

Family-Based Association Study of the Serotonin Transporter Gene Polymorphisms in Korean ADHD Trios

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The dopamine (DA) system has been implicated in attention deficit hyperactivity disorder (ADHD) based on pharmacologic evidence. Because of an interaction between the serotonin (5-HT) and DA systems, the serotonin transporter gene (*SLC6A4*) has been considered as a candidate ADHD susceptibility gene. Two common polymorphisms, 5-HTTLPR and the intron 2 VNTR, have been studied for association in ADHD, with both positive (increased frequency of long allele of 5-HTTLPR and decreased frequency of 12 repeats of the intron 2 VNTR) and negative findings. However, there has not been an association study in an East Asian ADHD population. In this study, we examined the genotypes of these two polymorphisms in 126 Korean ADHD families and investigated linkage disequilibrium (LD) between *SLC6A4* and ADHD, using the transmission disequilibrium test (TDT) and haplotype analysis. Additionally, association with quantitative measures of inattention, hyperactivity-impulsivity, and overall severity was tested using logistic regression and QTDT analysis. TDT of both polymorphisms and haplotype analysis failed to detect LD. However, after excluding ADHD NOS subtype, TDT revealed nominally significant LD between 5-HTTLPR and ADHD ($\chi^2=4.9$, $P=0.036$). QTDT revealed positive association between 12 repeats of the intron 2 VNTR and attention ($P=0.031$), but case-control and TDT logistic regression analyses were negative. These markers have low

heterozygosity in the Korean population, which would be expected to reduce the power of association. This result suggests that future studies should include more polymorphic markers and subjects to thoroughly investigate a potential association between *SLC6A4* and ADHD in the Korean population. © 2005 Wiley-Liss, Inc.

KEY WORDS: ADHD; serotonin transporter gene; polymorphisms; TDT; association

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common childhood-onset psychiatric disorder characterized by persistent pattern of inattention and/or hyperactive and impulsive behavior, with prevalence rate of 3%–9% in the US school-aged children and 2%–7.6% in the Korean school-aged children [Cho and Shin, 1994; Kim and Chae, 1998; Kim et al., 1999; Todd, 2000b; Pyo et al., 2001]. Although the etiology of ADHD is not well understood, evidence from the family, twin, and adoption studies suggests that ADHD is familial and highly heritable with an estimated heritability from 0.6 to 0.9 [Thapar et al., 1999; Todd, 2000a]. ADHD is likely to be a complex genetic disorder involving multiple genes of small to moderate effect [Smalley, 1997].

SLC6A4 has been proposed as a susceptibility gene in ADHD and has been investigated in several association studies, with both positive and negative reports. There are several positive studies showing the long allele of the 5-HTTLPR imparts risk for ADHD [Manor et al., 2001; Seeger et al., 2001; Zoroglu et al., 2002; Beitchman et al., 2003], while significant excess of the short (s) allele and the s/s genotype was reported in violent individuals with a childhood history of ADHD-related symptomatology [Retz et al., 2004]. Interestingly, Cadoret et al. [2003] observed differential interaction between the 5-HTTLPR and externalizing behavior in a subgroup of adoptees from the Iowa Adoption cohorts, depending on their biological parentage and gender, which may explain conflicting transmission results. One study also found that the genotype 12/12 of intron 2 VNTR was significantly less frequent in the subjects with ADHD compared to control subjects [Zoroglu et al., 2002]. There are also negative association studies for both the 5-HTTLPR and the intron 2 VNTR [Johann et al., 2003; Langley et al., 2003], although Kent et al. [2002] found a small but significant association between the 5-HTTLPR and ADHD (combined

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odds ratio = 1.33, 95% CI = 1.06–1.66, $P = 0.01$) by pooling data from three recent studies.

Until now, the majority of the association studies have been conducted in European subjects and there has not been an association study for *SLC6A4* in an East Asian ADHD population. In present study, 126 ADHD families were genotyped for both the 5-HTTLPR and the intron 2 VNTR in order to examine association between *SLC6A4* and ADHD. The transmission disequilibrium test (TDT) and haplotype analyses were carried out to detect transmission disequilibrium. Additionally, we carried out two more analyses to examine the association with quantitative measures of inattention, hyperactivity-impulsivity, and overall severity using logistic regression [Waldman et al., 1999] and QTDT [Abecasis et al., 2000]. The secondary aim of this study was to describe distribution of genotypes and allele frequencies of these two polymorphisms in the Korean children with ADHD.

