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COMT Val158Met Genotype as a Risk Factor for Problem Behaviors in Youth

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Abstract

Objective—To test the association between the catechol-O-methyltransferase (COMT) Val158Met polymorphism and both aggressive behavior and attention problems in youth. We hypothesized that youth carrying a Met allele would have greater average aggressive behavior scores, and youth exhibiting Val-homozygosity would have greater average attention problems scores.

Method—Complete data on maternal-rated Child Behavior Checklist (CBCL) measures of aggressive behavior (AGG) and attention problems (AP), COMT polymorphism data, demographics and maternal parenting quality were available for 149 youth (6 to 18 years old). Multivariable linear regression models were used to test the degree to which youth COMT Val158Met genotype was associated with AGG and AP while statistically controlling for age, gender, parental socioeconomic status (SES), and maternal parenting quality from the Alabama Parenting Questionnaire.

Results—Mothers of Met-carriers rated their children higher on average AGG scores when compared to mothers of Val-homozygotes ($p = .016$). Further analyses revealed that this association was even more robust for maternal ratings of direct aggression ($p = .007$). The hypothesized association between Val-homozygosity and higher average AP scores relative to average AP scores of Met-carriers did not quite reach statistical significance ($p = .062$).

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This article represents one of several articles published in the August issue of the *Journal of the American Academy of Child and Adolescent Psychiatry* that explores the intersection of genetics and mental health disorders in children and adolescents. The editors invite the reader to investigate the additional articles on this burgeoning area of developmental psychopathology.

Disclosure: Drs. Harder, Althoff, Rettew, Davies, Stanger, and Hudziak, and Mr. Albaugh, Mr. Ehli, Ms. Lengyel-Nelson, Ms. Ayer, and Ms. Sulman report no biomedical financial interests or potential conflicts of interest.

Conclusions—After controlling for demographics, SES, and maternal parenting quality as confounders, there remains a strong association between youth carrying a Met allele and higher average AGG scores relative to Val-homozygotes.

Keywords

youth; COMT; aggressive behavior; attention problems; parenting quality

INTRODUCTION

The enzyme, catechol-O-methyltransferase, or COMT, catabolizes catecholamine neurotransmitters, including dopamine, in the central nervous system and allelic variation in the COMT gene is believed to influence dopamine regulation in prefrontal regions of the brain. Lachman et al. (1996)¹ first reported a common biallelic single nucleotide polymorphism (SNP) at codon 158 in the gene coding for COMT, involving a substitution of valine (Val) for methionine (Met). This SNP at codon 158 in the COMT gene has been found to affect the thermostability of the COMT enzyme. Consequently, the Met allele of this polymorphism has been associated with a two- to four-fold reduction in COMT enzyme activity.²⁻⁴ Given the relative dearth of dopamine transporters in the human prefrontal cortex, COMT is believed to play a particularly important role in regulating dopamine levels in the prefrontal cortex.^{5,6} Thus, a reduction in COMT activity, conferred by inheritance of the Met allele, may increase dopamine availability in regions of the prefrontal cortex,^{2,6} whereas increased COMT activity due to the Val allele may reduce dopamine availability in prefrontal regions.

Numerous studies have investigated the relationship between the Val158Met polymorphism and behavioral phenotypes. In both adult human and animal studies, COMT activity and the dopaminergic system have been associated with aggressive behavior. COMT knockout mice, possessing higher levels of extracellular dopamine, have been reported to exhibit elevated levels of aggressive behavior, although this association was observed only in male mice.⁷ Administration of the dopamine agonist, apomorphine, has led to increased aggression in rodents and several human studies have reported putative associations involving the Met allele and aggressive behavior in adult clinical samples.⁸⁻¹³ Despite such findings in animal and adult human samples, the precise role of the Val158Met polymorphism in childhood aggression remains unclear, with several recent studies reporting associations between the Val allele and increased aggressive behavior.^{14,15}

Separate from aggression, the COMT Val158Met polymorphism has also been implicated in attention problems, including symptoms of ADHD. Past studies have revealed associations between the Val allele and forms of distractibility, and “off-task” behavior.^{16,17} Others have reported an association between the Val allele and ADHD diagnosis.^{18,19} Some groups, however, have found associations between the Met allele and increased ADHD symptom count, or severity, in youth samples.^{20,21} Thus, there is inconsistency in the literature regarding the role of the Val158Met polymorphism in youth attention problems.

