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Association between the *HTR2B* gene and the personality trait of fun seeking

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ABSTRACT

Previous research reported that a rare serotonin receptor 2B gene (*HTR2B*) stop codon mutation predisposes subjects to severe impulsivity and novelty seeking. In this study, we expanded this previous work by testing six single nucleotide polymorphisms (SNPs) within the *HTR2B* gene for potential associations with the behavioral inhibition system (BIS) and the three components of the behavioral approach systems (BAS: fun seeking, drive, and reward responsiveness) in a Han Chinese sample ($N = 478$). Association analysis for individual SNPs indicated that four of the six SNPs (i.e., *rs6437000*, *rs10194776*, *rs16827801*, and *rs1549339*) were significantly associated with BAS fun seeking ($p = .0003$ – $.0022$). Haplotype-based association analysis revealed that fun seeking was positively associated with haplotype A–A–G–A for SNPs *rs6437000*–*rs10194776*–*rs16827801*–*rs1549339* ($p = .0002$), which survived Bonferroni correction. Except for the association between BAS reward responsiveness and *rs16827801* ($p = .005$), no other association was found for BAS drive, BAS reward responsiveness, or BIS. This study provides the first evidence for the involvement of the *HTR2B* gene in BAS fun seeking. A better understanding of the genetic basis of the BIS and BAS would allow us to develop more effective diagnosis, treatment, and prevention of impulsive behavioral problems.

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1. Introduction

According to Gray's reinforcement sensitivity theory (Gray, 1987), there are two major behavioral systems, i.e., the behavioral approach system (BAS) and the behavioral inhibition system (BIS). The BAS is sensitive to potential rewards, while the BIS is sensitive to potential punishment. Highly active BAS leads to high impulsivity, such as acting on the spur of the moment. Greater BIS sensitivity is reflected in greater proneness to anxiety (Corr, 2004).

Derived from Gray's theory, the BIS/BAS scales were developed to provide one scale of the BIS and three subscales of the BAS (i.e., fun seeking, drive, and reward responsiveness) (Carver & White, 1994). BAS fun seeking refers to impulsive approach of rewards and sensation seeking, BAS drive refers to the persistent pursuit of desired goals, and BAS reward responsiveness refers to the positive response to reward. Recent studies suggested that BAS fun seeking is more closely linked to rash impulsiveness, while BAS drive and reward responsiveness are more closely related to

reward sensitivity (Heym & Lawrence, 2010; Leone & Russo, 2009; Smillie, Jackson, & Dalgleish, 2006). For example, BAS fun seeking has been found to have substantial positive correlations with impulsive behaviors such as drug and alcohol abuse in both clinical and community samples (Alloy et al., 2009; Franken & Muris, 2006; Johnson, Turner, & Iwata, 2003).

The BIS/BAS scales have been used in previous research on the biological basis of personality. Twin studies showed that the BAS and BIS were stable personality traits with moderate heritability (e.g., Takahashi et al., 2007). Researchers have reported associations between various neurotransmitter genes and the BAS. For example, consistent with the notion that the dopamine system provides the neurobiological mechanism underlying the BAS (Carver & White, 1994; Gray, 1990), researchers found that variation in the *DRD2* gene was associated with BAS reward responsiveness in a Korean sample (Lee, Ham, Cho, Lee, & Shim, 2007), and that this variation interacted with variation in the catechol-O-methyltransferase (*COMT*) gene to influence the BAS in a German sample (Reuter, Schmitz, Corr, & Hennig, 2006). Most recently, a study showed that the dopamine D4 receptor (*DRD4*) variable number tandem repeat (VNTR) moderated the effect of childhood adversity on BAS fun seeking in an Australian sample (Das, Cherbuin, Tan, Anstey, & Easteal, 2011).

In addition to the dopamine system, the serotonin system also plays an important role in personality traits. For example, several

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recent studies have shown that variation in the serotonin receptor 2B (*HTR2B*) gene is associated with impulsivity, a trait highly related to BAS fun seeking as mentioned earlier. Bevilacqua et al. (2010) reported that an *HTR2B* stop codon (Q20*) predisposed individuals to severe impulsivity and higher novelty seeking in a Finnish sample. They also found that knocking-out the *HTR2B* gene increased impulsive behavior in mice. Moreover, a polymorphism in exon 2 of *HTR2B* was associated with drug abuse vulnerability in Caucasians (Lin, Walther, Yu, Drgon, & Uhl, 2004). Researchers suggested that the *HTR2B* gene may function by modulating levels of both serotonin and dopamine in the brain regions involved with impulsivity (Cardinal, 2006; Doly et al., 2008).

