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Clinical involvement in daughters of men with fragile X-associated tremor ataxia syndrome

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Abstract

Women with the fragile X mental retardation 1 (*FMRI*) premutation often have concerns about neurological and medical problems, as they become older and if their fathers experience fragile X-associated tremor/ataxia syndrome (FXTAS). We therefore determined the prevalence of these problems in 110 daughters of men with FXTAS [mean age of 44.8 years (SD 8.2)]. We compared them with 43 female controls with normal *FMRI* alleles [mean age of 43.8 years (SD 8.1)] and 36 premutation carrier daughters of parents with the premutation, but without FXTAS [mean age of 43.5 years (SD 7.7)]. Overall, daughters of men with FXTAS have a higher prevalence of neurological symptoms including tremor, balance problems, memory problems, and dizziness, menopausal symptoms, and psychiatric involvement including sleep problems and anxiety when compared with non-carrier female controls. Reported balance problems and menopausal symptoms were significantly higher in daughters of men with FXTAS than in carrier daughters of parents without FXTAS, suggesting the potential influence of background gene effects. Therefore, neurological, psychological and gynecological surveillance should be warranted to better provide

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Conflict of interest

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appropriate counseling, management and care for daughters of men with FXTAS. Biological markers of additional gene effects that predispose individuals with the premutation to FXTAS need to be developed.

Keywords

anxiety; depression; fragile X; FXTAS; POI

There is an increased risk for medical problems such as hypothyroidism (1, 2), hypertension, fibromyalgia (1), menstrual dysfunction [primary ovarian insufficiency (POI)] (3–5), psychological issues such as depression and anxiety (6–8) and late onset neurological problems characteristic of the fragile X-associated tremor ataxia syndrome (FXTAS) (9–11) in female individuals with the *FMRI* (fragile X mental retardation 1, fragile X gene) premutation (55–200 CGG repeats), compared with age-matched controls. These women often have concerns about these issues, particularly neurological and medical problems, as they become older and/or if their fathers experienced FXTAS. “Will I have any neurological and/or medical problems since my father has FXTAS?” is a common question asked in a clinic. However, the prevalence of neurological and other problems has not been studied specifically in the subgroup of premutation carrier women who are daughters of men with FXTAS, and it is unknown if a parent with FXTAS predisposes to these clinical problems. Therefore, we examined the prevalence and the age of onset of neurological symptoms, medical conditions, menstrual dysfunction and psychological issues in women who have fathers with FXTAS compared with controls who have normal *FMRI* alleles and also with premutation carrier women who have parents with the premutation, but without FXTAS symptoms. Additionally, we examined whether there is any association between the characteristics of FXTAS in the father, including age of tremor and/or ataxia onset and molecular measures, and symptoms in the carrier daughter, after adjusting for age.

Furthermore, we used the Symptom Checklist-90-Revised (SCL-90-R) (12), a self-report of current psychological symptoms and the CATSYS system (13), a set of computer-assisted diagnostic instruments useful for quantitative assessment of movement abnormalities in particular postural sway (14), to validate the psychological and balance problems, respectively, which were both mainly obtained by the interview in our study.

Materials and methods

Subjects

Study subjects included 110 daughters with an age range of 30–65 years, carrying the *FMRI* premutation who have fathers with definite FXTAS (11), another group of 36 daughters with an age range of 35–66 years who also carry the *FMRI* premutation, but their parents who are the premutation carriers have not experienced any neurological symptoms which suggested FXTAS and 43 non-carrier female controls with an age range of 30–55 years. All were recruited through research studies related to FXTAS. Subjects were recruited at the MIND Institute, University of California-Davis, Sacramento and Rush University Medical Center, Chicago, between 2007 and 2009. There were 135 premutation carrier fathers who

experienced neurological symptoms which suggested FXTAS in the combined databases from both sites. These fathers had 251 daughters collectively and we were able to contact 139 of them. However, 29 daughters were excluded because of the fact that their fathers had not been formally diagnosed with definite FXTAS at our centers.

Thirty-six daughters who have parents with the premutation, but without any neurological symptoms that suggested FXTAS, were identified by thorough review of all pedigrees in the databases at our centers to make sure that the parents who carry the *FMRI* premutation were old enough (>50 years), but they have not developed any neurological symptoms yet at the time of this ascertainment. Ascertainment of this cohort of daughters is challenging because asymptomatic parents with the premutation are less probable to come in to participate in research studies at our centers. Asymptomatic parents have often not been tested for an *FMRI* mutation and do not have any medical history in the database because they were not primarily evaluated.

