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The Monoamine Oxidase B Gene Exhibits Significant Association to ADHD

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Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatric condition with strong genetic basis. Recent work in China indicated that ADHD may be linked to Xp1–2 in the Han Chinese population. The gene encoding monoamine oxidase B (MAOB), the main enzyme degrading dopamine in the human brain, is located in this region. The current study sequenced the exons and the 5′ and 3′ flanking regions of the MAOB gene and found four common variants including 2276C>T and 2327C>T in exon 15, rs1799836 in intron 13 and rs1040399 in 3′-UTR. We assessed the association of these variants with ADHD in 548 trios collected from 468 males and 80 females probands. TDT analysis showed that alleles of each polymorphism were preferentially transmitted to probands (rs1799836, $P = 3.28E\text{-}15$; rs1040399, $P = 1.87E\text{-}6$; 2276T>C or 2327T>C, $P = 2.20E\text{-}6$) and haplotype-based TDT analyses also found distorted transmission. In conclusion, this study provides the strongest evidence for the involvement of MAOB gene in the etiology of ADHD to date, at least in Han Chinese population. **© 2007 Wiley-Liss, Inc.**

KEY WORDS: gene; ADHD; X chromosome; sequence; monoamine oxidase B

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatric condition [Faraone et al., 2003]. The genetic contribution is prominent, as indexed by a heritability of 0.75 computed in a review of 20 twin studies [Faraone et al., 2005]. Since ADHD is four to nine times higher in males than in females, it is reasonable to hypothesize that X-linked genes might be involved. Although genome-wide scan studies of ADHD [Bakker et al., 2003; Ogdie et al., 2003; Arcos-Burgos et al., 2004] have not provided significant evidence for linkage to the X-chromosome, these studies may not have had sufficient power to detect genes of small effect. Jiang et al. [2006] used the transmission/disequilibrium test (TDT) to test for linkage and association between VNTR polymorphisms at 48 markers of X-chromosome and DSM-III-R diagnosed ADHD from 84 nuclear families from the Chinese population. The mean genetic distance between consecutive VNTRs was 4.5 cM. The TDT analysis revealed linkage between ADHD and the DXS1214 (Xp21, $P < 0.01$), DXS8102 (Xp11.4-Xp21, $P < 0.05$), DXS1068 (Xp11.4-Xp21, $P < 0.01$) and DXS8015 (Xp11.4-Xp21, $P < 0.05$). These data suggested that susceptibility loci for ADHD might reside at chromosome Xp11.4-Xp21. Monoamine oxidase (MAO), one of the most important enzymes in the metabolism of monoamines, exists as 2 isozymes, A and B, both of which are located at this region (Xp11.23 to Xp22.1). However, results of previous studies focusing on the role of polymorphisms of these two genes in ADHD are not consistent. Most studies revealed a positive association between MAOA gene polymorphisms and ADHD. Payton et al. [2001] analyzed MAOA CA repeats and found a trend for the increased transmission of the 122 bp allele, but in Jiang et al.'s [2000] study, the preferentially transmitted allele was the 114 bp allele. Another common polymorphism is a 30-bp VNTR in the promoter region of MAOA gene. Both Manor et al. [2002] and Lawson et al. [2003] reported an association between this polymorphism and ADHD. DXS7, which is about 1.2 Mb to the two MAO genes, has been studied by two groups. Jiang et al. [2000] reported an association between DXS7 and ADHD, but Lowe et al. [2001] did not replicate the finding. As for the MAOB gene, only two polymorphisms, a GT repeat sequence and rs1799836 have been previously studied and no association with ADHD was found [Jiang et al., 2001; Domschke et al., 2005].

