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FMR1 CGG repeat length predicts motor dysfunction in premutation carriers

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Abstract

Background—Fragile X–associated tremor/ataxia syndrome (FXTAS) is a recently described, underrecognized neurodegenerative disorder of aging fragile X mental retardation 1 (*FMR1*) premutation carriers, particularly men. Core motor features are action tremor, gait ataxia, and parkinsonism. Carriers have expanded CGG repeats (55 to 200); larger expansions cause fragile X syndrome, the most common heritable cause of mental retardation and autism. This study determines whether CGG repeat length correlates with severity and type of motor dysfunction in premutation carriers.

Methods—Persons aged ≥50 years with a family history of fragile X syndrome underwent structured videotaping. Movement disorder neurologists, blinded to carrier status, scored the tapes using modified standardized rating scales. CGG repeat length analyses for women incorporated the activation ratio, which measures the percentage of normal active chromosome X alleles.

Results—Male carriers (n = 54) had significantly worse total motor scores, especially in tremor and ataxia, than age-matched male noncarriers (n = 51). There was a trend toward a difference between women carriers (n = 82) and noncarriers (n = 39). In men, increasing CGG repeat correlated with greater impairment in all motor signs. In women, when activation ratio was considered, increasing CGG correlated with greater ataxia.

Conclusions—CGG repeat size is significantly associated with overall motor impairment in premutation carriers. Whereas this association is most pronounced for men and covers overall motor

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impairment—tremor, ataxia, and parkinsonism—the association exists for ataxia among women carriers. This is the first report of a significant correlation between the premutation status and a motor feature of fragile X–associated tremor/ataxia syndrome in women.

Fragile X–associated tremor/ataxia syndrome (FXTAS)[1] occurs in premutation carriers of the fragile X mental retardation 1 (*FMR1*) gene, predominantly in men over age 50 years. Premutations are expanded CGG repeats (55 to 200) and are also associated with premature ovarian failure.[2] Larger expansions (>200) result in transcriptional inactivation and fragile X syndrome,[3] the most common heritable form of mental retardation and autism.

Common manifestations of FXTAS are progressive intention tremor, cerebellar gait ataxia, parkinsonism, working memory impairment, and frontal executive dysfunction.[1,4–11] Other signs include hyperintensity of the middle cerebellar peduncles on MRI,[11] peripheral neuropathy,[6,12] and autonomic dysfunction.[6,13] The mediantimetodeathis 21years, butlifeexpectancy is variable.[14] Some female carriers have classic FXTAS,[15–17] but most are less affected,[7,8] likely secondary to a diluting effect from the second normal X chromosome.[18] Neuropathology shows generalized brain atrophy and intranuclear inclusions,[19,20] perhaps related to increased levels of abnormal *FMR1* messenger RNA (mRNA).[21,22]

The focus of this article is to study variables associated with the major motor signs in FXTAS. Previous studies found that increasing age and male sex strongly correlated with increased risk of FXTAS,[7,8] and that increasing CGG repeat length correlated with earlier age at onset.[23] A recent study suggested carriers of low premutation range (<70) repeats have atypical or milder FXTAS signs.[24] Now we report a prospective, quantitative, cross-sectional study of the association between specified variables (CGG repeat length, mRNA level, age, and sex) and the severity of major motor signs of FXTAS in a large cohort of premutation carriers.

METHODS

Patient recruitment and selection

The only inclusion criteria were family history of fragile X syndrome and age ≥ 50 years. Eligible family members were encouraged to participate regardless of the presence of neurologic symptoms and carrier status; those with normal *FMR1* repeat sizes served as controls. Families were recruited from local and national fragile X syndrome support groups in the United States or from fragile X clinics associated with one of three centers—the University of California at Davis, the University of Colorado at Denver and Health Sciences Center, and the Rush University Medical Center in Chicago—from 2002 to 2005. All eligible subjects who agreed to participate were included (n = 233). Carriers were not categorized into published diagnostic categories of possible, probable, and definite FXTAS, because these criteria are based on MRI findings, which many of our subjects did not undergo. All study procedures were conducted according to approved institutional review board protocols at each participating institution.

