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The *FMR1* Premutation and Attention-Deficit Hyperactivity Disorder (ADHD): Evidence for a Complex Inheritance

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Abstract

We recently reported elevated symptoms associated with attention-deficit hyperactivity disorder (ADHD) among adult female carriers of the *FMR1* premutation. To gain insight into the contribution of this mutation in the context of polygenes, we examined the proportion of variation in these symptoms due to residual genetic factors after adjustment for the effect of the premutation. To accomplish this, we performed a familial aggregation analysis of ADHD symptoms among 231 females from 82 pedigrees using scores from the Connors Adult ADHD Rating Scales. Results indicate that after accounting for the effect of *FMR1*, there are significant residual polygenic effects on self-reported symptoms of ADHD, as measured by the ADHD Index ($p = 0.0117$) and problems with self-concept ($p = 0.0110$), one specific symptom domain associated with ADHD. For both measures, *FMR1* accounts for ~5% of the variance while polygenes account for ~50% of the residual variance, suggesting that the premutation acts in concert with additional genetic loci to influence the severity of ADHD symptoms.

Keywords

CGG repeat; Triplet repeat; *FMR1*; Fragile X syndrome; ADHD; Familial aggregation

Introduction

The most common alleles of the X-linked fragile X mental retardation gene (*FMR1*) contain roughly 30 CGG repeats in the 5' untranslated region of exon 1 (Snow et al. 1993). Rare expansions of this repeat region are associated with different clinical disorders, depending on repeat size. Alleles with 200 repeats or more, termed full mutation alleles, are associated with fragile X syndrome (FXS). These alleles are typically hypermethylated which leads to a loss of gene expression (Sutcliffe et al. 1992). Premutation alleles, alleles with 55–199 repeats as defined by the American College of Medical Genetics (Sherman et al. 2005), remain unmethylated but are associated with elevated levels of *FMR1* transcript and reduced levels of FMRP (Kennerson et al. 2001; Primerano et al. 2002; Tassone et al. 2000a, b; Tassone and Hagerman 2003). Older males (>50 years) who carry the premutation are at an increased risk for fragile X-associated tremor/ataxia syndrome (FXTAS) (Hagerman et al. 2003) while premutation females are at an increased risk of fragile X-associated primary ovarian insufficiency (FXPOI) (Sherman 2000). Neither of these disorders is seen in conjunction with FXS, and is therefore thought to be caused by a toxic gain-of-function effect of increased levels of the expanded *FMR1* transcripts.

Recently, there have been suggestions that the premutation allele may lead to other disorders in addition to FXTAS and FXPOI. For example, in a nationwide survey, parents reported higher rates of attention problems, anxiety, aggression, autism, depression, developmental delay, and seizures for children age 6 and older who carried a premutation allele compared with non-carrier siblings (Bailey Jr. et al. 2008a). Using the self-report Connors Adult ADHD Rating Scales (CAARS) (Conners et al. 1999), we recently assessed the severity of symptoms associated with attention-deficit hyperactivity disorder (ADHD) among females aged 18–50 years ascertained from families with a history of FXS as well as from the general population (Hunter et al. 2008a). Results indicated that premutation carriers as a group had significantly elevated scores for three ADHD-related symptom domains compared to non-carriers: inattention and memory problems, impulsivity and emotional lability, and problems with self-concept, compared to non-carrier controls. Interestingly, premutation carriers were not significantly different from non-carriers for a fourth symptom associated with ADHD: hyperactivity and restlessness.

