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Co-occurring diagnoses among *FMR1* premutation allele carriers

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Abstract

Following the discovery of two disorders associated with premutation alleles of the fragile X mental retardation gene (*FMR1*), primary ovarian insufficiency [fragile X-associated primary ovarian insufficiency (FXPOI)] and a tremor/ataxia syndrome [fragile X-associated tremor/ataxia disorder (FXTAS)], numerous studies have examined other potential co-morbid conditions, including neuropsychological deficits. Here, the frequency of self-reported diagnoses obtained through medical history interviews from *FMR1* premutation carriers and non-carriers aged 18–50 were analyzed. Study subjects included 537 women, 334 of whom carry the premutation and 151 men, 37 of whom carry the premutation. Men with the premutation did not report any medical conditions at higher rates compared with non-carriers, controlling for age, ethnicity/race, and household income. Women with the premutation reported mental health disorders [i.e. attention deficit hyperactivity disorder (ADHD), anxiety, depression] significantly more often than non-carriers. However, after adjusting for covariates, these increased rates were not statistically significant. Additional follow-up analyses examined the consequence of ovarian dysfunction as a cause of co-occurring conditions. Women with an indication of ovarian insufficiency (i.e. irregular cycles) reported higher rates of thyroid problems and depression/anxiety. Because only women, not men, reported these conditions more often, the relationship between FXPOI and hormone irregularities in women should be explored for a potential link with the increase in the reported medical conditions.

Keywords

CGG repeat; *FMR1*; fragile X syndrome; FXPOI; FXTAS; premutation

The fragile X mental retardation gene (*FMR1*) 5' untranslated region contains a CGG repeat that in rare cases may become unstable and expand in the next generation (1–4). Repeats in the range of about 55–199, termed as premutation alleles, are associated with increased levels of mRNA as well as decreased protein levels (5–10). In addition, these alleles are associated with two clinical disorders: fragile X-associated primary ovarian insufficiency (FXPOI) (11, 12) and a fragile X-associated tremor/ataxia disorder (FXTAS) (13, 14). For both disorders, the premutation allele is incompletely penetrant and, when expressed, there is a range of severity. An RNA gain-of-function toxicity mechanism has been proposed to explain the pathophysiology of FXTAS (15).

Numerous studies have been published reporting other neurocognitive and psychiatric phenotypes associated with premutation alleles among carriers that do not meet diagnostic criteria of FXTAS with inconclusive results (16). However, two recent reports have

examined other medical conditions among women that are not part of the FXTAS or FXPOI symptom spectrum. Coffey et al. examined premutation carrier women without definite or probable FXTAS ($n = 128$) and found an increased medical history of chronic muscle pain, sensory loss, and tremor compared to controls ($n = 69$) (17). They also examined premutation carrier women with symptoms of FXTAS ($n = 18$) and found an increased history of hypertension, seizures and thyroid disease compared to age-matched controls ($n = 39$) (17). Most recently, Rodriguez-Revenga et al. reviewed the medical histories of 180 premutation carrier women and found an increased risk for thyroid disease and chronic muscle pain compared with the general population (18). Similar studies have not been done among adult men with the premutation.

In light of these recent reports of increased rates of co-occurring conditions among premutation allele carriers, we performed an exploratory analysis using self-report medical histories in an independent sample of adult women and, for the first time, among adult men. These diagnostic self-reports were provided by participants as part of a larger project to assess neuropsychological outcomes of premutation allele carriers (19–21) and included individuals, aged 18–50 years, with varying *FMR1* repeat lengths.

Methods

Subjects

Subjects included 151 men and 537 women between 18 and 50 years of age who spoke English as their primary language. Repeat length ranges and median values for all participants are shown in Table 1. Premutation carriers had a wide range of repeat length alleles, with 41% of males and 42% of females carrying alleles with greater than 90 repeats. The majority of participants were unrelated, although some were ascertained from the same pedigree. Participants from the general population were identified from various public sites, including health fairs, churches, and sports events. Participants from families with a history of fragile X syndrome (FXS) were identified through clinics, internet postings, parent groups, and word of mouth. Once the family member with FXS was identified, all relatives were surveyed to identify premutation carriers and non-carriers without knowledge of their phenotype. The protocols and consent forms for ascertainment were approved by the Institutional Review Board at Emory University.