Of 36 daughters of parents without FXTAS, 13 (36.1%) inherited the premutation from their fathers, 15 (41.7%) from their mothers and 8 (22.2%) inherited the premutation from either the father or the mother, but neither has ever had any neurological symptoms suggestive of FXTAS. Non-carrier women were females recruited from staff at the MIND Institute or their mothers (14/43, 32.6%), normal female controls from the local community who participated in the research at our centers (6/43, 13.9%), wives of men with the fragile X premutation, with and without FXTAS who were unrelated to both groups of daughters (11/43, 25.6%), female family members with normal alleles who were identified by cascade testing (11/43, 25.6%), and a biological mother of one daughter of a man with FXTAS (1/43, 2.3%).

Methods

All subjects completed either an interview over the phone (daughters of men with FXTAS *vs* daughters of parents without FXTAS *vs* normal female controls, 57% *vs* 0% *vs* 20%) or in person (daughters of men with FXTAS *vs* daughters of parents without FXTAS *vs* normal female controls, 43% *vs* 100% *vs* 80%) after informed consent was obtained. This interview covered the following clinical domains along with the age of onset for each problem with a response of yes, no or I don't know: neurological symptoms including tremor (any tremor or shakiness of the hands or any other body parts, if so we also asked whether the tremor of the hand is related to hand movement; resting *vs* moving, any difficulty with activities of daily living); balance problems (problems with balance, difficulty walking, loss of equilibrium or falls); memory problems (problems with memory, foggy thinking or confused easily); dizziness, weakness of the legs, neuropathy symptoms (burning or pain in the legs, numbness or tingling in the arms or legs); autonomic problems (problems with controlling bladder or bowel function, difficulty achieving orgasm, etc.); medical problems including thyroid problems, hypertension, migraine headache, autoimmune disorders (lupus, rheumatoid arthritis, fibromyalgia, Sjogren's syndrome, Raynaud's phenomenon, etc.); ovarian and menstrual dysfunction including POI, menopausal symptoms (any hot flashes or night sweats or irregular periods), and infertility (>1 year without getting pregnant when trying to become pregnant); psychiatric and behavioral symptoms including sleep problems (problems falling asleep or waking in the night), anxiety (any problems with anxiety or any

anxiety disorders), depression (any symptoms of depression), psychiatric medications and/or counseling for depression and anxiety, etc. These problems were self-reported and had to be characterized specifically during the interview either by phone or in person using similar medical data format. The status of FXTAS in the parent was not totally blinded. However, most of those who were interviewed in person at our centers were interviewed not because of their parents' problems, but because they participated in our premutation studies while accompanying their children (probands with fragile X syndrome) for a clinical evaluation at our centers. Table 1 has the list of variables interviewed in clinical domains that were evaluated statistically.

To be described as having medical or psychological problems, the subject had to have sought medical or psychological help for their symptoms and to have been treated for the psychological problems (physician-documented medical and psychological conditions). Furthermore, the SCL-90-R was obtained in some subjects who were seen at the MIND Institute in each group. The SCL-90-R questionnaire consisted of 90 questions which are clustered into the following symptom domains including somatization, obsessive-compulsive behaviors, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. The SCL-90-R depression and anxiety indices were used to validate the self-reported anxiety and depression obtained from interviews.

The CATSYS system (13) was used to evaluate the balance problems in those who were seen at the MIND Institute. This is a quantitative system that has shown utility in those with the premutation who have neurological problems (14). We utilized the sway assessment at 30 and 60s with the eyes open to assess balance condition. This study was approved by the University of California, Davis and Rush University Medical Center Institutional Review Boards.

Molecular analysis

A blood sample for measurement of CGG repeat number and methylation status were obtained from fathers with FXTAS, both groups of the daughters and normal female controls who were evaluated at our centers. Southern Blot and PCR-based genotyping were performed as previously described in Tassone et al. (15). *FMRI* mRNA expression levels were determined by quantitative RT-PCR as detailed in Tassone et al. (16).

