

Association of the Catechol O-Methyltransferase Val158-Met Polymorphism and Reduced Interference Control in Korean Children with Attention-Deficit Hyperactivity Disorder

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Objective We tested for association of the catechol-O-methyltransferase (COMT) Val¹⁵⁸-Met (rs4680) polymorphism with attention-deficit hyperactivity disorder (ADHD) using family-based test in Korean trios.

Methods A total of 181 subjects with ADHD along with both of their biological parents were recruited from University Hospitals in Korea. We performed a transmission disequilibrium test (TDT) on 181 trios.

Results In the TDT, we found the over-transmission of the Val allele in children with ADHD ($\chi^2=4.21$, $p=0.040$).

Conclusion These results suggest that the COMT Val158-Met polymorphism is associated with ADHD among the Korean population. However, this study must be replicated in larger populations.

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Key Words Attention-deficit hyperactivity disorder, COMT.

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a common disorder that has about 4–10% prevalence rate among elementary school children¹ and has an estimated heritability of approximately 80%.² Dysregulation of the central dopaminergic and noradrenergic systems is known to be involved in pathophysiology of ADHD.³ Catechol-O-methyltransferase (COMT) degrades synaptic dopamine and noradrenaline and plays a specific role in the catabolism of prefrontal cortical dopamine.⁴ The COMT gene has a functional polymorphism at codon 158 that results in a single amino acid change [methionine (Met) for valine (Val)]. The enzyme activities are high-

est in Val/Val homozygotes and lowest in Met/Met homozygotes.⁵ Due to its important role in the prefrontal dopamine and norepinephrine neurotransmission, COMT is considered as an essential candidate gene for the etiology of ADHD.

To date, studies on the association between the COMT Val¹⁵⁸-Met polymorphism and ADHD reported conflicting findings.⁶ Various races/ethnicities of the analysis population and different designs for genetic associations across studies have potential for conflicting results. For example, the COMT Val¹⁵⁸-Met polymorphism was found significantly associated with ADHD, with the over-transmission of Met allele in a family-based association study carried out in 166 German children.⁷ In contrast, other family-based association study carried out in 48 Jewish children claimed an association in completely the opposite direction (over-transmission of Val allele in ADHD probands).⁸ In a Korean study, there was no difference in COMT allele frequencies between 60 patient group recruited from Cheonan City and Jeonju and 100 control group recruited from Pyungtaek City, although there was a significant difference of COMT genotype frequencies (lower frequencies of Met/Met genotype and Val/Val genotype in

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Table 1. Allelic transmission calculated by extended transmission disequilibrium test for COMT Val¹⁵⁸-Met polymorphism (number of trios=181)

Markers	Minor allele	Major allele	T:NT	$\chi^2/df=1$	p	RR
rs1191454	Met	Val	73:100	4.21	0.040	0.73

NT: not-transmitted minor allele count, RR: relative risk, T: transmitted minor allele count

ADHD children).⁹ This study is limited by small sample size of ADHD population and non-matching for geographic region between the patient and control populations that might cause the problem of population stratification.^{10,11}

The transmission disequilibrium test (TDT) is a commonly used method for controlling for confounding due to unaccounted population admixture in genetic association studies.^{11,12} TDT avoids the problem of population stratification by using un-transmitted alleles as internal controls for transmitted alleles from heterozygous parents to affected offspring. Therefore, in this study, we investigated the association between the COMT Val¹⁵⁸-Met genotype and ADHD through the TDT, in a larger Korean population than the previous study.⁹

METHODS

Subjects

Subjects with ADHD and both biological parents were recruited from child psychiatric clinics in Korea. In order to confirm ADHD diagnoses and any comorbid disorders, all subjects were administered the Korean Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version.¹³ Exclusion criteria included the following: 1) a history of pervasive developmental disorder, mental retardation, bipolar disorder, psychotic disorder, obsessive compulsive disorder, or Tourette's syndrome; 2) a history of neurological disorder; 3) an intelligence quotient (IQ) below 70; and 4) the presence of learning disabilities or language disorders. We provided detailed information about the study to the parents and children and then obtained written informed consent before any child entered the study. The study protocol was approved by the institutional review board of the Seoul National University Hospital.

