 2003]. Subjects in the control group were age-matched to both premutation groups (Table I).

Methods

All subjects underwent a full medical history and examination including a detailed neurological examination after informed consent was obtained. The medical history included a detailed review of systems, and questions regarding medical conditions, neurological problems, surgical history, and medications. To be classified as having a medical diagnosis, we required that the subject had been previously diagnosed and treated by a physician for each disorder (i.e., hypertension, hypothyroidism,

TABLE I. Characteristics of Study Subjects

Characteristic	Control ^d	Premutation non-FXTAS	Size ^b n _c /n _p	P-value ^c	Control ^d	Premutation FXTAS	Size n _c /n _p	P-value
Age	45.8 ± 14.86 ^e (21–78 years) ^f	42.3 ± 11.54 (20–75 years)	69/128	0.0641	57.1 ± 8.91 (42–78 years)	59.2 ± 10.3 (42–74 years)	39/18	0.4451
Ethnicity (%)			68/125	—			38/18	—
Caucasian	76.47	84.80			—	94.44		
Hispanic	7.35	8.80			—	5.56		
African-American	1.47	1.60			—	0.0		
Asian	11.76	0.80			—	0.0		
American Indian ^g	0.00	1.60			—	0.0		
Other	2.94	2.40			—	0.0		
CGG repeat	32.6 ± 10.81	93.4 ± 21.35	47/120	<0.0001	34.0 ± 15.23	92.4 ± 11.34	23/17	<0.0001
<i>FMRI</i> RNA	1.4 ± 0.26	2.6 ± 0.85	25/118	<0.0001	1.3 ± 0.29	2.8 ± 1.08	16/17	<0.0001
<i>FMRP</i>	85.3 ± 10.47	87.3 ± 8.31	4/53	0.6441	—	84.3 ± 10.81	—/8	0.3784*
Activation ratio	—	0.54 ± 0.16	—/112	—	—	0.53 ± 0.15	—/17	0.9189*

P values based on *t* tests are for comparisons between corresponding controls with premutation carriers with or without FXTAS. Specific relevant comparisons between premutation carriers with and without FXTAS are indicated by a superscript *.

^aTotal number of subjects is as follows: control subjects is n = 69, premutation carriers without FXTAS is n = 128, and premutation carriers with FXTAS is n = 18. Total n less than 69, 128, and 18, respectively, is due to missing data.

^bGroup-specific sample size n_c/n_p (control/premutation group).

^c*P*-value for comparing corresponding controls to premutation group.

^dSubset of control subjects with similar age range (42–78) to premutation carriers with FXTAS.

^eMean ± SD.

^fAge range.

^gAmerican Indian or Alaskan Native.

**P* values for comparisons between premutation carriers with and without FXTAS.

type II diabetes mellitus, fibromyalgia, rheumatoid arthritis, peripheral neuropathy, multiple sclerosis, etc.). Subjects who presented with mild symptoms but who had not yet been diagnosed by a medical professional were not considered to have those diagnoses in the current statistical analysis. Specific criteria were established for neurological symptoms in the review of systems and on physical examination. Muscle pain was defined as persistent myalgia for greater than 2 months, unrelated to injury. Sensory loss was defined as persistent or intermittent numbness in the face or extremities for greater than 2 months, unrelated to injury or surgery. On physical examination, sensory loss was scored as present when a deficit was seen in response to proprioceptive stimulation. A description of the neurological exam can be found in Jacquemont et al. [2003]. The University of California, Davis Institutional Review Board Administration approved this study.

Molecular Analysis

A blood sample for determination of CGG status and *FMRI* mRNA level was obtained from each subject. Genomic DNA and total RNA were isolated from peripheral blood leukocytes (5 ml of whole blood) using standard methods (Puregene and Purescript Kits, Gentra, Inc., Minneapolis, MN; Tempus Tubes, Applied Biosystems, Foster City, CA). *FMRI* mRNA quantification, Southern Blot, and PCR-based genotyping were performed as described previously [Tassone et al., 2000a, 2004; Saluto et al., 2005]. Analysis and calculation of trinucleotide

expansion allele size, as well as the determination of the activation ratio (AR = fraction of normal *FMRI* allele as the active allele), were conducted using an Alpha Innotech FluorChem 8800 Image Detection System.

