

Variation in the catechol-O-methyltransferase Val¹⁵⁸Met polymorphism associated with conduct disorder and ADHD symptoms, among adolescent male delinquents

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Objective Variation in the catechol-O-methyltransferase gene (*COMT*) has been associated with antisocial behavior in populations with attention deficit/hyperactivity disorder (ADHD). This study examined whether *COMT* would predict antisocial behavior in a sample with high levels of behavior problems, not necessarily ADHD. In addition, because previous research suggests that *COMT* may be associated with ADHD in males, association between *COMT* and ADHD symptoms was examined.

Method This study tested whether variation in three polymorphisms of the *COMT* gene was predictive of symptoms of conduct disorder and ADHD, in a sample of 174 incarcerated Russian adolescent male delinquents.

Results The Val allele of the Val¹⁵⁸Met polymorphism was significantly associated with conduct disorder diagnosis and symptoms, whereas the Met allele was associated with ADHD symptoms.

Conclusion The Val¹⁵⁸Met polymorphism of the *COMT* gene shows a complex relation to behavior problems,

influencing conduct disorder and ADHD symptoms in opposite directions in a high-risk population. *Psychiatr Genet* 20:20–24 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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The *COMT* gene produces catechol-O-methyltransferase, an enzyme that breaks down catecholamines, including dopamine and norepinephrine, thus clearing them from the synapse. In the prefrontal cortex, it is the primary mechanism of dopamine clearance (Meyer-Lindenberg *et al.*, 2006). *COMT* contains a single nucleotide polymorphism (SNP) at codon 158 in the fourth exon of the membrane-bound form of *COMT*, which is the form expressed in the brain (Lachman *et al.*, 1996). This polymorphism (known as Val¹⁵⁸Met or rs4680) consists of a guanine (G) to adenine (A) mutation and results in an amino acid substitution of methionine (Met) for valine (Val) in enzyme synthesis. The Val¹⁵⁸Met polymorphism has been the subject of many studies because of its reported functional consequences for the *COMT* enzyme (Lachman *et al.*, 1996). The Val variant of the enzyme shows approximately 40% more activity than does the Met variant, with the result that individuals with the Met variant shows higher brain levels of dopamine, especially in the prefrontal cortex, (Chen *et al.*, 2004). These differences in dopaminergic function are presumed to underlie the demonstrated phenotypic differences in

cognitive function (Meyer-Lindenberg *et al.*, 2006), and these differences in cognitive function are likely to have consequences for behavior.

Variation in *COMT* has been associated with risk of antisocial behavior in individuals diagnosed with attention deficit/hyperactivity disorder (ADHD) (Caspi *et al.*, 2008). Specifically, the Val allele of the *COMT* Val¹⁵⁸Met polymorphism was associated with higher levels of antisocial behavior in three ADHD samples, but not in the general population not diagnosed with ADHD. The primary purpose of this study was to test whether the Val allele is a risk factor for higher levels of antisocial behavior in a population identified by behavior problems other than ADHD. To this end we investigated the genotypes of a sample of incarcerated adolescent male delinquents, who were assessed for conduct disorder and ADHD. An all-male sample is appropriate because disruptive behavior problems are far more prevalent in males than females (Bauermeister *et al.*, 1994). An incarcerated sample is of interest because it is likely to include many individuals with high levels of antisocial behavior.

Caspi *et al.* (2008) found that *COMT* variation was not associated with ADHD, despite predicting antisocial behavior in the presence of ADHD. However, a recent meta-analysis suggested that *COMT* variation may predict ADHD in male populations (Cheuk and Wong, 2006). Although this meta-analysis of 13 studies found no significant association between *COMT* Val¹⁵⁸Met variation and ADHD in mixed-sex samples, the subset of two studies examining only males did show an association between the Met allele and ADHD. This finding was supported by another study that explicitly tested for sexual dimorphism and found that the Met allele was associated with ADHD in males but not females (Biederman *et al.*, 2008). *COMT* has been associated with sexual dimorphism in other phenotypes as well, including psychiatric disorders and brain function (Harrison and Tunbridge, 2008). In our sample of male delinquents, we could not directly test for sexual dimorphism, but we did test whether *COMT* was associated with symptoms of ADHD as well as conduct disorder.