To date, no study has examined possible associations between *HTR2B* genetic variants and the BAS and BIS. In the current study, we analyzed six single nucleotide polymorphisms (SNPs) selected to cover the whole *HTR2B* gene, in order to explore whether there exists an association of the *HTR2B* gene with the BAS and BIS in a Han Chinese sample.

2. Materials and methods

2.1. Participants

Four hundred and seventy eight healthy undergraduates were recruited (mean age = 20 years, *SD* = 1, range 18–22 years old;

57% female) from Beijing Normal University (BNU) in China. All subjects were Han Chinese with no neurological or psychiatric history based on their self-report. They all signed written informed consent. This study was approved by the IRB of BNU, China.

2.2. Genotyping

A 4 ml venous blood sample was collected from each subject. Genomic DNA was extracted according to standard methods within 2 weeks after the blood sample was collected. All samples were genotyped using the standard Illumina GoldenGate Genotyping protocol (see <http://www.southgene.com.cn> for details).

As described in Fig. 1 and Table 1, six SNPs in the *HTR2B* gene on chromosome 2 were selected based on the HapMap data (<http://www.hapmap.org>; International HapMap Consortium, 2007), including rs17619600, rs6437000, rs10194776, rs16827801, rs1549339, and rs17586428. The *HTR2B* gene contains 4 exons and 3 introns. All six SNPs met the criteria of a call rate of >95%, Minor Allele Frequency (MAF) of >0.05, and Hardy–Weinberg equilibrium (HWE) of $p > 0.05$. The allele frequencies in our sample were very similar to those of the Chinese in the HapMap dataset (see Table 1). These six SNPs were chosen to cover most of the linkage disequilibrium (LD) blocks in *HTR2B*, as defined for the samples of Chinese included in the HapMap Project (<http://www.hapmap.org>) and in the 1000 Genomes Project (<http://www.broadinstitute.org/1000genomes.org>; The 1000 Genomes Project Consortium, 2010).

Fig. 1. Schematic representation of the *HTR2B* gene and linkage disequilibrium map of the six SNPs used in the current sample. The *HTR2B* gene has 4 exons and 3 introns. The position of a previously reported exon 2 glutamine-to-stop mutation (Q20*) associated with severe impulsivity is noted (Bevilacqua et al., 2010). Regions of high LD are shown in dark grey. Markers with lower LD are shown in light grey with the intensity decreasing with decreased r^2 value. Regions of low LD are shown in white. The numbers indicate the r^2 statistic value between the corresponding two SNPs. The haplotype associated with BAS fun seeking consisted of the four boxed SNPs.

Table 1Allele frequencies of six candidate SNPs in the *HTR2B* gene shown by ethnic groups. Data were from the present study and the HapMap data set (<http://www.hapmap.org>).

SNP	Base-pair position	Location	Reference/ other allele ¹	Reference allele frequencies					
				Present study Han Chinese (<i>N</i> = 478)	HapMap data				
					Chinese		Japanese	European	African
					CHB	CHD	JPT	CEU	ASW
<i>rs17619600</i>	231684704	Intron 3	G/A	.202	.167 (<i>N</i> = 168)	.224 (<i>N</i> = 170)	.238 (<i>N</i> = 172)	.084 (<i>N</i> = 226)	.047 (<i>N</i> = 106)
<i>rs6437000</i>	231685771	Intron 3	C/A	.404	.435 (<i>N</i> = 168)	.423 (<i>N</i> = 168)	.347 (<i>N</i> = 170)	.748 (<i>N</i> = 226)	.245 (<i>N</i> = 106)
<i>rs10194776</i>	231688263	Intron 2	G/A	.392	.415 (<i>N</i> = 164)	.417 (<i>N</i> = 168)	.355 (<i>N</i> = 172)	.659 (<i>N</i> = 226)	.208 (<i>N</i> = 106)
<i>rs16827801</i>	231689021	Intron 2	G/A	.495	.440 (<i>N</i> = 168)	.518 (<i>N</i> = 170)	.529 (<i>N</i> = 172)	.243 (<i>N</i> = 226)	.594 (<i>N</i> = 106)
<i>rs1549339</i>	231691070	Intron 2	G/A	.399	.423 (<i>N</i> = 168)	.418 (<i>N</i> = 170)	.355 (<i>N</i> = 172)	.717 (<i>N</i> = 226)	.387 (<i>N</i> = 106)
<i>rs17586428</i>	231697099	Intron 1	G/A	.217	.178 (<i>N</i> = 90)	NA	.167 (<i>N</i> = 90)	.025 (<i>N</i> = 118)	NA