Data collection

The primary focus of the research project from which this sample was drawn was to determine whether premutation carriers differed on neuropsychological outcomes compared with non-carriers (19–21). All participants were administered a self-report medical history by study personnel using a structured questionnaire used to determine eligibility for neuropsychological testing. The questionnaire was designed in 1999 prior to the identification of FXTAS and was not developed to assess premutation-associated medical conditions; thus, it provides an unbiased self-assessment of a participant's health concerns.

Subjects were queried about a broad range of medical conditions and were given examples of common conditions within diagnostic categories to ensure a complete history. Subjects were asked if a doctor or other health professional ever told them they had the following: allergies, stroke or transient ischemic attack, Parkinson disease, visual impairment, brain tumor, seizures or epilepsy, metabolic disorders (such as phenylketonuria), ADHD, developmental delay, learning disability, anxiety disorders, depression, obsessive-compulsive disorder (OCD), Tourette or other tic disorder, schizophrenia, cancer, endocrine disorders (such as hypothyroidism and hyperthyroidism), alcoholism or drug addiction, diabetes, immune system disorders (such as rheumatoid arthritis, lupus, multiple sclerosis,

chronic fatigue, and Grave's disease), and neuromuscular disorders (such as muscular dystrophy and myotonic dystrophy). Subjects were then asked to report any other past or present diagnoses not covered by the above headings. Subjects reported all current prescription medications and the reason(s) for their administration. Positive diagnoses for each condition were defined by either the subject's report of being diagnosed with the condition by a physician or other health professional, or by the subject's report of taking prescription medication(s) that were prescribed by a physician or other health professional as treatment for a particular condition.

In later versions of the questionnaire, subjects were also asked to provide a comprehensive report of any past or current cigarette smoking and alcohol use. For a subject to be considered as having a history of smoking or drinking, he/she must have reported smoking 100 or more cigarettes or drinking 50 or more alcoholic drinks, respectively, during their lifetime. Those who reported a history of smoking or drinking were asked more detailed questions regarding duration and quantity. Using this detailed history, variables for lifetime alcohol consumption (frequency of drinking multiplied by the number of drinks consumed) and pack years (the number of packs of cigarettes a person smokes per day times the number of years a person has smoked) were calculated. Data for alcohol consumption were obtained for 60 men and 254 women.

Women were asked to complete an additional questionnaire regarding their reproductive history. This questionnaire, completed by 520 women, asked about menstrual cycle characteristics and hormone medication use. We specifically used the following question concerning cycle length changes to determine if a woman was experiencing menopause transition or ovarian insufficiency (terms being dependent on age): Did you experience changes in the length of your menstrual cycle during the most recent five years that you were cycling naturally and not taking hormone medication. Cycle length variability is one characteristic of transition based on the classification of Soules et al. (2001) (22) and is an indicator of overall reproductive health (23). Among the women who completed the reproductive history questionnaire, 158/323 (48.9%) premenutation carriers and 66/192 (34.4%) of non-carriers reported evidence for ovarian insufficiency.

Statistical analysis

Subjects were divided into two groups based on CGG repeat length, non-carriers (less than 55 repeats) and premutation allele carriers (55–199 repeats). Demographic data are provided in Table 1. Using χ^2 tests for dichotomous variables and *t*-tests for continuous variables, significant differences in demographic variables between groups were examined. To be consistent across the study population, age, ethnicity, and income, but not education, were included as covariates in all adjusted models for men and women. We also examined ascertainment method (general population *versus* FXS families) as a potential confounder, but found no such evidence and did not include it in any of the models.

Fisher's exact test was used to evaluate associations between premutation carrier status and medical diagnoses using the crude data counts. Generalized estimating equation (GEE) models were then used to account for potentially correlated outcomes due to shared environmental and genetic effects among participants from the same family (Tables 2 and 3) (24). These models were also adjusted for age, ethnicity, and income. For several diagnostic outcomes, the number of diagnoses was too small to allow the model outlined above to converge and provide accurate estimates of the odds ratio (OR).

Follow-up analyses were performed based on the marginal and significant results of the models above. First, cigarette smoking and alcohol consumption were included as predictors in GEE models to test their potential contribution to the onset of all medical conditions.