The MAOA and B genes are similar. The deduced amino acid sequences of human liver MAOA and B share 70% identity and the MAOA and B genes have similar genomic structures, both of which comprise 15 exons and are identical in their exon–intron organization [Bach et al., 1988; Hsu et al., 1988]. Despite these differences, these two enzymes have different substrates in the brain: MAOB preferentially metabolizes dopamine, while MAOA preferentially metabolizes serotonin

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and norepinephrine. Each of these three substrates, has been implicated in ADHD, especially dopamine, which has been more extensively studied [Faraone, 2004]. Several sources of evidence implicate dopaminergic dysfunction in ADHD. For example, the psychostimulant drugs that treat ADHD inhibit the activity of the dopamine transporter and increase synaptic levels of dopamine. Moreover, there is substantial neuroimaging evidence for increased dopamine transporter density in the striatum of ADHD patients and structural and functional imaging studies of ADHD patient demonstrate abnormalities in other neuroanatomical areas with rich dopamine innervations [Faraone, 2004].

Early studies found that ADHD patients had low platelet MAO activity (being exclusively MAOB) [Shekim et al., 1982, 1986; Stoff et al., 1989]. We hypothesized that MAOB gene may be associated with ADHD. To testify this hypothesis, the present study was designed to detect new MAOB polymorphisms and to determine if they were associated with ADHD.

