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802 *Current Neuropharmacology,* **2015**, *13,* **802-814**

The Role of the Catechol-o-methyltransferase (*COMT*) Gene Val158Met in Aggressive Behavior, A Review of Genetic Studies

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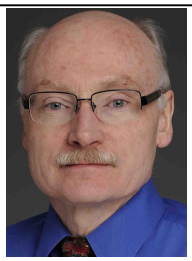

J.L. Kennedy

Abstract: Aggressive behaviors have become a major public health problem, and early-onset aggression can lead to outcomes such as substance abuse, antisocial personality disorder among other issues. In recent years, there has been an increase in research in the molecular and genetic underpinnings of aggressive behavior, and one of the candidate genes codes for the catechol-O-methyltransferase (COMT). COMT is involved in catabolizing catecholamines such as dopamine. These neurotransmitters appear to be involved in regulating mood which can contribute to aggression. The most common gene variant studied in the *COMT* gene is the Valine (Val) to Methionine (Met) substitution at codon 158. We will be reviewing the current literature on this gene variant in aggressive behavior.

Keywords: Aggression, attention-deficit hyperactivity disorder (ADHD), catechol-0-methyltransferase (COMT), genetics, schizophrenia, Val158Met (rs4680).

INTRODUCTION

Evolutionarily, aggression serves important roles in securing land and resources to increase an individual's chances of survival. It also helps parents to protect their offspring from intruders, predators, and hostile environments. However, excessive or inappropriate aggression can have devastating consequences [1]. For instance, in children aggression has been found to be associated with substance abuse, antisocial personality disorder, and violent outbursts [2]. Aggressive behavior is often observed in mental illnesses such as schizophrenia [3], attention-deficit hyperactivity disorder, borderline personality disorder, among others. Therefore, aggressive behavior is a serious public health issue, and research into its etiology and how it manifests can provide information on its treatment and prevention.

The mechanism underlying the development of aggressive behavior is unclear. Environmental factors seem to play a prominent role. For example, maternal stressors including exposure to alcohol, malnutrition, tobacco are associated with increased violent or criminal activities in the offspring [4]. Early-life stress has also been associated with the development of aggressive behaviors [5]. Aggressive behavior has also been shown to have a strong genetic component. Twin and adoption studies have shown aggressive behavior to be heritable [6-9]. Genetic factors explain as high as 40-50% of the risk for aggressive behavior [8, 10]. Craig and Halton [11] found that various genes have been associated with aggression, including dopamine system genes such as catechol-O-methyltransferase (*COMT*). This review is to summarize the current status of research conducted on how the functional Val158Met variant in the *COMT* gene has been implicated in aggressive behaviors in various psychiatric populations. It will also discuss limitations in the field, and offer a number of avenues that may help to resolve the mixed findings in the literature regarding this gene marker and aggressive behavior.

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MATERIALS AND METHODS

Literature search was conducted using PubMed and Google Scholar. Key words used included "COMT AND aggression", "COMT AND Val158Met AND aggression", "COMT AND violen*", and "COMT AND externalizing". Additional papers were collected from the reference lists of the articles from the primary internet searches. The review will begin with an introduction to COMT. We will be summarizing findings from association studies of *COMT* Val158Met with aggressive behavior, either by itself or in the context of schizophrenia, ADHD, and other psychiatric disorders. Studies that investigated the *COMT* Val158Met in aggression are summarized in Table **1**.

Catechol-O-Methyltransferase (COMT)

COMT is an enzyme that is involved in metabolizing various catecholamine neurotransmitters, including dopamine and epinephrine. The *COMT* gene is 27.22kb in length, and is located on chromosome 22q11.2 [12]. There are two isoforms expressed from two promoters, the soluble S-COMT isoform that is expressed in most tissues, such as liver, blood, and kidneys, and the membrane-bound form MB-COMT that is more common in the brain [13]. The MB-COMT form is of particular interest because of its role in regulating extracellular

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Table 1. Gene association studies between *COMT* Val158Met and aggression.