COMT genotyping

Genomic DNA was extracted from blood (stored frozen) using a G-DEX

TM II Genomic DNA Extraction Kit (Intron, Korea) according to the manufacturer's protocol. SNP detection was based on an analysis of primer extension products generated from previously amplified genomic DNA using a chip-based MALDI-TOF mass spectrometry platform (Sequenom, Inc., CA, USA). The general procedures were performed according to the manufacturer's standard protocol. The oligonucleotide

primers (5'-ACG TTG GAT GTT TTC CAG GTC TGA CAA CGG and 5'-ACG TTG GAT GAC CCA GCG GAT GGT GGA TTT) were used to generate polymerase chain reaction (PCR) products.

Statistical analysis

A family-based study was performed to assess the genetic association using transmission disequilibrium test (TDT) statistics. The '--perm' option was used to generate a single-point empirical p value (EMP1) to correct for the non-normal trait distribution using the adaptive permutation approach. The criterion for significance was set at an EMP1 of <0.05. Hardy-Weinberg equilibrium (HWE) and Mendelian errors were examined using the PLINK options '--hwe' and '--me'. Data handling and management were performed by R packages under the LINUX environment. Given the number and the structure of our ADHD families, we used the program Genetic Power Calculator¹⁴ to calculate power at the alpha level of 0.05.

RESULTS

A total of 181 children with ADHD (mean age=8.92±2.61 years, 152 boys and 29 girls) participated in this study. The combined type was the most common in our sample (59.7%), followed by the predominantly inattentive (27.1%) type. The ADHD, predominantly hyperactive-impulsive type and the ADHD, not otherwise specified (NOS) type were identified in 5.0% and 8.3% of the sample, respectively. The most common comorbidity was oppositional defiant disorder (14.4%), followed by anxiety disorder (7.7%), tic disorder (4.4%), and depressive disorder (3.9%), respectively.

The frequencies of Met (minor) allele and Val (major) allele were 0.301 and 0.691 for ADHD patients and 0.300 and 0.700 for their parents. The SNP passed the HWE test ($p \leq 1e-06$) and all of the family data were free from Mendelian errors. The TDT analysis of the COMT Val¹⁵⁸-Met polymorphism showed the biased transmission of the Val allele ($\chi^2=4.21$, $p=0.040$) (Table 1). This biased transmission of the Val allele was statistically significantly associated with adaptive permutations (EMP1=0.041).

DISCUSSION

In this study, we found preliminary evidence of the over-

transmission of the Val allele at the COMT Val¹⁵⁸-Met polymorphism in Korean children with ADHD. Although the results of pooled analysis of 18 studies investigating the association between the COMT Val/Met polymorphism and ADHD did not support an association between the COMT Val¹⁵⁸-Met polymorphism and ADHD (pooled OR=1.02, 95% CI 0.92–1.13, $p=0.727$), biochemical, animal, pharmacological, and neuroimaging studies indicate the involvement of the COMT gene in ADHD.⁶ Over-transmission of the high enzyme activity allele (Val) in children with ADHD is plausible because of its involvement in catecholamine metabolism and prefrontal dopamine-lowering effect.^{4,5}

Inconsistent with a previous Korean study that had reported no relationship between ADHD and the COMT gene,⁹ we found the over-transmission of Val allele in ADHD patients. Previous study used case-control association analyses and we used family-based association analyses. In the analysis of 93 investigations where both unrelated case-control and family-based design had been employed, Evangelou et al.¹⁵ concluded that unrelated case-control and family-based designs give overall similar estimates of association. Although population-based association studies are generally regarded as more statistically powerful than family-based studies,¹⁶ the much smaller sample size in previous study (60 ADHD patients) may mask a real association. Assuming the prevalence of 0.05, a Val allele frequency of 70%, and according to Eisenberg et al.,⁸ a genotypic relative risk of 0.97 and 1.86 for the Val/Met-genotype and the Val/Val genotype, respectively, the 181 families used in this study have a power of 80% to detect an association at the alpha level of 0.05. In contrast, the 60 cases and 100 controls used in previous study have a power of 47% to detect an association at the alpha level of 0.05. In addition, there is the possibility that population stratification, one problem with the case-control design,^{10,11} affected the negative results of previous study. However, we cannot completely rule out the possibility that inconsistent results between previous study and our study may be due to type I error of this family-based association study.

In conclusion, the results of this study suggest that the COMT Val¹⁵⁸-Met polymorphism is associated with ADHD in the family-based association study among the Korean ADHD population. However, we genotyped only one specific SNP of COMT, and this may have been insufficient to fully address the association between this gene and ADHD. The study must be replicated in a case-control association study

and with using more SNPs.

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