TABLE I. Primers Sequences Used in the Sequencing Procedures

Region	PCR primer	Sequence primer
Promoter	F: 5′GGCAATGAGGGTTAGAAGGA G3′	Same as it is PCR primer
−1,644 to −1,084	R: 5′CCCTGTATCTACCTGCTAGAAAG3′	560 bp
Promoter	F: 5′CCAAAGCAGGACAGATGGAAGT3′	Same as it is PCR primer
−1,244 to −683	R: 5′TGGTGGAAGCTGTTGAGGCTAG3′	561 bp
Promoter	F: 5′CCTGCTGCCACTAGTCTCCTG3′	Same as it is PCR primer
−730 to −132	R: 5′CGGAGAGGTCACCTAGGACTTC3′	598 bp
Promoter	F: 5′CCGTGCAGAAGGCTG AGGAGT3′	Same as it is PCR primer
−199 to intron1 +57	R: 5′AGGCAGCCACCTGTCCGAG3′	450 bp
−157 from exon2 to intron2 +154	F: 5′TGGGCCTCTATTGACAAACCGT3′	F′: 5′GTAACAATAGGCGGTGCA3′
	R: 5′GCAAACTGGGAGAGAGGCTGTG3′	R′: 5′AATGTTTCAGAGTTATTTTCACCCT 3′
		−116 from exon2 to intron2 +129, 340 bp
−225 from exon3 to intron3 +153	F: 5′AGCTCTTGCCTATTCAGAGTTCA3′	F′: 5′ ATTGATTTAATAACTAAGTCATGTG 3′
	R: 5′GAGAATGAATCTCAGAGTGGCTG3′	R′: 5′ TTTGCATCATCCAGAGATATAGAAG 3′
		−184 from exon3 to intron3 +110, 432 bp
−152 from exon4 to intron4 +215	F: 5′GGTTCTGAGGACACAAGGAGCTA3′	F′: 5′ TAACTCACATAATTTTGCTTGC 3′
	R: 5′AATCTCCTGCCCACTCATCAG3′	R′: 5′ TCTTATTATTGCAGAGGTT 3′
		−106 from exon4 to intron4 +166, 373 bp
−163 from exon5 to intron5 +167	F: 5′AAGCAATATTGGATGAATTTGGA3′	F′: 5′ GGTAGAGTTTTTAATACTATTTGAA 3′
	R: 5′GATATCTTCAGGGTAGGAGCCA3′	R′: 5′ ATTCCAATGGTTTTCAGC 3′
		−116 from exon5 to intron5 +145, 353 bp
−172 from exon6 to intron6 +133	F: 5′TCAAAAACCTCCGATGTCACG3′	F′: 5′ GATTCTAGTGACAATTTTTTGACCT 3′
	R: 5′TTGAGCTGCCATGGTAATGCT3′	R′: 5′ TTCCCACTTCAGCAGTTCAT 3′
		−138 from exon6 to intron6 +93, 373 bp
−127 from exon7 to intron7 +145	F: 5′AGCCACTATTCACTGCAGCAA3′	F′: 5′ TTTATGCCCATTCCTGCGTTTC 3′
	R: 5′CCCCATCCTGAAGCTACCTAG3′	R′: 5′ GCTGCCAGCCATCAATCA 3′
		−48 from exon7 to intron7 +122, 320 bp
−141 from exon8 to intron8 +144	F: 5′GGGCTACTTTAGGTTTCGACA3′	F′: 5′ AAGAGACTGAAAAGAATATAACGAT 3′
	R: 5′GCATCATGCAACATATCCATGT3′	R′: 5′ ACCCCTGAATCTAAAATAAAAG 3′
		−101 from exon8 to intron8 +105, 366 bp
−142 from exon9 to intron9 +209	F: 5′GTTTGCCTTCATATGTTTGGAG3′	F′: 5′ CTTTATTTGGCCTTTGGGCTTCTCA 3′
	R: 5′TGGTATTCTGCTTCCTACCTAGA3′	R′: 5′ TGGAAGACATTATTTAGAAAAGAAC 3′
		−111 from exon9 to intron9 +175, 383 bp
−265 from exon10 to intron10 +157	F: 5′GGTCAGCCATAGTGTTATCCA3′	F′: 5′TGATTCCTTGAAGTTAGAAAGTGCT 3′
	R: 5′ACACATATAATTAGGCAGTCCGT3′	R′: 5′ GCAGGCAAGTAGGTAGAAAAGAAGG 3′
		−206 from exon10 to intron10 +106, 366 bp
−126 from exon11 to intron11 +246	F: 5′TGAAATGCTGGAGTGGAATCA3′	F′: 5′ TTTCCCTCCCTTCTTTCCT 3′
	R: 5′CAGGGACAATGTAGCATCACCT3′	R′: 5′ GTTCCCTGACCTGCCACC 3′
		−51 from exon11 to intron11 +205, 314 bp
−110 from exon12 to intron12 +241	F: 5′TCCGAAATACATTGGTTTGACA3′	F′: 5′TACAAAGCCTACTAAACTGTTCGAT 3′
	R: 5′TGGTTATATTGATTGGAATTGCT3′	R′: 5′TTCCAGGGAAAAGCAGCACCATGAT 3′
		−87 from exon12 to intron12 +217, 402 bp
−162 from exon13 to intron13 +167	F: 5′ATGTAAGAGCTGGAGGAACCACA3′	F′: 5′ CAAAATTGCCAATGTCCT 3′
	R: 5′CGGGCTAAGGTGTTCACTTCAC3′	R′: 5′ CGGGCTAAGGTGTTCACT 3′
		−127 from exon13 to intron13 +167, 406 bp
−201 from exon14 to intron14 +164	F: 5′GGTAAGCCTAATGATTGGAACCT3′	F′: 5′ CCTCTTAAAGGTTGTATGGAGTGTT 3′
	R: 5′CTCACCTCTACCCTAACCCATGA3′	R′: 5′ CACTTAGGAAAAGGTATGTGAATAT 3′
		−101 from exon14 to intron14 +148, 312 bp
−191 from exon15 to 3′UTR +167	F: 5′GAAAGCCTCCCTGAGGAAGTGA3′	F′: 5′ AAGCAGAGGGAACATCGTG 3′
	R: 5′ACATATGCCACCCATGATGGA3′	R′: 5′ TGTGGGCTTCAGTTTGCT 3′
		−136 from exon15 to +644, 780 bp
		F′: 5′ ATGGCTTTGTGCTTGTTC 3′
		R′: 5′ TCCAGGCTTCAAGGAAAT 3′
		exon15 +487 to 3′UTR +122, 623 bp
From 3′UTR +106 to +620	F: 5′TTCCTTGAAGCCTGGATGATG3′	Same as it is PCR primer
	R: 5′TGCCACTGTAAAATCAGAAACTC3′	514 bp

F, forward primer; R, reverse primer; F′, primer used in forward directional sequencing; R′, primer used in reverse directional sequencing.