Statistical Analysis

Medical and neurological variables were rated dichotomously (presence or absence). Fisher's exact test for 2 × 2 contingency table analysis was used to assess the association between premutation carrier status and medical and neurological diagnosis. Control subjects (n = 69) were matched on age as a group with premutation carriers without FXTAS (non-FXTAS; n = 128). For the analysis of an association between FXTAS (n = 18) status and medical and neurological variables, an age-matched subset of older controls ages 42–78 (n = 39) was compared with subjects with FXTAS. (Details are given in the next section and Table I.) Continuous variables describing patient characteristics, including age, CGG repeat size, *FMRI* mRNA level, *FMRP* level, AR, and onset age of tremor and ataxia, were compared using *t* tests.

RESULTS

Patient Characteristics

Characteristics of the study subjects are summarized in Table I. The age range of controls (ages 21–78) was matched to that of the premutation carriers

(ages 20–75). There was no significant difference in mean age between the controls (45.8 ± 14.9) and premutation (42.3 ± 11.5) carriers ($P = 0.0641$). Similarly, a subset of older control subjects (ages 42–78) was selected to match the age of premutation carriers affected with FXTAS (ages 42–74). Again, there was no significant difference in age between the older control and FXTAS groups ($P = 0.4451$). As one would expect, there were significant differences in CGG repeat size and *FMR1* RNA levels for controls and premutation carriers with and without FXTAS ($P < 0.001$), but ARs were not different for the FXTAS and non-FXTAS groups ($P = 0.9189$). Data concerning medical and neurological findings can be found in Tables II and III.

Premutation Carriers in the Non-FXTAS Group

Premutation carriers in the non-FXTAS group ($n = 128$) had a significantly higher prevalence of muscle pain by history (25.6% vs. 8.9%; $P = 0.0097$), tremor history (11.7% vs. 1.5%; $P = 0.0123$), and persistent numbness and tingling in the extremities by history (45.2% vs. 11.9%; $P < 0.0001$) than did controls ($n = 69$) (see, Table II). Additional medical and neurological findings by history (e.g., thyroid problems, 17.3% vs. 10.1%; hypertension, 16.4% vs. 10.1%; neuropathy, 12.1% vs. 4.1%) were more

common in the non-FXTAS group than among controls, although these differences were not statistically significant.

Premutation Carriers With FXTAS

As expected, women with FXTAS differed significantly from age-matched controls, by both history and neurological examination with respect to the core features of FXTAS, including tremor and ataxia (see, Table III). In addition, compared with age-matched controls, patients with FXTAS had significantly higher prevalence by history of thyroid disorders (50% vs. 15.4%; $P = 0.0096$), hypertension (61.1% vs. 18%; $P = 0.002$), seizures (22.2% vs. 0%; $P = 0.0077$), diagnosed peripheral neuropathy (52.9% vs. 9.1%; $P = 0.004$), fibromyalgia (43.8% vs. 9.4%; $P = 0.0097$), and persistent muscle pain (76.5% vs. 10.7%; $P < 0.0001$). Some of these problems, including neuropathy and hypertension, have been noted previously in studies of FXTAS [Berry-Kravis et al., 2007a,b; Jacquemont et al., 2003, 2004a]; however, the associations of thyroid disease, fibromyalgia, and muscle pain are new findings.

