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Association Between Polymorphisms in Serotonin Transporter Gene and Attention Deficit Hyperactivity Disorder in Chinese Han Subjects

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Prior work has shown reduced serotonin transmission to be associated with impulsivity and behavioral problems. The current study assessed the association between ADHD and two variants of the serotonin transporter gene: the 44-bp deletion/insertion polymorphism (5-HTTLPR) and the 17 bp-repeat polymorphism in intron 2 (STin2.VNTR). We hypothesized that ADHD phenotypes associated with impulsivity would show an association with these variants. Two-hundred and ninety-three ADHD trios were genotyped and analyzed using transmission disequilibrium test (TDT) analysis and haplotype analysis. We found no association between the STin2.VNTR and ADHD, but did find preferential transmission of the S allele of the 5-HTTLPR polymorphism ($\chi^2 = 5.751$, $P = 0.016$) to probands with ADHD. Haplotype analysis found the L/10 haplotype was over-transmitted ($\chi^2 = 6.172$, $P = 0.013$), while L/12 was under-transmitted to probands with ADHD ($\chi^2 = 4.866$, $P = 0.027$). © 2006 Wiley-Liss, Inc.

KEY WORDS: genetics; ADHD; serotonin transporter; 5-HTT; polymorphism; linkage disequilibrium; haplotype

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INTRODUCTION

Attention deficit-hyperactivity disorder (ADHD) is a common behavioral disorder of inattention, hyperactivity, and impulsivity that affects between 4% and 7.4% of school-age children in China [Hu, 1998] and 3%∼6% of of school-aged children around the world [Faraone et al., 2003]. Although it is specific etiology has yet to be discerned, family, twin and adoption studies show ADHD to have a strong genetic component [Faraone and Doyle, 2001; Faraone et al., 2005].

Although much prior ADHD research has focused on dopaminergic and noradrenergic brain systems [Faraone and Biederman, 1998], the serotonergic system has also been implicated in the pathophysiology of the disorder. This shift in research focus has resulted from the work of Gainetdinov et al. [1999] on the role of serotonin in the paradoxical calming effect of psychostimulants on the hyperactivity of the dopamine transporter gene knockout mouse. Serotonin has been shown to influence a variety of behaviors relevant to ADHD, including impulsivity, aggression, disinhibition, and attention [LeMarquand et al., 1998; Lucki, 1998]. Platelet 5-HT content, being considered to reflect aspects of presynaptic reuptake, was lower in hyperactive school age boys [Rapoport et al., 1974], and was different between severe and mild ADHD [Spivak et al., 1999]. The number of ^{3}H-imipramine binding sites, an index of presynaptic 5-HTT activity, was decreased in children with mixed conduct disorder and ADHD [Stoff et al., 1987].

Recent research has focused on the 5-HT transporter (5-HTT) because of its pivotal role in the fine-tuning of 5-HT neurotransmission. The 5-HTT gene is located at 17q11.2, and three common polymorphisms have been studied in ADHD: (1) a 44 bp insertion/deletion in the promoter region (5-HTTLPR), resulting in a long (L) and a short (S) allele, (2) a 17 bp VNTR in intron 2 (STin2.VNTR), resulting in 9, 10, and 12 repeat variants in Caucasians, and (3) a 3′ untranslated region G/T SNP. A genomewide scan found modest evidence of linkage (LOD = 0.95) between ADHD and the 17q region harboring 5-HTT gene [Fisher et al., 2002]. Four studies suggested the L allele of the 5-HTTLPR polymorphism is risk factors for ADHD. Zoroglu et al. [2002] reported that S/S genotype was significantly lower and L/L and L/S genotype were predominant in ADHD patients compared with controls. Seeger et al. [2001] also reported an over-expression of the L/L genotype in hyperkinetic disorder with and without conduct disorder. Moreover, Manor et al. [2001] reported a significant decrease of the S/S genotype in ADHD patients having the combined subtype. Kent et al. [2002] described a trend of preferential transmission of the L allele in ADHD families. In contrast to these positive results, a multivariate linear regression analysis did not find an association between 5-HTTLPR and ADHD [Comings et al., 2000]. Langley et al. [2003] also failed to replicate the positive results in a case-control study and a family-based study.