Statistical analysis

Our primary analysis is based on Fisher's exact test and logistic regression analysis to compare the odds of specific clinical problems in *FMRI* premutation carrier daughters of men with FXTAS and normal female controls, within each clinical domain (neurological symptoms, medical problems, ovarian and menstrual dysfunction, and psychiatric and behavioral symptoms). In our primary analysis, adjustment for multiple testing was made based on the false discovery rate. Significant results (p-values) are indicated with an asterisk (Table 1). Descriptive statistics for the age of onset among these subjects with clinical involvement are provided in Table 2. Our secondary analysis involves comparing the daughters of men with FXTAS to carrier daughters of parents with the premutation, but without FXTAS, for each clinical domain (Table 3). Tertiary analysis examined the

association between characteristics of the fathers including onset of tremor, ataxia, and molecular measures with clinical involvement in the daughters. Early onset was defined as onset before the age of 60. The analysis adjusted for association within-family (fathers with more than one daughter) by utilizing empirical standard error estimates from general estimating equations methods (17, 18). For validation of self-reported medical and psychiatric symptoms from interviews, we performed *t*-tests comparing reported SCL-90-R depression and anxiety scores among those who reported presence/absence of these symptoms on interviews. Similarly, we compared quantitative measures of balance using the CAT-SYS system (14) to validate self-reported balance problems from interviews.

Results

Subject characteristics

The primary aim of this work is to assess broad clinical involvement in daughters of men with FXTAS relative to similar aged controls. The study subjects' age range is 30–65 with a mean age of 43.8 for controls (SD 8.1, $n = 43$) and a mean age of 44.8 (SD 8.2, $n = 110$) for daughters of men with FXTAS. There is no difference in age between these two groups ($p = 0.4906$). Our secondary analysis involves comparing the daughters of men with FXTAS to carrier daughters of parents with the premutation, but without FXTAS ($n = 36$, mean age 43.5, SD 7.7). With respect to molecular measures for each group of study subjects, daughters of men with FXTAS had a mean of CGG repeat length of 93.6 (SD 19.3, $n = 68$), a mean of mRNA level of 2.8 (SD 1.2, $n = 31$), and a mean of Activation Ratio (AR: a fraction of normal *FMRI* allele as the active allele) of 0.56 (SD 0.16, $n = 34$), which were not statistically significant from carrier daughters of parents with the premutation, but without FXTAS who had a mean of CGG repeat length of 93.2 (SD 19.6, $n = 25$, $p = 0.94$), a mean of mRNA level of 2.7 (SD 0.9, $n = 18$, $p = 0.66$), and a mean of AR of 0.54 (SD 0.14, $n = 18$, $p = 0.71$). Means of CGG repeats, and mRNA levels in normal female controls were 30.2 (SD 1.6, $n = 20$), and 1.42 (SD 0.2, $n = 9$), respectively, which were both significantly different from daughters of men with FXTAS ($p < 0.001$) as expected. Premutation parents without FXTAS were aged 54–77 (mean 65.7, SD 5.8) and was not statistically different from the mean age of fathers with FXTAS (mean 67.9, SD 5.9, $p = 0.113$), based on a subset of $n = 94$ of older daughters (from $n = 110$).

Clinical presentations in daughters of men with FXTAS and non-carrier female controls

As summarized in Table 1, daughters of men with FXTAS had significantly higher odds of certain neurological problems, including tremor (13.6% vs 0%; $p = 0.0065$), balance problems (27.3% vs 0%; $p < 0.001$), memory problems (38.9% vs 7.0%; $p < 0.001$), dizziness (28.4% vs 5.1%; $p = 0.0026$) and difficulty achieving orgasm (12.87% vs 0%; $p = 0.020$). Although not statistically significant, leg weakness showed trend toward increased prevalence in daughters of men with FXTAS (8.3% vs 0%; $p = 0.0628$). Although no significant difference was observed in terms of prevalence of neuropathy symptoms (17.43% vs 10.3%), the daughters of men with FXTAS appeared to report a fairly early age of onset of these symptoms including burning, numbness, or tingling in the extremities occurring in their early 40s, as showed in Table 2. Five of all daughters of men with FXTAS had also been diagnosed with FXTAS themselves at the time of this ascertainment and two

of these five women began to have FXTAS when they were over 50 years of age (the age of onset of these five women were 31, 31.5, 38, 56, and 59 years). Previous reports have found a relatively low risk for FXTAS in female carriers (8.3–16.5%) (1, 2). But with a mean age of 44.8 (SD 8.2) in the daughters of men with FXTAS in our study, most of them had not developed any neurological symptoms yet. Of those who were older than 50 years of age (28/110, 25.5% of the cohort) only two as mentioned has FXTAS symptoms although the rest may develop these symptoms over time. Furthermore, 112 of all 251 daughters of men with FXTAS cannot be contacted so we lacked the data of more females who were over 50 years of age. Therefore, we cannot properly estimate the prevalence of FXTAS in these targeted subjects.

