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Adrenergic neurotransmitter system transporter and receptor genes associated with atomoxetine response in attention-deficit hyperactivity disorder children

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Abstract Atomoxetine, a selective inhibitor of the norepinephrine transporter, exerts its therapeutic effect for attention-deficit hyperactivity disorder (ADHD) by increasing the concentration of synaptic norepinephrine. The objective of this study was to evaluate the association of the genetic variants of multiple genes of the noradrenergic neurotransmitter system with atomoxetine response. One hundred and eleven ADHD children and adolescents were enrolled in a prospective, open-label study of atomoxetine for 8–12 weeks. The dose was titrated to 1.2–1.4 mg/kg per day and maintained for at least 4 weeks. The primary efficacy measure was the investigator-rated ADHD Rating Scale-IV. Two categorical evaluations of treatment effects (defined as response and remission) were used. Twelve SNPs in *SLC6A2*, *ADRA2A*, and *ADRA1A* were genotyped to analyze their association with response or remission status. rs3785143 in *SLC6A2* was associated with responder status (nominal $P = 0.0048$; corrected by multiple test, $P = 0.0416$; OR 2.66, 95 % confidence interval (CI) 1.35–5.26). rs2279805 of *SLC6A2* was nominally significantly associated with the remission status. ($P = 0.0221$, OR 2.32, 95 % CI 1.13–4.75, multiple test $P = 0.2130$). The GG haplotype of rs1800544 and rs553668 in *ADRA2A* achieved nominal significance for association with non-remission ($P = 0.0219$, OR 2.82, 95 % CI 1.16–6.85, multiple test, $P = 0.2076$). The results of this study suggest that DNA variants of both *SLC6A2* and *ADRA2A* in the adrenergic neurotransmitter system might alter the response to atomoxetine, though further replication study in larger sample for validation of these findings is still needed.

Keywords Attention-deficit hyperactivity disorder · Atomoxetine · Gene · Adrenergic

Background

Attention-deficit hyperactivity disorder (ADHD) is a common behavior disorder in childhood, affecting 3–6 % of school-going children around the world (Faraone et al. 2003). It is clinically a heterogenous disorder with a complex etiology (Faraone and Mick 2010) that has a substantial impact on the patient's academic performance, occupation, social, and family relations as well as a substantial economic impact (Biederman and Faraone 2005).

The effectiveness of atomoxetine in the treatment of ADHD has been demonstrated among children and adolescents (Michelson et al. 2002; Kelsey et al. 2004). The symptom improvements assessed by parent, teacher, and investigator among atomoxetine-treated patients were superior to the improvement seen after placebo treatment. Mean reductions in the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) total scores were significantly greater for patients randomized to atomoxetine. Both inattentive and hyperactive/impulsive symptom domains were significantly reduced with atomoxetine, compared with placebo. The therapeutic effect

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began at the first week of treatment, and core symptoms continued to decrease throughout 8 weeks. The treatment effect size was estimated to be 0.71 for ADHD children.

Although the efficacy of atomoxetine for ADHD children and adolescents has been confirmed, the effect was not the same in all the patients. The treatment response rate (some defined as 40 % or more reduction from baseline ADHD-RS-IV scores) was only 45 % at the end of the sixth week of atomoxetine treatment (Newcorn et al. 2008). It is possible that this variability in drug response may be influenced by genetic variability.

Ramoz et al. (2009) investigated whether polymorphisms in the *SLC6A2* and *CYP2D6* genes might influence atomoxetine response in two independent cohorts of 160 and 105 ADHD children. The patients were treated with atomoxetine (0.5–1.8 mg/kg per day) for 6 weeks. One hundred and eight single nucleotide polymorphisms in *SLC6A2* and six mutant alleles of *CYP2D6* were genotyped; 20 SNPs of *SLC6A2* were significantly associated with clinical efficacy in atomoxetine responders, compared with non-responders. The genomic regions across exon 1 and exons 4–9 of *SLC6A2* were associated with treatment response in both cohorts.