MATERIALS AND METHODS

Subject

Consecutive subjects consenting to participate in a family-based association study for ADHD, and their biological parents, were studied between September 2000 and August 2002 at four, university-based, child psychiatry outpatient clinics (Seoul, Anyang, and Jinju) in South Korea. Included in the study were children between the ages of 6 and 12, with a full-scale IQ above 70, who met DSM-IV diagnostic criteria on the Diagnostic Interview Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime—Korean Version (K-SADS-PL-K). Individuals with neurological disorders, tic disorder, seizure disorder, pervasive developmental disorder, bipolar mood disorder, and psychotic disorder were excluded. The study protocol was approved by the Institutional Review Board at the Hallym University Sacred Heart Hospital (Anyang, South Korea).

Genotyping

DNA was extracted from whole blood using the PureGene DNA isolation procedure (Gentra Systems, Minneapolis, MN). PCR for 5-HTTLPR was carried out in a 10 μ l volume containing 50 ng of genomic template, 0.5 μ M of each primer, 200 μ M of each dNTP, 1 \times PCR buffer, 1.5 mM $MgCl_2$, and 0.3 U of DyNAzyme™ EXT DNA polymerase (Finnzymes Oy, Espoo, Finland), with 0.5 M GC-melt (Clontech, Palo Alto, CA). For the intron 2 VNTR, 0.25 U of HotStar Taq DNA polymerase (Qiagen, Valencia, CA) was used instead of DyNAzyme™ EXT DNA polymerase and 0.5 M GC-melt. Primer sequences were as follows: For 5-HTTLPR, 5'-FAM-CTGAATGCCAGCACCTAACCCCTAATGT-3' and 5'-GGGGAATACTGGTAGGGTGCAAGGAGAA-3'. For the intron 2 VNTR, primer sequences were 5'-HEX-TGGATTTCTCTCTCAGTGATTGG-3' and 5'-TCATGTTCTAGTCTTACGCCAGTG-3'. Post PCR products were injected and detected by laser-induced fluorescence on an ABI PRISM 3700 Genetic Analyzer at the University of Chicago DNA Sequencing and Genotyping Core. Electropherograms were processed and alleles called with Genotyper software (version 3.7 NT) (Applied Biosystems, Foster City, CA), blind to all but a number, which is consecutively assigned and is not related to the subject whether the subject is a child, father or mother and without any indication of pedigree relationship to adjacent numbers.

Statistical Analysis

Hardy–Weinberg equilibrium (HWE) was calculated with PEDSTATS [Wigginton et al., 2005]. Descriptive statistics were used to examine clinical characteristics, distribution of

genotypes, and allele frequencies in Korean children with ADHD. Sib_tdt test was used for TDT (ASPEX, version 2.2), and TDTPHASE [Dudbridge et al., 2000] was used for the haplotype analysis. The odds ratio (OR) was calculated using the method of Lohmueller et al. [2003]. This method treats the number of transmissions of each allele as the number of occurrences of that allele in cases. We assumed hypothetical control group that is very large population (10,000) with equal numbers of each allele (to reflect the expected 50:50 transmission ratio). For the quantitative analysis, symptom severity was computed from each ADHD item in K-SADS-PL-K. Each item was scored as 2 for threshold symptoms, 1 for sub-threshold symptoms, and 0 for no symptom. Inattention severity was computed from the summing of 9 items (2 from screening module and 7 from supplement module) and hyperactivity-impulsivity from 12 items (2 from screening module and 10 from supplement module). The associations between those genotypes and the quantitative measures were tested using logistic regression. This method is similar to that described in Waldman et al. [1999]. The quantitative traits were the independent variables and the dependent variable was either the genotype an individual carried (case-control) or the allele that was transmitted from a heterozygous parent (TDT). Sex and age were entered as covariates. Additionally, quantitative transmission disequilibrium test (QTDT) was performed to examine the association between the genotypes and the ADHD subscale severity scores. QTDT incorporates variance components methodology in the analysis of family data and includes exact estimation of P -values for analysis of small samples and non-normal data [Abecasis et al., 2000]. Sex and age were entered as covariates. For the alleles of which P -value was significant in QTDT, empirical significance levels were provided.