METHODS

Subjects

ADHD probands were recruited from the ADHD outpatient clinic at the Child and Adolescent Psychiatry Division of the Sixth Hospital, Peking University in Beijing, PRC. All probands fulfilled DSM-IV diagnostic criteria for ADHD based on interviews by at least two different child psychiatrists with the aid of information from both biological parents and teachers. All the subjects were of Han Chinese descent. Written informed consent was obtained from parents. The study was reviewed and approved by the Ethics Committee of Peking University. Of the 548 ADHD probands, 223 (40.7%) probands met criteria for ADHD combined type (ADHD-C), 30 (5.5%) met criteria for ADHD hyperactive-impulsive type (ADHD-HI) and 295 (53.8%) met criteria for ADHD inattentive type (ADHD-I). The age of the probands ranged from 6 to 17.5 years, with a mean age of 10.0 ± 2.9 years. Within the total sample, 422 (77.0%) probands met diagnostic criteria for other disorders as follows: 287 (52.5%) had comorbid oppositional defiant disorder (ODD) or conduct disorders (CD), 80 (14.6%) had a tic disorder, and 202 (36.9%) had learning disabilities (LD).

Screening of MAOB Gene

The screening sample included 48 biological mothers of male ADHD probands. Forty-eight chromosomes will provide nearly 100% probability of detecting alleles having a population frequency greater than or equal to 10%. The promoter region, 15 exons and exon–intron junctions and partial sequences of 3′UTR were amplified by polymerase chain reaction (PCR) with primers given in Table I. PCR primers were designed on the basis of the MAOB sequence published at www.ensembl.org. Ten-microliter PCR products was purified by the use of Millpore Montage PCR96 Plates (Millipore Corporation, Bedford, MA) and used as template in the sequencing reaction. Sequencing primers used in the forward and reverse directions are also given in Table I. Sequencing reactions comprised 1-μl purified PCR product, 1-μl sequencing primer (1 pM/μl), 2-μl MagaBase DYEnamic ET Dye Terminator (Amersham Biosciences Corporation, Piscataway). PCR thermal cycling condition for sequencing reaction was as following: 25 cycles of 96°C for 20 sec, 53°C for 20 sec and 60°C for 60 sec, and soak at 4°C. When cycling was complete, the sequencing reactions were precipitated using ammonium acetate and ethanol to concentrate the reactions and to purify the products. Sequences were analyzed on an ABI 3730 DNA sequencer (Perkin–Elmer, Norwalk, CT) and then the data were analyzed with DNAstar software.

Genotyping Variants in ADHD Trios

Variants of interest detected in this study were genotyped by restriction fragment length polymorphism (RFLP) in 548 ADHD trios (468 unrelated male ADHD probands and their biological mothers, as well as 80 females ADHD probands and both biological parents). The method for genotyping these variants were given in Table II.

Statistical Methods

Linkage disequilibrium (LD) between variants was estimated by the EH program. The Transmission Disequilibrium Test (TDT) and the extended Transmission Disequilibrium Test (ETDT) [Spielman et al., 1993] were performed to test for distorted transmission of alleles or haplotypes. In TDT analyses, only heterozygous parents are useful. Because MAOB is located on the X chromosome, fathers are hemizygous and not informative so were excluded from the analyses. We used Holm's [1979] sequential Bonferroni procedure to correct for multiple testing.

RESULTS

The genotype distribution and allelic frequencies are presented in Table III. Four variants with >10% heterozygosity rates in biological mothers of ADHD probands were identified. Two of these, A>G in intron13 (rs1799836) and C>T in the 3′UTR (rs1040399), had previously been deposited in the dbSNP database in the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/SNP/). The other two, 2276T>C and 2327T>C in exon15, were new variants. We also detected four new infrequent variants: −113G>A, −1126C>A, −1583C>T and −1648G>A in the promoter region.