Atomoxetine is a highly selective inhibitor of the norepinephrine transporter, which may exert its therapeutic effect through change of the norepinephrine concentration in the synapse. Others have suggested that ADHD may be a noradrenergic disorder (Biederman and Spencer 1999). This hypothesis comes, not only from pharmacological evidence, but also from the fact that the noradrenergic system regulates many higher cognitive functions including attention (Solanto 1998). Animal studies revealed that norepinephrine enhanced cognitive function through actions at α2A receptor in the prefrontal cortex (Arnsten et al. 1996). In consideration of above neurobiological evidence, any functional DNA variants in the noradrenergic neurotransmitter system might change the response to atomoxetine in the treatment of ADHD.

We hypothesized that any DNA variants of genes in the noradrenergic system might regulate atomoxetine response in ADHD children. We selected four single nucleotide polymorphisms (SNPs) of *SLC6A2* (rs3785143, rs5569, rs2242447, and rs28386840), three SNPs of *ADRA1A* (rs17426222, rs573514, and rs3808585), and two SNPs of *ADRA2A* (rs1800544 and rs553668), which had been either confirmed or suggested to be associated with ADHD in previous studies (Kim et al. 2008; Retz et al. 2008; Elia et al. 2009; Kiive et al. 2010; Wang et al. 2006; Cho et al. 2011; Sengupta et al. 2012) to analyze their association with multiple assessments of atomoxetine response. As the association of *SLC6A2* gene with ADHD was replicated in several studies, and the coded protein was the target site of atomoxetine as well, we added three SNPs (rs3785152, rs2279805, and rs36009) to increase the coverage of this gene.

Materials and methods

Subjects

Children and adolescents who met the ADHD criteria of the Diagnostic and Statistic Manual of Mental Disorders, fourth edition (DSM-IV) were recruited from the Child and Adolescent Psychiatric Outpatient Department of Peking University Sixth Hospital. The diagnosis was first made by a child psychiatrist, and then validated by a semi-structured interview with the parents and the child, using Barkley's Clinical Diagnostic Interview Scale (Barkley 1998). This scale was based on DSM-IV criteria. It included questions about the 18 items of ADHD symptoms, onset of age, impairment of function, and exclusion criteria. We had used this scale in our previous pharmacogenetic study (Yang et al. 2004). All patients were required to meet the following symptom severity thresholds: The total score of investigator rated ADHD Rating Scale-IV was no less than 25 for boys or 22 for girls, or the subtype corresponding subscale score was equal to or more than 12 (Wang et al. 2007; DuPaul 1998). The subjects were unmedicated, or had been medicated with methylphenidate preparations or atomoxetine, but had stopped for at least 1 or 4 weeks, respectively. All patients and their parents were Han Chinese. The exclusion criteria were (1) allergy to atomoxetine; (2) combined treatment with other psychotropic drugs or non-drug intervention for ADHD; and (3) noncompliant with the blood withdrawal. The study was approved by the Peking University Sixth Hospital Institutional Review Board. Parents signed written informed consent.

Clinical trial

The subjects received open-label treatment with atomoxetine for 8–12 weeks. The dose was titrated from 0.5 mg/kg per day in the first week, 0.8 mg/kg per day in the second week, and to 1.2 mg/kg per day in the third to fourth week. If necessary, the dose could be increased to 1.4 mg/kg per day in the fifth week. Then the last dose was maintained at least for 4 weeks. Those with side effect at any stage of titration could be maintained at the dose for 1–2 weeks. The total course of treatment was no more than 12 weeks. Treatment response was assessed at baseline, and at the end of the first, second, fourth, eighth weeks, or the end of the trial. Medication compliance was assessed by directly asking the parent at every visit. Patients who missed the whole or partial dose for three consecutive days or ten total

days were defined as non-compliant and were withdrawn from the trial.