In an attempt to integrate the relations between COMT and behavior, Bilder and colleagues applied the tonic-phasic dopamine hypothesis to COMT, postulating that Met-carriers possess increased prefrontal dopamine levels, leading to increased high frequency, low amplitude tonic dopamine firing.^{22,23} This increase in high frequency, low amplitude tonic dopamine firing affords for enhanced stability of cortical activation states. They predicted that increased stability of cortical representations may lead to the excessive rigidity that characterizes some patients' externalizing symptoms. As explained by the authors, patients exhibiting excessive rigidity, “may `skip' the gradual buildup of hostility,” leading to more

sudden and dramatic shifts in behavior.²³ Thus, in this theory excessive cognitive rigidity may impede the ability to smoothly transition to other cognitive states, resulting in abrupt “jumps” in activation states—including impulsive acts of aggression. Following this tonic-phasic hypothesis, the Met allele may confer risk to excessive cognitive rigidity, resulting in an increased likelihood of aggressive behavior. Conversely, Bilder and colleagues hypothesized that low levels of dopamine in the prefrontal cortex, conferred by carrying the Val allele, results in subsequent increases in low frequency, high amplitude phasic dopamine firing. This increase in low frequency, high amplitude phasic dopamine firing facilitates the updating of information and plasticity of activation states.²³ Following, diminished stability of cortical representations may lead to increased distractibility and difficulty remaining focused on particular tasks. Thus, the Val allele may confer risk to the diminished stability of cortical representations, leading to increased distractibility and difficulty sustaining attention.

In testing for associations between Val158Met genotype and psychopathology in youth, variation in parenting quality has generally not been controlled for in previous studies. Low parenting quality, however, has been associated with aggressive behavior and attention problems in children. The Multimodal Treatment Study of Children with ADHD (MTA) has provided evidence that reductions in negative parental behaviors are associated with decreased disruptive behaviors in school, but only for children who receive concomitant pharmacologic and behavioral interventions.²⁴ The MTA has also reported that reduction of child ADHD symptoms—whether through behavioral intervention alone, pharmacologic intervention alone, or combined behavioral and pharmacologic intervention—involves significant reductions in negative parental behaviors.²⁵ Similarly, parents who underwent an intervention aimed at child conduct problems invoked less physical punishment in response to hypothetical vignettes.²⁶ What is more, there is recent evidence suggesting that poor parenting quality may interact with the COMT gene, contributing to attention problems in children.²⁷

In the present study, following from the COMT tonic hypothesis, we test two *a priori* hypotheses regarding the relationships between Val158Met genotype (Val-homozygotes versus Met-carriers) with both aggressive behavior and attention problems. First, we test whether Met-carriers possess higher average scores on the Child Behavior Checklist (CBCL) Aggressive Behavior scale (AGG). We expand this primary hypothesis to test if Met-carrier status in youth is differentially associated with two subtypes of aggressive behavior: relational and direct aggression, following from work by Crick and Grotpeter.²⁸ Second, we test whether Val-homozygotes have higher average scores on the CBCL Attention Problems (AP) scale. Further, given research cited above, maternal parenting quality will be statistically controlled for in testing these hypothesized associations.

METHOD

Sample

Participants in the present study were from the Vermont Family Study which aimed to examine genetic and environmental factors influencing AGG and AP.²⁹ In the Vermont Family Study, four target groups of probands were sought based on the CBCL: subjects with (1) T scores equal to or greater than 67 on the AP scale and less than 60 on the AGG scale; (2) T scores equal to or greater than 67 on AGG but less than 60 on AP; (3) T scores equal to or greater than 67 on both scales; and (4) T scores less than 60 on both scales. The family study was approved by an institutional review board, and all consent requirements were fulfilled. Families participating in the study were recruited through the use of newspaper advertisements and posters, as well as by local pediatricians and psychiatrists practicing in a university-based outpatient clinic. Three demographic inclusion criteria were applied during

the initial screening of families: (1) proband was between 6 and 18 years of age; (2) proband was living with at least one biological parent; and (3) proband had at least one sibling between 6 and 18 years of age. A total of 206 families participated in the study, and data were obtained for 205 probands (126 boys, 79 girls; mean age 10.99 years; SD, 3.66 years). In the present study, all probands with complete mother-rated CBCL AGG and CBCL AP data were initially included ($n = 166$). Of these probands with mother-rated CBCL data, 149 youth had genotype data for the COMT Val158Met polymorphism as well as maternal parenting quality data. Thus, the regression models used in testing the aforementioned hypotheses were on this subset of 149 participants.