For the STin2.VNTR polymorphism, Zoroglu et al. [2002] found the 12/12 genotype was less expressed in ADHD patients than controls, but Langley et al. [2003] did not. Research on the 3′ UTR SNP found that the T allele was preferentially transmitted to ADHD offspring [Kent et al., 2002]. By using

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haplotype analysis, Kent et al. [2002] found significant preferential transmission of haplotypes L/10/T to ADHD probands. In contrast, Langley and colleagues were not able to conclude that haplotypes composed of the 5-HTTLPR and STin2.VNTR polymorphisms were related to ADHD.

In summary, prior studies provided evidence for the involvement of 5-HTT gene in ADHD, especially those examining the 5-HTTLPR polymorphism in Caucasian samples. The frequencies of the S and L alleles are approximately 72% and 28% among Chinese [Chong et al., 2000], compared with 40% and 60% respectively among Caucasian samples [Kent et al., 2002]. Therefore, we hypothesized that 5-HTT gene may be involved in the pathogenesis of ADHD; but, that it may play a different role in Han Chinese compared with Caucasian samples. The aim of the current study was to further assess the relationship between both of the 5-HTTLPR and STin2.VNTR polymorphisms and ADHD as well as individual DSM-IV ADHD subtypes in a large Han Chinese sample.

MATERIALS AND METHODS

Subjects

Two hundred and ninety-three unrelated complete trios, composed of ADHD probands and both biological parents were recruited from the child psychiatric clinics at Peking University Institute of Mental Health from September 1999 to December 2002. Affected children were diagnosed by experienced clinicians according to the diagnostic and statistical manual of mental disorders (DSM-IV) [American Psychiatric Association, 1994] criteria for ADHD. Children were excluded if they showed evidence of bipolar affective disorder, childhood schizophrenia, autism, mental retardation, or other neurological or complex medical illnesses. All non-Han families were excluded. All subjects agreed to participate and parents signed informed consent. Both the informed consent and research protocol were reviewed and approved by the Ethics Committee of the Institute of Mental Health, Peking University (6th affiliated Hospital of Peking University).

Diagnostic and Assessment Instruments

Diagnoses of ADHD and subtypes of ADHD were based on the American Clinical Diagnostic Interview Scales (CDIS) [Barkley, 1998], a structured interview derived from the DSM-IV. The CDIS assesses many behavioral and emotional disorders of childhood, including ADHD, conduct disorders (CD), emotional disorders, affective disorder, tics, and learning disabilities (LD). The CDIS was translated into Chinese by bilingual member of our group. This rating scale has shown a high degree of sensitivity (97.2%) and specificity (100%). The test–retest reliability was 0.89. The inter-rater reliability Kappa coefficient was 0.74 ($P < 0.01$). The CDIS allows for the diagnosis of DSM-IV subtypes of ADHD, including ADHD inattentive type (ADHD-I), ADHD hyperactive-impulsive type (ADHD-HI) and ADHD combined type (ADHD-C). Two psychiatrists, one of whom was of senior status, interviewed all parents separately. Additionally, teachers completed Rutter's Scale to evaluate the children's behaviors at school. Based upon data collected from the CDIS, parent interviews and teacher reports, consensus diagnoses were assigned to all probands. Of the 293 ADHD trios, 120 (41.0%) probands met criteria for ADHD-C, 19 (6.5%) met criteria for ADHD-HI and 154 (52.5%) met criteria for ADHD-I. The age of the probands ranged from 6 to 17 years, with a mean age of 10.3 ± 2.5 years. The gender composition of the sample included 242 (82.6%) male probands and 51 (17.4%) female probands. Within the total sample, 223 (76.1%) probands met diagnostic criteria for other disorders: 38.6% had comorbid oppositional defiant disorder (ODD) and/or conduct disorder (CD), 9.6% had an emotional disorder, 17.4% had a tic disorder, 9.6% had an affective disorder, 8.5% had obsessive–compulsive disorder (OCD), and 36.9% had a learning disability (LD).

The intelligence quotient (IQ) was estimated using the Chinese-Wechsler Intelligence Scale for Children (C-WISC, standardized by Gong Yaoxian). The full scale IQ ranged from 72 to 142 (mean = 100.2, SD= 13.7). Other supplementary assessment instruments included the Achenbach Child Behavior Checklist (CBCL), the Rutter Child Behavior Questionnaires, Conner's Parent and Teacher Rating Scales, and a child mental health scale.