With respect to medical problems, we did not see statistically significant differences between daughters of men with FXTAS and non-carrier female controls, although we do note some interesting trends based on the observed proportions of these medical problems including thyroid problems (20.2% vs 9.3%), hypertension (18.2% vs 7.0%) and migraine headaches (35.2% vs 26.3%).

We also observed significantly higher odds of psychiatric and behavioral symptoms in daughters of men with FXTAS relative to non-carrier controls including sleep problems (62.7% vs 32.6%; $p = 0.001$) and anxiety (65.1% vs 34.9%; $p < 0.001$). With respect to ovarian and menstrual dysfunction, we observed significantly higher menopausal symptoms (74.1% vs 38.5%; $p = 0.0003$). Although not statistically significant, there was an observed increased trend toward primary ovarian insufficiency (14.1% vs 0%; $p = 0.0589$) in daughters of men with FXTAS compared to control women without the premutation. We note that because our cohort also includes young women, their necessary exclusion from analysis limits our power to detect differences. For example, POI status cannot be determined in women if they are younger than 40 years of age. Thus, the necessary exclusion of women under 40 years from analysis reduces the effective sample size.

Daughters of men/parents with and without FXTAS

In our secondary analysis, comparing the age-matched daughters of men with FXTAS ($n = 94$ – lower n related to age matching) to daughters of a parent with the premutation, but without FXTAS ($n = 36$), the fathers were between the age of 54 and 77, as described above. Table 3 summarizes the results. Although the observed percentages of neurological problems were typically higher in daughters of men with FXTAS, only the increase in balance problems was significant (27.7% vs 5.6%; $p = 0.0075$). There is an increased trend with respect to memory problems (37.6% vs 16.7%; $p = 0.0222$), although this is not statistically significant after p-value adjustment. There were no differences with respect to the medical problems surveyed. With respect to the ovarian and menstrual dysfunction, there were significantly higher menopausal symptoms (71.6% vs 36.1%; $p = 0.0007$) in the daughters of men with FXTAS, and a trend toward increased infertility, although not statistically significant after p-value adjustment. We note that the results in this analysis should be cautiously interpreted and require further research, because of the challenge of an incomplete observation period in the group of men who have not yet developed FXTAS but

who may develop FXTAS later in their lives. We expand on this limitation in Discussion section.

Daughters of parents without FXTAS and non-carrier female controls

We note that analysis comparing non-carrier female controls to daughters of parents without FXTAS indicates no significant differences in any of the clinical symptoms after p-value adjustment for multiple comparisons. Lower prevalence in tremor ($p = 0.04$), POI ($p = 0.02$), and anxiety ($p = 0.01$) were observed in the non-carrier female control group compared with daughters of parents without FXTAS group, although these trends are not statistically significant after p-value correction.

Association of tremor/ataxia onset to daughters' anxiety problems

Our tertiary analysis examined the association between the early onset of tremor and ataxia (onset <age 60) in fathers and their daughters' clinical involvement, adjusted for the age of daughters. The results suggest a positive association between early onset of ataxia in fathers and prevalence of anxiety in daughters (OR = 5.38, 95% CI: 1.02–28.31; $p = 0.0468$). This result is based on the available data on 57 daughters from 40 fathers. Although early onset of tremor in father was positively associated with the anxiety problems in daughters, the result was not statistically significant (OR = 3.98, $p = 0.0896$). We note that models that included CGG and *FMRI* mRNA expression indicate that both the variables were not significant. However, we point out that given the limited sample size, more precise estimation of the effects of these additional molecular parameters needs to be further assessed in future larger studies. Furthermore, the age of tremor and ataxia onset contains measurement error as it is generally difficult to ascertain precisely the age of onset based on recall (19).