Sample Characteristics	Diagnosis	Assessment Tools for Aggression	Findings	Refs.
149 youths, 58% males (6-18yo)	N/A	Mother-rated CBCL	Met- > ValVal (aggression scale (p=0.016), direct aggression (p=0.007) and relational aggression (p=0.041))	Albaugh *et al.* [24]
379 male air force recruits	N/A	Aggression Questionnaire	Not significant	Avramopoulos *et al.* [26]
144 majority European, 72% males (6-16yo)	N/A	Pervasive aggression (CBCL and TRF) vs healthy adult controls	Not significant	Hirata *et al.* [27]
37, 86% males, mixed ethnicity (40.6yo)	Schizophrenia	RAD	MetMet higher risk than ValVal (p=0.003)	Strous *et al.* [33]
55, 62% males, European	Schizophrenia or schizo-affective	27 with history of multiple assaults vs 28 non-violent patients	Met associated with risk (p=0.02)	Lachman *et al.* [35]
92, 63% males, Jewish (39.1yo)	Schizophrenia	30 homicidal vs 62 non-violent	Trend for Met associated with risk (p<0.1)	Kotler *et al.* [36]
122, 77% males, Jewish	Schizophrenia	LHA	MetMet with higher scores than Val- (p=0.005; aggression p=0.007; self-directed aggression p=0.033)	Strous *et al.* [37]
168 male East Asian	Schizophrenia	OAS	MetMet associated with highest scores on physical aggression against other people (p=0.02)	Han *et al.* [39]
132 male East Asian	First-episode schizophrenia	OAS	MetMet associated with highest scores on physical aggression against other people and total OAS scores (both p<0.001)	Han *et al.* [41]
80, 51% males, European	Schizophrenia	OAS	MetMet with higher total OAS scores than ValVal (p=0.045)	Tosato *et al.* [42]
180 European (75.6% males)	Schizophrenia	OAS	ValVal with higher total scores than Met- (p<0.05); lowest scores in ValMet (p<0.01)	Jones *et al.* [43]
330 European (180 from Jones *et al.*)	Schizophrenia	OAS	Not significant	Zammit *et al.* [44]
All males (18-65yo)	Schizophrenia	93 Homicidal vs 100 non-homicidal	Not significant	Hong *et al.* [45]
198, 47% males, East Asian	Schizophrenia	Aggressive behavior or gestures 2wks before hospital admission	Not significant	Liou *et al.* [46]
70 males various ethnicities from South Africa	Schizophrenia	40 violent vs 30 non-violent (OAS)	Not significant	Koen *et al.* [47]
165, 58% males, East Asian (38.4yo)	Schizophrenia	61 aggressive vs 104 non-aggressive (MOAS)	Met- with higher scores in verbal aggression within aggressive patients (p=0.032)	Kim *et al.* 2008 [48]
East Asian, 59% males (36.8yo)	Schizophrenia	99 criminal/ 133 homicidal patients vs healthy controls	Not significant	Koh *et al.* [49]
Chinese, all males	Schizophrenia	252 violent vs 332 non-violent patients; MOAS	Not significant with Val158Met; haplotypic association	Gu *et al.* [115]
516, 77% males, Brazilian majority European	ADHD	CD or ODD	ValVal > Met- (p=0.016; OR=1.58; CI95%=1.07–2.35)	Salatino-Oliveira *et al.* [61]
240, 89% males, European children	ADHD	Comorbid CD	ValVal associated with risk	Thapar *et al.* [56]

Table 1. contd….

Sample Characteristics	Diagnosis	Assessment Tools for Aggression	Findings	Refs.
(1) 241 British (2) 2232 British birth cohort (3) 1037 New Zealand cohort	ADHD	(1) CD symptoms in ADHD; (2) CBCLs in general population and ADHD; (3) adolescents followed to adulthood	(1) ValVal with higher CD symptom scores than Met1 (p=0.05); (2) ValVal with pervasive aggression in ADHD subgroup (p=0.04); (3) ValVal with higher scroes on antisocial behavior index than Met- in ADHD subgroup (p=0.03)	Caspi *et al.* [57]
444, 58% males, mainly European (6-55yo)	ADHD	Comorbid CD	Not significant with CD; ValVal with more aggressive subtype symtpoms than Met- (p=0.03)	Monuteaux *et al.* [58]
171 East Asian boys	ADHD	Comorbid ODD	ValVal associated with ODD (p=0.019)	Qian *et al.* [59]
4365, 51% males, European (7.5yo)	ADHD	Antisocial behavior symptoms	ValVal associated with highest loading of antisocial behavior symptoms (p<0.001)	Langley *et al.* [60]
166, 84% males, German (6-13yo)	ADHD	Lifetime history of comorbid CD	Not significant with CD; Met- associated with highest ADHD symptom severity	Palmason *et al.* [62]
446, 53% males, youths mostly Italian ancestry (10-14yo)	N/A	CBCL	Not significant with conduct behavioral problems; ValVal children in families of low socioeconomic status with highest ADHD symptom severity	Nobile *et al.* [63]
94 Finnish/ 54 US	Schizophrenia/ Schizo-affective	Suicide attempt	Met allele associated with risk (p=0.015); male-specific association (p=0.008)	Nolan *et al.* [67]
393, 79% males, Croatian	Alcoholism	Suicide attempt	MetMet associated with risk in males (p<0.001)	Nedic *et al.* [68]
477, 42% males, German	N/A	149 suicide attempters vs 328 healthy controls; STAI	Met allele over-represented in violent attempters vs non-violent attempters; Val allele associated with state anger, anger-in, and Met allele associated with anger-out	Rujescu *et al.* [69]
107 Swiss/ 320 French (42% males, 18-75yo)		427 suicide attempters vs 185 controls	Val associated with risk (p=0.019)	Baud *et al.* [73]
305 small nuclear families; 38% males, mainly European	Bipolar disorder	Suicide attempt	Not significant	De Luca *et al.* [75]
270, 73% males, mainly European	Schizophrenia	92 suicide attempters	Not significant	De Luca *et al.* [74]
486	Mood disorder	201 suicide attempters	Not significant	Zalsman *et al.* [76]
163, 69% males, East Asian	N/A	Suicide completers	ValVal male-specific association with low risk (p=0.016)	Ono *et al.* [79]
German, 50% males	BPD	161 cases vs 156 healthy controls	MetMet associated with risk (adjusted p=0.034)	Tadic *et al.* [81]
Italian	BPD	19 cases vs 36 controls	Met associated with risk (p=0.02)	Lazzaretti *et al.* [82]
(1) 99 US young adults from low-income families; (2) 136 Hungarian; 29% males	(1) N/A; (2) mood disorder	BPD	Not significant	Nemoda *et al.* [83]
296 Chinese female	Heroine dependence	61 BPD vs 235 without BPD	Not significant	Yang *et al.* [84]
Male inmates convicted of violent impulsive crimes	APD	47 cases vs 43 healthy controls	Not significant for Val158Met; significant for Ala146Val with Val- associated with violent cases	Vevera *et al.* [85]
Colombian male inmates	APD	310 cases vs 200 controls	Met allele associated with APD (p=0.002)	Cuartas Arias *et al.* [86]