Treatment response assessment

The primary efficacy measure was the investigator-rated ADHD-RS-IV (DuPaul 1998)]. It was rated based on both parent and teacher reports. The ADHD-RS-IV consists of 18 items corresponding to DSM-IV criteria for ADHD. The total symptom score as well as the inattention and hyperactivity–impulsivity subscales scores were used to evaluate the core symptoms of ADHD. This scale had been translated into Chinese. The validity and reliability of the Chinese version were demonstrated by Su et al. (2006).

In this study, we used a categorical definition of treatment response. Response was defined as at least a 25 % decrease from baseline on the ADHD-RS-IV total score (Dickson et al. 2011; Swanson et al. 2001; Ramoz et al. 2009; Steele et al. 2006). Remission was defined as each ADHD-RS-IV item score ≤ 1 at the end of the treatment (Stein et al. 2003; Steele et al. 2006).

Genotyping

Genomic DNA was extracted from 2 ml peripheral blood using a standard protocol (Omega Bio-tek Inc., Doraville, GA, USA). Twelve SNPs in three candidate genes—*SLC6A2*, *ADRA2A*, and *ADRA1A*—were selected via the ABI SNP browser. Genotyping was performed by Taqman® on the ABI 7900HT Fast Real-time PCR System (Applied Biosystems, Foster City, CA, USA). The PCR reaction was performed following a standard protocol with 5 ng DNA in 5-ml reaction volumes for each sample. Thermal cycle included 95 °C for 10 min, followed by 92 °C 15 s, and 60 °C 1 min for 40–45 cycles. SDS version 2.3 software (Applied Biosystems) was used for genotype identification. For quality control, 1 % of the samples were genotyped as duplicates. Conflicting calls were excluded from the analyses (0.1 %). The call rates ranged from 94 to 100 %. Two to four negative test controls were set in every 384-well plate.

Statistical analysis

The SNPs were tested for Hardy–Weinberg equilibrium using Haploview 4.0. Only one (rs28386840) of the 12 SNPs significantly deviated from HWE ($P < 10^{-5}$), and was excluded from the analysis. The Haploview 4.0 software was also used to generate the linkage disequilibrium (LD) map. The allele and haplotype distribution difference between patients who did or did not meet the criteria for response or remission was analyzed by Haploview 4.0. The level of significance was 0.05 for all analyses. Five thousand permutation tests were used to control multiple comparisons. The odds ratio was calculated as the measure of effect size.

Results

One hundred and eleven subjects completed 8–12 weeks of treatment and provided both baseline and endpoint assessments. The demographic and clinical features at baseline and endpoint of atomoxetine treatment were presented in Table 1.

Using an ADHD-RS score decrease of 25 % or more as the response criterion, 81 patients were responders, and 30 were non-responders. Among the 11 SNPs used in the analysis, rs3785143 in SLC6A2 had a nominally significant association with responder status ($P = 0.0048$, OR 2.66, 95 % CI 1.35–5.26). The significance was maintained after 5,000 permutations performed for multiple test correction ($P = 0.0416$). The T allele was associated with being a non-responder (T: 44.2 vs. C: 22.9 %, Table 1). Using remission criteria, 28 patients achieved remission, and 83 did not. The rs2279805 of SLC6A2 was nominally significantly associated with the status of remission. (C: 29.8 vs. T: 15.5 %, $P = 0.0221$, OR 2.32, 95 % CI 1.13–4.75). However, the significance disappeared after permutation test correction ($P > 0.05$).

There were two LD blocks detected in *ADRA1A* and *ADRA2A*, respectively (Fig. 1). However, no haplotype was associated with responder status ($P > 0.05$). The GG haplotype of Block2 in *ADRA2A* achieved nominal significance for association with non-remission ($P = 0.0219$, OR 2.82, 95 % CI 1.16–6.85), but was not significant after permutation test ($P > 0.05$) (Table 2).

Discussion

One *SLC6A2* SNP, rs3785143, was significantly associated with atomoxetine response in Chinese ADHD children. The T allele was associated with being a non-responder. The other SNP, rs2279805, and an *ADRA2A* haplotype showed nominal association with remission.