Laboratory Procedures

5-HTTLPR polymorphism typing. The venous blood samples were refrigerated at 4°C in EDTA-test tubes. Genomic DNA was extracted using standard method within 2 weeks. Forward primer 5′-GGC GTT GCC GCT CTG AAT TGC-3′ and reverse primer 5′-GAG GGA CTG AGC TGG ACA ACC AC-3′ were used to generate 484 bp and 528 bp fragments of 5-HTTLPR polymorphism. A 25-μl reaction was performed according to the protocol previously described [Collier et al., 1996] on a PE-9700 or a PE-2400 thermal cycle (Perkin Elmer, USA). After initial denaturation at 95°C for 4 min, 35 cycles were carried out at 96°C for 45 sec, 61°C for 90 sec, and 72°C for 90 sec, followed by a final step of elongation at 72°C for 10 min, then the PCR products were run out on a 2% agarose gel stained with ethidium bromide for 3 hr. They were then analyzed with Gel Doc 2000 imaging system to detect and record the genotype of each sample. The L variant represented the fragment of 528 bp and the S allele represented the fragment of 488 bp. Genotypes were read by at least two researchers, ambiguous or unidentifiable results were reamplified and re-scored. Samples that continued to amplify poorly were eliminated from the study.

STin2.VNTR typing. Forward primer 5′-GTC AGT ATC AAC AGG CTG CGA G-3′ and reverse primer 5′-TGT TCC TAG TCT TAC GCC AGT G-3′ were used to generate 300 bp and 267 bp fragments of STin2.VNTR polymorphism. A 25-μl reaction was performed according to the protocol previously described [Lesch et al., 1994]. After initial denaturation at 95°C for 4 min, 35 cycles were carried out at 96°C for 45 sec, 58°C for 90 sec, and 72°C for 90 sec, followed by a final step of elongation at 72°C for 10 min, then the PCR products were run out on a 2% agarose gel stained with ethidium bromide for 3 hr. The 12-repeat variant represented the fragment of 300 bp and the 10-repeat variant represented the fragment of 267 bp.

Statistical Methods

The transmission disequilibrium test (TDT) [Spielman et al., 1993] was performed to explore the possible linkage and association of the two polymorphisms with ADHD. In addition, we also performed haplotype analysis by using the TRANSMIT program [version 2.5; Clayton, 1999].

RESULTS

Parental allele and genotype frequencies of the two polymorphisms of the 5-HTT gene are listed in Table I. We also compared them with those reported in other studies of Han Chinese [Chong et al., 2000; Li et al., 2002] and European-American Caucasian samples [Bellivier et al., 1998]. The allele and genotype frequencies described in the current study were consistent with other Chinese research, but were significantly

TABLE I. Parental Allele and Genotype Frequencies of Serotonin Transporter Gene Polymorphisms in the Current and Previous Study

	5-HTTLPR					Stin2.VNTR					
	L	S	L/L	L/S	S/S	12	10	9	12/12	12/10	10/10	9/others
Current study	269 (0.24)	847 (0.76)	34 (0.06)	201 (0.36)	323 (0.58)	1079 (0.92)	93 (0.08)	0	494 (0.84)	91 (0.16)	1 (0.0002)	0
Chinese normal controls from prior studies	58 (0.28)	148 (0.72)	13 (0.13)	32 (0.31)	58 (0.56)	209 (0.91)	21 (0.09)	0	95 (0.82)	19 (0.17)	1 (0.01)	0
Caucasian normal controls from prior study	116* (0.59)	82* (0.41)	29* (0.29)	58* (0.59)	12* (0.12)	120* (0.63)	70* (0.37)	2* (0.01)	38* (0.40)	43* (0.45)	13* (0.14)	2* (0.02)

Allele and genotype frequencies of 5-HTTLPR in previous study in Chinese are from the reports of Chong et al. [2000] in normal controls.
Allele and genotype frequencies of Stin2.VNTR in previous study in Chinese are from the reports of Li et al. [2002] in normal controls.
Allele and genotype frequencies of two 5-HTT gene polymorphisms in previous study are from the reports of Bellivier et al. [1998] in adult normal controls.
*Allele or genotype frequency was significantly different with that in the current study, P-value < 0.05.

different with research about European-American Caucasians ($P < 0.05$).