Next, we examined whether the ovarian insufficiency, using reports of variable menstrual cycle length as an indicator (see above for rationale), influenced co-morbid conditions. Lastly, we included a variable for raising a child with FXS in GEE models as a predictor of psychiatric disorders to account for any potential psychosocial impact on these conditions.

Because of the number of statistical tests performed, a simple Bonferroni correction with the number of major diagnostic categories as the denominator was used. Based on this correction, a p value of <0.01 indicates statistical significance at the 5% level. We conducted follow-up analyses on all statistically significant ($p < 0.01$) and marginally significant ($0.05 > p \geq 0.01$) initial analyses. SAS V9.1 was used for all statistical analyses.

Determination of *FMR1* CGG repeat number

All subjects were asked to provide a blood or buccal brush sample for molecular analysis of *FMR1* repeat length. DNA was extracted from samples with the Qiagen QiAmp DNA Blood Mini Kit. A fluorescent sequencer method using an ABI Prism 377 DNA sequencer, and most recently an ABI 3100 Genetic Analyzer, was used to determine *FMR1* CGG repeat length (25). When no repeat length band for males or only one band for females was present, an alternative polymerase chain reaction-based, hybridization technique was used to identify larger premutation or full mutation alleles (26). For heterozygous females, CGG repeat length from the larger repeat allele was used in subsequent statistical analyses.

Results

No evidence for the presence of major co-morbid conditions among males with the premutation

In general, men with or without the premutation reported few diagnostic conditions and there was no evidence of differential reporting of medical conditions by carrier status (Table 2). This was true irrespective of the ability to use the GEE regression models adjusting for age, ethnicity and income or the use of the Fisher's Exact test on the crude data. We also investigated smoking and alcohol consumption histories and found that fewer premutation males reported having smoked ($p = 0.01$), whereas there was no difference in reports of a history of alcohol consumption ($p = 0.69$).

Females with the premutation report a higher rate of co-morbid conditions

Overall, women reported a higher frequency of medical conditions than men (Table 3). Among the mental health disorders, only ADHD differed among groups in the GEE models. Although the comparisons of the crude data indicated higher reporting of anxiety disorders and depression among premutation carriers ($p = 0.01$), once covariates were included, no significance differences were found. In addition, reporting of learning disabilities (LD) was marginally increased and reporting allergies was decreased among premutation carriers compared with non-carriers. Lastly, women with the premutation reported having a history of smoking more often than non-carriers with marginal significance (Table 3).

Given ADHD was elevated among female carriers of the premutation, we examined the medications being taken by all women who reported ADHD. Among the non-carriers, one was currently being treated with stimulants (i.e. Ritalin or Adderall), and one was not currently taking medication for ADHD, but had been treated with stimulants as a child and with a selective serotonin reuptake inhibitor as a teenager. Among the carriers, four were never treated, three were treated with stimulants as a child or teenager but were not currently being treated, two were currently taking stimulants, and six were currently taking both stimulants and some type of selective serotonin or norepinephrine reuptake inhibitor (i.e. Effexor, Strattera, Celexa, or Prozac).

In follow-up analyses, smoking and alcohol consumption were not significant predictors for any diagnoses. In follow-up analyses including a measure of ovarian insufficiency as a predictor, depression and anxiety were combined because they were often reported by the same women. In addition, although not significant in our analyses ($p = 0.06$), we included thyroid disorders due to significant associations with premutation alleles reported in other studies (17, 18). We found that ovarian insufficiency was a marginally significant predictor for depression/anxiety and thyroid problems, but not for ADHD or LD (Table 4). Interaction terms for ovarian insufficiency and carrier status were not significant in any of the models. In a further stratified analysis, ovarian insufficiency remained marginally significant for predicting depression/anxiety (OR: 1.79; 95% CI: 1.11–2.10 $p = 0.02$) and thyroid disease (OR: 2.28; 95% CI: 1.15–4.55 $p = 0.02$) among premutation carriers only. Although the pattern of OR was the same for non-carriers, ovarian insufficiency was not a significant predictor for either condition (depression/anxiety – OR: 1.33; 95% CI: 0.65–2.73; $p = 0.44$; thyroid disease – OR: 2.45; 95% CI: 0.61–9.89; $p = 0.21$). Lastly, raising a child with FXS was not a significant predictor of anxiety, depression, ADHD, or all mental health disorders combined.