Structured videotape and FXTAS Rating Scale administration

Subjects underwent a structured videotaped examination, designed to capture the major motor features of FXTAS: tremor, cerebellar dysfunction, and parkinsonism. Participating movement disorders specialists trained study personnel to produce acceptable standardized videos at each site. These neurologists, blinded to the subjects' premutation status, scored the videotapes using the FXTAS Rating Scale.[25]

The FXTAS Rating Scale was developed for this study. Initially the scale was composed of all items from the Clinical Rating Scale for Tremor,[26] the International Cooperative Ataxia Rating Scale,[27] and the Unified Parkinson's Disease Rating Scale (part III).[28] In addition, the

tandem test,[29] a sensitive and important (but not specific) test for cerebellar gait dysfunction,[30] was added. This large composite scale was reduced to the final FXTAS Rating Scale by elimination of items that were repetitive and items that had unacceptable interrater reliability. Clinimetric testing of the final scale among the three movement disorders neurologists showed all items had a weighted kappa statistic of good to excellent (≥0.4).[31] Three subdomain scores to measure each motor feature of interest—tremor, ataxia, and parkinsonism—were designated, and their sum represented the total FXTAS score.

Molecular analyses

Genomic DNA was isolated from peripheral blood leukocytes using standard, previously published methods.[7] *FMR1* DNA analysis was performed using both PCR and Southern blot as described previously,[7,22] which provides determination of allele size, methylation status, and, thus, estimation of the X-activation ratio in women. The activation ratio, which measures the percentage of cells that carry the normal allele on the active chromosome X, was the ratio of the intensity of the normal *FMR1* unmethylated band over the sum of the intensities of the normal unmethylated and methylated bands, as previously described.[7] Quantifications of *FMR1* mRNA were performed as described previously.[21]

Statistical analysis

The two-sample *t* test was used to compare the total and subdomain FXTAS Rating Scale scores between the premutation and control groups. Data from the entire cohort were analyzed, and data from men and women were studied separately, because women carriers have a second normal *FMR1* allele that is predicted to dilute the expression of neurologic signs. Associations between variables of CGG repeat length, age, and mRNA level (independent variables) and the rating scale scores (dependent variable) were analyzed by multiple regression. Regression analyses included all subjects, encompassing the entire CGG range, from normal through premutation. The CGG repeat length regression analysis was controlled for age. For women, the association between CGG repeat length and rating scale scores was reanalyzed with a term to control for activation ratio (AR), with $(1 - R) \times (CGG)$, AR, and age as the independent variables. Throughout the analysis, the alpha = 0.05 nominal level was used.

Seven subjects had alleles that fell within the “gray-zone” range of 41 to 54 repeats. Data from gray-zone carriers are included in regression analyses performed across the full range of allele sizes for carriers and controls. There is uncertainty regarding the boundaries of the gray zone, e.g., 41 to 54 vs 45 to 54, and whether alleles in this range produce neurologic signs. Therefore, we used the broader category for the regression analysis, and we excluded these subjects from the control group in group-wise comparisons.

Lexin Li, PhD, Department of Statistics, North Carolina State University, conducted the statistical analysis.

RESULTS

Demographic data for premutation carriers and controls are shown in table 1. The total and all subdomain FXTAS Rating Scale scores were significantly worse in the entire group of carriers compared with controls (table 2). This also held true when men were analyzed separately (figure). Whereas all three subdomain scores showed impairment, differences in parkinsonism were less marked than the other two subdomains. In contrast to the findings in men, there was only a trend toward a difference in motor scores between women carriers and controls.

CGG repeat length, with control for age, was positively and highly correlated with impairment on motor scores in the entire cohort, ranging from noncarriers through premutation subjects

(table 3). This correlation was primarily driven by the strong correlation between increasing CGG and motor impairment in men, and the correlation was more robust for tremor and ataxia than for parkinsonism. Women carriers showed only a trend toward worsening of motor scores with increasing CGG repeat length. However, when the activation ratio (percent of normal alleles that are active) was included in the analyses, ataxia strongly correlated with increasing CGG repeat length ($p = 0.03$).

Increasing age also correlated strongly with worsening of all motor scores in the entire cohort (table 3), and analyses of each sex separately showed that the correlation was highly significant in both, more so in men than in women. In the latter, the degree of correlation was parkinsonism > ataxia > tremor. Last, there was no relationship between mRNA level and rating scale scores.