While ADHD is one of the most common psychiatric disorders among children, the disorder is also prevalent among adults with roughly 60% of childhood cases persisting into adulthood (Faraone et al. 2006). Prevalence rates of adult ADHD are estimated at 2.9% for a narrow definition of ADHD (defined as meeting DSM-IV criteria for childhood and adulthood) and 16.4% for a broad definition of ADHD (which includes cases that meet sub-threshold criteria for ADHD) (Faraone and Biederman 2005). Twin studies in children point to a large overall impact of genetics on ADHD, with heritability estimates typically in the range of 0.6–0.8 for both males and females (Larsson et al. 2004; Rietveld et al. 2004; Willcutt et al. 2000). However, to date, there is surprisingly little information on the heritability of ADHD symptoms that persist into adulthood. Recently, two twin studies have been published using the Netherlands Twin Registry to assess ADHD heritability in male and female young adults (Boomsma et al. 2010; van den Berg et al. 2006). Van den Berg et al. (2006) used longitudinal assessments of attention problems only among twin pairs aged 18–30 using the attention subscale of the Young Adult Self-Report to obtain heritability estimates of roughly 0.40 for both males and females. Boomsma et al. (2010) analyzed CAARS ADHD Index scores from adult twins, along with their siblings and parents, and obtained a heritability estimate of 0.30 for both males and females.

The goal of the current study is to understand the contribution of the *FMR1* premutation toward ADHD symptoms in the context of polygenes to better understand the genetic

architecture of the complex disorder. Thus, we determined the heritability of self-reported ADHD symptoms among adults that remains after adjusting for the effects of the *FMR1* premutation. Importantly, this is the first study to date to examine the heritability of ADHD in the presence of a single gene effect as well as the first study to analyze the heritability of a range of specific symptom domains of ADHD in an adult population. Here, we use CAARS scores from 231 women from 82 pedigrees first to confirm the association between ADHD symptoms and the *FMR1* premutation and second to examine the residual heritability of symptoms after adjustment for the premutation effect using a familial aggregation analysis (Therneau and Atkinson 2007). The overarching goal of this study is to gain essential evidence for novel ADHD-susceptibility genes in this sensitized population of premutation carriers as well as aid in risk prediction.

Materials and methods

ADHD measurement

Symptoms associated with ADHD were measured using the self-report, long form of the Conners' Adult ADHD Rating Scales (CAARS-S:L) (Conners et al. 1999). The CAARS provides an ADHD Index score that is intended to distinguish ADHD adults from nonclinical adults. The CAARS also provides factor-derived scales to assess four domains of ADHD symptoms: inattention and memory problems, hyperactivity and restlessness, impulsivity and emotional lability, and problems with self-concept. Increasing scores indicate increasing severity of ADHD symptoms. The CAARS has high internal reliability (Cronbach's α estimates ranging from 0.79 to 0.90 for the four factor scores and ADHD Index) and test-retest reliability (correlations in the range of 0.88–0.91) (Conners et al. 1999). In addition, the CAARS has been shown to be most accurate in predicting clinical diagnoses among adults with ADHD compared to other self-report measures (Sandra Kooij et al. 2008). The CAARS also includes an Inconsistency Index to account for random or careless responding, where values >7 indicate inconsistency among answers. Thus data from any participant with an inconsistency score greater than this threshold were removed from analysis to improve reliability of the data. Any score above 65 is considered indicative of elevated symptoms associated with ADHD. Gender- and age-adjusted T-scores were used for analysis.

Study participants

Study participants were ascertained either through a relative with a fragile X-associated disorder or from the general population as part of an ongoing research project to determine neuropsychological phenotypes associated with *FMR1* premutation alleles among young adults (Allen et al. 2005; Hunter et al. 2008a, b). Participants were aged 18–50 and had English as their primary language. After removing participants with missing genotype or phenotype data, as well as subjects with a CAARS inconsistency index >7, our study sample included 231 women from 82 pedigrees. Among these pedigrees, the number of females per pedigree ranged from 2 to 8. The types of relationships among these females were highly variable among pedigrees (e.g. mothers and daughters, aunts and nieces, first and second cousins). Only 40 of the 82 family clusters analyzed consisted of full siblings only (35 pedigrees with 2 full sisters and 5 pedigrees with 3 full sisters). The protocols and consent forms for ascertainment were approved by the Institutional Review Board at Emory University.