Outcome Measures

Child Behavior Checklist (CBCL) AGG and AP—The CBCL,^{30,31} one of the most extensively used instruments for assessing child psychopathology and competence worldwide, asks parents to report on specific behaviors exhibited by their child within the past 6 months. In the present study, CBCL AGG and AP were selected as the two continuous dependent variables based on *a priori* hypotheses outlined above. Mother-rated CBCLs were collected on 166 probands (97 boys, 69 girls; mean age 10.93 years; standard deviation: 2.77 years).

Relational and Direct Aggression—There is evidence to suggest that the CBCL AGG scale measures two distinct subtypes of aggressive behavior. Employing principal components analysis, we previously identified two subtypes of aggression within the CBCL/4–18 AGG scale.³² One subtype within AGG, referred to as Relational Aggression, consists of 14 items that generally pertain to hostile and negativistic behaviors. This subtype includes CBCL items such as, “*Easily jealous*,” “*Teases a lot*,” and, “*Bragging, boasting*.” The second subtype within AGG, labeled Direct Aggression, consists of 6 items that involve more direct, physically aggressive behaviors. This subtype includes CBCL items such as, “*Physically attacks people*,” “*Gets in many fights*,” and, “*Destroys his/her own things*.” These two subtypes of CBCL AGG were used as outcome measures in an attempt to further characterize the predicted relationship between Met-carrier status and aggressive behavior.

Predictor Measures

Alabama Parenting Questionnaire (APQ)—The APQ is a 42-item self-report questionnaire that can be scored to yield measures of Positive Involvement, Negative/Ineffective Discipline, and Deficient Monitoring.^{25,33} The internal consistency of these scales is high, with Cronbach's alphas ranging from 0.81 to 0.92.²⁵ The Positive Involvement scale assesses the extent to which a parent exhibits interest in their child's activities, as well as offers praise, reward, affection, and other forms of positive reinforcement in response to their child's behavior. Items pertaining to the Positive Involvement scale include, “You reward or give something extra to your child for obeying you or behaving well,” and “You compliment your child when he/she does something well.” Negative/Ineffective Discipline assesses both the consistency and severity of parental disciplinary practices. Items on this scale include, “You threaten to punish your child and then do not actually punish him/her,” and “You let your child out of a punishment early (lift restrictions earlier than you originally said).” Deficient Monitoring assesses the extent to which a child does not receive sufficient parental supervision. Items on this scale include, “Your child goes out with friends you do not know,” and “Your child goes out without a set time to be home.” Parenting variables were entered continuously into our regression models in order to control for maternal parenting quality.

AGG and AP—Previous research suggests that the CBCL AGG and AP syndrome scales are highly correlated in nature.³⁴ In an attempt to control for the shared variance between

these two constructs, AP was entered as a control variable in our models of AGG. Similarly, in our model of AP, AGG was entered as a control variable.

Child's age and gender—The age and gender of each child were controlled for in the regression analyses. Age, in years, was entered as a continuous variable, whereas gender was entered as a binary variable (Table 1). Females were coded as “0” and males were coded as “1.”

Parental SES—We utilized parental employment as a measure of parental socioeconomic status (SES), following the Hollingshead 9-point scale for parental occupation.³⁵ Parental SES was entered as a continuous control variable in each of the regression analyses. Hollingshead scores ranged from 10 to 90, with higher scores representing higher socioeconomic level (Table 1).