RESULTS

One hundred twenty-six children with ADHD were ascertained by K-SADS-PL-K. The reliability and validity of K-SADS-PL-K have been examined previously, which suggested K-SADS-PL-K is an effective instrument for diagnosing major child psychiatric disorders, including ADHD, behavioral disorders, and tic disorders in Korean children [Kim et al., 2004b]. Among 126 families, 19 trios did not have complete genotyping, because one or two of family members did not complete blood collection (1 family with missing proband, 15 families with 1 missing parent, 3 families with 2 missing parents). When clinical characteristics (gender, age, IQ-total, verbal, and performance, ADHD subtype, etc.) were compared between completely genotyped trios ($n = 107$) and incompletely genotyped trios ($n = 19$), no significant difference was found. 110 probands were boys (87.3%) and 16 probands were girls (12.7%). Mean age of the probands was 8.3 years (± 1.8 years) and the mean IQ was 104 (± 16). The ADHD subtypes included inattentive type 27.8% ($n = 35$), hyperactive-impulsive type 7.9% ($n = 10$), combined type 28.6% ($n = 36$), and NOS 35.7% ($n = 45$). Comorbidity in the study subjects was low. The only comorbid conditions observed were depressive disorders ($n = 6$) and anxiety disorders ($n = 4$). Interestingly, comorbidity with oppositional defiant disorder (ODD) or conduct disorder (CD) was not observed in this study population, probably due to very strict inclusion/exclusion criteria and/or it could be a population-specific finding. Detailed description of the characteristics of study subjects is discussed elsewhere [Kim et al., 2004c].

5-HTTLPR and the intron 2 VNTR were genotyped in all available subjects. Three trios were incompatible for the 5-HTTLPR and one trio for the intron 2 VNTR. Dropping these trios from further analysis resulted in 104 completed trios for the 5-HTTLPR and 106 trios for the intron 2 VNTR.

TABLE I. The Genotype Frequencies of 5-HTTLPR and VNTR for Present Study Populations, Compared With Findings From Previous Studies

Polymorphisms	Study	Types of population	No. of subjects	Allele frequency		Genotype frequency		
				S	L	S/S	S/L	L/L
5-HTTLPR	Present study (Korean)	Total	125	183 (73.2)	67 (26.8)	66 (52.8)	51 (40.8)	8 (6.4)
		(1) ADHD-I ^a	35	51 (72.9)	19 (27.1)	17 (48.6)	17 (48.6)	1 (2.9)
		(2) ADHD-HI ^b	9	11 (61.1)	7 (38.9)	3 (33.3)	5 (55.6)	1 (11.1)
		(3) ADH nD-C ^c	36	49 (68.1)	23 (31.9)	18 (50.0)	13 (36.1)	5 (13.9)
	(4) ADHD-NOS ^d	45	72 (80.0)	18 (20.0)	28 (62.2)	16 (35.6)	1 (2.2)	
	Pae et al. [2003] (Korean)	Normal control	208	336 (80.8)	80 (19.2)	139 (66.8)	58 (27.9)	11 (5.3)
Kim et al. [2000] (Korean)	Normal control	252	377 (74.9)	127 (25.1)	137 (54.4)	103 (40.9)	12 (4.8)	
Kim et al. [2004a] (Korean)	Normal control	211	332 (78.7)	90 (21.3)	130 (61.6)	72 (34.1)	9 (4.3)	
VNTR				10	12	10/10	10/12	12/12
	Present study (Korean)	Total	125	24 (9.6)	226 (90.4)	0 (0.0)	24 (19.2)	101 (80.8)
		(1) ADHD-I ^a	35	7 (10.0)	63 (90.0)	0 (0.0)	7 (20.0)	28 (80.0)
		(2) ADHD-HI ^b	9	3 (16.7)	15 (83.3)	0 (0.0)	3 (33.3)	6 (66.7)
		(3) ADHD-C ^c	36	8 (11.1)	64 (88.9)	0 (0.0)	8 (22.2)	28 (77.8)
	(4) ADHD-NOS ^d	45	6 (6.7)	84 (93.3)	0 (0.0)	6 (13.3)	39 (86.7)	
	Kim et al. [2000] (Korean)	Normal control	252	48 (9.6)	456 (90.4)	4 (1.6)	40 (15.9)	208 (82.5)

^aADHD-inattentive type.^bADHD-hyperactive impulsive type (original number of probands was 10, but genotype was not obtained from one proband).^cADHD-combined type.^dADHD-not otherwise specified.

5-HTTLPR was slightly deviated from HWE. The P -value of HWE among all genotyped individuals was 0.0851 and P -value among founders was 0.0629, with an excess of 340 homozygotes.

The genotype frequencies of the 5-HTTLPR and the intron 2 VNTR in the study population were presented in Table I. The allele frequencies were comparable to the previous reports from Korean populations [Kim et al., 2000, 2004a; Pae et al., 2003] without significant statistical difference (5-HTTLPR allele frequencies: $\chi^2 = 2.60$, $df = 1$, $P = 0.11$; Intron 2 VNTR allele frequencies: $\chi^2 = 0.001$, $df = 1$, $P = 0.97$). The frequencies of the alleles and genotypes did not differ among ADHD subtype groups excluding ADHD NOS subtype (5-HTTLPR allele frequencies: $\chi^2 = 2.70$, $df = 2$, $P = 0.60$; Intron 2 VNTR allele frequencies: $\chi^2 = 0.64$, $df = 2$, $P = 0.73$).