Additional conditions self-reported by subjects

As part of the medical history questionnaire, subjects were asked to report additional diagnoses not specifically queried. There were a variety of disorders reported, although none were differentially reported by premutation carrier status among men or women (data on request). Although fibromyalgia has been reported to be increased among women with the premutation carriers (17), in this study there was no difference between carriers and non-carriers in this unsolicited reporting (1NC and 3 PM, $p = 1.00$).

Discussion

Based on recent studies that reported increased frequency of medical conditions among premutation carriers (17, 18, 27), we examined the self-reported medical histories of male and female premutation carriers aged 18–50 years. This history was taken as part of a larger protocol to examine neuropsychological outcomes and was used to determine eligibility to perform psychological testing (19–21). Overall, men with the premutation did not report a history of any medical conditions in higher frequencies compared to non-carriers. In contrast, women with the premutation reported higher rates for four times as many conditions as did non-carriers (adjusted OR >1 *versus* <1) disregarding statistical significance. However, there was no statistically significant differential reporting by carrier status. There was a marginal increase in reporting of ADHD and LD and decreased reporting of allergies by women with the premutation.

Women with the premutation in our dataset reported mental health conditions more often than non-carriers, including depression, anxiety and ADHD. These self-reports are consistent with our previous reports based on assessment of such conditions through psychometric testing (19, 20) and are important as they indicate one's own assessment of their mental health. In our study of mood and anxiety, repeat length was not only associated with anxiety, but also was marginally associated with negative affect in women (19). Using that assessment battery, we also found that repeat length in men was marginally associated with negative affect as well as depression; however, we had no indication of an increase of these conditions among men with the premutation based on self-report (Table 2). In addition, a separate study on the same population indicated significant associations of premutation alleles and symptoms associated with ADHD among women including memory, impulsivity and emotional lability, and problems with self-concept, but not for hyperactivity and restlessness (28). These problems were not associated with men, although there were 37 males with the premutation compared to 334 females. Taken together, the

self-recognition of reduced mental health and our test battery (19, 20) suggest that women, and perhaps men, with the premutation may be at risk for emotional morbidity. These data are partially consistent with a recent report based on a nationwide parent survey of families with a child diagnosed with FXS (29) which suggested higher rates of anxiety and depression for children aged 6 and older with a premutation allele. Both studies are limited by the lack of follow-up with medical records. Also, no information was available for subjects who did not participate. In our study, if subjects chose not to participate because of medical or psychiatric conditions, their missing data could affect the results.

A slightly higher prevalence of thyroid disease in premutation carrier women is consistent with the findings from Coffey et al. (17), although they found this increase primarily among women with FXTAS, as did Rodriguez-Revenga et al. (18). However, this higher prevalence of thyroid disease was not reported in Hundscheid et al. (27) and was not significantly elevated in this study. Thus, additional studies with more detailed medical review are warranted. Further, Coffey et al. reported elevated chronic muscle pain and persistent paraesthesias in extremities among non-FXTAS premutation carrier women and elevated hypertension, seizures, peripheral neuropathy, and fibromyalgia among women with FXTAS symptoms (17). Although we did not ask specifically about most of these conditions, women did not mention these when asked about 'other medical conditions'. The difference between studies may relate to the difference in age between studies; the sample reported in Coffey et al. was older on average than the group reported here. Also, we did not have any men or women with probable or definite FXTAS in our sample.

With respect to lifestyle behaviors, premutation carrier women, but not carrier men, reported a history of alcohol consumption more often than non-carriers, although this increase was not statistically significant when adjusting for covariates. Increased rates of substance abuse compared to non-carrier controls from the general population has been reported among men (not studied among women) (30). More data are needed to confirm these intriguing, but non-significant, results.

The increased reporting of medical conditions among premutation carrier women in this age range may be the consequence of stress related to caring for relatives with fragile X-associated disorders, over-reporting due to the fact of being a gene carrier, or of the underlying effects of ovarian insufficiency. We were unable to find evidence for the potential effects of raising a child with FXS by simply using a covariate in the model. Using presence of irregular menstrual cycles as a surrogate for ovarian insufficiency, we found that this variable was a marginally significant predictor of thyroid disease and depression/anxiety.