FMR1 repeat length measurement

All participants provided a biological sample, either buccal or blood, for molecular analysis of *FMR1* CGG repeat length using methods reported in Allen et al. (2005). Briefly, DNA extracted with the Qiagen QiAmp DNA Blood Mini Kit is genotyped using a PCR reaction

with fluorescent primers that amplifies across the *FMRI* repeat region and creates a fluorescent product for analysis on an automated sequencer (Meadows et al. 1996). Alleles with up to 90 repeats can be identified with this method. Alleles with expansions longer than 90 repeats and alleles from homozygous females are analyzed with an alternative PCR-based, hybridization technique (Brown et al. 1993).

Statistical analysis

Demographic variables were obtained through a standardized questionnaire and included age at the time of testing (continuous variable), self-reported race (dichotomous: 0 = Caucasians and Asians, 1 = other races), level of education achieved (ordinal: 1 = high school not completed, 2 = high school completed, 3 = trade or vocational school completed, 4 = college not completed, 5 = college completed, 6 = graduate or professional school completed), total household income (ordinal: 1 = <\$10,000, 2 = \$10,000–25,000, 3 = \$25,000–50,000, 4 = \$50,000–75,000, 5 = \$75,000–100,000, 6 = >\$100,000), and method of ascertainment (dichotomous: 0 = ascertained from the general population, 1 = ascertained from a family with a history of fragile-X associated disorders). Table 1 shows the comparison of these variables by repeat group. Statistical differences across repeat groups were determined using models that allowed adjustment for correlation among relatives: linear mixed models for continuous and ordinal variables and generalized estimating equation (GEE) models for dichotomous variables. Participants were also assessed for ADHD medication use. However, only one participant reported taking any medications for ADHD symptoms, and thus models were not adjusted for this factor.

The goal of this study was to measure the contribution of the residual additive genetic component, or polygenes, on CAARS scores after accounting for the effect of *FMRI* repeat length. Thus we used the *lme4* function within the *kinship* package of R (Therneau and Atkinson 2007) which provides a linear mixed-model framework that allows modeling of the polygenic variance component. This approach models the CAARS score for the i th subject as:

$$y_i = X_i\beta + b_i + \varepsilon_i,$$

where y_i is the CAARS score, X_i is the vector of all fixed effects (*FMRI* repeat length and additional covariates), β is the parameter vector for all fixed effects, b_i is the subject's random effect due to shared additive polygenes among relatives, and ε_i is the subject's residual error. The distribution of the random additive polygenetic effects is assumed to follow a multivariate normal distribution with mean zero and the variance–covariance matrix Σ :

$$\Sigma = 2\Phi\sigma_p^2,$$

where Φ is the kinship matrix, structured based on the familial relationships among subjects, and σ_p^2 is the variance due to shared additive polygenes among relatives. To determine whether polygenes have a significant effect on particular CAARS score, we maximized the likelihood under the null hypothesis ($H_0: \sigma_p^2 = 0$) and the alternative hypothesis ($H_A: \sigma_p^2 > 0$). We then calculated a likelihood-ratio statistic, which is twice the difference between the maximized likelihoods under the null and alternative hypotheses. The likelihood-ratio statistic follows a 50:50 ratio of χ_0^2 and χ_1^2 distributions (Self and Liang 1987). To account for multiple testing of various CAARS scores, we used a Cheverud–Nyholt approach to

estimate the effective number of tests as 3.71, based on the correlation among the five outcome scores (Cheverud 2001; Nyholt 2004). In order to account for correlation of scores among women within pedigrees, one participant per pedigree was randomly selected to be included in the estimation of the effective number of tests. Applying 3.71 as the denominator in a Bonferroni correction, we rejected H_0 at the 0.05 significance level with a p -value threshold of $p < 0.0135$.