Isolation of DNA

All DNA extractions and genotyping were performed at the Avera Institute for Human Behavioral Genetics. DNA was extracted from saliva saturated cotton spit wads using a column purification method.³⁶ DNA was extracted from buccal cells using the QIAamp DNA Blood Midi kit large volume protocol (Qiagen) with few modifications. Briefly, the spitwad was incubated at 7°C in a Protease/Lysis buffer mixture (200ul Qiagen Protease/ 2.4ml buffer AL) for 30 minutes. The lysate was separated from the spit wad using centrifugation by placing the spit wad in the barrel of a 5ml syringe (Becton Dickson) that was seated in a conical 15ml tube (Fisher) and centrifuged for 10 minutes at 12,000 rpm. 2ml ethanol was added to the lysate to precipitate DNA and was mixed thoroughly. The lysate was transferred to a Qiagen Midi column, and the column placed in a clean 15ml conical tube. The column was centrifuged @ $1850 \times g$ for 3 minutes. The filtrate was discarded and the column washed twice with buffer AW1 and AW2 according to manufacturer's instructions. DNA was eluted from the column in a clean 15ml conical tube with consecutive washes with 200ul buffer AE. DNA concentration and yield were determined using UV spectrophotometry (Nanodrop). All genomic DNA was either diluted or concentrated to a final concentration of 50ng/ul.

Genotyping

COMT Val158Met genotypes were determined as described previously.³⁷ Briefly, a 109-base-pair fragment was amplified via PCR with the following pair of primers; COMTforward, 5'-CTCATCACCATCGAGATCAA-3' and COMTreverse, 5'-CCAGGTCTGACAACGGGTCA-3'. PCR reactions were performed using a PCR Master Mix (Promega) containing a final concentration of 1.5 mM MgCl₂, 1× reaction buffer, 200μM of each dNTP, 40ng purified genomic DNA, 1.25 units *Taq* DNA polymerase, and 5pmols of each primer in a 25ul reaction. PCR cycling conditions consisted of an initial denaturation at 95°C for 15 minutes, 35 cycles each consisting of 30 s at 94°C, 30 s at 54°C, and 40 s at 72°C. Elongation was continued for 15 min at 72°C after the last cycle. The Val and Met alleles were determined using restriction fragment length polymorphism (RFLP) with the restriction endonuclease *Nla*III at 37°C for 2 hours. The fragments were separated on a 3% agarose gel supplemented with ethidium bromide (0.02%, Fisher) and visualized on a UV transilluminator. The fragments used to discriminate each genotype are as follows; Val-homozygotes (86 and 23 base pairs), Val/Met heterozygotes (86, 68, 23, and 18 base pairs), and Met homozygotes (68 and 18 base pairs). Of the 200 probands that were genotyped for this polymorphism as part of the Vermont Family Study, genotype calls were obtained for 198 participants (99% call rate). In the present study, Met/Val and Met/Met genotypes were grouped together as Met-carriers and Val-homozygotes (Val/Val) were coded as the reference group.

Statistical Analyses

The testing of models was performed using multiple linear regressions. Model 1 explored the relation between Met-carrier status and CBCL AGG while linearly controlling for the effects of age, sex, parental SES, CBCL AP and the three parenting variables (Positive Involvement, Negative/Ineffective Discipline, and Deficient Monitoring). The same variables were entered in Model 1A and Model 1B, however, the outcome measure of CBCL AGG was replaced with Direct Aggression and Relational Aggression, respectively. In Model 2, the same variables included in Model 1 were used, however, CBCL AP served as the outcome measure and CBCL AGG served as a predictor.

In post hoc analysis, effect size for the primary predictor of interest, COMT Val158Met genotype, was calculated using Cohen's f^2 statistic. More specifically, this effect size statistic relates to the unique variance in the outcome variable that is associated with Met-carrier status, above and beyond the variance accounted for by remaining control variables.

