Association of the catechol-O-methyltransferase polymorphism with methylphenidate response in a classroom setting in children with attention-deficit hyperactivity disorder

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It has been postulated that the prefrontal cortex plays a key role in attention-deficit hyperactivity disorder (ADHD). The catechol-O-methyltransferase (COMT) enzyme degrades synaptic catecholamines and plays a specific role in the catabolism of prefrontal cortex dopamine. We investigated the association between the COMT valine (Val) 108/158 methionine (Met) polymorphism and the response to treatment with methylphenidate (MPH) in children with ADHD. This study included 124 children with ADHD in South Korea. Those patients who had an improvement after 8 weeks of treatment greater than or equal to 50% compared with the baseline ADHD rating scale scores before treatment were considered to be the ‘good response’ group. After performing genotyping for COMT, we examined the correlation of the COMT polymorphism with response to treatment with MPH using the $\chi^2$ test. We found that whereas 62.5% of the patients showing a good response to MPH treatment had the Val/Val genotype, 41.7 and 11.7% of the patients showing a poor response to MPH treatment as assessed by their teachers had the Val/Met and Met/Met genotypes ($\chi^2 = 6.58, \text{d.f.} = 2, P = 0.035$). Our findings provide evidence of an association between the COMT genotype and MPH response as assessed by the teachers of children with ADHD. Int Clin Psychopharmacol 23:291–298 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Introduction

Many neurobiological theories of attention-deficit hyperactivity disorder (ADHD) have postulated that the prefrontal cortex (PFC) plays a primary role in this disorder through such impairments as a deficit in PFC inhibition, resulting in deficits in the four executive functions: nonverbal working memory, internalization of speech (verbal working memory), self-regulation of affect, and reconstitution (Barkley, 1997). As one of the bases of the neurodevelopmental theories of ADHD, Sonuga-Barke (2003) and Sagvolden \textit{et al}. (2005) postulated deficits in the dopaminergic PFC-subcortical systems, including the mesocortical, mesolimbic, and nigro-striatal circuits. Seamans and Yang (2004) reviewed the principles of the dopamine functional mechanisms at the PFC, and identified the key features of dopamine modulation of the PFC neurons in patients with ADHD. These include a distinct bell-shaped dose–response profile of postsynaptic effects, and biphasic bidirectional modulation of the N-methyl-D-aspartate receptors by D1 stimulation, with implications for the cellular aspects of working memory. In contrast, data obtained from striatal neurons suggest that dopamine acts via D1 receptors to depolarize \(\gamma\)-amino-butyric acid interneurons directly, yet acts presynaptically via D2 receptors to inhibit \(\gamma\)-amino-butyric acid release onto the dorsal and ventral spiny output neurons.

The catechol-O-methyltransferase (COMT) enzyme degrades synaptic catecholamines and plays a specific role in the catabolism of PFC dopamine, because of the relative lack of dopamine transporters in the PFC (Napolitano \textit{et al}. , 1995; Weinshilboum \textit{et al}. , 1999; Moron \textit{et al}. , 2002). The COMT gene resides on the q11 region of chromosome 22 (Grossman \textit{et al}. , 1995; Lachman \textit{et al}. , 1999). Individuals can be homozygous for the Met or Val alleles, or they can possess one of each allele. The Met allele results in a four-fold decrease in enzymatic activity relative to the Val allele, resulting in functional significance increases in PFC catecholamine activity (Lotta \textit{et al}. , 1995; Lachman \textit{et al}. , 1996). There have been no reports of the COMT gene in the genome-wide scan on the COMT region, even though interest in the genome-wide scan for the COMT region...
has been increasing. However, one recent report (Xing et al., 2007) identified cis-acting influences on the gene expression level. The researchers then performed a genome-wide linkage scan for trans-acting regulators across the genome conditional on the cis-acting effect at chromosome 22q11 (Xing et al., 2007).