Table 1. contd….

Sample Characteristics	Diagnosis	Assessment Tools for Aggression	Findings	Refs.
2 treatment-seeking samples (293 German, 190 Polish); >=18 years of age	Alcoholism	Violent or non-violent crimes; LHA, BDHI, SSAGA	Not significant	Soyka *et al.* [34]
97 male Korean	Alcoholism	History of violence	Met associated with violence (p=0.012)	Kweon *et al.* [90]
38, 39% males, children	22q11 deletion	CBCL	Val allele associated with higher scores (p<0.01)	Bearden *et al.* [91]
174 adolescent male Russian delinquents	N/A	CD	MetMet associated with highest ADHD symptom counts, and ValVal associated with highest symptom counts for CD (p<0.01)	DeYoung *et al.* [92]
112 female German	BPD	BDHI	ValVal and history of childhood sexual abuse associated with lowest BDHI scores (p<0.05)	Wagner *et al.* [100]
191, 87% males, European (6-12yo)	ADHD	Antisocial behaviour symptom severity	Not significant	Sengupta *et al.* [102]
430 mainly European (15-20yo)	N/A	CBCL	ValVal and maternal smoking associated with adolescent aggression	Brennan *et al.* [103]
Turkish, 63% males	Intellectual disability	36 Violent criminals with MR vs 36 non-MR controls	Not significant	Isir *et al.* [116]
112, 68% males, European	Axis II personality disorder	BDHI	Not significant with Val158Met; 3'UTR marker rs165599 associated	Flory *et al.* [117]
Male Afro-Caribbean adults	N/A	29 Convicted vs 26 never	Not significant	Vinkers *et al.* [118]

ADHD attention-deficit hyperactivity disorder; CD conduct disorder; BPD borderline personality disorder; APD antisocial personality disorder; ODD oppositional defiant disorder; BDHI Buss-Durkee Hostility Inventory; CBCL child behavior checklist; OAS Overt Aggression Scale; AQ Aggression Questionnaire; LHA Life History of Aggression Scale; RAD Risk Assessment for Dangerousness; TRF Teacher Report Form.

dopamine levels in the prefrontal cortex [14, 15]. A common non-synonymous single-nucleotide polymorphism (rs4680) changes the 158th amino acid residue of the membrane-bound isoform (or 108th amino acid of the soluble form) from Valine (Val) to Methionine (Met). The presence of the Met variant leads to a four-fold reduction in COMT enzyme activity due to increased thermolability at physiological temperature [16, 17]. This in turn increases the dopamine levels in the prefrontal cortex [16].

COMT in Aggression

While the etiopathophysiology of aggression is unclear, previous research indicates the dopamine neurotransmission system to play a prominent role. For example, dopamine levels are elevated before, during, and after aggressive social encounters in rodents [18]. In addition, dopamine-augmenting pharmacological agents, including amphetamine and apomorphine, have been associated with the induction of aggressive behavior [19, 20]. Furthermore, frontal cortical dopamine depletion by 6-hydroxydopamine-induced lesions resulted in diminished foot-shocked induced fighting behavior in rats [21]. The role of COMT in aggression was first suggested by Kuperman *et al.* [22], where the authors followed up on 31 men who were seen for issues of hyperactivity as children. They found that COMT activity was negatively correlated to a measure of hostility and positively correlated to a measure of impulsivity. Animal models have provided further support for a role of COMT in aggressive behavior. More specifically, male mice lacking one copy of the *comt* gene displayed enhanced fighting behavior toward one another [23]. These previous observations, as well as the role of the COMT enzyme in the degradation of dopamine, support the study of the *COMT* gene in aggressive behavior.