DISCUSSION

The current data confirm previous reports[5,7,8] and find that male premutation carriers have markedly more tremor and ataxia, and moderately more parkinsonism, than age-matched, noncarrier controls. This study shows that in men, increasing CGG repeat length is a powerful risk factor for the motor signs common in FXTAS. In addition, increasing age correlates with the severity of motor features of FXTAS.

Women carriers, conversely, have relatively few motor signs compared with male carriers. However, when the percent of active mutant alleles is factored into the analysis, increasing CGG repeat length is a significant risk factor for ataxia in women. This intriguing observation suggests that a threshold number of neural cells with elevated mRNA levels—those in which the abnormal allele is active—may be sufficient to trigger the neurologic dysfunction underlying FXTAS. Previous work[15–18] had shown clear cases of FXTAS in women, but a controlled study[7] found that symptoms were generally milder in women carriers compared with men. Besides the activation ratio, there may be other sex-related effects on phenotype, including hormonal status. Although women have milder FXTAS motor signs than men, they are more common than in noncarriers, and their children are at high risk for fragile X syndrome. Because the classic syndrome was first described in men, the focus has been on tremor, ataxia, and parkinsonism. Further study of the clinical expression of the premutation in women may reveal other features of diagnostic importance specific to this sex.

Leukocyte *FMR1* mRNA levels did not correlate with motor symptoms in this study. At first glance, the finding seems surprising because *FMR1* mRNA has been identified within the brain intranuclear inclusions,[32] high levels of abnormal mRNA are postulated to play an important role in the pathophysiology of FXTAS,[1,7] and one study found a correlation between leukocyte mRNA levels and psychological features in premutation carriers.[33] However, other studies have not reported similar associations between phenotype and leukocyte mRNA level.[10,34–36] These observations likely reflect the fact that although regional brain levels of mRNA are elevated in FXTAS,[22] blood levels do not closely correlate with brain levels. More specifically, because brain levels of *FMR1* mRNA vary widely across different brain regions,[22] leukocyte values may not accurately reflect expression levels in the relevant brain regions. However, the significant associations between CGG repeat length and the severity of movement disorder likely reflect the overall trend in brain mRNA levels.

Correct diagnosis of FXTAS is vital because ensuing generations are at high risk for fragile X syndrome. However, the first clinical description of FXTAS was published only 6 years ago,[1] and physicians are just gradually learning about the syndrome. A recent study[37] showed that only 4% of persons diagnosed with FXTAS had been previously seen by a movement disorders neurologist; the majority had been followed by general neurologists or primary care physicians. Increasing knowledge of the disorder by the latter physicians would prompt them to ask

appropriate patients (table 4)[20] about a family history of fragile X syndrome. Although it is important to obtain a family history, doing so may not be helpful in making the diagnosis, because the affected man may not have daughters or the daughters may not have children with a correct diagnosis of fragile X syndrome. Another obstacle to diagnosis of FXTAS is that the presentation may be nonspecific, e.g., progressive balance difficulty, cognitive dysfunction, and mild tremor in an aging male, and these findings are often ascribed to multiple strokes or simply aging. Our experience and studies suggest that typical FXTAS patients will not seek medical care; instead, they are brought into the clinic by a spouse frustrated by the patient's change in behavior (e.g., agitation, poor insight) or cognitive decline. On examination, patients generally at least have impaired tandem gait. Many affected persons deny tremor and have minor tremor on examination.

This study used a newly developed instrument, the FXTAS Rating Scale,[25] to effectively discriminate between the type and severity of major motor signs in carriers vs controls. One advantage of the scale is its reliance on items of interest selected directly from scales that are already familiar to movement disorder neurologists. The scale is also easily applied with standard neurologic tests (quiet observation, eye movements, simple motor tasks, and walking) that are feasible to rate from a videotape or in person. In its current form, however, the scale has 44 items. Further clinimetric study may allow elimination of duplicative items. Our long-term goal is to provide a comprehensive, but practical, tool for conduct of therapeutic and longitudinal trials in FXTAS.