RESULTS

Preliminary Analyses

COMT genotype frequencies were consistent with Hardy-Weinberg equilibrium ($\chi^2 = .89, p = .344$). No significant differences were found for age, gender, parental SES, and the three maternal parenting qualities when comparing between Val-homozygotes and Met carriers. Looking at the simple associations between the three parenting variables, Positive Involvement was negatively correlated with Deficient Monitoring ($r = -.38, p = 5.66 \times 10^{-7}$) and Negative/Ineffective Discipline ($r = -.42, p = 2.41 \times 10^{-8}$), whereas Deficient Monitoring was positively correlated with Negative/Ineffective Discipline ($r = .40, p = 1.87 \times 10^{-7}$). As expected, a significant positive correlation was found between AGG and AP raw scores ($r = .63, p = 6.89 \times 10^{-20}$). Consistent with previous findings, Relational Aggression scores were highly correlated with Direct Aggression scores ($r = .81, p = 1.53 \times 10^{-37}$).

Model 1: AGG

Multiple linear regression analysis controlling for confounders showed that Met-carriers possessed an AGG raw score that was on average 2.9 points higher ($p = 0.016$) than Val-homozygotes. Table 2 lists standardized beta coefficients and respective p values for all covariates in Model 1. Post hoc analysis revealed that the effect size associated with the additional unique variance accounted for by Met-carrier status was small ($f^2 = .04$). In addition to Met-carrier status, parental SES ($p = .019$), maternal Negative/Ineffective Discipline ($p = .027$) and CBCL AP ($p = 6.99 \times 10^{-16}$) were also found to account for unique portions of variance in CBCL AGG.

Model 1A: Direct Aggression

Further analysis revealed that Met-carriers had Direct Aggression raw scores that were on average 1.0 point higher than Val-homozygotes with a slightly stronger statistical significance than reported for the overall AGG score ($p = 0.007$). Compared with findings from Model 1, the effect size associated with Met-carrier status was larger for direct aggression ($f^2 = .06$), albeit still small. In addition to Met-carrier status, maternal Negative/Ineffective Discipline ($p = .012$) and CBCL AP ($p = 1.42 \times 10^{-11}$) were also found to account for unique portions of variance in Direct Aggression ratings. There was a non-significant trend suggesting that parental SES was associated with Direct Aggression ($p = .073$).

Model 1B: Relational Aggression

Met-carriers were found to have Relational Aggression raw scores that were on average 1.9 points higher ($p = 0.041$) than Val-homozygotes. Further analysis revealed that the effect size associated with the additional unique variance accounted for by Met-carrier status was small ($f^2 = .03$). In addition to Met-carrier status, parental SES ($p = .039$), maternal Negative/Ineffective Discipline ($p = .023$) and CBCL AP ($p = 4.66 \times 10^{-17}$) were also found to account for unique portions of variance in Relational Aggression.

Model 2: AP

Multiple linear regression analysis controlling for confounders yielded a non-significant trend showing that Val-homozygotes possessed nearly 1.4 points higher CBCL AP raw scores relative to Met-carriers ($p = 0.062$). Again, Table 2 lists standardized beta coefficients and respective p values for all covariates in Model 2. No significant associations were revealed between any of the maternal parenting qualities and AP raw score. Interestingly, an exploration of the simple association between COMT genotype and AP raw score resulted in an effect estimate much closer to the null. Through further examination using step-wise regression exploration and simple associations, the APQ parenting variables were found to be negative confounders of the association between COMT genotype and AP raw score. CBCL AGG raw score was the only predictor in this model that accounted for a unique portion of variance in CBCL AP ($p = 6.99 \times 10^{-16}$).

DISCUSSION

The primary aim of the present study was to test the association between Val158Met genotype and two behavioral phenotypes commonly linked with child psychopathology: attention problems and aggressive behavior. Following from previous work by Grace, and Bilder et al., we predicted that the Val and Met alleles would be differentially associated with attention problems and aggressive behavior in youth. Given that allelic variation in this polymorphism is believed to result in countervailing patterns of dopaminergic signaling, we hypothesized that Met-carrying youth would be rated as more aggressive relative to Val-homozygotes. In contrast, we hypothesized that Val-homozygotes would possess higher ratings of attention problems relative to Met-carriers. These hypotheses were partially supported. Youth Met-carriers were found to possess significantly higher CBCL AGG scores when compared to Val-homozygotes. In order to better characterize this association between Met-carrier status and aggressive behavior, we investigated the extent to which the Met allele was differentially associated with two subtypes of aggressive behavior measured by the CBCL AGG scale: Direct Aggression and Relational Aggression. Although Met-carrier status was significantly associated with both subtypes of aggressive behavior, our findings suggest that Met-carrier status may be more closely associated with Direct Aggression compared to Relational Aggression. In regards to the hypothesized association between Val158Met genotype and attention problems, a trend was revealed suggesting that Val-homozygote youth possess higher CBCL AP scores relative to Met-carriers.