Our results suggest that the hormonal relationship between ovarian function, the thyroid, and mood and anxiety should be further explored (Table 4). Irregular thyroid hormone levels, specifically hypothyroidism, are associated with abnormal menstrual cycles (29) and increased symptoms of depression and anxiety (31, 32). Although autoimmune disorders, in general, were not elevated in this study population, autoimmune causes of hypothyroidism in premutation women should be explored (28).

There are some potential limitations of this study not already addressed. First, the use of self-report questionnaires is not as reliable as use of medical records. Although both carriers and non-carriers were interviewed with a structured questionnaire, there is the potential of reporting and possibly recall bias. Second, a history of irregular cycles among the female participants, obtained from the reproductive questionnaires, represents only one symptom of ovarian insufficiency. Further, studies that use better indicators of ovarian insufficiency would be valuable. A limitation, and perhaps strength, of this study is that the questionnaire

was developed prior to the reporting of various health conditions, including FXTAS. Thus, it was unbiased in its representation of questions asked and provides results that substantiate previous reports for some conditions, but does not add evidence for others.

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Table 1

Demographic information stratified by gender and repeat length group

Gender	Repeat length group	N	Median repeat length (range)	Mean age (SD)	Ethnicity, % Caucasian/Asian	Education, % college completed	Income, % \$50,000
Males	All	151	31 (20–180)	35.9 (9.2)	81.3	80.1	70.9
	NC (<55 repeats)	114	30 (20–54)	36.3 (9.1)	77.9	82.5	69.2
	PM (55–199 repeats)	37	89 (55–180)	34.9 (9.8)	91.9	73.0	76.5
Females	All	537	75 (20–160)	35.4 (9.4)	78.6	85.1	63.3
	NC (<55 repeats)	203	32 (20–54)	32.5 (10.1) ^a	60.9 ^a	87.7	53.4 ^a
	PM (55–199 repeats)	334	89 (55–160)	37.1 (8.4) ^a	89.4 ^a	83.5	69.2 ^a

NC, non-carriers; PM, premutation allele carriers; SD, standard deviation.

^aNC and PM groups differed significantly, $p < 0.001$.

Table 2

Male premutation carriers and non-carriers: Fisher's Exact test of the repeat group comparisons and odds ratio (OR) adjusted for age, income and ethnicity and 95% confidence interval (CI) for repeat size group based on Generalized estimating equation (GEE) regression analysis

	NC (N = 114)	PM (N = 37)	Adjusted OR (95% CI)
Mental health disorders	16 (14%)	3 (8.1%)	0.48 (0.13–1.82)
ADHD	3 (2.6%)	0	–
Anxiety disorder	3 (2.6%)	2 (5.4%)	–
Depression	15 (13.2%)	2 (5.4%)	0.33 (0.06–1.69)
OCD	2 (1.8%)	1 (2.7%)	–
Schizophrenia	0	0	–
Tourette's or Tic disorder	0	0	–
Alcoholism or drug addiction	2 (1.8%)	1 (2.7%)	–
Neurological issues			
Developmental delay	0	0	–
Learning disability	5 (4.4%)	1 (2.7%)	–
Parkinson's disease	0	0	–
Seizures/epilepsy	0	0	–
Vision problems	17 (15%)	3 (8.1%)	0.43 (0.11–1.72)
Endocrine problems	4 (3.5%)	2 (5.4%)	–
Diabetes	4 (3.5%)	2 (5.4%)	–
Thyroid	0	0	–
Hypothyroidism	0	0	–
Hyperthyroidism	0	0	–
Stroke	0	0	–
Musculoskeletal conditions	0	0	–
Cancer/tumors	2 (1.8%)	0	–
Autoimmune disorders	1 (0.9%)	0	–
Rheumatoid arthritis	0	0	–
Lupus	0	0	–
Chronic fatigue syndrome	0	0	–
Multiple sclerosis	1 (0.9%)	0	–
Allergies	40 (35%)	13 (35%)	1.03 (0.47–2.23)
Metabolic disorders	0	0	–
Lifestyle^a			
Alcohol	40 (85%)	12 (80%)	0.75 (0.10–5.52)
Smoking	22 (47%)	1 (6.7%) ^b	–

NC, non-carriers; PM, premutation allele carriers; ADHD, attention deficit hyperactivity disorder; OCD, obsessive-compulsive disorder; MVP, mitral valve prolapse.