In addition to the Val¹⁵⁸Met polymorphism, at least two other polymorphisms in *COMT* are of interest (Meyer-Lindenberg *et al.*, 2006; Shifman *et al.*, 2002). The rs737865 SNP appears in the first intron of *COMT* and the rs165599 SNP appears in the 3' region. Importantly, like Val¹⁵⁸Met, rs165599 is transcribed in the human brain and has been shown to affect gene expression (Bray *et al.*, 2003). The rs737865 SNP is not transcribed but may be associated with functional outcomes because it is in linkage disequilibrium with an SNP in the nearby P2 promoter region of the gene that influences *COMT* activity (Meyer-Lindenberg *et al.*, 2006). This study therefore examined rs737865 and rs165599 in addition to Val¹⁵⁸Met and used multiple regression and haplotype analysis to examine the combined effects of these three SNPs (a haplotype is a pattern of alleles on a single chromosome). We formed no specific hypotheses regarding rs737865 and rs165599, but it is unlikely that either of these two polymorphisms are associated with conduct disorder, because Caspi *et al.* (2008) found no association between them and antisocial behavior.

Methods

Participants

Participants ($n = 174$) were chosen from a larger sample used in previous studies, based on the availability of *COMT* genotypes (Ruchkin *et al.*, 2002, 2003, 2005). Participants with genotype data were slightly younger than the rest of the larger sample, $t_{473} = 3.27$, $P < 0.01$ (mean age 16.23 years, $SD = 0.82$ vs. 16.50, $SD = 0.87$), but they did not differ significantly in conduct disorder or ADHD symptoms, all $t_{426} < 0.28$, $P > 0.78$. Participants were recruited over a period of 6 months from a group of male adolescent inmates who had been court-ordered to the only juvenile detention facility in the Arkhangelsk region of northern Russia, a catchment area with a

population of 1.5 million. The region is ethnically homogeneous, with approximately 98% of the population of Russian ancestry, which reduces the risk of genomic population stratification.

Most participants had multiple convictions, with the most severe violations including property crimes (e.g. theft, car theft; 51%), violent crimes (e.g. assault or robbery; 38%), rape or other forms of sexual violence (6%), and murder (5%). No differences in *COMT* were detectable between offenders whose most severe crimes were property crimes and those whose crimes involved aggression; nonetheless, we controlled for this variable in regressions. At the time of the study, the mean length of sentence was 4.3 years, and all participants had been incarcerated for at least 6 months.

This sample from a special population is relatively small by the standards of genetic research. However, it is similar in size to the ADHD samples in which Caspi *et al.* (2008) showed the association of Val¹⁵⁸Met with antisocial behavior, a fact which suggests that our sample should be adequately powered to detect the effects of interest.

Conduct disorder and ADHD diagnosis and symptom counts

Conduct disorder and ADHD diagnoses and symptom counts were determined using the *Schedule for Affective Disorders and Schizophrenia for School-Age Children*, a widely used, extensively validated, semistructured psychiatric interview (Kaufman *et al.*, 1999), carried out by two psychiatrists, who received the standard *Schedule for Affective Disorders and Schizophrenia for School-Age Children* training from the author of the instrument. Interrater reliability for this measure is high, with interrater agreement on screens and diagnoses ranging from 94 to 100% (Kaufman *et al.*, 1999). Diagnoses were based exclusively on information collected from the participants. Participants were scored positively for conduct disorder if they received a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth edition, diagnosis of either current or past conduct disorder. They were scored positively for ADHD if they received a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth edition, diagnosis of either current or past ADHD. For the symptom count variables, each symptom was scored as positive if it reached threshold either in the past or in the present. Not surprisingly for an incarcerated population, 128 (73.6%) of the participants were diagnosed with conduct disorder, whereas only 27 (15.5%) were diagnosed with ADHD. The results reported below for conduct disorder remained substantively the same when participants diagnosed with ADHD were excluded from the analyses. As there were so few diagnoses of ADHD, and because they were based exclusively on self-reports, we focus on ADHD symptom counts in our statistical tests.