Despite some early suggestive findings (Eisenberg et al., 1999), most studies that have investigated the possible association between COMT genes and ADHD have subsequently yielded negative etiological findings, despite the apparent role of COMT in the dopamine metabolism of the PFC (Faraone et al., 2005). As reviewed by Faraone et al. (2005), there have been seven family-based association studies, which have evaluated the Val/ Met polymorphisms in ADHD. Five of these found no significant association (Barr et al., 1999; Hawi et al., 2000; Manor et al., 2000; Tahir et al., 2000; Payton et al., 2001), whereas the other two studies reported significant associations, although the authors of one of these studies subsequently corrected their report to show less over-transmission of the Val allele than originally reported (Eisenberg et al., 1999), and the other study, which involved Han Chinese, was significant only when limited to male cases (Qian et al., 2003). Accordingly, the cumulative analyses showed no evidence of a significant association between ADHD and COMT genes. In terms of there being an association between the PFC and COMT, however, it has been hypothesized that ADHD patients with the more active Val/Val genotype would have fewer available synaptic catecholamine neurotransmitters and concomitant worse performance on neuro-psychological measures of executive functioning (Castellanos and Tannock, 2002). One study conducted in normal adults found decreased performance at baseline on the Wisconsin Card Sorting Task and greater degrees of improvement with amphetamine in individuals with the more active allele (Martay et al., 2003). In normal individuals who have Val/Val COMT polymorphisms (and lower basal dopamine levels), the administration of psychostimulants such as methylphenidate (MPH) increases the dopamine levels and this allows for increased prefrontal cortical efficiency (Seamans and Yang, 2004).

Recently, many studies have investigated the possible association between polymorphisms in the dopamine candidate genes involved in ADHD and the response to psychostimulant treatment (McGough, 2005). The most frequently performed pharmacogenomic studies in ADHD have, however, concerned the dopamine transporter gene 10-repeat polymorphism (Winsberg and Comings, 1999; Roman et al., 2002; Kirley et al., 2003; Cheon et al., 2005). Pharmacogenomic studies regarding other dopamine candidate genes, including dopamine receptors and COMT, were limited by their small sample sizes and/or inconsistent research design, although our earlier study recently showed a significant association between the four-repeat allele of the dopamine D4 receptor gene and the response to MPH treatment in children with ADHD (Cheon et al., 2007).

The main aim of this study was to evaluate the association between the COMT and the treatment response to MPH in children with ADHD reported by both their parents and teachers. It was hypothesized that the Val/Val COMT polymorphisms would be associated with a good response to treatment with MPH in ADHD, because those patients with the Val/Val genotype would have a more efficient prefrontal cortical activation response.

**Materials and methods**

**Patients**

This study included 124 children with ADHD (8.6 ± 1.8 years), consisting of 106 boys and 18 girls, who were recruited over 3 years from a child psychiatric clinic in Myong-Ji Hospital affiliated with Kwandong University College of Medicine in South Korea. All children were assessed through an interview with the parent and, for children aged 6 years and older, a direct interview was carried out after interviewing the parent. All patients originated from one generation.

The children selected for the ADHD group were those: (i) who were diagnosed as having ADHD through the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997), which was conducted by a board-certificated child psychiatrist; (ii) who were aged 6–12 years; (iii) whose parents/guardians agreed to participate in the study, with the provision of informed consent before inclusion; (iv) who had never been exposed to psychostimulants such as MPH. We excluded those children: (i) who had a past history or were currently suffering from brain damage or convulsive disorder; (ii) who were mentally handicapped (IQ score lower than 70) or had autistic-spectrum disorder, language difficulties, or developmental problems including learning disability; (iii) who or whose parents/guardians did not agree to the study. This study was approved by the Institutional Review Boards for Human Subjects at the Myong-Ji Hospital affiliated with Kwandong University College of Medicine in Seoul Korea.

**Diagnostic and evaluation tool of clinical symptoms**

(1) K-SADS-PL (Kaufman et al., 1997): K-SADS-PL was the tool used for the diagnosis of ADHD in this study. This is a semistructured interview tool designed to evaluate the severities of ADHD symptoms and to evaluate the current state and affected state throughout the lifetime of 32 different psychiatric disorders included in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV using objective diagnostic criteria. The validity and
reliability of K-SADS-PL were proven by its developer. The Korean version of K-SADS-PL was translated by Kim et al. (2004) and its validity and reliability for the evaluation of ADHD, tic disorder, and oppositional defiant disorder were established earlier.