Our finding that Met-carrying youth possess higher CBCL AGG scores relative to Val-homozygotes is consistent with Bilder et al.'s proposed role of the Val158Met polymorphism in the context of dopamine tonic-phasic firing. This model postulates that elevated dopamine levels in the prefrontal cortex leads to cognitive inflexibility and increased risk for exhibiting aggressive behaviors. Interestingly, evidence from a number of recent functional neuroimaging studies suggests that the Met allele is positively associated with neural activity in prefrontal and amygdala regions during the processing of emotional stimuli.^{38–41} Moreover, this heightened activity in prefrontal and limbic regions exhibited by Met-carriers appears to be specific to the processing of negative as opposed to positive

emotional stimuli. These imaging findings are particularly intriguing given that the brain regions influenced by the Met allele during the processing of unpleasant stimuli (e.g., orbital frontal cortex, ventromedial prefrontal cortex, amygdala) overlap with areas implicated in the exhibition of direct aggression.⁴² Davidson and colleagues have argued that the proclivity to engage in impulsive aggression is closely associated with a “low threshold for activating negative affect.”⁴² Williams and colleagues recently reported that brain regions found to exhibit Met allele dose effects during the processing of negative emotional stimuli were also associated with self-reported bias toward both anticipating and attending to negative information and events.⁴¹ Thus, it is plausible that the Met allele confers risk for aggressive behavior by facilitating the activation of negative affect.

Our results indicate that Met-carrier status is associated with both Direct and Relational subtypes of CBCL Aggressive Behavior. The results of the present study further suggest that the association between Direct Aggression and Val158Met genotype may be more robust when compared to the association between Relational Aggression and Val158Met genotype. We have previously reported that the genetic factors associated with these two subtypes of aggression, contained in the CBCL AGG scale, only partially overlap and possess a genetic correlation of .54 for boys and .43 for girls.³² Thus, it is possible that the Val158Met polymorphism may constitute a specific genetic factor that is differentially associated with these two subtypes of aggressive behavior.

Several recent studies have reported an association between the Val allele and symptoms of conduct disorder in youth. Although the present study did not specifically look at symptoms of conduct disorder, we have previously noted that the CBCL items comprising the Direct Aggression factor more closely correspond to symptoms of conduct disorder, whereas items comprising the Relational Aggression factor are more consistent with symptoms of oppositional defiant disorder.³² Caspi et al.¹⁴ found that Val-homozygotes were more aggressive and exhibited more symptoms of conduct disorder, but only for those children diagnosed with ADHD. Monuteaux et al.¹⁵ found that the Val allele was associated with overtly aggressive symptoms of conduct disorder in children diagnosed with ADHD, but this finding was non-significant after correcting for multiple comparisons. In the present study, quantitative, empirically-derived phenotypic measures were utilized to more fully capture variation in youth attention problems and aggression. This difference in methodology may account, in part, for the apparent inconsistency between these past reports and our current findings.

Our hypothesized association between CBCL AP and Val-homozygosity was significant only at the trend level but in the predicted direction. This result is also in accordance with the COMT dopamine tonic-phasic hypothesis which contends that low dopamine levels in the prefrontal cortex, conferred by the Val allele, result in an increase in phasic dopaminergic signaling. This increase in phasic dopaminergic signaling is believed to facilitate cognitive flexibility and set-shifting. Interestingly, our finding parallels reports by other groups suggesting that the Val allele is associated with ‘off-task’ behaviors and, more specifically, distractibility.¹⁶ Exclusion of the parenting variables from the regression of AP on COMT genotype revealed that the parenting variables acted as negative confounders; the unadjusted estimate moved closer to the null hypothesis.⁴³ Therefore, other studies that fail to control for the hypothesized confounding effect of maternal parental qualities may underestimate the association between the Val allele and average AP raw score.