Genotyping

All participants gave their consent after being given a detailed description of the study and informed of the voluntary and confidential nature of their involvement. The appropriate ethics committees in Russia, Sweden, and the United States approved the study. Two nurses obtained blood samples from participants' arm veins. In Dr Orelan's laboratory, DNA was extracted from samples collected through 5 ml vacutainer tubes containing ethylenediaminetetraacetic acid. An aliquot of DNA was sent to Dr Grigorenko's laboratory, where it was subsequently amplified with Repli-G technologies (Qiagen, Valencia, California, USA). Once a sufficient amount of DNA was available for each sample, three SNPs within the COMT gene (Val¹⁵⁸Met, rs737865, rs165599) were genotyped using the ABI TaqMan platform (Applied Biosystems, Foster City, California, USA). Genotyping of Val¹⁵⁸Met was unsuccessful for 15 participants, of rs737865 for 11 participants, and of rs165599 for one participant. This left 149 participants with all variables of interest for our regression analyses. None of the groups analyzed deviated significantly from Hardy-Weinberg equilibrium (tested using the HAPLO program; Hawley and Kidd, 1995).

Results

Genotype frequencies for the different diagnostic categories are presented in Table 1. As predicted, Val¹⁵⁸Met was associated with diagnosis of conduct disorder. The number of Val alleles was positively associated with conduct disorder, $\chi^2_{(2)} = 11.08$, $P < 0.01$, and the association was linear, $\chi^2_{(1)} = 9.78$, $P < 0.01$. Chi-square tests for the association of ADHD diagnosis with Val¹⁵⁸Met could not be performed because of a violation of the assumptions of the test: the expected count was less

than 5 for one cell (this was not the case for conduct disorder, despite the fact that one cell had an observed count less than 5).

Logistic regression was used to determine the independent contributions of the three polymorphisms to conduct disorder diagnosis (Table 2). Age and the type of participants' most severe crime (violent = 1, non-violent = 0) were included as covariates. Neither variable was correlated with diagnosis, $r < 0.08$, $P > 0.35$, but there was a weak association of age with Val¹⁵⁸Met genotype, $F_2 = 3.17$, $P < 0.05$. Mean ages in years (with standard deviations), for Val¹⁵⁸Met genotypes, were as follows: Val/Val: 16.48 (0.85), Val/Met: 16.08 (0.84), Met/Met: 16.37 (0.78). Total ADHD symptom count was also included as a covariate. Conduct disorder and ADHD symptoms were significantly correlated, $r = 0.21$, $P < 0.01$. Number of G(Val) alleles for Val¹⁵⁸Met, rs737865, and rs165599 were entered as predictors. Val¹⁵⁸Met was a significant predictor, with an odds ratio of 2.49. In addition, ADHD symptoms significantly predicted conduct disorder. Genotypes for rs737865 and rs165599 did not predict diagnosis, nor did the most severe type of crime that participants had committed.

Haplotype analysis was carried out using HAPLO (Hawley and Kidd, 1995), which provides a test of significant differences in estimated haplotype frequency across groups, considering all haplotypes simultaneously (significance tests are not provided for individual haplotypes). Haplotype analysis revealed significant differences in COMT haplotype frequency between participants with and without conduct disorder, $\chi^2_{(7)} = 19.7$, $P < 0.01$. Estimated haplotype frequencies (available from the authors on request) were consistent with the

Table 1 Genotype frequencies by diagnosis, at three COMT polymorphisms

	Val ¹⁵⁸ Met			rs737865			rs165599		
	GG (n=23)	AG (n=87)	AA (n=49)	GG (n=11)	AG (n=54)	AA (n=98)	GG (n=22)	AG (n=77)	AA (n=74)
CD-positive	0.20	0.54	0.26	0.06	0.34	0.60	0.14	0.47	0.39
CD-negative	0.00	0.56	0.44	0.09	0.30	0.61	0.09	0.39	0.52
ADHD-positive	0.04	0.44	0.52	0.00	0.40	0.60	0.07	0.41	0.52
ADHD-negative	0.16	0.57	0.27	0.08	0.32	0.60	0.14	0.45	0.41

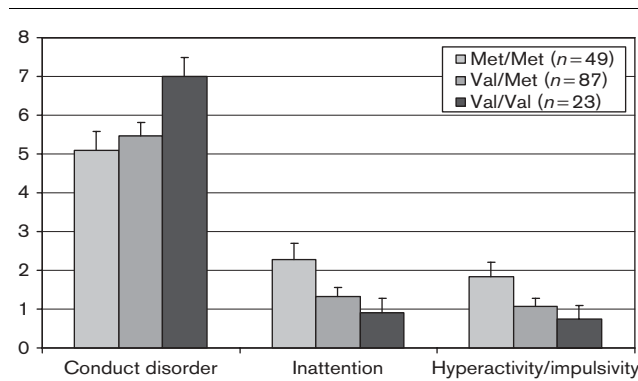
A, adenine (Met); ADHD, attention deficit/hyperactivity disorder; CD, conduct disorder; COMT, catechol-O-methyltransferase; G, guanine (Val); N, 174.