Table II shows the TDT analysis for 5-HTTLPR in ADHD and subtypes of ADHD in 279 trios. We found preferential transmission of the S allele to ADHD offspring ($\chi^2 = 5.8$, $P = 0.016$) but analyses of subtypes did not reach statistical significance. Due to the small sample size, we did not do the TDT analysis in ADHD-HI trios. Table III shows the TDT analysis for the STin2.VNTR locus in 293 trios. No significant biased transmission of any allele was observed for ADHD or subtypes of ADHD.

Data from 250 trios were informative for the two locus haplotype analysis (see Table IV). For the diagnosis of ADHD, the global χ^2 test for haplotype transmission was not significant ($\chi^2 = 6.307$, $P = 0.10$). The haplotype analysis was also not significant for ADHD-C offspring ($\chi^2 = 5.8$, $P = 0.12$) and ADHD-I offspring ($\chi^2 = 3.6$, $P = 0.31$). Moreover, the haplotype of L/10 was over-transmitted ($\chi^2 = 6.172$, $P = 0.013$), while the haplotype of L/12 was under-transmitted ($\chi^2 = 4.866$, $P = 0.027$) to probands of ADHD. As for three subtypes of ADHD, under-transmission of haplotype L/12 ($\chi^2 = 4.866$, $P = 0.027$) was found in families with probands of ADHD-C.

DISCUSSION

We found over-transmission of the S allele of 5-HTTLPR in ADHD, with a trend for this to be more pronounced among ADHD-I patients. Results from the present study once again provide evidence for the involvement of 5-HTTLPR in the etiology of ADHD. Our results contrast with reports from the west, most of which described high expression of the L/S or L/L genotype [Seeger et al., 2001; Zoroglu et al., 2002], and low expression of S/S genotype [Manor et al., 2001; Zoroglu et al., 2002] in ADHD by case-control study and over-transmission of the L allele to ADHD probands [Kent et al., 2002] in a family-based study. For the STin2.VNTR locus, we found no biased transmission of any allele for ADHD or subtypes of ADHD.

Differences between studies in the 5-HTTLPR association results may be due to differences in allele frequencies between the Chinese Han and European-American populations. For example, the frequency of the S allele in parents of ADHD children was 0.76 in Chinese and 0.4 in Caucasians [Kent et al., 2002]. In ADHD patients, the frequency of the S allele was 0.79 in Chinese and 0.37 in Caucasians [Kent et al., 2002].

The Han Chinese and Japanese populations are closely related to each other, and the frequencies of alleles and genotypes of 5-HTTLPR in these two populations are similar [Kunugi et al., 1997]. In pharmacogenetic studies examining the relationship between 5-HTTLPR and antidepressant response to fluvoxamine in depressed patients, Smeraldi et al. [1998] reported that Caucasian patients with the S/S genotype had a poorer response to treatment compared with other Caucasian patients. In contrast, Yoshida et al. [2002] found the opposite results in Japanese patients.

In fact, the ethnic differences were common at the genetic study of ADHD. For example, research continues to show that the 7-repeat allele is the most prevalent allele of 48-bp repeat polymorphism in exon III of the DRD4 gene in Caucasians, while is the rarest allele in Chinese. As for its role in ADHD, European-American studies suggested the 7-repeat allele was a risk factor for ADHD [Swanson et al., 1998; Faraone et al., 1999], but this has not been seen in Chinese samples [Zhang et al., 2001; Qian et al., 2003].

Lesch et al. [1996] reported that the S variant of 5-HTTLPR reduced the transcriptional efficiency of the 5-HTT gene promoter and the L/L genotype differed from L/S and S/S genotypes by having 40% more 5-HTT binding sites in transformed lymphoblastoid cells. Based on the work of Lesch

TABLE II. The Number of 5-HTTLPR Alleles Transmitted or not Transmitted From Heterozygous Parents to ADHD Offspring

Phenotypes	Number of trios	T/NT†	Alleles S	Alleles L	χ^2	*P*-value
ADHD	279	T	118	83	5.751	0.016*
		NT	83	118		
ADHD-C	111	T	46	31	2.545	0.111
		NT	31	46		
ADHD-I	149	T	67	48	2.817	0.093
		NT	48	67		

†T, transmitted; NT, not transmitted.
*P-value < 0.05.