(2) ARS-IV: composed of a total of 18 items, ARS is the ADHD symptom severity scale designed by DuPaul et al. (1998) according to the DSM-IV Diagnostic Criteria of Mental Disorders. Each item has a 4-point scale ranging from 0 to 3. The 18 items are composed of nine items reflecting the symptoms related to inattention and nine items reflecting the symptoms related to hyperactivity and impulsivity. Either parents or teachers can complete the scale for the ADHD child and both scales have the same items. The Korean version of ARS was standardized by So et al. (2002).

Protocol
All of the ADHD patients were administered MPH for 8 weeks. The dosages were increased up to a dose that was sufficient to achieve the therapeutic effect, based on the parents’ reports of symptom improvement and side effects. These dosage levels were maintained for 8 weeks. The ARS scores were assessed by both parents and teachers who evaluated ADHD symptoms in both the home situation and classroom setting before and after the 8-week course of treatment with MPH, to assess the improvement in the ADHD symptoms.

A clinical response to treatment with MPH was defined as a decrease of at least 50% in mean basal scores of the ARS, suggesting robust improvement (Roman et al., 2002; Cheon et al., 2005, 2007). After 8 weeks of treatment, an improvement in the ARS score of greater than or equal to 50% compared with the baseline ARS score before the treatment was considered a ‘good response’, whereas an improvement of less than 50% was considered a ‘poor response’. All of the procedures were performed by medical staff blinded to the results of the COMT genotyping.

Preparation of genomic DNA
Genomic DNA was extracted from blood lymphocytes using a Genomic DNA Extraction kit (Bioneer, Korea).

Catechol-O-methyltransferase genotype determination
Polymerase chain reactions of the COMT polymorphism (Val158Met) were performed using the primers and conditions described by Norton et al. (2002). Twenty-four nanograms of genomic DNA were amplified with 1.4 pmol of each primer: forward, 5′ ACT GTG GCT ACT CAG TGT G 3′ and reverse, 5′ CCT TTT TCC AGG TCT GAC AA 3′, 1X Qiagen buffer (Perkin Elmer Life Science Products, Boston, MA, USA), 1.5 mmol/l magnesium chloride, 100 mmol/l each dNTP, 1 unit Qiagen taq polymerase, in a final volume of 12 ml, for one cycle of 94°C for 3 min, 40 cycles of 94°C for 30 s and 578°C for 30 s, and finally one cycle of 728°C for 5 min. Two units of the restriction enzyme Nla III, 0.2 ml 100 × BSA, 2 ml 10 × NEB3 buffer, and 5.6 ml water were added to the PCR product to give a final volume of 20 ml. The PCR product was digested overnight at 378°C to give fragment sizes of 114 base pairs (allele 1, Val) and 105 base pairs (allele 2, Met). The digested PCR product was electrophoresed on 2% metaphor agarose, 1% agarose.

The Val 108/158 Met polymorphism was genotyped by single nucleotide primer extension using a template-directed dye terminator incorporation assay with fluorescence polarization detection based on AcyloPrime reagents (Perkin Elmer Life Science Products, Boston, Massachusetts, USA) according to the manufacturer’s recommendations.

Statistical analysis
Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 12.0 for Windows (SPSS, Chicago, Illinois, USA). Chi-square analyses were used for the correlation between the COMT Val 108/158 Met polymorphism and the response to treatment with MPH. The patients were divided into three groups according to their genotype (Val/Val, Val/Met, and Met/Met). The significance level accepted was 5% (two-tailed).

Results
Patient characteristics
The patients were 124 children with ADHD (mean age = 8.6 ± 1.8 years) comprising 106 boys (mean age = 8.6 ± 1.9 years) and 18 girls (mean age = 8.6 ± 1.4 years). The average total IQ of the ADHD patients was 106.3 ± 17.1. The average score of the overall symptoms of ADHD according to ARS as measured by the parents and teachers of the ADHD children decreased from 33.18 ± 8.13 and 30.87 ± 8.17 at baseline to 16.34 ± 5.00 and 16.19 ± 4.68, respectively, after 8 weeks of treatment with MPH. Thirty-one per cent (49) of the patients had ADHD-inattentive type, 36.7% (58) had ADHD-combined type, 36.7% (58) had ADHD-hyperactive/impulsive type. In terms of comorbidity, 19.4% (24) of children had mood disorder, 12.1% (15) had anxiety disorder, 5.6% (7) had oppositional defiant disorder, 2.4% (3) had conduct disorder, and 9.7% (12) had tic disorder (Table 1).