Albaugh *et al.* [24] reported that youths carrying at least one copy of the low-activity Met allele had higher aggression scores on the mother-rated Child Behavior Checklist (CBCL; [25]) than the ValVal genotype carriers, particularly in aggression scale, direct aggression and relational aggression. In a sample of 379 male air force recruits, aggression scores measured by Aggression Questionnaire were not significantly different across the three Val158Met genotypes [26]. Hirata *et al.* [27] analyzed the *COMT* gene for possible association with pervasive aggression assessed by Child Behavior Checklist (CBCL; [25]) (both mother and teacher rated), but did not find Val158Met to be associated with risk for aggression. The results remained not significant when the analysis was stratified by gender or ADHD diagnosis.

The inconsistent findings across these studies suggest that the relationship between *COMT* Val158Met and aggression may not be straightforward. It is especially relevant as these studies were conducted on samples of different ages, different sex ratios using different assessments of aggressive behaviors, making these studies not directly comparable. Thus, it was not surprising that a recent meta-analysis did not find Val158Met to be significantly associated with aggression in general [28]. Many studies attempted to control for this disparity by narrowing the focus of Val158Met in aggression to within specific psychiatric populations, with schizophrenia being often considered.

COMT and Aggression in Schizophrenia

In numerous studies, aggression and the *COMT* gene have been examined was in the context of schizophrenia. Part of the reason was the dopamine hypothesis of schizophrenia, as well as the use of antipsychotics in the treatment of aggressive behaviors in various populations [29-31], including schizophrenia [32]. The first genetic study examined the role of Val158Met in aggressive or potential dangerous behaviors, as measured using the Risk Assessment for Dangerousness (RAD), in schizophrenia inpatients [33]. The dangerous behaviors included having caused bodily harm, alcohol/cocaine abuse, violent crime, and/or threatening behaviors. The authors reported that homozygotes for the low-activity MetMet allele had higher risk for these dangerous behaviors than the high-activity ValVal homozygotes. The small sample of 37 patients, and the mixed ethnicity meant that these findings were preliminary. Nonetheless, it was a novel finding implicating *COMT* Val158Met to aggressive behavior in schizophrenia.

A number of studies have attempted to replicate the original Strous *et al.* [33] finding of an association between *COMT* MetMet genotype and aggression in schizophrenia/ schizoaffective disorder patients (*e.g.*, reviewed in [34]). Lachman *et al.* [35] reported a significant over-representation of the low-activity Met allele in 27 patients with documented history of multiple assaults compared to 28 non-violent patients. Similarly, Kotler *et al.* [36] found a trend for the MetMet genotype to be more frequently observed in 30 homicidal patients than in 62 nonviolent patients. In the Strous *et al.* [37] study, the authors used the Life Time History of Aggression scale (LHA; [38]) which has a variety of measures of aggression including self-directed aggression, antisocial behavior subscale, and aggression. The authors found in a Jewish sample that the low-activity MetMet genotype carriers had significantly higher LHA scores than carriers of the other genotypes, particularly due to the Aggression and Self-directed aggression subscales [37]. Han *et al.* [39] studied an East Asian sample of 168 male schizophrenia patients from South Korea. In this study, they assessed aggressive behavior with the Overt Aggression Scale (OAS; [40]). The OAS included subscales for verbal aggression, aggression against objects, physical aggression against self, and physical aggression against other people. The authors found that among the *COMT* genotypes, the homozygous MetMet genotype was associated with the highest scores on the subscale measuring physical aggression against other people. Han *et al.* [41] followed up with another paper examining only first-episode male patients and reported the similar results for physical aggression against other people and total OAS scores. More recently, Tosato *et al.* [42] studied a cohort of schizophrenia patients comparing the MetMet homozygotes with the ValVal homozygotes, taking into consideration substance use as well as antipsychotic use and dosage. They also found that the MetMet patients had the higher total OAS scores than the ValVal patients.

As described above, there have been numerous reports of the low-activity Met allele being associated with aggression in schizophrenia patients; however, there have also been a number of studies reporting negative or opposite findings. Jones *et al.* [43] measured aggressive behavior in a European sample of 180 schizophrenia patients using OAS. They reported that homozygotes for high-activity (ValVal) allele showed higher total OAS scores than the other two genotypes. They also found the lowest scores in heterozygotes. Zammit *et al.* [44] continued on with Jones *et al.* [43] with an additional 150 schizophrenia patients, but the results were not significant for either this stage-two sample or the combined sample. Hong *et al.* [45] found that the frequencies of Val158Met genotypes and alleles did not differ significantly between schizophrenia patients who had committed homicides and non-homicidal schizophrenia patients. Liou *et al.* [46] investigated incidents of aggressive behavior towards others or threatening gestures in the two weeks before hospital admission in a sample of 198 Chinese schizophrenia patients, and failed to find an association with Val158Met. Koen *et al.* [47] examined male schizophrenia patients of various ancestries from South Africa and did not report significant association between Val158Met and violent behaviors. Kim *et al.* [48] studied a group of 61 aggressive and 104 non-aggressive schizophrenia patients. They found that the *COMT* Val158Met polymorphism had no significant effect on the presence of aggression in the Korean schizophrenia sample; however they found the Met-allele carriers to score higher in verbal aggression within the aggressive schizophrenia subgroup. Koh *et al.* [49] examined inpatients from a forensic psychiatric hospital in Korea. When they compared the frequencies of criminal or homicidal schizophrenia patients with healthy controls, they did not find Val158Met to be associated.