There has been only one prior pharmacogenetic study of atomoxetine. Ramoz et al. (2009), in France, reported significant associations between 20 *SLC6A2* SNPs and the clinical efficacy of atomoxetine. The most significant SNP implicated by our study, i.e., rs3785143, was corresponding to the SNP 15 in Ramoz et al.'s study. The LD block that this SNP located was consistently associated with atomoxetine response status in their two independent cohorts, with the haplotype containing the C allele of SNP 15 associated with responder status. As for the results of

Table 1 Demographic and clinical features of the ADHD cohorts at baseline and end point of atomoxetine treatment ($n = 111$)

Features	Overall	Response status			Remission status		
		Responder	Non-responder	*P*	Remission	Non-remission	*P*
Male (%)	92 (82.9 %)	69 (85.2 %)	23 (76.7 %)	0.290	25 (89.3 %)	67 (80.1 %)	0.298
Mean age (years ± SD)	9.6 ± 2.2	9.7 ± 2.2	9.3 ± 2.2	0.400	9.5 ± 2.4	9.7 ± 2.1	0.773
ADHD subtype							
Combined type	56 (50.5 %)	36 (44.4 %)	20 (66.7 %)	0.097	10 (35.7 %)	46 (55.4 %)	0.109
Inattentive type	53 (47.7 %)	43 (53.1 %)	10 (33.3 %)		18 (64.3 %)	35 (42.2 %)	
Hyperactive-impulsive type	2 (1.8 %)	2 (2.5 %)	0 (0 %)		0 (0 %)	2 (2.4 %)	
Psychiatric comorbidity							
Oppositional defiant disorder (ODD)	36 (32.4 %)	25 (30.9 %)	11 (36.7 %)	0.562	8 (28.6 %)	28 (33.7 %)	0.614
Conduct disorder (CD)	1 (0.9 %)	1 (1.2 %)	0 (0 %)	0.541	0 (0 %)	1 (1.2 %)	0.560
Tic disorder	35 (31.5 %)	22 (27.2 %)	13 (43.3 %)	0.103	11 (39.3 %)	24 (28.9 %)	0.307
Generalized anxiety disorder	2 (1.8 %)	2 (2.5 %)	0 (0 %)	0.385	0 (0 %)	2 (2.4 %)	0.407
Social phobia	2 (1.8 %)	2 (2.5 %)	0 (0 %)	0.385	0 (0 %)	2 (2.4 %)	0.407
Specific phobia	6 (5.4 %)	4 (4.9 %)	2 (6.7 %)	0.721	2 (7.1 %)	4 (4.8 %)	0.638
Baseline ADHD-RS-I score (mean ± SD)	31.9 ± 8.4	31.5 ± 8.1	33.2 ± 9.2	0.323	29.7 ± 8.7	32.7 ± 8.2	0.099
Inattentive symptoms	18.3 ± 3.6	18.0 ± 3.4	19.0 ± 3.9	0.184	17.8 ± 3.4	18.4 ± 3.6	0.452
Hyperactive-impulsive symptoms	13.7 ± 6.6	13.5 ± 6.6	14.2 ± 6.7	0.592	11.9 ± 6.5	14.3 ± 6.6	0.093
Baseline CGI-S (mean ± SD)	4.8 ± 1.2	4.8 ± 1.3	4.9 ± 1.2	0.709	4.4 ± 1.4	4.9 ± 1.2	0.084
Endpoint ADHD-RS-I score (mean ± SD)	19.5 ± 9.8	15.6 ± 6.5	29.9 ± 9.8	<0.001	10.7 ± 4.7	22.4 ± 9.3	<0.001
Inattentive symptoms	11.4 ± 5.1	9.4 ± 3.6	16.7 ± 4.8	<0.001	6.8 ± 2.4	12.9 ± 4.9	<0.001
Hyperactive-impulsive symptoms	8.1 ± 5.8	6.2 ± 4.3	13.2 ± 6.2	<0.001	4.0 ± 3.1	9.5 ± 5.8	<0.001
Endpoint CGI-S (mean ± SD)	2.9 ± 1.4	2.5 ± 1.2	4.0 ± 1.4	<0.001	1.9 ± 1.1	3.3 ± 1.4	<0.001