Validation of interview data

There are some limitations to self-reported clinical symptoms obtained from telephone interview. Future studies, based on a more reliable quantitative assessment tools, will be able to provide additional validation of our results. However, for some of the reported symptoms, specifically anxiety and depression, we were able to validate self-reported data from interviews with data from the Symptom Checklist-90-Revised (SCL-90-R) for 56 of the study patients. More specifically, the mean SCL-90 depression score was 51.4 (SD 8.6) and 59.6 (SD 9.1) for subjects who reported that they did not and did have depression, respectively ($p = 0.002$). Similarly, the mean SCL-90 anxiety score was 47.5 (SD 8.9) and 59.2 (SD 9.1) for subjects who reported that they did not and did have anxiety, respectively ($p < 0.0001$).

We also validated self-reported balance problems with a quantitative measure of sway area using the CATSYS system (in $n = 43$ subjects). In both 60- and 30-s tests of sway (eyes open), individuals who reported balance problems [mean 14.8 (SD 16.8); 30-s test] have significantly higher average level of sway compared to those who reported no balance problems [mean 6.0 (SD 4.5), $p = 0.0286$]. Similar results were observed for 60-s sway test.

Discussion

All daughters of men with premutation are obligate carriers. When their fathers develop FXTAS, these women are very concerned about their own health problems, in particular, neurological and medical problems. Although an increased risk of various neurological, medical, ovarian and psychological problems has been well established in women with the premutation (1, 2, 4–11, 20), neither the health and FXTAS status of the father nor family history of FXTAS was extensively considered in previous studies. We hypothesized that the presence of FXTAS in the father is associated with higher levels of neurological symptoms as well as other clinical involvement in the daughter. We also hypothesized that earlier onset of neurological or other problems in the daughter are associated with the early onset of FXTAS in the father. This is the first study that not only compared clinical involvement in daughters of men with FXTAS with non-carrier female controls, but also with carrier daughters of parents with the premutation, but without FXTAS.

As expected, various neurological/medical symptoms including tremor, balance problems, memory problems, dizziness, difficulties achieving orgasm, menopausal symptoms, psychiatric and behavioral symptoms including sleep problems and anxiety appeared to be more prevalent in the daughters of men with FXTAS than non-carrier female controls after p-value adjustment.

Neurological symptoms are relatively common in female premutation carriers regardless of whether FXTAS is present in a family, but they may not be identified during clinical visits when the age is below 50. Although neurological symptoms observed in female carriers may be sufficiently patchy and mild that they do not meet the criteria for FXTAS, these symptoms may still be related to RNA toxicity. Increased reports of memory problems in these daughters may be related to subtle cognitive impairments in many areas including working memory, executive function, selective attention and social cognition in premutation carriers without FXTAS compared with controls (21–23). Neurological findings should not be interpreted as early FXTAS because these symptoms may not necessarily lead to FXTAS, particularly in women who are relatively protected from full FXTAS. Additionally, the daughters' perception of symptoms could be altered as a result of anxiety or as a result of seeing FXTAS in the father, worrying about it and reading about it. Therefore, these neurological concerns should be taken into account and thoroughly assessed in carrier daughters to clarify whether there are any significant problems.

Our daughters of men with FXTAS reported a higher rate of anxiety (65.1% vs 29%) and depression (53.2% vs 47%) than what was reported by Roberts et al. (2009) (8). This difference probably results from the use of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) in the Roberts et al. study which is a more rigid research documentation of mood and anxiety disorders than what was obtained by the interview through this study. However, partial validation of data obtained from the interview was accomplished by comparing results from the SCL-90-R in the same subjects, supporting the interview results in the three subgroups of subjects. The documented higher rate of anxiety in daughters of men with FXTAS compared to controls supports the concept of a

vulnerability to psychiatric symptoms in female carriers, which is hypothesized to be associated with toxicity to the limbic system from the higher levels of *FMRI*-mRNA (6, 7).