Among the 18 premutation carriers with FXTAS, nine (50%) indicated a history of thyroid problems. Of these nine with thyroid problems, six reported a history of hypothyroidism of unspecified etiology requiring treatment. The remaining three patients,

TABLE II. Comparisons Between Controls and Non-FXTAS Premutation Carriers

	Control % (n_c)	Premutation non-FXTAS % (n_p)	Total % (n) ^a	<i>P</i> -value
POF	5.6 (36)	19.0 (63)	14.1 (99)	0.0772
Thyroid problems	10.1 (69)	17.3 (127)	14.8 (196)	0.2101
Diabetes	0.0 (69)	3.9 (127)	2.6 (196)	0.1639
Lupus	0.0 (61)	2.4 (125)	1.6 (186)	0.5520
Hypertension	10.1 (69)	16.4 (128)	14.2 (197)	0.2875
Seizures	0.0 (69)	2.3 (128)	1.5 (197)	0.5531
MS	0.0 (61)	0.80 (125)	0.5 (186)	1.0000
Work-up for MS	0.0 (56)	4.0 (125)	2.8 (181)	0.3260
Peripheral neuropathy	4.1 (49)	12.1 (116)	9.7 (165)	0.1529
Fibromyalgia	5.0 (60)	8.3 (121)	7.2 (181)	0.5491
Muscle pain	8.9 (56)	25.6 (125)	20.4 (181)	0.0097*
Tremor history	1.5 (68)	11.7 (128)	8.6 (196)	0.0123*
Probs. walk/ataxia hist.	1.5 (68)	8.6 (128)	6.1 (196)	0.0604
Sensory loss (Hx)	11.9 (67)	45.2 (126)	33.7 (193)	<0.0001*
Tremor exam	12.7 (63)	5.6 (125)	8.0 (188)	0.1508
Intention tremor exam	11.1 (63)	4.0 (125)	6.4 (188)	0.1091
Dysmetria exam	1.6 (63)	2.4 (125)	2.1 (188)	1.0000
Resting tremor exam	1.6 (63)	2.4 (126)	2.1 (189)	1.0000
Gait problem exam	3.2 (63)	4.0 (125)	3.7 (188)	1.0000
Gait ataxia	1.6 (63)	3.2 (125)	2.7 (188)	0.6654
Gait listing	0.0 (63)	2.4 (124)	1.6 (187)	0.5520
Gait broad based	1.6 (62)	1.6 (124)	1.6 (186)	1.0000
Sensation loss in LE (exam)	6.7 (60)	7.6 (118)	7.3 (178)	1.0000

Medical, neurological, and hypertensive problems, and FXTAS-related symptoms in controls patients ($n_c = 69$) and premutation carriers ($n_p = 128$) in the non-FXTAS group. Given are the percentages for controls and carriers with group-specific totals, overall total number of subjects (n), and Fisher's exact *P* values.

^aTotal number of subjects combined is $n = 197$. Total n less than 197 is due to missing data.

*Significant tests at level 0.05.

TABLE III. Comparisons Between Controls and Premutation Carriers With FXTAS

	Control % (n _c)	Premutation with FXTAS % (n _p)	Total % (n) ^a	P-value
POF	5.9 (34)	13.3 (15)	8.2 (49)	0.5764
Thyroid problems	15.4 (39)	50.0 (18)	26.3 (57)	0.0096*
Diabetes	0.0 (39)	11.1 (18)	3.5 (57)	0.0959
Lupus	0.0 (33)	5.9 (17)	2.0 (50)	0.3400
Hypertension	18.0 (39)	61.1 (18)	31.6 (57)	0.0020*
Seizures	0.0 (39)	22.2 (18)	7.0 (57)	0.0077*
MS	0.0 (33)	5.9 (17)	2.0 (50)	0.3400
Work-up for MS	0.0 (29)	11.8 (17)	4.4 (46)	0.1314
Peripheral neuropathy	9.1 (22)	52.9 (17)	28.2 (39)	0.0040*
Fibromyalgia	9.4 (32)	43.8 (16)	20.8 (48)	0.0097*
Muscle pain	10.7 (28)	76.5 (17)	35.6 (45)	< 0.0001*
Tremor history	0.0 (38)	89.0 (18)	28.6 (56)	< 0.0001*
Probs. walk/ataxia hist.	2.6 (38)	83.3 (18)	28.6 (56)	< 0.0001*
Sensory loss (Hx)	18.9 (37)	83.3 (18)	40.0 (55)	< 0.0001*
Tremor exam	11.4 (35)	77.8 (18)	34.0 (53)	< 0.0001*
Intention tremor exam	8.6 (35)	64.7 (17)	26.9 (52)	< 0.0001*
Dysmetria exam	2.9 (35)	35.3 (17)	13.5 (52)	0.0034*
Resting tremor exam	2.9 (35)	50.0 (18)	18.9 (53)	< 0.0001*
Gait problem exam	5.7 (35)	100.0 (18)	37.7 (53)	< 0.0001*
Gait ataxia	2.9 (35)	94.4 (18)	34.0 (53)	< 0.0001*
Gait listing	0.0 (35)	52.9 (17)	17.3 (52)	< 0.0001*
Gait broad based	2.9 (35)	52.9 (17)	19.2 (52)	< 0.0001*
Sensation loss in LE (exam)	12.5 (32)	58.8 (17)	28.6 (49)	0.0018*