CAARS scores were transformed (natural-log) to improve normality and homoscedasticity. Each of the individual CAARS scores was analyzed as the outcome variable in separate models. *FMR1* repeat length was used as the main predictor in all models and was modeled as a five-level categorical variable: non-carriers (< 40 repeats), intermediate allele carriers (41–60 repeats), low premutation allele carriers (61–80 repeats), middle premutation allele carriers (81–100 repeats), and high premutation allele carriers (>100 repeats). These repeat length categories were used in our previously published analysis of CAARS scores in our study population. These studies indicated that *FMR1* repeat length modeled as categories was a more significant predictor of ADHD symptoms compared to repeat length as a continuous variable (Hunter et al. 2008a). This is consistent with our previous studies that showed a non-linear effect of *FMR1* repeat length on premutation-associated phenotypes (Allen et al. 2007; Sullivan et al. 2005). As long repeat tracks, or premutation alleles, are associated with molecular pathology (Allen et al. 2004), the repeat length of the larger allele was used to categorize the females into repeat length groups. Models were adjusted for age, race, level of education achieved, household income, and method of ascertainment to account for potential confounding.

To complement our findings, we performed power calculations to determine our sample's ability to detect different values of narrow-sense heritability for a particular CAARS score. For a specific value for the narrow-sense heritability, we determined the appropriate value of σ_p^2 assuming the variance component due to subject-specific environment (residual error) was 1. We then used the values of these variance components to calculate the variance–covariance matrix of trait symptoms for our familial sample of 231 female participants. Using this matrix, we applied the R *mvnrm* function to generate multivariate outcomes for simulated datasets with the same size and pedigree configuration as observed in our sample. We then tested for a significant additive polygenic component in the dataset using the mixed model described in the previous paragraphs using the same $p < 0.0135$ threshold for statistical significance discussed above. For a given narrow-sense heritability value, we evaluated empirical power of our sample to detect the value using 1,000 replicate datasets.

The models described above do not account for any potential effect associated with shared environment within families, which could affect heritability estimates. Though previous studies of ADHD symptoms in children indicated a negligible impact of shared environment (e.g. Nikolas and Burt 2010). We performed follow-up analyses that examined the impact of shared environment on ADHD symptoms to ensure our heritability estimates were robust to the inclusion of such additional effects. Using the mixed model framework described earlier, we reanalyzed the data assuming random effects due to both shared polygenes as well as shared environment. We analyzed shared environment in a variety of different ways. In particular, we considered the effects of shared environment within families (random effect for each family), within full siblings (random effect for all full siblings within the same family), and a more innovative model of shared environment proposed by Schork (1993).

Linear mixed models and simulations were run in the statistical package R 2.12.0 (www.r-project.org). All other analyses were performed using SAS 9.2.

Results

Demographic data for the study population stratified by repeat group is shown in Table 1. Three participants were missing data for race and seven participants were missing data for household income. Repeat groups differed for age at testing ($p = 0.04$) and method of ascertainment ($p < 0.01$). Fourteen women were removed prior to analyses due to CAARS inconsistency index scores >7 : 2 non-carriers, 2 intermediate allele carriers, 3 low premutation carriers, 4 mid premutation carriers, and 3 high premutation carriers. A Chi square test indicated no significant association between repeat group and inconsistent reporting on the CAARS ($p = 0.58$).

Mean CAARS scores stratified by *FMR1* repeat length group are shown in Table 2. Analysis of the current study population of 231 females confirmed a significant association between *FMR1* repeat length and CAARS scores as previously published on a larger dataset which included women from the pedigrees analyzed in the current analysis (Hunter et al. 2008a). That is, *FMR1* repeat group was a significant predictor of ADHD Index, with participants in the low premutation group scoring significantly higher compared to the non-carrier group (Table 3). As presented previously (Hunter et al. 2008a), we explored specific ADHD symptom domains to better understand the effect of repeat size. The group of low premutation carriers scored significantly higher compared to the non-carrier group for inattention and memory problems, impulsivity and emotional lability, and problems with self-concept, indicative of elevated symptoms associated with ADHD in this premutation range (Table 3). In addition, the high premutation group scored significantly higher compared to the non-carrier group for severity of inattention and memory problems only (Table 3).