Note: On the HapMap Website (Hapmap genome browser released 2 [phase 3]), these specific alleles of SNPs have different labels, due to different coding based on either the forward primer or the reverse primer. For example, the alleles of *rs17619600* are A and G in the present study (the standard Illumina GoldenGate Genotyping protocol), but they are T and C on the HapMap Website; the alleles of *rs10194776* are A and G in the present study (the standard Illumina GoldenGate Genotyping protocol), but they are T and C on the HapMap Website. In this table, we used the coding of all alleles based on the coding system of the Illumina system.

Population descriptors: CHB: Han Chinese in Beijing, China; CHD: Chinese in Metropolitan Denver, Colorado; JPT: Japanese in Tokyo, Japan; CEU: Utah residents with Northern and Western European ancestry from the CEPH collection; ASW: African ancestry in Southwest USA.

2.3. Behavioral assessment

The BAS/BIS scales were designed to measure individual differences in the sensitivity of the BAS (behavioral approach system) and BIS (behavioral inhibition system) (Carver & White, 1994). There are three BAS subscales (i.e., fun seeking [BAS-FS; 4 items], drive [BAS-D; 4 items], and reward responsiveness [BAS-RR; 5 items]) and a BIS scale (7 items). The BAS regulates appetitive motives, i.e., moving toward something desired. For example, a sample BAS-FS item is “I crave excitement and new sensations”; a BAS-RR item is “When I’m doing well at something I love to keep at it”; a BAS-D item is “When I want something I usually go all-out to get it”. The BIS regulates aversive motives, i.e., moving away from something unpleasant. For example, a sample BIS item is “I worry about making mistakes”. Each item is answered using a four point Likert scale, ranging from 1 (strongly disagree) to 4 (strongly agree). Previous research has shown that the scales have satisfactory reliability and construct validity. Similar to previous studies, the Cronbach alpha values were .64 for BAS-FS, .77 for BAS-D, .58 for BAS-RR, and .78 for BIS in the current study.

2.4. Data analyses

Quantitative trait genetic association analysis was carried out by using Plink v1.07 (Purcell et al., 2007), including allelic association tests between individual SNPs and behavioral measures, and associations between haplotype and behavioral measures. In order to test the group differences between different genotypes, ANOVA and the Fisher’s least significant difference post hoc tests (*t*-tests) were performed in SPSS 17.0. Pair-wise LD between all SNPs was assessed using the Haploview 4.2 program (Barrett, Fry, Maller, & Daly, 2005).

The three BAS score (fun seeking, drive, and reward responsiveness) and the one BIS score were analyzed separately. All significant associations were corrected for multiple testing by the max(T) permutation approach in Plink (1000 permutation) for individual SNP analysis, considering all tests that were done for all behavioral traits, and by applying a Bonferroni correction by dividing the significance level by the number of major haplotypes for haplotype-based association analysis.

3. Results

In the current study, the means and standard deviations of the scales were 12.58 (*SD* = 2.20) for BAS fun seeking, 11.81 (*SD* = 2.32) for BAS drive, 17.74 (*SD* = 1.74) for BAS reward responsiveness, and

20.34 (*SD* = 3.40) for BIS. Pair-wise correlations were moderate among the three BAS subscales (*r* = .31–.38). The BIS scale was correlated at $-.05$ with fun seeking, $-.10$ with drive, and $.25$ with reward responsiveness. These results were similar to those obtained in previous studies of non-clinical samples (Cooper, Gomez, & Aucote, 2007; Jorm et al., 1998).

