

# Catechol O-Methyltransferase Gene Variant and Birth Weight Predict Early-Onset Antisocial Behavior in Children With Attention-Deficit/Hyperactivity Disorder

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**Context:** Early-onset antisocial behavior accompanied by attention-deficit/hyperactivity disorder is a clinically severe variant of antisocial behavior that is associated with a particularly poor outcome. Identifying early predictors is thus important. Genetic and prenatal environmental risk factors and prefrontal cortical function are thought to contribute. Recent evidence suggests that prefrontal cortical function is influenced by a valine/methionine variant in the catechol O-methyltransferase (COMT) gene.

**Objective:** To test the a priori hypothesis that this genetic variant predicts early-onset antisocial behavior in a high-risk sample and further examine the effects of birth weight, an environmentally influenced index of prenatal adversity previously linked to childhood disruptive behaviors and genotype  $\times$  birth weight interaction.

**Design, Setting, and Participants:** A family-based genetic study was undertaken between 1997 and 2003. Participants were prospectively recruited from child and adolescent psychiatry and child health clinics in the United Kingdom and included 240 clinic children who met di-

agnostic criteria for attention-deficit/hyperactivity disorder or hyperkinetic disorder. Participants underwent comprehensive standardized assessments including measures of antisocial behavior and IQ.

**Main Outcome Measure:** DSM-IV symptoms of childhood-onset conduct disorder rated by trained interviewers using a standard diagnostic interview.

**Results:** The results show main effects of the COMT gene variant ( $P = .002$ ), birth weight ( $P = .002$ ), and a significant gene  $\times$  environment (COMT  $\times$  birth weight) interaction ( $P = .006$ ).

**Conclusions:** Early-onset antisocial behavior in a high-risk clinical group is predicted by a specific COMT gene variant previously linked with prefrontal cortical function and birth weight, and those possessing the val/val genotype are more susceptible to the adverse effects of prenatal risk as indexed by lower birth weight.

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**E**ARLY-ONSET ANTISOCIAL behavior accompanied by attention-deficit/hyperactivity disorder (ADHD) is a severe variant of antisocial behavior that is associated with a poor outcome. The origins of antisocial behavior are not fully understood, yet identifying risk factors and early predictors, particularly in a high-risk clinical group, is important so that resources and interventions are appropriately targeted. Biological processes play a key role in the genesis of antisocial behavior with specific evidence of brain involvement and contribution of genetic and early environmental risk factors, including prenatal factors.<sup>1</sup>

Specifically, the prefrontal cortex (PFC) has been implicated in the etiology of antisocial behavior.<sup>1</sup> This hypothesis has been supported by different types of evidence, from studies of head injury, functional and structural neuroimaging studies, and neuropsychological research.<sup>1</sup> Descriptions of patients who have sustained damage to the PFC specifically support a link between the PFC and childhood-onset antisocial behavior.<sup>2,3</sup> The most recent detailed report of 2 patients with PFC lesions acquired in childhood found that subjects showed conduct disorder symptoms (eg, stealing, violence). These features have not generally been noted in adult-onset lesions,<sup>2</sup> suggesting that there may be important

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**Table. Multiple Regression Analysis of Conduct Symptom Scores Based on Possession of *COMT* Val/Val Genotype and Birth Weight in Grams**

	Standardized β Coefficients	t Test	P Value
Sex	-0.093	-1.393	.16
Age, mo, at time of assessment	-0.026	-0.387	.70
Verbal IQ	-0.026	-2.003*	.046*
Performance IQ	-0.046	-0.646	.52
<i>COMT</i>	1.220	3.140*	.002*
Birth weight	-0.934	-3.078*	.002*
<i>COMT</i> × birth weight	1.324	2.753*	.006*

Abbreviations: *COMT*, catechol *O*-methyltransferase; val, valine.  
\*Indicates significance.

developmental considerations in the neurobiological origins of antisocial behavior.