The four frequent variants were genotyped in 548 ADHD trios. 2276T>C and 2327T>C were in complete linkage disequilibrium, rs1040399 and 2276T>C/2327T>C were in strong linkage disequilibrium ($D' = 0.89$, $\chi^2 = 648.75$, $P < 0.001$), rs1799836 was in moderate to weak linkage disequilibrium with rs1040399 ($D' = 0.59$, $\chi^2 = 21.58$, $P < 0.001$), and 2276T>C/2327T>C ($D' = 0.38$, $\chi^2 = 12.59$, $P < 0.001$). For each SNP, the allele-based TDT analysis found significantly biased transmitted to ADHD offspring, even when the P value was at 0.00625 after Holm Bonferroni correction (Table IV). Consistent with the allele-based analyses, the haplotype-based TDT analyses found distorted transmission of haplotypes from parents to probands (Table V).

DISCUSSION

We found two novel polymorphisms in the MAOB gene, 2276C>T and 2327C>T, which were in complete linkage disequilibrium with each other. We also found a significant association between MAOB gene alleles and haplotypes and ADHD. Given that dysregulated dopamine metabolism is believed to be part of ADHD's pathophysiology, our data suggested that MAOB maybe a susceptibility gene for ADHD. In fact, early studies found changed level of platelet MAO,

TABLE II. PCR Amplification and Genotyping Methods of MAOB Variants

Variants	Primers(5′-3′)	TA (°C)	PCR product size (bp)	RE	Allele size (bp)
rs1799836	GGA ACCTCTTATACCACAGG GACTGCCAGATTTCATCCTC	54	232	Tsp45I	G(232), A(146,86)
rs1040399	ATGCAGTTCCTTGCCTTCACTAC ATGAAAACTGACGGTGGGAG	59	265	TaqI	T(265), C(242,23)
2276T>C	GAGCCACAATAAGCCACTGGT ATGCATCATCCAGGCTTCAAG	53	472	StyI	T(472), C(408,64)
2327T>C	As above	53	472	Tth111I	T(472), C(355,117)

TA, annealing temperature; RE, restriction enzyme.

TABLE III. Genotypic and Allelic Distribution of MAOB Variants in 48 Parents

Variants	Genotype count (frequency)			Allele count (frequency)	
rs1799836	AA	AG	GG	A	G
	31(0.65)	16(0.33)	1(0.02)	78(0.81)	18(0.19)
rs1040399	CC	CT	TT	C	T
	31(0.65)	14(0.29)	3(0.06)	76(0.79)	20(0.21)
2276T>C	TT	CT	CC	T	C
	29(0.61)	15(0.31)	4(0.08)	73(0.76)	23(0.24)
2327T>C	TT	CT	CC	T	C
	29(0.61)	15(0.31)	4(0.08)	73(0.76)	23(0.24)
−113G>A	GG	GA	AA	G	A
	47(0.98)	1(0.02)	0(0.00)	95(0.99)	1(0.01)
−1126C>A	CC	AC	AA	C	A
	47(0.98)	1(0.02)	0(0.00)	95(0.99)	1(0.01)
−1583C>T	CC	CT	TT	C	T
	45(0.94)	0(0.00)	3(0.06)	90(0.94)	6(0.06)
−1648G>A	GG	AG	AA	G	A
	46(0.96)	2(0.04)	0(0.00)	94(0.96)	2(0.04)