TDT for both polymorphisms and haplotype analysis failed to detect transmission disequilibrium. However, the long allele of 5-HTTLPR appeared more frequently transmitted than the short allele. The OR of the long allele (transmitted vs. not-transmitted) was 1.4 with 95% confidence interval (CI) of 0.9-2.2 (P -value for OR = 0.09), although it was not nominally significant (Table II). The haplotype consisting of the short allele of 5-HTTLPR and 12 repeats of the intron 2 VNTR (S-12) had a trend for less frequent transmission than expected

(OR = 0.7, 95% CI = 0.5–1.0, P -value for OR = 0.06), while there was a trend for the haplotype of the long allele of 5-HTTLPR and 12 repeats of the intron 2 VNTR (L-12) appeared more commonly transmitted than expected (OR = 1.6, 95% CI = 1.0–2.5, P -value for OR = 0.06) (Table II). Subtype specific TDT was not performed in this study, because of small sample sizes of each subtype. However, we performed TDT after excluding ADHD NOS subtype and presented this data in Table II together with the original TDT/Haplotype results.

Case-control and TDT logistic regression revealed no association with the quantitative measures of inattention, hyperactivity-impulsivity, or severity. However, QTDT analysis revealed positive association between 12 repeats of the intron 2 VNTR and attention. QTDT analysis excluding ADHD NOS was negative (Table III).

There was weak but statistically significant linkage disequilibrium between the 5-HTTLPR and the intron 2 VNTR in our study population ($D' = 0.39$, $P < 0.000017$, $r^2 = 0.045$).

DISCUSSION

To our knowledge, this is the first association study of *SLC6A4* and ADHD in East Asian population (China, Japan, or Korea). In this study, we examined LD between *SLC6A4* and

TABLE II. 5-HTTLPR, the Intron 2 VNTR, and Haplotype TDTs With and Without ADHD NOS Subtype

Allele or haplotype	ADHD pooled together			ADHD without ADHD NOS subtype		
	Transmitted	Not-transmitted	P -value	Transmitted	Not-transmitted	P -value
5-HTTLPR						
S	36	52	0.11	21	38	0.036
L	52	36		38	21	
VNTR						
10	17	14	0.72	14	7	0.2
12	14	17		7	14	
Haplotype			Global $P = 0.2$			Global $P = 0.07$
S-10	8	5	0.14	7	4	0.4
S-12	40	59	0.056	23	44	0.010
L-10	9	9	1.00	7	3	0.2
L-12	44	28	0.06	32	18	0.049

TABLE III. QTDT Analysis of the Quantitative Measures of ADHD Symptoms Subscales and 5-HTTLPR and Intron 2 VNTR Polymorphisms Individual Alleles

Tested allele	Inattention severity		Hyperactive-impulsive severity	
	F	P-value	F	P-value
5-HTTLPR				
Long	-0.167	0.667	2.254	0.132
Intron 2 VNTR				
12 repeats	-2.54	0.047*	1.839	0.288

*Bonferroni significance level: $P = 0.0918$.
QTDT, quantitative transmission disequilibrium test.

ADHD using TDT and haplotype analysis. We also examined association between *SLC6A4* and the quantitative traits of our study population. The TDT is less powerful than case-control studies, but the TDT is robust to population stratification. Many of the positive findings of association between 5-HTTLPR and ADHD have come from case-control studies [Seeger et al., 2001; Retz et al., 2002; Zoroglu et al., 2002; Beitchman et al., 2003].

In this study, we performed TDT with and without excluding ADHD NOS subtype, because ADHD NOS subtype may contain more heterogeneous population than other subtype. TDT without excluding ADHD NOS subtype failed to reveal LD between *SLC6A4* and ADHD. However, TDT with excluding ADHD NOS subtype revealed nominally significant association between 5-HTTLPR and ADHD. Because of small sample size in each subtype, we did not perform subtype-specific TDT, although this would increase homogeneity of the sample. Haplotype analysis with excluding ADHD NOS subtype revealed similar but somewhat stronger trend than haplotype analysis without excluding ADHD NOS subtype.