Table 2 Binary logistic regression predicting conduct disorder diagnosis from variation in COMT polymorphisms

Criterion	Predictor	B	SE	Wald χ^2	P value	OR	R ²
Conduct disorder							0.20
		Val ¹⁵⁸ Met	0.91	0.29	9.90	0.00	2.49
		rs737865	-0.30	0.22	1.95	0.16	0.74
		rs165599	-0.05	0.23	0.05	0.82	0.95
		ADHD symptoms	0.15	0.06	6.50	0.01	1.16
		Crime type	0.15	0.42	0.12	0.73	1.16
		Age	0.20	0.24	0.70	0.40	1.23

ADHD, attention deficit/hyperactivity disorder; COMT, catechol-O-methyltransferase; N, 149; OR, odds ratio.

Fig. 1



Mean symptom count (with standard errors) by catechol-O-methyltransferase Val¹⁵⁸Met genotype, for conduct disorder, inattention, and hyperactivity/impulsivity. Met, methionine; Val, valine.

Table 3 Poisson regressions predicting symptom counts from variation in *COMT* polymorphisms

Criterion	Predictor	B	SE	Wald χ^2	d.f.	P value
Conduct disorder	Val ¹⁵⁸ Met			17.87	2	0.00
	AA	-0.62	0.15	16.11	1	0.00
	AG	-0.39	0.11	12.68	1	0.00
	rs737865			3.48	2	0.18
	AA	0.35	0.19	3.48	1	0.06
	AG	0.32	0.20	2.66	1	0.10
	rs165599			1.24	2	0.54
	AA	0.04	0.14	0.09	1	0.76
	AG	-0.07	0.13	0.30	1	0.58
	ADHD symptoms	0.04	0.01	19.97	1	0.00
Crime type				1.38	1	0.24
	Age	0.04	0.06	0.54	1	0.46
Inattention	Val ¹⁵⁸ Met			6.64	2	0.04
	AA	1.34	0.57	5.45	1	0.02
	AG	0.72	0.53	1.81	1	0.18
	rs737865			0.78	2	0.68
	AA	0.09	0.84	0.01	1	0.92
	AG	0.31	0.84	0.14	1	0.71
	rs165599			1.45	2	0.48
	AA	0.40	0.57	0.49	1	0.48
	AG	0.61	0.55	1.23	1	0.27
	CD symptoms	0.17	0.04	18.73	1	0.00
Crime type				0.11	1	0.74
	Age	0.17	0.18	0.89	1	0.35
Hyperactivity/impulsivity	Val ¹⁵⁸ Met			8.79	2	0.01
	AA	1.45	0.59	5.95	1	0.01
	AG	0.57	0.56	1.00	1	0.32
	rs737865			0.89	2	0.64
	AA	0.18	0.87	0.04	1	0.84
	AG	0.45	0.89	0.25	1	0.61
	rs165599			3.93	2	0.14
	AA	-0.14	0.57	0.06	1	0.80
	AG	0.49	0.53	0.86	1	0.35
	CD symptoms	0.19	0.05	14.30	1	0.00
Crime type				1.38	1	0.24
	Age	0.14	0.21	0.42	1	0.52

GG is omitted as a redundant predictor.

ADHD, attention deficit/hyperactivity disorder; A, Met allele; G, Val allele; N, 149.

results of the logistic regression, in that haplotypes containing the Val allele were more frequent in participants diagnosed with conduct disorder.