After adjusting for the effect of *FMR1* and potential confounders (age, race, education, income, and ascertainment), we tested for residual additive genetic effects on CAARS scores. We detected statistically significant polygenic components for ADHD Index and problems with self-concept scores (Table 3). *FMR1* adjusted R^2 values associated with these scores were 0.0579 and 0.0527, respectively, while narrow-sense heritability estimates for these scores were 0.5153 and 0.5060, respectively. The narrow-sense heritability estimates for inattention and memory problems, hyperactivity and restlessness, and impulsivity and emotional lability were 0.1418, 0.2078, and 0.4038, respectively, although these were not statistically different from zero in this sample. A possible reason why these tests did not achieve statistical significance is that our sample is underpowered to detect modest heritability values. For example, the power of our sample to detect a heritability of 0.40 at our chosen significance level is 34%. Thus we likely lacked empirical power to detect a significant additive genetic component for these scores.

Lastly, we performed follow-up analyses in the CAARS ADHD Index that included an additional random effect to account for shared environmental effects. Using the Schork (1993) model for shared sibling environment, we observed that shared environment accounted for 10.0% of the variance but this estimate was not significantly different from 0 ($p = 0.31$). The estimate of heritability was 51.0%, which was similar to our earlier results. Similarly, shared sibling environment contributed negligibly to the problems with self-concept, accounting for $<0.01\%$ of the variance ($p = 0.50$) while the heritability estimate remained 50.6%. We observed similar findings for models that assumed effects due to shared full-sibling environment as well as shared family environment (data not shown).

Discussion

This study is the first to analyze familial aggregation of ADHD symptoms in adults in the presence of a major gene effect. We previously reported an effect of the *FMR1* premutation on symptoms associated with ADHD among 506 adult females including 293 carriers of a premutation allele (defined as 60–199 repeats), 96 carriers of an intermediate allele (41–60 repeats), and 117 non-carriers (40 repeats or less) (Hunter et al. 2008a). In the current study, we confirmed this effect and that it behaved in a non-linear way with respect to repeat size. We then tested for an additive polygenic effect on self-reported ADHD and specific ADHD-associated symptom domains after adjusting for the effect of the *FMR1* premutation allele. Overall, narrow-sense heritability estimates of ADHD symptoms were large. Models using the CAARS ADHD Index, designed to be an indicator of clinical ADHD, estimated that roughly 50% of the variability in ADHD symptoms reported in our population could be attributed to an additive genetic component, compared to roughly 6% of variability of these symptoms attributable to *FMR1*.

Though heritability estimates of ADHD in the general population have been high, the genetic etiology of this disorder of combined behavioral symptoms has remained unclear and no major genes have been identified. This suggests that ADHD is due to small effect sizes of multiple genes (Franke et al. 2009) and/or to many different rare mutations of larger effect. Most association studies for genes involved in ADHD have used a candidate gene approach; the most significant gene variants identified had odds ratios of about 1.3 (Banaschewski et al. 2010). Our results here indicate that *FMR1* is one of the more rare mutations that increases the risk for symptoms associated with clinical ADHD, as measured by the CAARS ADHD Index, but does so in combination with a significant polygenic component.

The heritability estimates reported in this study are higher than the two previously published studies on heritability of ADHD in adult populations. Boomsma et al. (2010), using the same CAARS ADHD Index score, obtained an estimate of 0.30, while van den Berg et al. (2006) used an assessment on attention scores only and obtained an estimate of 0.40. There are several explanations for differing heritability estimates of this study and those previously published. For example, the previous studies both used twin data from the Adult Netherlands Twin Registry, while our study population is taken from United States-based recruitment with a focus on relatives from families with a history of fragile X-associated disorders. Thus the two study populations could differ in background genetic composition. Also, both previous studies assessed heritability in males and females together, while our study assessed females only. While epidemiological studies of ADHD in children tend to indicate lower heritability among girls compared to boys (Freitag et al. 2010), the relative contribution of polygenes on ADHD between the sexes might be different in adulthood.