which was exclusively the B-type, in ADHD patients [Shekim et al., 1982, 1986; Stoff et al., 1989]. However, whether platelet MAO activity can reflect central MAOB activity is not clear. A previous study using positron emission tomography indicated that brain and platelet MAOB activity were highly correlated [Bench et al., 1991], even though it was unclear if brain MAOB activity was changed in ADHD patients. Platelet MAOB levels are stable within individuals over time but vary over 50-fold between individuals [Murphy et al., 1976]. Pedersen et al. [1993] reported a heritability of 76% for platelet MAOB activity. Rice et al. [1984] proposed that a single major locus was the main determinant of platelet MAOB activity. Subsequently, the A>G polymorphism in intron 13 (rs1799836) of MAOB was associated with platelet MAOB activity [Garpenstrand et al., 2000]. Balciuniene et al. [2002] reported an association between rs1799836 and brain MAOB activity in 31 British male post-mortem samples, however, the direction of the association was opposite to Garpenstrand et al.'s. The sample size of the above two studies is relatively small, so the true effect of rs1799836 on MAOB activity needs further study, although both of the above two studies reported a role of rs1799836 in MAOB activity.

Researchers postulated that there may be a cis-regulatory element in the MAOB gene in linkage disequilibrium with rs1799836 that alters MAOB activity. However, this hypothesis has not been confirmed. Costa-Mallen et al. [2004] performed a sequencing study in Parkinson's disease and only found the −1114C>T variant with an allelic frequency of 3.5% apart from the rs1799836. In the current study, on the one hand, three SNPs associated with ADHD were in relatively moderate or weak linkage disequilibrium with rs1799836. On the other hand, we found no functional SNPs, for example, rs1040399 occurs in 3'UTR, although 2276T>C/2327T>C is located at exon 15, the position is at the download of termination codon, resulting in no functional change.

TABLE IV. Allele-Based TDT Analyses of 548 Trios

Variants	Phenotype	Alleles	T/NT T	T/NT NT	McNemar χ^2	P
rs1799836	ADHD	A	164	49	62.09	3.28E−15*
		G	49	164		
rs1040399	ADHD	C	97	41	22.72	1.87E−6*
		T	41	97		
2276T>C	ADHD	C	41	95	20.65	2.20E−6*
2327T>C		T	95	41		

T, transmitted; NT, not transmitted.
*$P < 0.05$.

TABLE V. Haplotype-Based TDT Analyses of 548 Trios

Alleles	T/NT T	T/NT NT	McNemar χ^2	P
CCA	19	19	0.00	1.000
TCA	31	59	8.71	0.003*
CTA	199	57	78.77	6.978E−19*
TTA	15	14	0.03	0.862
CCG	6	9	0.60	0.439
TCG	0	23	23.00	1.620E−6*
CTG	42	127	42.75	6.220E−11*
TTG	1	5	2.67	0.102

The haplotype is denoted as "rs1040399-2276T>C- rs1799836."
T, transmitted; NT, not transmitted.
*$P < 0.05$.

Although the role of rs1799836 in MAOB activity is not clear, the strongest association for ADHD we found was for rs1799836, which is discrepant to Domschke et al. [2005] who found an equal number of transmitted and untransmitted alleles in 178 Irish nuclear families for this SNP. Among the probands involved in Domschke's study, 143(80%) met criteria for ICD-10 or DSM-IV ADHD, others had a clinical diagnosis of ADHD but failed to meet the above criteria. So, besides ethnicity, other reasons contributing to the discrepancy between the current study and Domschke's study may include the diagnostic criteria. The only other study examining MAOB studied a GT- repeat polymorphisms in intron2 [Jiang et al., 2001] in a Han Chinese sample. Jiang et al. using a global TDT analysis reported a negative result. However, based on the data published at Jiang's report, a preferential transmission of the six repeat allele ($\chi^2 = 8.73$, $P = 0.003$) can be observed by the use of single allele test. In another study of Jiang et al.'s [2006], at least four VNTR polymorphisms within or near MAOB were reported to be positively associated with ADHD. So, adding the current study and Jiang et al.'s study together, it is reasonable to postulate that MAOB gene polymorphisms may play a role in ADHD, at least in Han Chinese population.

In conclusion, our work has provided two new polymorphisms for the study of MAOB and also suggests these SNPs and others nearby are associated with ADHD. Although it is premature to conclude that rs1799836 is an ADHD susceptibility SNP, given its strong association with ADHD and prior evidence suggesting it is functional, it should be included in future studies.

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