Medical, neurological, and hypertensive problems, and FXTAS-related symptoms, in age-matched controls patients (n_c = 39) and premutation carriers with FXTAS (n_p = 18). Given are the percentages for controls and premutation carriers with FXTAS with group-specific totals, overall total number of subjects (n), and Fisher's exact *P* values.

^aTotal number of subjects combined is n = 57. Total n less than 57 is due to missing data.

*Significant tests at level 0.05.

of the nine with thyroid problems, indicated hyperthyroidism (one with a thyroid nodule, one with Graves Disease, and one without a specific diagnosis).

Comparison of AR and Thyroid Problems in Premutation Carriers

The FXTAS and non-FXTAS groups showed no significance difference in AR (see, Table I). In all premutation carriers, both with and without FXTAS, there was no significant difference in AR between those with and without thyroid problems. Similar analyses for FXTAS and non-FXTAS separately also show no significant difference (Table I).

Prevalence of Probable or Definite FXTAS

Family studies utilizing cascade testing introduce an ascertainment bias that may yield different prevalence estimates than is the case for carriers who are seen in a neurology clinic without a family history of fragile X syndrome. Studies in which a pedigree is examined following identification of a fragile X proband are more likely to include carriers with larger CGG repeat number because the allele has expanded to a full mutation in at least one family member, compared to research with carriers who present without a family history of FMR1 trinucleotide repeat expansion. Eighteen of the 146 carriers

(12.3%) were found to have probable or definite FXTAS. However, 15 of these women were self-referred or were more likely to participate in our studies due to the presence of neurological symptoms. Of the 15 self-referred women, 12 were subsequently diagnosed with FXTAS, and 3 did not meet criteria for a FXTAS diagnosis. If the 12 self-referred women with FXTAS are eliminated in order to reduce ascertainment bias related to neurological symptoms, then a total of 6 women out of 134 total (4.5%), or 6 out of 72 women over age 40 (8.3%), had FXTAS in a sample of female carriers assessed through family studies.

DISCUSSION

FXTAS has been defined primarily in terms of its core features of tremor and gait ataxia; however, neuropathy, psychiatric symptoms, autonomic dysfunction, and cognitive decline are also common among male premutation carriers with FXTAS, and are now generally regarded as part of a broader FXTAS complex (i.e., related to the neurological dysfunction of FXTAS). The FXTAS complex encompasses both central and peripheral neurological features, including neuropathy related to neurodegeneration or demyelination [Berry-Kravis et al., 2007b].

In the current work, we have broadened the features of the FXTAS complex in females to include

neuropathy, muscle pain, and hypertension, which were significantly higher in females with FXTAS compared to age-matched controls. The neuropathy often includes pain in the extremities and loss of vibration sensation in the lower extremities on exam; however, some individuals present with muscle pain, which has been diagnosed as fibromyalgia by medical professionals, with a quality of myositis. These myalgias warrant further investigation, because they can be chronic and non-specific conditions and different etiologies of the pain (i.e., neuropathy vs. myositis) require different treatment approaches. There may be a continuum of effects of mRNA toxicity in individuals with the premutation, some of which are linked to FXTAS, while others (e.g., thyroid dysfunction or POF) may be less directly related to the neurodegenerative phenotype, but rather reflect the effects of some pathological process on other systems, especially the endocrine system. We documented significant differences in muscle pain, tremor history, and sensory loss in female premutation carriers without FXTAS compared to controls, which is likely related to the continuum of RNA toxicity in premutation carriers.