Despite the mixed findings of *COMT* Val158Met in aggressive behavior in schizophrenia samples, a number of recent meta-analyses showed an overall effect of the low-activity Met allele carrying genotypes in risk for violence (pooled odds ratio for the MetMet genotype = 1.737, 95% confidence interval = 1.103 to 2.735, p=0.017) [50, 51].

Besides schizophrenia, there have been a considerable number of studies looking at how *COMT* Val158Met may play a role in aggressive behavior in attention-deficit hyperactivity disorder (ADHD).

COMT and Aggression in Attention-Deficit Hyper-activity Disorder

ADHD and disruptive behavior disorders are highly co-morbid (reviewed in [52]), and longitudinal studies demonstrate that ADHD is often antecedent to antisocial behavior [53]. The dopamine system has been studied

extensively in ADHD due to the efficacy of medications that regulate the levels of catecholamines [54]. A number of studies have investigated for possible association between *COMT* Val158Met and ADHD diagnosis, though a recent meta-analysis reported negative findings [55]. Nonetheless, many papers also examined whether Val158Met plays a role in conduct or aggressive behavior in ADHD children and adolescents.

Thapar *et al.* [56] first reported an association between the ValVal genotype in risk of comorbid conduct disorder in a sample of 240 ADHD children of European ancestry. Caspi *et al.* [57] carried out a large study to further support the relationship between Val158Met and aggressive behavior in three independent samples. Firstly, they examined conduct disorder symptoms in children with ADHD before treatment commencement. They found the ValVal homozygotes to score higher in conduct disorder symptoms than Met-allele carriers. When the authors followed up with a general population sample, they found that the association of ValVal with pervasive aggression, as measured by CBCL by multiple informants, was specific for children with ADHD. These association findings were not observed in children without ADHD. The authors further examined this relationship in a third cohort, where adolescents were followed to adulthood. Similar to the other two samples, higher scores on an antisocial behaviors index in ValVal genotype carriers in comparison to Met-allele carriers were observed only in individuals with ADHD. ADHD individuals with the ValVal genotype were also more likely to have been convicted of a crime at age 32. These replicated findings suggest that the association of *COMT* high-activity ValVal genotype with aggressive behavior may be dependent on underlying psychiatric diagnosis, as in this case ADHD.

Monuteaux *et al.* [58] attempted to further replicate the previous findings by examining conduct disorder symptoms in 444 ADHD patients extracted from four studies. Although *COMT* Val158Met was not associated with risk of conduct disorder, ValVal subjects reported more aggressive subtype symptoms than Met-allele carriers. Nonetheless, these findings are consistent with those reported by Caspi *et al.* [57]. Similarly, Qian *et al.* [59] looked at a sample of 171 Chinese ADHD boys and also found the ValVal genotypes to be observed more frequently in the group with comorbid oppositional defiant disorder than expected by chance. In another large study of 4365 children, the highest loading of antisocial behavior symptoms was found in ADHD children with the high-activity ValVal genotype (odds ratio: 2.82; 95% confidence interval: 2.02-3.94; P <0.001) [60]. Salatino-Oliveira *et al.* [61] studied on a sample of 516 Brazilian youths and adolescents with ADHD. They found the ValVal genotype to be at higher risk for conduct or oppositional defiant disorder (p=0.016; OR=1.58; CI95%=1.07–2.35).

In contrast, Palmason *et al.* [62] could not replicate the earlier findings when they analyzed symptom severity and risk for conduct disorder with Val158Met in a sample of 166 ADHD children. They reported the high-activity Met-carrying genotypes to be associated with higher ADHD symptom severity, and did not find Val158Met to be associated with lifetime history of comorbid conduct disorder in their sample. Nobile *et al.* [63] investigated 446 youths of mostly Italian ancestry using the CBCL/6-18 checklist. They found that children with the ValVal genotype in families of low socioeconomic status scored highest in the ADHD symptom severity compared to children of other genotypes and socioeconomic statuses. However, they did not find Val158Met to be associated with conduct behavioral problems. Future studies looking into specific aggressive symptoms within conduct disorder may be required to better address the role of Val158Met in aggressive behavior exhibited by ADHD children.

COMT and Suicidal Behavior (Reviewed in [64])

Aggression has been linked to suicidal behavior across psychiatric diagnoses (reviewed in [65]). Impulsive aggression, as measured by Barratt Impulsiveness Scale and the Brown-Goodwin History of Aggression, has been shown to be a predictor of suicide completion [66].