^aAlcohol and smoking data available for 60 males (47 NC and 15 PM).

^bp <0.05.

Table 3

Female premutation carriers and non-carriers: Fisher's Exact test of the repeat group comparisons and OR adjusted for age, income and ethnicity and 95% confidence interval (CI) for repeat size group based on GEE regression analysis

	NC (N = 203)	PM (N = 334)	Adjusted OR (95% CI)
Mental health disorders	40 (20%)	107 (32%) ^d	1.57 (0.99–2.50)
ADHD	2 (1.0%)	15 (4.5%) ^c	6.01 (1.16–31.25) ^c
Anxiety disorder	13 (6.4%)	45 (13%) ^c	1.85 (0.97–3.54)
Depression	31 (15%)	84 (25%) ^c	1.53 (0.91–2.56)
OCD	5 (2.5%)	9 (2.7%)	1.02 (0.28–3.70)
Schizophrenia	0	1 (0.3%)	–
Tourette's or Tic disorder	0	0	–
Alcoholism/drug addiction	0	3 (0.9%)	–
Neurological issues			
Developmental delay	1 (0.5%)	2 (0.6%)	2.02 (0.06–65.05)
Learning disability	3 (1.5%)	16 (4.8%)	5.60 (1.02–30.92) ^c
Parkinson's disease	0	0	–
Seizures/epilepsy	0	3 (0.9%)	–
Vision problems	21 (10%)	53 (16%)	1.51 (0.83–2.74)
Endocrine problems	20 (9.9%)	48 (14%)	1.26 (0.66–2.42)
Diabetes	11 (5.4%)	21 (6.3%)	1.13 (0.47–2.68)
Thyroid	11 (5.4%)	34 (10%)	1.47 (0.61–3.59)
Hypothyroidism	10 (5.0%)	31 (9.3%)	1.49 (0.60–3.72)
Hyperthyroidism	1 (0.5%)	3 (0.9%)	–
Stroke	0	1 (0.3%)	–
Musculoskeletal conditions	0	0	–
Cancer/tumors	5 (2.5%)	6 (1.8%)	0.46 (0.10–2.19)
Autoimmune disorders	0	3 (0.9%)	–
Rheumatoid arthritis	0	2 (0.6%)	–
Lupus	0	0	–
Chronic fatigue syndrome	0	1 (0.3%)	–
Multiple sclerosis	0	0	–
Allergies	104 (51%)	143 (43%)	0.55 (0.37–0.83) ^d
Metabolic disorders	0	0	–
Lifestyle			
Alcohol ^a	22 (50%)	155 (74%)	2.32 (1.20–4.48) ^c
Smoking ^b	4 (9.3%)	55 (26%)	2.63 (0.93–7.42)

NC, non-carriers; PM, premutation allele carriers; ADHD, attention deficit hyperactivity disorder; OCD, obsessive-compulsive disorder; MVP, mitral valve prolapse.

^aAlcohol data available for 254 females (44 NC and 210 PM).

^bSmoking data available for 251 females (43 NC and 208 PM).

^c $p < 0.05$.

^d $p < 0.01$.

Table 4

Examination of the influence of ovarian insufficiency on medical conditions in women using GEE models (ORs adjusted for age, income and ethnicity)

	NC (N = 195)	PM (N = 325)	<u>Adjusted odds ratio (95% confidence interval)</u>	
			Repeat group	Irregular menstrual cycles
Mental health disorders	38 (19%)	103 (32%)	1.45 (0.90–2.34)	1.58 (1.05–2.38) ^a
ADHD	2 (1.0%)	15 (4.6%)	5.86 (1.08–31.87) ^a	1.01 (0.38–2.70)
Depression/anxiety	35 (18%)	97 (30%)	1.45 (0.88–2.37)	1.67 (1.12–2.50) ^a
Learning disability	3 (1.5%)	16 (4.9%)	5.50 (0.95–31.79)	0.53 (0.18–1.58)
Thyroid problems	11 (5.4%)	34 (10%)	1.65 (0.67–4.07)	2.11 (1.04–4.26) ^a

NC, non-carriers; PM, premutation allele carriers; ADHD, attention deficit hyperactivity disorder.

^a p < 0.05.