The prevalence of POI and medical problems including diabetes, thyroid problems and hypertension were similar to what was reported previously in other studies of carrier females (1, 2, 24). A higher rate of balance and menopausal problems in the daughters of men with FXTAS group when compared with the daughters of parents with the premutation, but without FXTAS may be related to the influence of background gene effects which may interplay with the mRNA toxicity from the premutation and other biomarkers/factors contributing to these problems. Comparison of daughters of men with FXTAS with a larger sample size of daughters of parents without FXTAS, using FXTAS Rating Scale (9), and/or other reliable assessments to document movement abnormalities particularly postural sway or balance problems, as well as more detailed assessments to detect menopausal symptoms early, is needed in future studies.

With respect to the age of onset for various clinical problems, descriptive analysis did not suggest earlier onset for each problem in the targeted subjects when compared with both groups of controls as we hypothesized. Therefore, the presence of FXTAS in a family may not be associated with the onset of individual specific clinical symptoms, but rather predispose to a general increase in the risk of any clinical involvement.

One strength of the current work is the fairly large number of daughters of men with FXTAS, and, although our non-carrier female controls are not different in age on average to the daughters, more control subjects are needed. An important limitation of the results reported is in our secondary analysis comparing: (A) daughters of fathers with FXTAS to (B) daughters of parents with the premutation, but without FXTAS. This limitation relates to the fact that one does not know with certainty that the premutation fathers who have not yet had FXTAS (group B) will remain so unless we follow them (longitudinally) until the end of their lives. We have tried to increase this probability as much as feasible in this cross-sectional study by including only older men (aged 54–77). Alternatively, future studies may consider a larger retrospective study of daughters of premutation carrier fathers who have died and in whom FXTAS diagnosis is known in a case–control design. For this reason and also because of the smaller sample size ($n = 36$), the results in this secondary analysis should be interpreted with caution. Future studies will be able to shed further light on our preliminary findings.

Furthermore, the non-carrier female controls were not representative of a general population-based sample because some of them were wives of men with the premutation, with and without FXTAS. Therefore, they might be expected to have higher rates of psychiatric symptoms than the general population (8). However, even compared with this higher-risk non-carrier control group, the prevalence of anxiety and sleep symptoms was still significantly higher in the daughters of men with FXTAS group.

Why some carriers develop FXTAS and others do not is thought to relate to background gene and environmental effects which may be protective or deleterious. Although we incorporate the genetic background when FXTAS was in the family, many subjects were too

young to accurately observe the prevalence of FXTAS in this study. Therefore, we cannot thoroughly address the association between background gene effects and development of FXTAS and our study represents just the first step in this direction.

In conclusion, daughters of men with FXTAS have significantly higher rates of neurological, psychiatric, and menopausal symptoms compared to non-carrier female controls. Therefore, neurological, psychological and gynecological surveillance are warranted in addition to the medical interview/assessment to better provide appropriate counseling, management, and care for these women. Furthermore, the finding that daughters of men with FXTAS are more prone to balance and menopausal problems than carrier daughters of asymptomatic parents suggests that biological markers of additional gene effects that predispose certain individuals and families with the premutation to neurological and ovarian symptoms from RNA toxicity need to be developed. The relationship between early psychological symptoms and the eventual development of FXTAS also requires further investigation.

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Prevalence of neurological symptoms, medical problems, ovarian and menstrual dysfunction, and psychiatric and behavioral symptoms in daughters of men with FXTAS compared to non-carrier female controls

Table 1

Variables	Daughters of men with FXTAS (n = 110)			Controls (n = 43)		
	n	Percentage	n	Percentage	p-Value	
Neurological symptoms						
Tremor	15	13.64	0	0.00	0.00653*	
Balance problems	30	27.27	0	0.00	0.00002*	
Memory problems	42	38.89	3	6.98	0.00006*	
Dizziness	29	28.43	2	5.13	0.00257*	
Burning or pain in the leg	19	17.43	4	10.26	0.43972	
Weakness of the leg	9	8.26	0	0.00	0.06277	
Problems in orgasm	13	12.87	0	0.00	0.01995*	
Medical problems						
Diabetes	4	3.64	0	0.00	0.57717	
Thyroid problems	22	20.18	4	9.30	0.15112	
Hypertension	20	18.18	3	6.98	0.12879	
Migraine headache	38	35.19	10	26.32	0.42228	
Ovarian and menstrual dysfunction						
Menopausal symptoms	60	74.07	15	38.46	0.00025*	
POI	10	14.08	0	0.00	0.05888	
Infertility	20	26.67	4	14.29	0.29420	
Psychiatric and behavioral symptoms						
Sleep problems	69	62.73	14	32.56	0.00106*	
Anxiety	71	65.14	15	34.88	0.00099*	
Depression	58	53.21	20	46.51	0.47667	
Psychiatric medications and/or counseling	67	63.21	25	58.14	0.58139	

FXTAS, fragile X-associated tremor/ataxia syndrome; POI, primary ovarian insufficiency.