Interestingly, all *FMR1* premutation groups had mean CAARS T-scores within the normal range, including the ADHD Index T-scores (Table 2). Thus, though we showed that the low, premutation group scores significantly higher compared to the non-carrier group, this group as a whole did not score within the clinically elevated range (a T-score of 65 or higher). Overall, the results of this study suggest that the *FMR1* premutation increases the risk for elevated ADHD symptoms, but does so in concert with other ADHD susceptibility genes. Future studies will focus on better defining the characteristics of the premutation that elevate the risk symptoms of ADHD and identifying these other genes that contribute significantly to ADHD symptom severity.

Additional factors specific to women who carry an *FMR1* premutation allele could impact symptoms of ADHD and should be discussed. First, females who carry a premutation allele

are at risk of having a child with FXS (Nolin et al. 2003). Caring for a child with the intellectually disability and behavioral issues characteristic of this disorder has been shown to be associated with increased stress and decreased quality of life (Bailey Jr. et al. 2008b). However, the previously published analysis of ADHD symptoms among our female study population indicated that raising a child with FXS was not predictive of symptom severity (Hunter et al. 2008a). Second, some published studies have reported an elevation of mood and anxiety disorders and certain medical conditions (e.g. thyroid disease and fibromyalgia) among women who carry a premutation (e.g. Coffey et al. 2008; Roberts et al. 2009). However, previous analyses of our female study sample have not shown significantly elevated rates of these disorders (Hunter et al. 2008b, 2010). Based on our previous studies, none of these factors were accounted for in the current analyses since they do not appear to impact the severity of ADHD symptoms in our study population and are thus likely have little impact on the heritability estimates reported.

There are some limitations of this study. First, our small sample size resulted in reduced power to detect low to moderate effect sizes of the additive genetic component. In addition, the CAARS is a self-report questionnaire which relies on the subject's insight into her experience of symptoms associated with ADHD as well as her accuracy in reporting her symptomology. Lastly, our models did not account for shared environmental effects. Our follow-up analyses that added shared environmental effects to the model did not alter heritability estimates and indicated that the shared environmental effects were minimal, if present at all. However, our sample size was limited and our analyses may have lacked the power to detect such small shared effects. More pedigrees and more pedigrees with extended relationships would be informative for future follow-up studies.

Overall, the models outlined in this study provide significant evidence that the *FMR1* premutation, a relatively rare mutation, contributes to the risk of ADHD symptoms. Once adjusting for this gene effect, other additive genetic effects play a significant role in defining risk, particularly for the CAARS ADHD Index, a measure of clinically significant symptoms of ADHD. This finding is important in that it motivates the next stage in research: the identification of additional genes that contribute to symptoms associated with ADHD in both carriers of *FMR1* premutation alleles and in the general population.

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Table 1

Demographic data for 231 females in study population stratified by *FMR1* allele groups defined by CGG repeat length (education and income ordinal measures were dichotomized for presentation purposes)

Repeat group	N	Mean age (in years)	Race (% Caucasian or Asian)	Education (% at least some college completed)	Income (% >\$50,000)	Ascertainment (% FXS families)
NC (40)	40	34.4	85.0	85.0	61.5	97.5
IM (41–60)	16	33.9	100.0	93.8	68.8	43.8
Low PM (61–80)	48	33.8	91.7	81.3	70.2	89.6
Mid PM (81–100)	97	37.5	85.6	78.4	73.1	100.0
High PM (>100)	30	33.9	96.4	80.0	65.5	100.0
All	231	35.5*	88.3	81.4	67.1	93.5**

NC non-carrier, IM intermediate allele, PM premutation allele, FXS fragile X syndrome

* Repeat groups significantly different for demographic variable at $p < 0.05$ level

** Repeat groups significantly different for demographic variable at $p < 0.01$ level

Table 2
Means and standard deviations of raw CAARS scores stratified by *FMR1* repeat length group