Individual SNP analysis using Plink revealed significant associations for *rs17619600*, *rs6437000*, *rs10194776*, *rs16827801*, and *rs1549339* with BAS fun seeking ($p = .0003$ – $.0298$, see Table 2 for details). Except for *rs17619600*, the other four associations remained significant after correcting for multiple testing by max(T) permutation. Corrected empirical *p*-values (max(T)/familywise) were .002 for *rs1549339*, .004 for *rs6437000*, .004 for *rs16827801*, and .015 for *rs10194776*. The respective effect sizes (Cohen’s *d*) were .337, .318, .318, and .282. As shown in Fig. 1, a haplotype block across *HTR2B* was revealed from the linkage disequilibrium (LD) data for these six SNPs. The block contains four SNPs *rs6437000*, *rs10194776*, *rs16827801*, and *rs1549339*, which covered 5 kb. The mean pair-wise r^2 value of these four SNPs within *HTR2B* was .77.

Haplotype-based association analysis was performed for different combinations of SNPs within *HTR2B* in the current sample. As shown in Table 3, we found a major haplotype A–A–G–A (with a frequency of 48%) for *rs6437000*–*rs10194776*–*rs16827801*–*rs1549339* that showed a significant positive association with BAS fun seeking ($p = .0002$, Cohen’s *d* = .344). The haplotype C–G–A–G for these same SNPs (with a frequency of 39%) showed a significant inverse association with BAS fun seeking ($p = .0013$, Cohen’s *d* = $-.295$). These associations remained significant after Bonferroni correction. No other significant associations were found between the six SNPs in the *HTR2B* gene with BAS-D, BAS-RR or BIS measures ($p > .05$), except for that between BAS-RR and *rs16827801* ($p = .005$, Cohen’s *d* = .258, $A < G$). In addition, the effects of gender and age were not significant for all four behavioral measures ($p > .05$), except for the gender effects on BAS-RR and BIS ($p < .05$, female > male). Therefore, we also conducted individual SNPs analysis association using gender as a covariate. The significant associations between SNPs and behavioral measures as reported above remained significant with gender as a covariate.

4. Discussion

In the present study, we chose six SNPs in the *HTR2B* gene to investigate their associations with the behavioral approach and inhibition (BAS and BIS) systems in a Han Chinese sample. Results showed that four of the six SNPs (i.e., *rs6437000*, *rs10194776*,

Table 2Associations between six SNPs of the *HTR2B* gene and BAS fun seeking.

SNP	Effective allele	Allelic test		maj	M	SD	N	het	M	SD	N	min	M	SD	N	LSD ($p < .05$)
		<i>t</i>	<i>p</i>													
<i>rs17619600</i>	G	2.18	.0298	AA	12.43	(2.23)	299	AG	12.76	(2.13)	165	GG	13.57	(2.24)	14	
<i>rs6437000</i>	A	3.47	.0006	AA	13.16	(2.19)	166	AC	12.25	(2.18)	238	CC	12.35	(2.04)	74	AA > AC, CC
<i>rs10194776</i>	A	3.08	.0022	AA	13.11	(2.18)	174	AG	12.22	(2.21)	233	GG	12.46	(1.98)	71	AA > AG, GG
<i>rs16827801</i>	G	3.47	.0006	AA	12.31	(1.93)	120	AG	12.37	(2.29)	243	GG	13.30	(2.14)	115	GG > AG, AA
<i>rs1549339</i>	A	3.69	.0003	AA	13.18	(2.18)	170	AG	12.22	(2.18)	235	GG	12.34	(2.05)	73	AA > AG, GG
<i>rs17586428</i>	G	1.59	.1121	AA	12.49	(2.12)	288	AG	12.62	(2.33)	173	GG	13.65	(2.18)	17	

Note: Significant *p*-values after correction for multiple comparisons by max(T) permutation are shown in bold. maj, majority; het, heterozygote; min, minority; LSD, Fisher's least significant difference post hoc test.

Table 3Associations between the major haplotypes of the *HTR2B* gene and BAS fun seeking.