We found no significant differences in the average daily dose of MPH among the subjects with the Val/Val, Val/Met, and Met/Met genotypes of COMT (Table 2). We found no significant correlation between the ADHD subtype and response to treatment according to both
parent-rated improvement and teacher-rated improvement (parent: $\chi^2 = 0.927$, d.f. = 2, $P = 0.629$, teacher: $\chi^2 = 3.023$, d.f. = 2, $P = 0.221$). Neither was any significant correlation between the COMT genotype and the ADHD subtype found ($\chi^2 = 6.883$, d.f. = 4, $P = 0.142$).

No significant correlation between the comorbidity and response to treatment according to both parent-rated improvement and teacher-rated improvement was found (parent: $\chi^2 = 2.59$, d.f. = 1, $P = 0.108$, teacher: $\chi^2 = 1.031$, df = 1, $P = 0.310$). No significant correlation between the comorbidity and the COMT genotype ($\chi^2 = 0.663$, d.f. = 2, $P = 0.718$) was observed.

**Genetic polymorphisms of catechol-O-methyltransferase**

Among the 124 patients, the Val and Met alleles of COMT were identified in 184 (74.2%) and 64 (25.8%) of the 248 chromosomes, respectively. The distribution of the three genotypes for the COMT enzyme was in agreement with the expected values of the Hardy–Weinberg equilibrium (goodness of fit $\chi^2 = 0.014$, d.f. = 1, $P = 0.90$). To perform the quality control of the genotyping method used in this study, we selected 10 samples randomly and reanalyzed them in a blind manner. No discrepancies were found. The Val/Val genotype was observed in 68 ADHD children (54.8%), the Val/Met genotype in 48 (38.7%), and the Met/Met genotype in eight (6.5%) children.

**Correlation between the Val 108/158 Met polymorphism of catechol-O-methyltransferase and the response to treatment with methylphenidate**

We found no significant differences in the demographic characteristics, clinical characteristics, or the average daily dosage of MPH between the ADHD patients with the Val/Val, Val/Met, and Met/Met genotypes at COMT (Table 2). We found that whereas 54.2% (39 of 72) of the patients who showed a good response to treatment with MPH had the Val/Val genotype, 40.4% (21 of 52) and 3.8% (two of 52) of the patients who showed a poor response to treatment with MPH according to ARS assessed by their parents had the Val/Met and Met/Met genotypes at COMT, respectively ($\chi^2 = 1.02$, d.f. = 2, $P = 0.60$) (Table 3). In contrast, we found that whereas 62.5% (40/64) of the patients who showed a good response to treatment with MPH had the Val/Val genotype, 41.7% (25/60) and 11.7% (7/60) of the patients who showed a poor response to treatment with MPH according to ARS assessed by their teachers had the...
Val/Met and Met/Met genotypes at COMT, respectively ($\chi^2 = 6.58$, d.f. = 2, $P = 0.035$) (Table 4) (Fig. 1).

Follow-up between-group comparisons revealed a significant difference for Met/Met genotype frequency between treatment responder and nonresponder groups ($\chi^2 = 5.238$, d.f. = 1, $P = 0.029$). Only a trend-level significance of difference for Val/Val genotype frequency, however, between the good responder and poor responder groups ($\chi^2 = 3.135$, d.f. = 1, $P = 0.077$) was observed. If the Bonferroni correction were applied with the genotypes and treatment response groups, the $\alpha$-threshold would be 0.017 ($= 0.05/3$), and none of the above results would be statistically significant.

### Discussion

This study showed the existence of a significant association between the COMT Val 108/158 Met polymorphism and the response of Korean children with ADHD to treatment with MPH in a school setting as assessed by their teachers. In particular, the Val/Val genotype of COMT was significantly associated with a good response to treatment with MPH for the children with ADHD in a school setting according to the ADHD rating scale as assessed by their teachers. No significant association, however, was found between the genotype of COMT and the response to treatment with MPH according to the ARS assessed by their parents. These findings demonstrate that the COMT polymorphism might modulate the response of ADHD patients to treatment with psychostimulants in structured settings such as the classroom.