This report helps to further define the clinical features of *FMR1* carriers, in particular, showing that motor signs are associated with increasing CGG repeat length in men and with increasing percentage of active mutant *FMR1* alleles in women. Further research in defining the clinical manifestations of *FMR1* carriers is needed, because FXTAS often goes unrecognized. The disorder is estimated to be similar in prevalence to atypical parkinsonian disorders such as progressive supranuclear palsy (6 per 100,000) and multiple system atrophy (2 to 5 per 100,000) and is a noteworthy cause of ataxia[38] (1 to 2 per 6,000) in aging men.[39]

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GLOSSARY

AR
: activation ratio

FXTAS
: fragile X-associated tremor/ataxia syndrome

MCP
: middle cerebellar peduncle

mRNA
: messenger RNA

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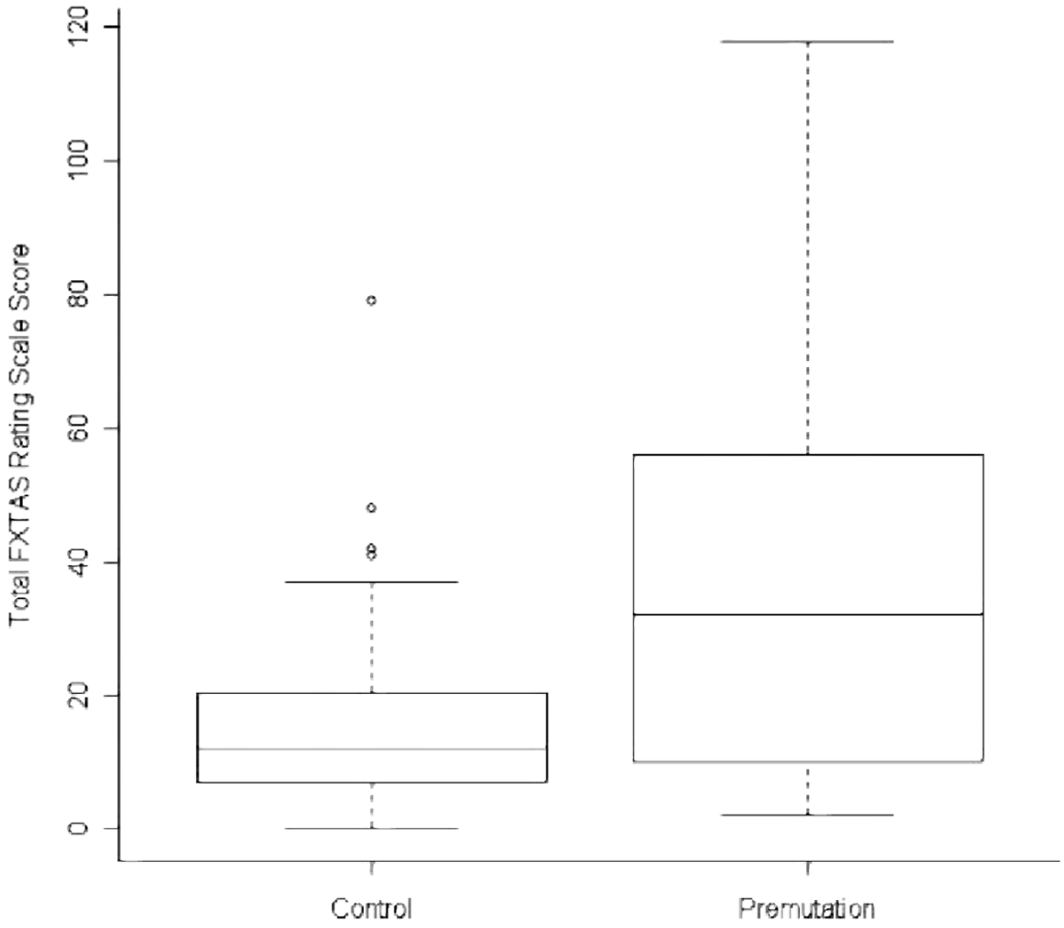

Figure. Box plot showing the distribution of total Fragile X–Associated Tremor/Ataxia Syndrome Rating Scale scores (score range 0 to 226) in male controls vs carriers

The horizontal line in the middle of each box indicates the median, whereas the top and bottom borders of the box mark the 75th and 25th percentiles. The vertical lines above and below the box extend to the 90th and 10th percentiles. The single points are outliers beyond the 90th and 10th percentiles.