<i>rs6437000</i> – <i>rs10194776</i> – <i>rs16827801</i> – <i>rs1549339</i>			
Haplotype	Frequency	<i>t</i>	<i>P</i>
A–A–G–A	.48	3.76	.0002
C–G–A–G	.39	–3.23	.0013
A–A–A–A	.12	–0.57	.5697

Note: On the HapMap website, these specific SNPs alleles have different labels due to different coding based on either the forward primer or the reverse primer (see note to Table 1 for more details).

rs16827801, and *rs1549339*) were significantly associated with BAS fun seeking after multiple testing corrections. Furthermore, we found that the haplotype A–A–G–A (frequency of 48%) for these SNPs (*rs6437000*–*rs10194776*–*rs16827801*–*rs1549339*) was linked to high scores on BAS fun seeking, whereas the haplotype C–G–A–G for these SNPs (frequency of 39%) was linked to low scores on BAS fun seeking. These haplotype associations were still significant after Bonferroni correction. These effects were also independent of subjects' age and gender. These results suggest a critical role of *HTR2B* variation in BAS fun seeking.

These findings can be integrated with multiple lines of human and animal research (including biochemical, pharmacological, and genetic studies) on the *HTR2B* gene and BAS fun seeking. *HTR2B* encodes one of the serotonin receptors, which mediate many of the central and peripheral physiologic functions of serotonin. Central serotonin neurotransmission is believed to underlie impulsivity, a trait closely related to BAS fun seeking. Previous studies showed that lowered serotonin signaling led to impulsive action (Pattij & Vanderschuren, 2008), whereas 5-HT_{2B} receptor antagonist decreased impulsive behavior (Talpos, Wilkinson, & Robbins, 2006). *HTR2B* knockout mice show increased impulsive behavior. A possible biochemical mechanism for this increase is that *HTR2B* knockout male mice show a high level of the hormone testosterone (Bevilacqua et al., 2010). Alternatively, *HTR2B* might influence BAS fun seeking through its modulation of the interaction between the serotonin and dopamine pathways (Kelsoe, 2010).

In the current study, we identified four *HTR2B* SNPs (*rs6437000*–*rs10194776*–*rs16827801*–*rs1549339*; located in introns 2 and 3) and a four-marker haplotype of A–A–G–A that were significantly associated with high BAS fun seeking. Among these significant markers, two of four markers (i.e., *rs6437000* and *rs1549339*) were reported to have high linkage disequilibrium (LD) with the rare *HTR2B* stop codon in exon 2 identified in the study of Bevilacqua et al. (2010). As discussed above, Bevilacqua et al. (2010) identified a glutamine-to-stop substitution (i.e., Q20*) in the *HTR2B* gene, which was associated with severe impulsivity and novelty seeking. The *HTR2B* Q20* mutation led to variable nonsense-mediated RNA decay and blocked expression of the receptor protein. According to Bevilacqua et al. (2010), this mutation appears unique to the Finnish population with a frequency of .012. *HTR2B* Q20* was found on

a single haplotype background A–G–A–(G/A)–A–A for *rs6437000*–*rs4973377*–*rs1549339*–(stop codon)–*rs17586428*–*rs3806545*. Consistent with their findings, our Chinese subjects with allele A for *rs6437000* and *rs1549339* (as underlined above) had high scores on BAS fun seeking. While Bevilacqua et al. (2010) reported that *HTR2B* Q20* was associated with severe impulsivity and novelty seeking in a Finnish sample, we found that a haplotype block containing several adjacent SNPs reported to be in high LD with *HTR2B* Q20* were positively associated with the impulsivity-related trait BAS fun seeking in a Han Chinese sample. While Bevilacqua et al. (2010) speculated that this *HTR2B* Q20* haplotype block was related to the recent origin of the Finnish population investigated, the finding of a similar haplotype block associated with BAS fun seeking in a different population (Han Chinese) suggests that variation in this genomic region may contribute to impulsivity in many populations. It should be noted, however, that the SNPs used in this study have different minor allele frequency (MAF) in different ethnic populations based on HapMap Data (<http://www.hapmap.org>, see Table 1). Hence, potential replication of the current association of *HTR2B* and BAS fun seeking in other populations should acknowledge these differences.

In conclusion, the current study provided the first evidence of an association between variation in the *HTR2B* gene and BAS fun seeking. This result helps our understanding of the genetic basis of the behavioral approach system in general, and fun seeking in particular. It is a first step toward the development of more effective diagnosis, treatment, and prevention of impulsive behavioral problems and its related prevalent neuropsychiatric disorders.

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