* Significant after p-value adjustment.

Descriptive summaries of age of onset for each problem in daughters of men with FXTAS, daughters of parents without FXTAS, and non-carrier female controls

Table 2

Variables	Daughters of men with FXTAS				Daughters of parents without FXTAS				Controls			
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Neurological symptoms												
Hand tremor	13	37.73	12.97	4	44.25	13.74	0					
Balance problems	24	41.88	11.00	2	33.00	11.31	0					
Memory problems	31	39.29	7.84	3	46.00	8.54	2	43.75	5.30			
Dizziness	27	36.20	12.94	4	38.00	10.10	2	37.50	24.75			
Burning or pain in the leg	16	40.44	9.95	7	40.86	8.72	0					
Numbness or tingling in the arms or legs	28	41.20	8.92	9	39.11	5.33	5	40.80	5.40			
Leg weakness	6	51.00	10.47	0			0					
Bladder or bowel incontinence	14	39.93	12.83	0			0					
Problems in orgasm	6	28.33	9.91	3	45.00	8.89	0					
Medical problems												
Diabetes	1	60.00		0			0					
Thyroid problems	17	33.59	11.55	2	34.50	7.78	2	48.50	2.12			
Hypertension	18	42.36	8.94	2	36.50	27.58	1	49.00				
Migraine headache	28	29.79	12.86	7	32.93	16.54	8	25.50	13.12			
Ovarian and menstrual dysfunction												
Menopause	47	43.01	6.45	13	42.04	5.31	9	49.22	4.41			
Infertility	19	29.29	3.26	1	35.00		4	32.00	4.00			
Hormonal replacement therapy	31	41.74	8.10	4	38.50	6.66	4	49.75	5.38			
Psychiatric and behavioral symptoms												
Sleep problems	41	36.62	11.73	4	47.00	10.55	9	33.39	10.14			
Anxiety	33	29.32	11.93	11	37.27	7.17	6	30.67	6.62			
Depression	37	28.80	10.36	13	37.73	10.56	12	31.54	11.32			
Counseling	38	37.55	10.07	11	39.86	5.79	10	33.35	9.72			
Psychiatric medications	29	28.48	10.45	9	36.61	8.139	13	31.85	8.52			

Prevalence of neurological symptoms, medical problems, ovarian and menstrual dysfunction, and psychiatric and behavioral symptoms in daughters of men with FXTAS compared to daughters of parents with the premutation, but without FXTAS

Table 3

Variables	Daughters of men with FXTAS (<i>n</i> = 94)			Daughters of parents without FXTAS (<i>n</i> = 36)		
	<i>n</i>	Percentage		<i>n</i>	Percentage	<i>p</i> -Value
Neurological symptoms						
Tremor	13	13.83		4	11.11	0.77907
Balance problems	26	27.66		2	5.56	0.00753*
Memory problems	35	37.63		6	16.67	0.02218
Dizziness	24	27.59		7	19.44	0.49381
Burning or pain in the leg	17	18.28		8	22.22	0.62495
Weakness of the leg	7	7.53		0	0.00	0.18929
Problems in orgasm	11	12.09		1	2.78	0.17669
Medical problems						
Diabetes	3	3.19		0	0.00	0.56016
Thyroid problems	18	19.35		4	11.11	0.30913
Hypertension	17	18.09		3	8.33	0.27603
Migraine headache	29	31.52		11	30.56	1.00000
Ovarian and menstrual dysfunction						
Menopausal symptoms	48	71.64		13	36.11	0.00070*
POI	6	10.53		5	21.74	0.28003
Infertility	15	23.81		1	2.86	0.00858
Psychiatric and behavioral symptoms						
Sleep problems	58	61.70		15	41.67	0.04891
Anxiety	62	65.96		23	63.89	0.83908
Depression	49	52.13		18	50.00	0.84698
Psychiatric medications and/or counseling	55	60.44		23	65.71	0.68364

* Significant after *p*-value adjustment.