In a combined sample of Finnish and US schizophrenia/ schizoaffective disorder patients, the low-functioning Met allele was found more frequently in suicide attempters, especially in male attempters or violent attempters [67]. The low-activity MetMet genotype appeared to be over-represented in suicide attempters in a Croatian alcoholism sample [68]. A German study investigated constructs of aggression to test if the *COMT* gene could have more complex effects on aggression [69]. This study had a sample of 149 suicide attempters and 328 healthy control subjects. The low-activity Met allele was found to be over-represented in violent suicide attempters compared to the nonviolent attempters. In addition, the authors administered the State-Trait Anger Expression Inventory (STAI, [70, 71]) for various components of aggressive behavior. After controlling for age, sex, educational levels, and suicide attempter versus healthy control status, the high-activity Val allele appeared to be associated with State Anger and Anger-in or inwardly directed anger, and the low-activity Met allele appeared to be associated with Anger-out or externalizing anger. There have been many other studies investigating Val158Met in suicidal behavior. The first meta-analysis of Val158Met in suicide utilizing earlier studies pointed to the low-activity Met variant to be associated with risk for suicidal behavior [72]. However, more recent meta-analyses with additional samples (*e.g.*, [73-76]) failed to confirm this association [77, 78]. Interestingly, a number of studies reported the sex-specific association of Val158Met with suicidal behavior [67, 79], and sex ratios appeared to influence the overall findings [72, 77], warranting further studies involving sex-stratified analyses. As different associations have been observed for ADHD and schizophrenia, it would be prudent to conduct these suicide-related analyses within specific psychiatric diagnoses. In addition, as suicidal behavior is an outcome, examining aggression measures may be fruitful in this population.

COMT and Aggression in other Psychiatric Disorders or Contexts

Aggressive behavior is also commonly observed in patients with borderline personality disorder (reviewed in

[80]). With regard to personality disorders, several groups have investigated whether the low-activity Met allele or MetMet genotype is associated with antisocial (APD) or borderline personality disorders (BPD), both of which involve impulsive aggressive behaviors. The MetMet genotype was associated with risk for BPD when comparing between 161 BPD patients and 156 healthy controls in a study on a German sample [81]. In an Italian sample, Lazzaretti *et al.* [82] showed that *COMT* low-functioning MetMet genotype was more frequent in 19 BPD patients compared to 36 healthy controls (47.4% vs. 22.2%). However, these initial association findings between *COMT* Val158Met and BPD could not be replicated in a sample of young adults from low-income families in the US, a sample of Hungarian mood disorder patients [83], or a sample of female heroin-dependent patients in China [84]. Vevera *et al.* [85] examined a Caucasian sample of 47 male inmates convicted of violent crimes with high impulsivity. These participants had a diagnosis of APD. The authors did not find genotype frequencies of the Val158Met in these cases to differ significantly from those in 43 healthy control subjects. They, however, found a different polymorphism, Ala146Val to be significant, where the Val-carrying genotypes were over-represented in the violent antisocial cases. Cuartas Arias *et al.* [86] showed in a study in Colombia that the Met allele was more frequently observed in 310 male inmates with APD than in 200 male inmates without APD. With the few studies conducted on Val158Met in BPD or APD so far, it is premature to draw conclusions from the mixed findings reported thus far.

Alcohol use has been linked to violent and aggressive behavior at home [87, 88] and in the workplace [89]. Few studies have investigated specifically the role of Val158Met and aggression in alcohol dependence. Neither violent nor non-violent crimes were associated with Val158Met in two treatment-seeking alcoholic patient samples [34]. Moreover, Val158Met was found not to be associated with criminal or aggressive behavior as assessed using the Brown Goodwin Life History of Aggression, Buss-Durkee Hostility Inventory, or the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) in a German sample and a Polish replication sample [34]. However, Kweon *et al.* [90] found the Met allele to be associated with history of violence in a Korean sample of 97 male alcoholics.

Bearden *et al.* [91] looked at behavioral problems in 38 children with 22q11.2 deletion; that is, with only one copy of the *COMT* gene. They found individuals carrying the Val allele to score significantly higher than Met allele carriers in various components of the CBCL, including externalizing and internalizing behaviors, delinquency, withdrawal, and social problems, but not in aggressive behavior. In a study on Russian delinquents, while the MetMet genotype was associated with the highest symptom counts for ADHD, the ValVal genotype was associated with the highest symptom counts for conduct disorder [92].

DISCUSSION

Overall, the findings from association studies between *COMT* Val158Met and aggression have been mixed. A few interesting trends were observed. The low-functioning Met allele appeared to be associated with aggression in schizophrenia patients, while the high-functioning Val allele appeared to be associated with conduct behavioral problems in a majority of ADHD samples thus far. These trends seemed to be congruent with some of the medications used for treating aggressive behaviors in these two populations, more specifically the use of dopamine D_2 receptor-antagonizing antipsychotics in schizophrenia patients [93] and the use of dopamine-agonizing psychostimulants (*e.g.*, methylphenidate) in ADHD patients [94]. These results may be reflective of the mechanism of the underlying psychiatric disorders. In some cases, the use of psychotropic medication could have confounded these findings. Unfortunately, methodological issues to be discussed below make genetic studies of aggression hard to interpret.