The enzyme catechol *O*-methyltransferase (*COMT*) has been proposed to play a key role in prefrontal cortical functioning in that it accounts for most of the degradation of dopamine in the PFC.<sup>4</sup> Catechol *O*-methyltransferase-knockout mice, which lack function of the *COMT* gene, show increased levels of dopamine in the PFC but not the striatum where the dopamine transporter, which is largely absent from the PFC, appears to regulate dopamine levels.<sup>5-7</sup> Two isoforms of *COMT* exist, a short, soluble form and a longer, membrane-bound form predominating in the brain. A polymorphism exists at codon 108 of the short isoform (codon 158 of the longer isoform) resulting in the substitution of methionine (met) for valine (val). Short isoforms carrying the val allele have 3 to 4 times higher *COMT* activity than those carrying the met allele. While the biochemical effects of this polymorphism on the longer isoform have not yet been reported, it is nevertheless clear that the polymorphism contributes to variation in prefrontal cortical function and cognition.<sup>4</sup> Several studies have shown that the met allele (met/met and met/val genotypes) is associated with better performance on cognitive tasks assessing prefrontal cortical function.<sup>2</sup>

Given the links between prefrontal cortical deficits and antisocial behavior and between *COMT* and prefrontal cortical functioning, we hypothesized that the functional *COMT* variant would be associated with antisocial behavior. We specifically set out to examine the subtype of antisocial behavior purported to have the strongest neurobiological<sup>8</sup> and heritable origins,<sup>9</sup> that is, childhood-onset conduct disorder symptoms accompanied by ADHD. It was predicted that individuals with the “high-activity” val/val genotype, associated with poorer PFC function, would show increased antisocial behavior.

Genes coact and interact with early environmental factors<sup>10</sup> and both contribute to juvenile antisocial behavior.<sup>11</sup> There has been much work linking environmental adversity of prenatal origin with childhood-onset antisocial behavior.<sup>8,10</sup> Birth weight provides a particularly useful index of prenatal environment in that it has been reported to be associated with childhood disruptive behaviors,<sup>12,13</sup> is easily measured and readily available, and,

most importantly, unlike many other measures, mainly indexes maternally provided environment rather than genetic contribution.<sup>14</sup> This is an important consideration when testing for gene × environment interaction, which is more difficult to detect with heritable environmental measures.<sup>15</sup> Given the potential importance of gene × environment interaction whereby genes modify susceptibility to environmental factors, we tested for interaction as well as main effects of *COMT* variant and birth weight.

## METHODS

The participants were 240 British, white clinic children (213 boys, 27 girls; the expected sex distribution for clinic cases with this diagnosis) aged 5 to 14 years (mean [SD] age, 9 years 3 months [2 years 2 months]) who met *DSM-IV* criteria for ADHD or *International Statistical Classification of Diseases, 10th Revision* criteria for hyperkinetic disorder and who were living with at least 1 biological parent. North-West Multicenter Research Ethics Committee approved the study protocol. Children who had IQ test scores lower than 70, any neurological condition, autism, or Tourette syndrome were excluded. Assessments for ADHD, conduct disorder, and other psychiatric disorders were undertaken by trained, supervised interviewers using the Child and Adolescent Psychiatric Assessment—parent version,<sup>16</sup> a research diagnostic interview. Symptom reports were obtained prior to starting medication. *DSM-IV* conduct disorder symptoms were coded as present or absent and summed to yield a total antisocial symptom score. Items included behaviors such as “physical cruelty to other people,” “sets fires,” “nontrivial stealing,” and “crime involving confrontation with the victim.” All *DSM-IV* conduct disorder symptoms in this sample were of childhood onset (onset less than 10 years). Each child was also assessed using the Wechsler Intelligence Scale for Children<sup>17</sup> from which verbal and performance IQ test scores were obtained. Mothers were asked to report on the child’s birth weight. Previous work has shown that such reports are reliable.<sup>18</sup>

Genotyping was performed by single-nucleotide primer extension using a template-directed dye-terminator incorporation assay with fluorescence polarization detection<sup>19</sup> based on AcycloPrime reagents (Perkin Elmer Life Science Products, Boston, Mass). Association of *COMT* variant and birth weight with antisocial behavior was tested using multiple regression analysis in which the total *DSM-IV* conduct disorder symptom score was the dependent measure. Possession of at least 1 copy of the met allele (or val/val genotype) and birth weight were the independent (predictor) variables, adjusting for the effects of verbal and performance IQ, age, and sex, which are other potentially associated variables.<sup>1,8,10,12</sup> An interaction term (*COMT* × birth weight) was also included.