Table 1

Baseline characteristics of the study participants*

	Premutation carriers	Controls
Men, n	54	51
Women, n	82	39
Men, age, y (SD)†	66.9 (8.3)	64.6 (9.7)
Women, age, y (SD) †	63.0 (10.0)	64.9 (9.2)
Men, CGG repeat size (SD)	89.8 (19.1)	27.6 (5.0)
Women, CGG repeat size (SD)	82.4 (16.4)	29.9 (3.5)

* These data do not include the seven subjects with repeat sizes in the gray zone.

† There was no difference in age between the male carrier and control groups ($p = 0.20$) or the female carrier and control groups ($p = 0.31$).

Table 2

Group comparisons of Fragile X-Associated Tremor/Ataxia Syndrome Rating Scale scores*

	Premutation carriers, mean (SD)	Controls, mean (SD)	*p* Value
All subjects			
Total score	23.5 (22.9)	14.6 (13.4)	< 0.001
Tremor score	8.3 (8.8)	4.9 (4.7)	< 0.001
Ataxia score	7.8 (8.4)	4.6 (4.6)	< 0.001
Parkinsonism score	6.8 (8.6)	4.7 (5.8)	0.016
Men			
Total score	36.2 (28.2)	16.1 (14.7)	< 0.001
Tremor score	13.2 (10.9)	5.4 (5.3)	< 0.001
Ataxia score	12.4 (10.4)	4.9 (4.8)	< 0.001
Parkinsonism score	10.3 (10.9)	5.3 (6.4)	0.003
Women			
Total score	15.1 (13.3)	12.6 (11.2)	0.14
Tremor score	5.0 (4.8)	4.3 (3.7)	0.19
Ataxia score	4.8 (4.9)	4.2 (4.5)	0.24
Parkinsonism score	4.5 (5.5)	4.0 (4.9)	0.29

* These comparisons were not corrected for age because there was no significant difference in ages of carrier and control groups for either sex.

Table 3

P values for regression analyses of motor scores with CGG repeat length and age

	CGG repeat length*		Age	
	Regression coefficient	***p* Value**	**Regression coefficient**	***p* Value**
All subjects				
Total score	0.180	< 0.001	0.927	<0.001
Tremor score	0.068	< 0.001	0.263	< 0.001
Ataxia score	0.072	< 0.001	0.306	< 0.001
Parkinsonism score	0.039	0.006	0.360	<0.001
Men				
Total score	0.270	< 0.001	1.302	< 0.001
Tremor score	0.110	< 0.001	0.390	< 0.001
Ataxia score	0.109	< 0.001	0.404	< 0.001
Parkinsonism score	0.055	0.016	0.490	< 0.001
Women				
Total score	0.064	0.10	0.466	< 0.001
Tremor score	0.016	0.28	0.091	0.03
Ataxia score	0.025	0.10	0.165	< 0.001
Parkinsonism score	0.017	0.29	0.221	< 0.001
Women, with incorporation of the activation ratio				
Total score	0.43	0.15	0.43	0.03
Tremor score	0.08	0.50	0.06	0.47
Ataxia score	0.25	0.03	0.15	0.05
Parkinsonism score	0.11	0.34	0.26	0.001

*Regressions of scores against CGG repeat length were controlled for age.

Table 4

Phenotypic groups recommended for FXTAS testing*

1. Unexplained cerebellar gait ataxia, onset ≥ 50 years
2. Unexplained action tremor in person with parkinsonism or dementia, onset ≥ 50 years
3. MCP sign on MRI, family history of *FMR1* mutation, or premature menopause in self or family if have signs consistent with FXTAS† onset ≥ 50 years
4. Probable multiple system atrophy, cerebellar subtype

*Fragile X–associated tremor/ataxia syndrome (FXTAS) is less common in women.

†Signs consistent with FXTAS include cerebellar gait ataxia, action tremor, parkinsonism, cognitive decline, neuropathy, and autonomic dysfunction.

MCP =middle cerebellar peduncle.