Gene-Gene and Gene-Environment Interaction in Aggression

The mixed findings for Val158Met with aggressive behavior could have been due to the fact that multiple gene variants likely contribute to the function of the COMT enzyme [95, 96]. It is COMT activity, which may be informed by the sum and interactions of its gene variants, may be associated with aggressive behavior. For example, one study found that a functional Alanine substitution for Serine (Ala72Ser, rs6267, [97]) was associated with history of homicides in a Korean schizophrenia sample [45]. The association was strengthened when the Ala72Ser and Val158Met were considered in haplotypes. These findings while requiring replications, suggest that various polymorphisms could lead to changes in enzymatic activity that can influence the risk for aggressive behavior. Additional work with other functional *COMT* polymorphisms may address some of the discrepancies in the association findings. In addition to studies based on single genes, multiple genes may additively or interactively contribute to the development of aggressive behavior. Tadic *et al.* [81] found the genotype combination of *COMT* MetMet and short/short or short/long at the *SLC6A4* 5HTTLPR to be over-represented in BPD patients. There is growing evidence that decreased serotonin and increased dopamine is associated impulsive aggression [98, 99]. Thus, studies looking into gene variants that regulate dopamine levels in addition to *COMT* Val158Met, and serotonin levels, as well as the interactions among these gene variants are warranted.

In some studies, investigators have investigated if individuals' predisposition to aggressive behavior could be explained by the *COMT* gene in conjunction with environmental variables. In one study, Wagner *et al.* [100] aimed to see if aggressive behavior modulated the relationship between severe life events and BPD. In an exclusively female patient sample from Germany, aggression was assessed using the Buss-Durkee Hostility Inventory (BDHI; [101]). The authors found an interaction between *COMT* Val158Met and stressful life events. More specifically, ValVal genotype carriers with history of childhood sexual abuse had the lowest average BDHI sum scores, while the ValVal genotype carriers without such history had the highest scores. One study found an interaction of low birth weight with *COMT* Val158Met in predicting antisocial behavior symptom severity in a

European ADHD sample [56]. However, this finding failed to replicate in an independent sample of mostly Europeans [102]. Brennan *et al.* [103] investigated the effect of maternal prenatal cigarette smoking on psychopathology in the offspring in a large birth cohort study in Australia. They did not find Val158Met by itself to be associated with CBCL-rated aggressive behavior during adolescence. However, they found that ValVal carriers whose mothers smoked during pregnancy scored the highest in adolescent aggressive behavioral problems than other comparison groups. The interaction between Val158Met and maternal prenatal smoking in antisocial behavior was not observed in another study [56].

In order to further elucidate how the environment can contribute towards aggressive behavior, epigenetic studies could be included to see if methylation patterns can explain any changes in aggressive behavior. Thus far, the *COMT* gene has not been studied epigenetically at great depth. However, one study looked at the potential role of DNA methylation in the *COMT* gene in relation to PTSD. Norrholm *et al*. (2013) looked at a sample of patients with a history of PTSD from the inner cities of Atlanta Georgia. The study wanted to see if the environment can confer an impact on PTSD and fear response, specifically if the *COMT* promoter region methylation can have an effect on it. What they found was that the Met/Met genotype had higher fear response to a signal than the Val-allele carrying genotypes. This pattern also persisted in the Met/Met genotype with a diagnosis of PTSD. In addition, the Met/Met genotype was associated with methylation patterns at four CpG sites of which two sites also had an association with impaired fear inhibition to a safety signal [104]. These results highlight the complexity of the contribution of environmental variables to genetic studies of aggression, and encourage the inclusion of epigenetic analyses to the studies of *COMT*.

It is further likely that both gene-gene and gene-environment interactions will have to be considered in concert in studies of aggressive behavior. For example, van IJzendoorn *et al.* [105] studied a group of mother-toddler pairs where the children scored at least 75th percentile on the externalizing problem scale of the CBCL. They examined hassles experienced by the mothers and their sensitivity towards their toddlers during a series of problem-solving tasks. Mothers who carried a Val allele as well as a 7R allele of the *DRD4* exon-3 variable-number tandem repeat marker were more sensitive to their toddlers when they reported less hassle. The mothers with the same genotypes were less sensitive when they reported more hassle. These observations, though preliminary, demonstrate the presence of both gene-gene and gene-environment interactions in aggressive behavior.

Defining and Measuring Aggression

An important issue in summarizing the literature on the association findings of genetic variants with aggression is the variety of ways used to define aggressive behavior. Firstly, aggression has been studied in the context of various psychiatric disorders. For instance, ADHD children exhibiting aggressive behavior are commonly diagnosed with either Oppositional defiant disorder (ODD) or Conduct Disorder (CD). However, even in individuals diagnosed with either of the ODD or CD, there is considerable heterogeneity between them. ADHD comorbid with ODD appeared to be associated with lower risk of learning disability, while ADHD comorbid with CD appeared to be associated with increased anxiety, aggression, and maternal psychopathology [106]. In a ten-year follow-up study, boys with ADHD and ODD were at higher risk of depression, while boys with ADHD and CD were at higher risk of bipolar disorder, antisocial personality disorder, and smoking [107].