Repeat group	CAARS score				
	ADHD Index	Inattention and memory problems	Hyperactivity and restlessness	Impulsivity and emotional lability	Problems with self-concept
NC	45.4 (7.6)	47.5 (7.8)	48.3 (7.4)	44.6 (8.9)	43.6 (8.8)
IM	47.5 (6.8)	48.5 (7.1)	48.5 (7.6)	45.6 (6.9)	45.6 (5.7)
Low PM	52.0 (10.3)	53.2 (9.3)	52.2 (8.7)	51.2 (9.9)	49.7 (10.1)
Mid PM	48.3 (9.3)	50.2 (9.8)	47.4 (8.2)	47.4 (9.2)	46.9 (9.4)
High PM	49.3 (10.6)	53.7 (11.5)	46.8 (8.0)	49.5 (12.1)	47.3 (9.8)

CAARS Connors Adult ADHD Reporting Scales, *ADHD* attention-deficit hyperactivity disorder, *NC* non-carrier, *IM* intermediate allele, *PM* premutation allele

Table 3

Categorical models testing for additive genetic contribution to CAARS ADHD scores while adjusting for the effect of *FMR1* premutation

CAARS score	<i>FMR1</i> repeat group parameter estimates ^a	<i>FMR1</i> adjusted R^{2b}	Heritability estimate ^c	Test of polygenic variance component
ADHD Index	NC: reference IM: $\beta = 0.0873$, $p = 0.1664$ Low PM: $\beta = 0.1337$, $p = 0.0010^d$ Mid PM: $\beta = 0.0467$, $p = 0.1714$ High PM: $\beta = 0.0525$, $p = 0.3045$	0.0579	0.5153	$p = 0.0117^d$
ADHD symptoms				
Inattention and memory problems	NC: reference IM: $\beta = 0.0831$, $p = 0.1579$ Low PM: $\beta = 0.1252$, $p = 0.0010^d$ Mid PM: $\beta = 0.0510$, $p = 0.1166$ High PM: $\beta = 0.1115$, $p = 0.0089^d$	0.0618	0.1418	$p = 0.2769$
Hyperactivity and restlessness	NC: reference IM: $\beta = -0.0078$, $p = 0.8841$ Low PM: $\beta = 0.0740$, $p = 0.0313$ Mid PM: $\beta = 0.0257$, $p = 0.3813$ High PM: $\beta = -0.0600$, $p = 0.1173$	0.0612	0.2078	$p = 0.1619$
Impulsivity and emotional lability	NC: reference IM: $\beta = 0.0470$, $p = 0.4825$ Low PM: $\beta = 0.1424$, $p = 0.0010^d$ Mid PM: $\beta = 0.0452$, $p = 0.2157$ High PM: $\beta = 0.0864$, $p = 0.0680$	0.0517	0.4038	$p = 0.0318$
Problems with self-concept	NC: reference IM: $\beta = 0.1163$, $p = 0.0657$ Low PM: $\beta = 0.1205$, $p = 0.0031^d$ Mid PM: $\beta = 0.0448$, $p = 0.1903$ High PM: $\beta = 0.0357$, $p = 0.4186$	0.0527	0.5060	$p = 0.0110^d$

CAARS Connors Adult ADHD Rating Scales, ADHD attention-deficit hyperactivity disorder, NC non-carrier, IM intermediate allele, PM premutation allele

^a Models are adjusted for other fixed effects, including age, race, education, income, and ascertainment

^b Calculated as one minus the ratio of the sums of the polygenic and subject-specific variance in the presence and absence of *FMR1*

$$\left[1 - \frac{(s_{pg,with\ FMR1}^2 + s_{e,with\ FMR1}^2)}{(s_{pg,without\ FMR1}^2 + s_{e,without\ FMR1}^2)} \right]$$

^c Indicates the narrow sense heritability or the proportion of variance attributable to an additive genetic component

^d Significant at 5% level using $p < 0.0135$ to adjust for multiple testing