The genotype distribution and allele frequencies of both polymorphisms in this sample are similar to previous reports from normal control population in Korea, which may support that there was no significant sampling bias in this study. Not surprisingly, however, they are markedly different from non-Asian populations. Specifically, heterozygosity was lower in our study population compared to European populations [Manor et al., 2001; Seeger et al., 2001]. Since, the TDT counts transmissions from only heterozygous parents [Spielman et al., 1993], markers with low heterozygosity have low power to detect linkage disequilibrium.

Based on previous studies that reported the long allele of the 5-HTTLPR [Manor et al., 2001; Seeger et al., 2001; Zoroglu et al., 2002] and the 10 repeats of the intron 2 VNTR as risk alleles of ADHD susceptibility [Manor et al., 2001; Seeger et al., 2001; Zoroglu et al., 2002], we calculated the power of this study. In our analysis, our sample had ~80% power to detect an OR of 1.8 for the long allele of the 5-HTTLPR at $P < 0.05$. For the 10 repeats of the intron 2 VNTR, our sample had ~80% power to detect an OR of 2.4 at $P < 0.05$. Other studies have found ORs of 1.23–1.46 [Kent et al., 2002], thus our study was underpowered to find a similar genetic effect.

It was also noted that the long allele of 5-HTTLPR was more frequently transmitted than the short allele, and was nominally significant in the analysis excluding ADHD NOS. This finding may support previous studies [Manor et al., 2001; Seeger et al., 2001; Kent et al., 2002], however, this should be interpreted very carefully because of these two possibilities: (1) the Korean population is genetically different from non-Asian population. Therefore, it is possible that the susceptibility allele may be in linkage disequilibrium with either short or long allele of 5-HTTLPR depending on ethnicity and

(2) there are different allelic variants of 5-HTTLPR based on sequencing data [Nakamura et al., 2000]. However, these allelic variants are not identified through conventional genotyping procedures used to type the 5-HTTLPR. So it is also possible that some of these untyped allelic variants of the 5-HTTLPR may impart ADHD risk or be in linkage disequilibrium with susceptibility gene(s).

Interestingly, QTDT also revealed a positive association of 12 repeats of the intron 2 VNTR and attention. This may support the findings from Zoroglu et al. [2002]. We also performed QTDT excluding ADHD NOS to reduce heterogeneity. However this was negative possibly due to reduced power resulting from the smaller sample number. In any case, the positive association between 12 repeats of the intron 2 VNTR and attention needs careful interpretation, given negative results from both TDT and logistic regression analysis and the possibility of a false positive due to multiple comparisons.

The distribution of the allele frequencies of 5-HTTLPR deviated slightly from HWE, although it was not statistically significant. Deviation from HWE may suggest possibilities of genotyping error, assortative mating, population admixture, selection at the locus, genotypic association with the disease or chance. In case-control studies, HWE is often used to test for genotyping errors, since there is no way to systematically identify genotyping errors. On the other hand, in family-based studies, incompatible genotypes are more apparent. In this study, we found three incompatible trios for 5-HTTLPR, which were potentially consistent with non-paternity. We confirmed the incompatibility by redoing genotyping with independent PCR. Moreover, we felt confident that this HWE finding was more likely false positive rather than suggestive of genotyping errors, since (1) the genotyping process was carried out blind to clinical data, (2) genotyping error rates in our lab has been consistently low from our previous experiments with the same marker and other samples have not deviated from HWE [Cook et al., 1997; Kim et al., 2002], (3) In this sample, we genotyped four markers in the same study population, but only one marker was slightly deviated from HWE. Therefore, we need to consider the possibility of a false positive due to multiple comparisons.

Finally, we must consider *SLC6A4* may not be a susceptibility gene in the Korean ADHD population. However, it would be very difficult to determine this, since we only examined the 5-HTTLPR and VNTR in this study. Numerous polymorphisms in *SLC6A4* are reportedly in linkage disequilibrium with the 5-HTTLPR and the intron 2 VNTR [Kim et al., 2002]. Of note, there are many other polymorphisms in *SLC6A4* that may also influence function, although these have not been extensively investigated [Nakamura et al., 2000; Kim et al., 2002]. There are also many different allelic variants of 5-HTTLPR [Nakamura et al., 2000]. In order to thoroughly investigate this gene, it would be necessary to fully type the allelic variants of 5-HTTLPR not previously typed in 5-HTTLPR association studies and type variants in *SLC6A4* that could be more powerful due to higher polymorphism and possibly being in tighter linkage disequilibrium with a putative susceptibility variant within the gene than the variants that have been analyzed in this study. Since susceptibility genes for ADHD are likely to have a small effect size, large sample sizes may also be needed for adequate power.

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