Another issue comes in distinguishing between antisocial and aggressive behaviors. Aggressive behavior can be defined as behavior that is meant to harm other people and/or objects or it can be self-directed. Antisocial behaviors can be defined as behaviors where those affected are disadvantaged due to a violation of social norms and values. An example of antisocial behavior is stealing. By definition, aggressive behaviors represent one of the dimensions of antisocial behaviors but not all antisocial behaviors are acts of aggression. A longitudinal population-based twin study in Sweden reported difference in heritability of antisocial behavior between the sexes [108]. More specifically, while the genetic contribution to aggressive behavior was similar for both sexes, genes explain more of the variance in delinquency in females than in males. Moreover, while the genetic contribution to aggressive antisocial behavior appears to be stable from childhood to adolescence, its contribution to delinquent behavior fluctuates through this developmental period [109]. Conducting genetic analyses on aggressive and non-aggressive delinquent antisocial behaviors separately may help reduce the noise associated with heterogeneity of antisocial behavior.

Aggressive behaviors also fall under two broad subtypes, reactive and proactive aggression [110]. Reactive aggression can be defined as an impulsive act which is generally uncontrolled and is related to high levels of arousal and emotions. It is an angry, hostile reaction to a stimulus. An example is striking someone after being insulted. Proactive aggression directed at achieving an end. It can be seen as a means to use aggression instrumentally in order to attain a goal. Proactive aggression is characteristic of psychopaths as their behaviors are labeled as callous and unemotional. This distinction has been mostly ignored in past studies of Val158Met in aggression. A twin study using the Reactive-Proactive Aggression Questionnaire from multiple informants has shown that genetic factors appear to explain a significant variance in proactive aggression and reactive aggression, with larger variance explained for proactive aggression [6]. This genetic contribution also appears to be larger in males, warranting sex-stratified analyses of aggressive behavior.

Measuring aggression has been a challenge due to its heterogeneity. In the case of children, a common questionnaire that is used is the Child Behavior Checklist (CBCL; [25]). There are three versions, the parent- or guardian-rated CBCL, the Teacher Report Form, and the Youth Self Report. Some aggression studies discussed above were conducted only with single informants (only mothers or only participants) [58, 63], thus the aggressive phenotype might not have been pervasive across different settings and might have been more dependent on specific environmental stressors.

In this context it is worth noting that aggressive behavior can occur as a "state" or a "trait". In the former circumstances aggressive behavior occurs within a limited context, for example, within the family home when limits are placed on the child or adolescent. In contrast, when aggression is a trait, aggressive behavior will be evident in multiple situations and contexts, at home, at school, with friends and so on. In these circumstances the aggression would be considered pervasive. The intensity of the aggressive behaviors may fluctuate depending on the status of the underlying psychiatric illness, such as manic episodes in bipolar disorder [111, 112], or psychotic episodes in schizophrenia. None of the studies reviewed have explicitly dealt with this issue, and some of the contradictory findings may be attributed to the failure to differentiate between aggression as a trait versus aggression as a state.

The Overt Aggression Scale (OAS [40]), which is used for the assessment of aggressive behavior in adults, consists of subscales for verbal aggression, aggression against objects, physical aggression against self, and physical aggression against other people. It is interesting to note that OAS scores could be influenced by other personality traits such as sensation seeking and impulsivity, as well as environmental factors such as smoking [113]. Moreover, unlike BDHI and LHA, OAS assesses aggressive behavior occurring during the past week, thus it does not capture aggressive behavior across lifetime. To further complicate matter, one meta-analysis of genetic and environmental influence on aggression showed that self-reported and parent-rated aggression yielded different heritability measures from observational data [114], warranting the use of multiple tools of aggression assessment.

In summary, there have been many studies on *COMT* Val158Met in aggressive behavior. However, its role in aggression is still unclear. Aggressive behaviors have been observed in mood disorder patients, with bipolar I disorder appearing to be associated with higher levels of aggression than bipolar II disorder or unipolar depression [112]. Future studies of *COMT* aggression should include these populations, as well as intellectual disability, Alzheimer's disease, stroke victims, and other dementias. Future studies will also need to consider many approaches to help to resolve ininconsistencies in previous studies of *COMT* and aggression. They include testing additional genetic markers in *COMT* and other dopamine system genes, looking at genetic markers in other neurotransmitter systems (*e.g.*, serotonin), and exploring gene-gene interactions. Environmental variables also need to be considered in conjunction with epigenetic changes. More importantly, there needs to be consensus on the assessment and characterization of the different facets of aggressive behavior, including proactive or reactive, state or trait, self-reported or multi-informant. Overcoming these challenges will help to consolidate the various genetic findings and elucidate the biological mechanism underlying the development of aggressive behavior, leading to improved outcome through evidence-based prevention and intervention strategies.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

We thank Dr. Sheng Chen and Andrea Smart for their assistance in the preparation of this review.

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Received: April 27, 2015 Revised: May 22, 2015 Accepted: May 25, 2015