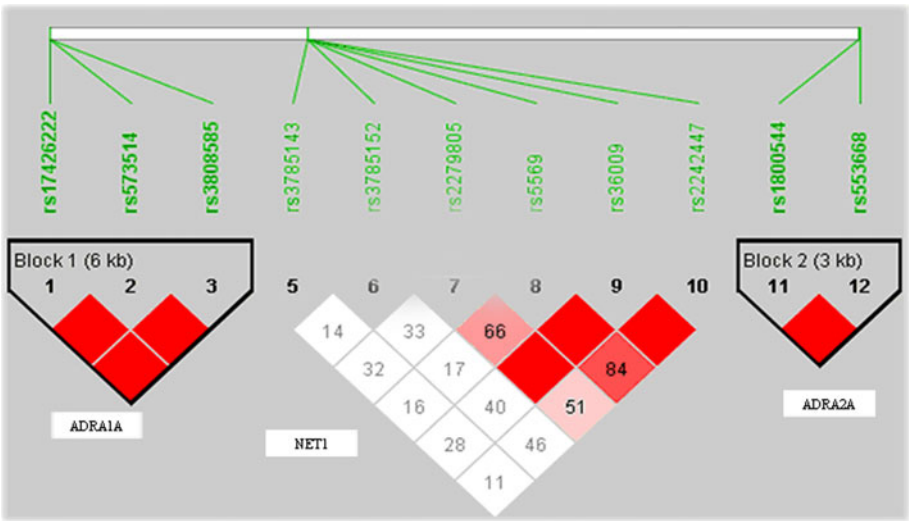

Fig. 1 Linkage disequilibrium plot of SNPs in the three norepinephrine receptor and transporter genes

this study, the T allele was associated with non-responder, while the C allele was associated with responder, which showed the same association direction with the previous report. The other SNP, rs2279805, which was nominal associated with atomoxetine response in our study is located in the sixth intron of *SLC6A2*. It was also among the genomic region across exons 4–9, which was associated with treatment response in Ramoz's study. Altogether, our results showed highly consistent evidence with previous study for the association between the *SLC6A2* gene and atomoxetine response. As for *ADRA2A*, this is the first study to report on its association with atomoxetine's efficacy (Table 3).

Atomoxetine is a highly selective inhibitor of the norepinephrine transporter (SLC6A2). The SLC6A2 reuptakes norepinephrine into the presynaptic terminal.

Table 2 Association of SNPs of norepinephrine transporter and receptor genes with atomoxetine response and remission status

Gene	SNP	Allele	Response				Remission			
			Allele counts		χ^2	*P*	Allele counts		χ^2	*P*
			Responder	Non-responder			Remission	Non-remission		
ADRA1A	rs17426222	C	114	43	0.036	0.8505	43	114	1.33	0.2487
		T	48	17			13	52		
	rs573514	A	87	33	0.03	0.8633	33	87	0.717	0.3973
		G	75	27			23	79		
	rs3808585	C	107	42	0.31	0.5779	35	114	0.723	0.395
		T	55	18			21	52		
SLC6A2	rs3785143	T	24	19	7.961	0.0048[a]	11	32	0.004	0.9522
		C	138	41			45	134		
	rs3785152	T	18	7	0.014	0.9074	6	19	0.022	0.881
		C	144	53			50	147		
	rs2279805	T	51	20	0.069	0.7928	11	60	5.242	0.0221[a]
		C	111	40			45	106		
	rs5569[b]	G	106	45	2.57	0.1089	43	108	2.002	0.1571
		A	54	13			13	54		
	rs36009	T	25	10	0.083	0.7739	9	26	0.02	0.8878
		C	135	48			45	138		
	rs2242447	C	63	30	2.019	0.1554	21	72	0.336	0.5623
		T	97	30			33	94		
ADRA2A	rs1800544	G	112	43	0.133	0.7152	39	116	0.001	0.9734
		A	50	17			17	50		
	rs553668	A	77	30	0.107	0.7437	33	74	3.454	0.0631
		G	85	30			23	92		