TABLE III. The Number of STin2.VNTR Alleles Transmitted or not Transmitted From Heterozygous Parents to ADHD Offspring

Phenotypes	Number of trios	T/NT*	Alleles 10	Alleles 12	χ^2	*P*
ADHD	293	T	44	47	0.044	0.834
		NT	47	44		
ADHD-C	120	T	18	15	0.121	0.728
		NT	15	18		
ADHD-I	154	T	25	29	0.167	0.683
		NT	29	25		

*T, transmitted; NT, not transmitted.

et al., we postulated that over-transmission of the S allele may result in reduction of 5-HTT binding sites in ADHD. This is consistent with the results reported by Stoff and colleagues' who found a reduction of ^{3}H-imipramine binding sites (an index for 5-HTT binding sites) on platelets from patients having ADHD and co-morbid conduct disorder. Fewer 5-HTT binding sites could result in reduced reuptake of 5-HT, which in turn would lead to increased levels of 5-HT in the synaptic cleft. This supports the idea that excess serotonergic transmission might contribute to the pathogenesis of ADHD.

Although this hypothesis is not consistent with findings associating decreased serotonergic transmission with impulsivity and related behavioral problems, these latter findings are drawn predominantly from studies of adult subjects. Many other studies have described excess serotonergic transmission in ADHD children. For example, CSF 5-HIAA levels were found to be positively related to hyperactivity and aggression in a relatively unaggressive sample of hyperactive prepubertal boys [Castellanos et al., 1994]. A greater proportion of children with ADHD and co-morbid CD or ODD had elevated whole-blood serotonin and children with elevated whole-blood serotonin were more hyperactive, had poorer social skills, and showed more oppositional behavior compared with children without elevated whole-blood serotonin [Cook et al., 1995].

Williams et al. [2003] reported a significant ethnicity X genotype interaction, which indicated the 5HTTLPR S/S genotype was associated with higher CSF 5HIAA levels in African Americans, but with lower levels in Caucasians and proposed opposite direction of linkage disequilibrium between 5-HTTLPR polymorphism and other 5-HTT gene polymorphism between African-Americans and Caucasians to explain opposite effect of 5-HTTLPR. Lesch et al. [1996] work documenting the increased transcriptional efficiency of the L allele has been done only in Caucasian samples, making it

TABLE IV. Results of 1 df Test for Individual Haplotype of the Two Polymorphisms in ADHD and Subtypes of ADHD

Phenotype	Haplotype	Observed	Expected	Var(O-E)	χ^2 (1 df)	*P*-value
ADHD	S/10	21.235	22.926	11.14	0.257	0.612
	L/10	371.77	354.07	50.714	6.1715	0.013*
	S/12	13.765	15.574	7.464	0.438	0.508
	L/12	93.235	107.43	41.39	4.866	0.027*
ADHD-C	S/10	8.669	9.835	4.798	0.286	0.595
	L/10	154.33	146.17	20.463	3.259	0.071
	S/12	7.331	5.665	2.713	1.022	0.312
	L/12	33.669	42.335	16.548	4.539	0.033*
ADHD-I	S/10	11.571	11.428	5.560	0.004	0.952
	L/10	187.43	179.07	27.382	2.551	0.110
	S/12	6.429	9.572	4.632	2.133	0.144
	L/12	54.571	59.928	22.81	1.258	0.262

*P-value < 0.05.

possible that in African-derived populations and other populations, such as Han Chinese population, the S allele could be in linkage disequilibrium with another locus that renders it more, rather than less transcriptionally efficient. So, although the risk allele of 5-HTTLPR for ADHD varied in different ethnic background, the effect of 5-HTTLPR in ADHD maybe the same in different ethnic background.

As for STin2.VNTR polymorphism, neither the current study nor the study conducted by Langley et al. [2003] were able to find biased over-transmission of any allele to ADHD probands or subtypes of ADHD using TDT analysis. However, Zoroglu et al. [2002] using a case-control study design found the frequency of the 12/12 genotype was less, while 12/10 and 10/10 genotype was more in ADHD patients than in controls.

In conclusion, the current study suggests that variants of the serotonin transporter gene may influence susceptibility to ADHD and subtypes of ADHD. The S allele and L/10 haplotype may increase susceptibility, while the L allele and L/12 haplotype may decrease susceptibility to ADHD and subtypes of ADHD. The results were not consistent with other reports, which may be due to ethnic differences between studies; therefore, additional studies with Chinese samples are needed to replicate our findings and other polymorphisms in serotonin transporter gene are also needed to further investigate in ADHD.

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