### Table 3  Correlation between COMT genotype and response of the ADHD children to treatment with methylphenidate according to the ARS, as assessed by their parents*$^a$

<table>
<thead>
<tr>
<th>COMT genotype</th>
<th>Poor (≤ 50%)</th>
<th>Good (≥ 50%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val/Val</td>
<td>29 (55.8%)</td>
<td>39 (54.2%)</td>
<td>68 (54.8)</td>
</tr>
<tr>
<td>Val/Met</td>
<td>21 (40.4%)</td>
<td>27 (37.5%)</td>
<td>48 (38.7)</td>
</tr>
<tr>
<td>Met/Met</td>
<td>2 (3.8%)</td>
<td>6 (8.3%)</td>
<td>8 (6.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>52 (41.9%)</td>
<td>72 (58.1%)</td>
<td>124</td>
</tr>
</tbody>
</table>

ADHD, attention deficit hyperactivity disorder; ARS, ADHD rating scale; COMT, catechol-O-methyltransferase; Met, methionine; MPH, methylphenidate; Val, valine.

*$^a$The $\chi^2$ test was used for correlation. Pearson $\chi^2 = 6.579$, d.f. = 2, $P = 0.035$ ($P < 0.05$) (by Fisher’s exact test), odds ratio = 1.905.

### Table 4  Correlation between COMT genotype and response of the ADHD children to treatment with methylphenidate according to the ARS, as assessed by their teachers*$^a$

<table>
<thead>
<tr>
<th>COMT genotype</th>
<th>Poor (≤ 50%)</th>
<th>Good (≥ 50%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val/Val</td>
<td>28 (46.7%)</td>
<td>40 (62.5%)</td>
<td>68 (54.8)</td>
</tr>
<tr>
<td>Val/Met</td>
<td>25 (41.7%)</td>
<td>23 (35.9%)</td>
<td>48 (38.7)</td>
</tr>
<tr>
<td>Met/Met</td>
<td>7 (11.7%)</td>
<td>1 (1.6%)</td>
<td>8 (6.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>60 (48.4%)</td>
<td>64 (51.6%)</td>
<td>124</td>
</tr>
</tbody>
</table>

ADHD, attention deficit hyperactivity disorder; ARS, ADHD rating scale; COMT, catechol-O-methyltransferase; Met, methionine; MPH, methylphenidate; Val, valine.

*$^a$The $\chi^2$ test was used for correlation. Pearson $\chi^2 = 6.579$, d.f. = 2, $P = 0.035$ ($P < 0.05$) (by Fisher’s exact test), odds ratio = 1.905.
Converging evidence that ADHD symptoms arise from the dysregulation of the PFC/striatal and cerebellar circuits (Arnsten and Castellanos, 2002) has been observed. The PFC uses working memory to guide behavior and attention, inhibiting inappropriate responses and sustaining attention over long delays, particularly under conditions of interference from distractors (Goldman-Rakic, 1996; Robbins, 1996). Deficits in PFC function lead to poor impulse control, distractibility, hyperactivity, forgetfulness, and poor organization and planning (Stuss and Knight, 2002). It is generally agreed that ADHD involves weakened PFC function (Barkley et al., 1992) and there has been speculation that MPH might strengthen PFC abilities as assessed. Consistent with this view, imaging studies have shown that MPH produces more efficient PFC function in both ADHD patients (Vaidya et al., 1998) and control patients (Mehta et al., 2000).