It is important to discuss our limitations as well as some offsetting strengths. First, in testing the above associations, we rely solely on maternal reports of child psychopathology. Thus, it is possible that the associations revealed in this study are confounded by maternal psychopathology as well as maternal genotype. Future studies testing similar hypotheses

would benefit from including data from multiple raters and also accounting for the contribution of parental genotype and psychopathology. Second, the cohort used in the present study includes a wide range of ages. Given that particular parenting qualities may be associated with certain psychopathologies at specific age ranges, future studies should utilize more developmentally homogenous samples, and/or larger cohorts to conduct age-specific sub-analyses. Third, although parenting quality is treated as an independent environmental factor that child participants are passively exposed to during their upbringing, this assumption belies the degree to which child behavior may serve to shape maternal parenting. Thus, the environmental factor of maternal parenting used in our analyses is undoubtedly influenced by children's biology and behavior. Fourth, other genes are likely to play significant roles in influencing the physiological underpinnings of aggressive behavior and attention problems. One of the strengths of the present study is our use of empirically-derived, quantitative phenotypic measures as opposed to DSM diagnoses, or symptom counts. By using continuous measures of aggressive behavior and attention problems, we were able to more effectively control for the co-occurrence of these behaviors in our analyses, while also increasing statistical power.

In conclusion, the results of the present study indicate that variation in the Val158Met polymorphism influences problem behaviors associated with psychopathology in youth. More specifically, our findings suggest that the Val and Met alleles of this polymorphism are associated with attention problems and aggressive behavior, respectively. Furthermore, our results indicate that the Met allele is associated with both Direct Aggression and Relational Aggression. The results of the present study may help future efforts to identify unique classes of externalizing disorders with distinct biological substrates.

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TABLE 1

Descriptive Statistics of Predictor Variables for Probands with Mother-rated Child Behavior Checklists

	M	SD
<u>Demographics</u>		
Age (in years) (<i>n</i> = 166)	10.93	2.77
Sex (% male) (<i>n</i> = 166)	58.43%	
Parental Socioeconomic Status (<i>n</i> = 159)	65.09	22.04
<u>COMT Genotype</u>		
Val158Met (% Val/Val) (<i>n</i> = 160)	31.25%	
<u>Parenting Qualities</u>		
Positive Involvement (<i>n</i> = 162)	63.51	7.59
Negative/Ineffective Discipline (<i>n</i> = 162)	21.29	4.75
Deficient Monitoring (<i>n</i> = 162)	12.90	4.52
<u>Child Behavior Checklist Measures</u>		
Aggressive Behavior (<i>n</i> = 166)	10.81	9.30
Direct Aggression (<i>n</i> = 161)	1.92	2.78
Relational Aggression (<i>n</i> = 164)	9.15	7.09
Attention Problems (<i>n</i> = 166)	6.47	5.23

Note: COMT = Catechol O-methyl transferase

TABLE 2

Model Summaries with Standardized Beta Coefficients

	AGG			Direct Aggression			Relational Aggression			AP		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Met Carrier Status	.146	.060	.016	.178	.065	.007	.123	.060	.041	-.122	.065	.062
Age	-.063	.076	.406	-.029	.082	.723	-.056	.076	.458	.023	.081	.779
Male Gender	.061	.060	.313	.115	.065	.080	.048	.060	.430	.048	.065	.456
Parental SES	-.144	.061	.019	-.118	.065	.073	-.126	.061	.039	-.002	.066	.972
AGG										.653	.072	6.99×10^{-16}
AP	.571	.063	6.99×10^{-16}	.499	.068	1.42×10^{-11}	.599	.062	4.66×10^{-17}			
Positive Involvement	-.014	.067	.839	-.089	.073	.224	.028	.067	.675	-.005	.072	.943
Deficient Monitoring	.104	.082	.204	-.028	.088	.755	.109	.081	.183	.006	.088	.942
Negative/Ineffective Discipline	.154	.069	.027	.194	.077	.012	.157	.068	.023	-.001	.075	.987

Note: AGG = Child Behavior Checklist Aggressive Behavior raw sum; AP = Child Behavior Checklist Attention Problems raw sum; β = standardized beta coefficient; SE = standard error; SES = socioeconomic status