Symptom counts for conduct disorder, inattention, and hyperactivity/impulsivity are presented according to Val¹⁵⁸Met genotype in Fig. 1. Poisson regressions were carried out using the generalized linear model, to examine effects of genotype on symptom counts (Table 3). Again, age and type of crime were controlled, though they were not significantly correlated with any symptoms, all $r < 0.14$, $P > 0.08$. Total ADHD symptom count for both inattention and hyperactivity/impulsivity was entered as a covariate in predicting conduct disorder symptoms, and conduct disorder symptom count was controlled when predicting inattention and hyperactivity/impulsivity. ADHD symptoms and conduct disorder symptoms were significantly correlated, $r = 0.33$, $P < 0.01$. Consistent with the analyses of diagnosis, of the three polymorphisms, only Val¹⁵⁸Met was associated with symptoms. The Val/Val genotype positively predicted conduct disorder symptoms, whereas the Met/Met genotype positively predicted ADHD symptoms.

Discussion

In a sample of incarcerated adolescent male delinquents, we found that the Val allele of the *COMT* Val¹⁵⁸Met polymorphism was associated with conduct disorder diagnosis and symptoms and that the Met allele was associated with ADHD symptoms. Interestingly, both findings are at least partially consistent with prior research. The finding that the Val/Val genotype group has the highest level of conduct disorder symptoms is related to the findings of Caspi *et al.* (2008), who found a similar association in three ADHD samples (where our finding is inconsistent with theirs is that Caspi *et al.* (2008) found no association of *COMT* with antisocial behavior in the group without a diagnosis of ADHD). Our finding that the Met allele is associated with ADHD is consistent with a meta-analysis and a subsequent study that found an association between Met and ADHD in males but not in females (Cheuk and Wong, 2006; Biederman *et al.*, 2008).

Our findings extend prior research in two ways. First, they show that these two results can be present in the same sample. It may seem counterintuitive that two forms of disruptive behavior (conduct disorder and ADHD) should be affected in opposite ways by the same polymorphism. However, our results indicate that previously reported findings are not necessarily incompatible. Future research will need to determine the mechanisms by which the increase in *COMT* enzyme efficiency associated with the Val allele can lead to more severe antisocial behavior while at the same time being associated with lower levels of inattention and hyperactivity. The low versus high levels of synaptic dopamine associated with the Val/Val versus Met/Met genotype may lead to qualitatively different patterns of disruptive behavior over the course of development, in the presence of other risk factors.

Second, our results extend those of Caspi *et al.* (2008) by showing that the increased risk for antisocial behavior associated with the Val allele is not confined to populations with ADHD. As noted above, Caspi *et al.* (2008) found that the Val allele was not a risk for antisocial behavior in populations with no ADHD diagnosis. Presumably, the ADHD diagnosis represents a background of additional environmental or genetic risks that must be present if *COMT* variation is to influence antisocial behavior. Our results suggest that these additional risk factors are not specific to ADHD. The number of Val alleles predicted conduct disorder diagnosis and symptoms even when controlling for ADHD symptoms (and even when all participants diagnosed with ADHD were excluded from the analyses). The risky background represented by incarceration for criminal behavior is apparently sufficient to produce a significant effect of Val¹⁵⁸Met variation on antisocial behavior.

Limitations

This study had several limitations. First, diagnoses were made exclusively on the basis of interviews with participants and, for ADHD at least, were therefore less reliable than diagnoses based on reports from teachers and/or parents (Smith *et al.*, 2000). However, because our findings for both conduct disorder and ADHD are consistent with prior research, we can be reasonably confident that they are not artifacts of using self-reports. Second, the sample included a relatively small number of individuals diagnosed with ADHD. This fact increased the importance of analyzing symptom scores. Third, the sample available to us was all male, so we could not test for sexual dimorphism. Nonetheless, our results are consistent with the possibility that the Met allele is a risk factor for ADHD only in males, which might explain past inconsistencies in findings of association between Val¹⁵⁸Met and ADHD.

Conclusion

Variation in the Val¹⁵⁸Met polymorphism of *COMT* is associated with behavior problems, in at least some high-risk populations. However, our findings indicate that this association is complex. In a sample of incarcerated adolescent male delinquents, the Val/Val genotype was associated with conduct disorder, whereas the Met/Met genotype was associated with ADHD. These findings suggest the complexity of the effects of specific polymorphisms, with their specific effects on molecular mechanisms, in the context of other risk factors that may help to determine how genetic variation influences behavior.

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