Recently, Arnsten and Dudley (2005) reported that the administration of low, oral doses of MPH to rats had effects on PFC executive function, such as working memory via the stimulation of the dopamine D1 receptor of the PFC, similar to those seen in humans and patients with ADHD. Therefore, in terms of the role of the COMT Val 108/158 Met polymorphism in PFC catecholamine activity, it was assumed that it might be useful to investigate the possible association between the COMT genotype and MPH response. A correlation between the Val/Val COMT genotype, which induces a lower basal dopamine level in the PFC, and a good response to MPH via an increase in the PFC efficiency, was found in normal participants in a study performed by Seamans and Yang (2004). Bilder et al. (2004) suggested that the COMT polymorphism was related to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. They also proposed the following: (i) The Val allele associated with high-activity COMT increases phasic and reduces tonic dopamine transmission in the subcortical region and decreases dopamine concentrations in the cortical region. This leads to an increase in D2 and a decrease in D1 transmission; as a result, there is decreased stability of the neural networks underlying working memory representations, including the maintenance of executive functions, but there is also facilitation of the switching or transition to alternate network states mediating the resetting of working memory traces and flexibility in behavioral programs (state 1). (ii) The Met allele associated with low-activity COMT decreases phasic and increases tonic dopamine transmission in the subcortical region, and increases dopamine concentrations in the cortical region: this is associated with increased D1 and decreased D2 transmission in the PFC. This increases the stability of the networks mediating sustained working memory representations, but makes it more difficult to switch or update the currently active networks that represent sustained working memory representations or ongoing behavioral programs (state 2). In terms of the pharmacogenomic predictions of the COMT polymorphism in ADHD, the Val allele (lower D1 activity in the PFC) would be expected to respond to a psychostimulant medication that increases extrasynaptic dopamine, and hence D1 stimulation, and allows increased working memory capacity, whereas the Met allele (higher D1 activity in the PFC) would result in narrowed or stereotypic cognitive activity. From the viewpoint of the relation between the COMT polymorphism and the psychostimulant response in ADHD, our finding that the Val/Val genotype was associated with a good response to treatment of ADHD children with MPH in a classroom setting as assessed by their teachers corresponds with these assumptions.

When evaluating and diagnosing children with ADHD, it is very important to use rating scales that are assessed by both parents and teachers. In particular, teacher ratings can often confirm parent-based assessments and are very useful in terms of evaluating the executive function in a more structured setting, such as classroom behavior, academic performance, and peer relationships. Tripp et al. (2006) reported that teacher ratings generally outperformed parent ratings when considering sensitivity, specificity, and overall classification accuracy, and are important to take into consideration when confirming and disconfirming diagnoses. Recently, one study demonstrated that there was a significant effect of MPH on listening comprehension for information passages, and on verbal and visual–spatial working memory skills, with significant dose–response relationships being evident for both domains (McInnes et al., 2007). These findings provide preliminary evidence that MPH affects higher-level language comprehension skills, which require sustained attention and mental effort. If they can be generalized to classroom listening skills, these findings have implications for the teachers involved with assessing treatment response in children with ADHD.

This study has a number of limitations that should be addressed in future studies. First, in assessing the treatment response to MPH, we did not use an objective assessment tool or neuropsychological test for evaluating executive function. Unfortunately, these procedures are subject to informant bias and are often technically inadequate (Stoner et al., 1994). Second, we did not control for the two types of MPH product (we used both immediate-release MPH and extended-release MPH), which were administered to children with ADHD. Actually, the response to treatment with MPH can differ because of the difference of the pharmacokinetic profile and drug compliance or adherence depending on which type of MPH is used. In addition, unfortunately, we cannot rule out the possibility that lack of adherence occurred to some extent in several samples and induced
poor MPH response in the patients involved, because MPH was administered with no control of drug adherence by the investigators. Third, our research design does not allow the exclusion of different placebo responses between the groups, because it is not a randomized placebo-controlled trial. Fourth, we could not find any statistically significant association between the COMT genotype and MPH response after multiple correction. We postulated that our sample might have been too small to detect a significant effect of the COMT polymorphism on the MPH response of the children with ADHD assessed by their teachers. Finally, these findings with the COMT gene might just reflect genetic stratification in our study groups. It has been argued that the high false-positive rates often seen in many candidate genetic association studies are likely a result of the low a priori probability that the polymorphism under investigation is causally related to study outcome (Risch, 2000). Therefore, in future studies, we need to genotype more single nucleotide polymorphisms around three genotypes of COMT (Val/Val, Val/Met, and Met/Met) and it requires significantly larger samples than earlier reported.

This study is the first ADHD pharmacogenomic study to investigate the possible association between the COMT genotype, which plays a key role in the PFC, and the treatment response as assessed by both parents and teachers. In the future, it will be necessary to replicate our results using a superior observational tool in larger samples and also to evaluate different neurotransmitter system genes involving PFC function in ADHD.

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