Although POF is not considered part of FXTAS, because it is generally associated with ovarian dysfunction, POF also may be linked to an RNA toxicity mechanism that affects long-term survival of the eggs, or perhaps the number of eggs created during development [Sullivan et al., 2005; Wittenberger et al., 2007]. Elevated FSH levels are thought to be related to ovarian failure; although, inclusions have been found in the anterior and posterior pituitary, as well as the hypothalamus [Louis et al., 2006; Greco et al., 2007]. In our study, POF occurred in 19% of the non-FXTAS women who carry the premutation, and in 13% of women with FXTAS; this difference was not significant, consistent with previous literature summarized by Sullivan et al. [2005]. Importantly, POF was not elevated in women with FXTAS compared to non-FXTAS women.

Here we report on thyroid disorders in females with FXTAS (50%) and without FXTAS (17.3%), the former being significantly different from controls (10.1%). In contrast, among the general population, the prevalence of hypothyroidism in women below age 30 is 1.5%, increasing to 7.5% for women in their 70s [Bjoro et al., 2000]. The cause of the high rate of thyroid disease in females with the premutation, especially those with FXTAS, is unclear. These endocrine problems may be related to direct RNA toxicity in the hypothalamic-pituitary axis, or to a direct effect of RNA toxicity on the thyroid-perhaps through an autoimmune mechanism or the induction of apoptosis in the thyroid cells. A skewed AR has been previously reported in patients with thyroid problems related to autoimmune disease [Brix et al., 2005; Ozcelik et al., 2006], but in this study there was no difference in the AR between those with and

without thyroid disease. Surprisingly, there was also no difference in the AR in females with and without FXTAS. Previous studies in smaller patient samples of female carriers with FXTAS have reported a skewed AR [Hagerman et al., 2004; Jacquemont et al., 2005; Berry-Kravis et al., 2007b].

Consequences of the thyroid dysfunction that can occur in some premutation carriers may be difficult to distinguish from, and may complicate, the direct effects of the premutation on neurological functioning, as hypothyroidism itself may also lead to both cognitive impairments and psychological symptoms of anxiety and depression [Baldini et al., 1997; Gunnarsson et al., 2001; Teixeira Pde et al., 2006]. Thus, since there is some overlap of the cognitive and psychological symptoms, it is important to recognize and treat thyroid disease in premutation carriers.

The results of this study also suggest that carriers of the premutation may have neurological problems that do not meet or are distinct from the diagnostic criteria for FXTAS. Some of these neurological signs are part of the currently documented FXTAS complex, but more-detailed studies are needed to determine if a number of the other problems (i.e., hypertension, fibromyalgia, and thyroid disease) we have observed are specific to the premutation, to FXTAS, or both, or are associated with psychological problems, such as anxiety and depression, which may be present in 25–30% of female carriers [Sobesky et al., 1996; Franke et al., 1998; Hessl et al., 2005]. Our data support the hypothesis that hypertension is part of the FXTAS complex. Seizures also are more common in women with FXTAS, and may be related to CNS disease secondary to RNA toxicity associated with FXTAS.

In conclusion, our results have important clinical implications for the treatment of female premutation carriers both with and without FXTAS. Thyroid function should be tested as a matter of routine in female carriers, and it is important to investigate possible neurological symptoms or emotional problems in the medical workup of women with the fragile X premutation. Undiagnosed hypothyroidism in carriers may exacerbate emotional difficulties, especially anxiety and depression, which are also common in carriers [Franke et al., 1999; Hessl et al., 2005] and may lead to cognitive deterioration [Teixeira Pde et al., 2006]. In addition, carriers should be routinely checked for hypertension, which can worsen white matter disease and cause further cardiovascular problems [Sierra and Coca, 2006].

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