## RESULTS

The frequencies of the met and val alleles were 52% (246 subjects) and 48% (230 subjects). Genotypic frequencies were met/met 25% (59 subjects), met/val 54% (128 subjects), and val/val 21% (51 subjects), and there was no evidence of departure from Hardy-Weinberg equilibrium ( $\chi^2=1.41$ ;  $P=.24$ ). Linear regression analysis showed there was significant evidence of main effects for the possession of the high-activity val/val genotype ( $P=.002$ ) and birth weight ( $P=.002$ ) and a significant interaction term ( $P=.006$ ). This association was independent of the effects of age, sex, verbal IQ ( $P=.046$ ), and performance

IQ (**Table**). Continuous data were used for the statistical analyses, but for ease of interpretation, we also display the results graphically in the **Figure** where birth weight is split into 2 categories: birth weight less than 2500 g, the standard clinical cutoff, and birth weight more than this cut point. The Figure shows that the mean conduct disorder symptom scores were higher in those possessing the val/val genotype and those with lower birth weight. It also suggests interaction effects where the impact of lower birth weight is much greater in those with the val/val genotype.

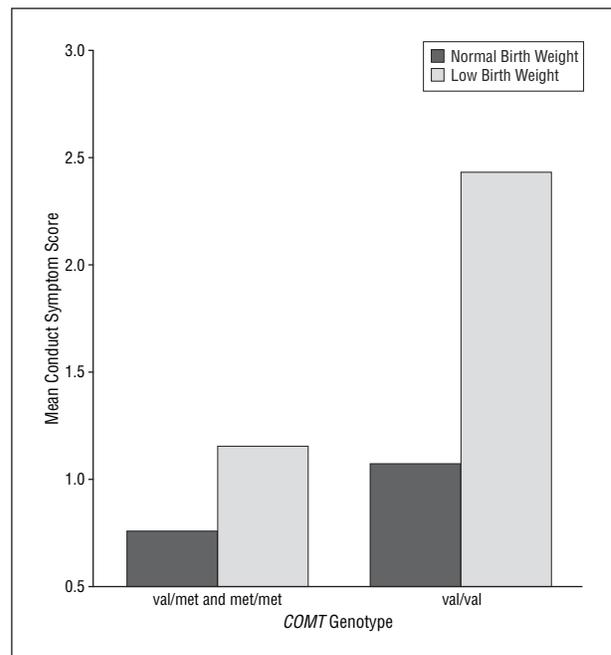
The results were independent of maternal smoking in pregnancy, the only other available measure of prenatal environment for which there was no evidence of interaction (results available on request). Birth weight was also found to be independent of *COMT* genotype ( $\beta=0.03$ ;  $t=0.498$ ;  $P=.62$ ). Finally, to test whether these results might have arisen as an artifact of scaling, we used *DSM-IV* conduct disorder ( $n=21$ ) as the dependent variable, bearing in mind the reduced power arising from using categorical data. Logistic regression analysis showed evidence of main effects for the val/val genotype ( $P=.02$ ), birth weight ( $P=.03$ ), and significant interaction ( $P=.04$ ).

## COMMENT

Based on previous research linking both the PFC and prenatal adversity with childhood-onset antisocial behavior and the links between variation in *COMT* activity and prefrontal cortical functioning, we predicted that the *COMT* "poor function" val/val genotype and lower birth weight would be associated with increased symptoms of conduct disorder. These predictions were confirmed. Moreover, we observed significant gene  $\times$  environment interaction. These results are of considerable interest because they suggest not only that *COMT* genotype and birth weight influence antisocial behavior in this high-risk group but also that those with the val/val genotype are particularly susceptible to the effects of lower birth weight. Several issues merit discussion.