[a] Nominal significant association

[b] The genotypes of two samples could not be identified

Table 3 Association of haplotypes of norepinephrine transporter and receptor genes and atomoxetine response and remission status

Haplotype	Frequency	Response				Remission			
		Haplotype counts		χ^2	*P*	Haplotype counts		χ^2	*P*
		Responder	Non-responder			Remission	Non-remission		
ADRA1A									
CAT	0.329	55	18	0.310	0.5779	21	52	0.723	0.3950
TGC	0.293	48	17	0.036	0.8505	13	52	1.330	0.2487
CAC	0.212	32	15	0.722	0.3954	12	35	0.003	0.9565
CGC	0.167	27	10	0.000	1.0000	10	27	0.076	0.7822
ADRA2A									
GA	0.482	77	30	0.107	0.7437	33	74	3.454	0.0631
CG	0.302	50	17	0.133	0.7152	17	50	0.001	0.9734
GG	0.216	35	13	0.000	0.9921	6	42	5.258	0.0219[a]

[a] Nominal significant association

Dopamine reuptake in the frontal cortex also depends on the SLC6A2 (Moron et al. 2002). Abnormalities in SLC6A2 function may disturb norepinephrine levels (and dopamine levels in frontal cortex) and increase the risk of ADHD (Biederman and Spencer 2000). It could be speculated that the efficacy of SLC6A2 blockers such as

atomoxetine may vary with variation in transporter density that is regulated by *SLC6A2* gene variants. SNP rs3785143 is located in intron 1, a region responsible for transcription level of *SLC6A2* (Kim et al. 1999). Although this SNP is not known to be functional, it may be in high LD with other functional SNP.

Animal studies show that norepinephrine acts through adrenergic α2 receptors in the prefrontal cortex to modulate multiple cognitive functions (Arnsten and Li 2005; Arnsten et al. 1996; Biederman and Spencer 1999); (Franowicz and Arnsten 1998). Several studies reported the *ADRA2A* gene to be associated with ADHD (Comings et al. 1999; Roman et al. 2003, 2006; Park et al. 2005; Stevenson et al. 2005; Wang et al. 2006; Schmitz et al. 2006; Deupree et al. 2006), and several drugs used to treat ADHD, such as guanfacine, clonidine and even methylphenidate, agonize the α2A receptor (Biederman and Faraone 2005; Andrews and Lavin 2006). Hence, it was reasonable to suppose that the α2A receptor might also be involved in the mechanism of action of atomoxetine. SNPs rs1800544 and rs553668 are two widely investigated functional polymorphisms in ADRA2A, which are also described as MspI and DraI. The G allele separately, and the GG haplotype were associated with increased risk for ADHD (Roman et al. 2003, 2006; Park et al. 2005; Schmitz et al. 2006; Deupree et al. 2006). Further evidence showed decreased radioligand binding of receptor coded by the G alleles of these two SNPs (Deupree et al. 2006). Therefore, the GG haplotype carrier might have malfunctioning α2A receptor, which could lead to less symptom improvement when treated with atomoxetine.

The advantage of this study included the prospective design, adequate dose titration, and evaluation of multiple genes in the adrenergic neurotransmitter system. As the primary measurement of efficacy, the investigator rated ADHD-RS-IV was comprehensive with dual informants, integrating both parent's and teacher's ratings. The limitation of this study was the open-label design without placebo control out of ethnic consideration, so that the efficacy measurement might be influenced by the placebo effect. We only investigated three genes and small amount of tag SNPs in the noradrenergic system, which might cause omission of other association signals. More variants in this system should be measured in future studies. This study only investigated efficacy-associated genes, leaving the side effects un-analyzed, which should be considered in further studies.

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Conflict of interest The authors declare they have no conflict of interest.

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