First, the term *antisocial behavior* encompasses a complex phenotype that is etiologically heterogeneous. However, there is now strong evidence to support the neurobiological distinction of childhood-onset antisocial behavior accompanied by ADHD. This subgroup of antisocial behavior shows a stronger association with neurocognitive deficits,<sup>20</sup> is a more strongly heritable variant of antisocial behavior,<sup>9</sup> and leads to a poorer clinical outcome.<sup>8,21</sup> Studies of brain injury have also indicated that prefrontal cortical damage may be more linked to antisocial behavior when it occurs in childhood.<sup>2,22</sup> Our results further support this subtype of childhood-onset antisocial behavior accompanied by ADHD as a useful phenotype for neurobiological and genetics research and highlight the importance of research into biological predictors of antisocial behavior in children with ADHD.

Second, is the association between the *COMT* val/met variant and antisocial behavior found in our study mediated by some other variable? Several studies,<sup>23-27</sup> although not all,<sup>28,29</sup> have found association of the *COMT*



**Figure.** Mean number of *DSM-IV* conduct symptoms by genotype and birth weight. Association with catechol *O*-methyltransferase (*COMT*) genotype using categorically defined low birth weight (birth weight <2500 g): normal birth weight, valine (val)/methionine (met) and met/met,  $n=161$ ; val/val,  $n=44$ ;  $\beta=0.099$ ;  $t=1.4$ ;  $P=.16$  and clinically defined low birth rate, val/met and met/met,  $n=26$ ; val/val,  $n=7$ ;  $\beta=0.34$ ;  $t=2.0$ ;  $P=.05$ .

val/met variant with prefrontal cognitive function. Specifically, possession of the met allele has been associated with better performance on different tasks dependent on prefrontal cognition, including the Wisconsin Card Sorting Test,<sup>23-26</sup> N-Back test,<sup>30</sup> and Dots-Mixed task,<sup>27</sup> as well as processing speed and attention.<sup>31</sup> These results have been found in normal subjects, patients with schizophrenia, and siblings of patients with schizophrenia. Interestingly, the association between the *COMT* variant and antisocial behavior in our sample was not mediated by cognitive performance on the task measures available<sup>32</sup> (verbal IQ, performance IQ, task measures of working memory, response inhibition, attention, and impulsiveness assessed in a subsample of this group) or clinical variables (including ADHD symptom severity), suggesting that it is conduct disorder symptom score that is the important dependent measure. One potential explanation for failing to find a cognitive mediating effect is that all of the sample consists of children with ADHD and thus the "comparison" group is also likely to have neurocognitive deficits.

Finally, the findings from our study underscore the importance of both environmental and genetic influences in the etiology of childhood-onset antisocial behavior and of interaction between the 2. This finding of significant gene  $\times$  environment interaction for childhood-onset antisocial behavior complements results of a recent study of adult antisocial behavior in which a significant interaction effect between variation in the monoamine oxidase A gene and childhood maltreatment<sup>33</sup> was found, although in that study, no main gene effect was detected. Prenatal environment has been hypothesized as playing an important role in the genesis of

antisocial behavior<sup>10</sup> but obtaining measures of prenatal adversity in humans is a challenge. We have used birth weight as a useful risk indicator in that it is a measure that is readily available and is known to index mainly prenatal environment rather than parental genes.<sup>14</sup> In this study, main effects of birth weight were detected but what was most interesting was the evidence of significant gene  $\times$  environment interaction. The results of this study have potentially important implications insofar as they suggest that among those with ADHD who are at high risk of early-onset antisocial behavior, possession of a specific risk genotype, the *COMT* variant val/val genotype, not only predicts antisocial behavior in itself but also increases susceptibility to the effects of prenatal risk as indexed by birth weight.

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