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

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\textbf{A B S T R A C T}

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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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 (Q20del) 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.southgene.com.cn), including rs17619600, rs64370000, 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.southgene.com.cn) and in the 1000 Genomes Project (http://www.southgene.com.cn) and in the 1000 Genomes Project (http://www.southgene.com.cn).

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 (Q20del) 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 1
Allele 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 | HapMap data Chinese | HapMap data Japanese | HapMap data European | HapMap data African |
|-----------|--------------------|------------|------------------------|----------------------|----------------------|----------------------|----------------------|
| rs17619600 | 231684704          | Intron 3    | G/A                    | .202                 | .167 (.N = 168)       | .224 (.N = 170)       | .238 (.N = 172)       |
|           |                    |            |                        |                      | .084 (.N = 226)       | .047 (.N = 106)       |                      |
| rs6437000  | 231685771          | Intron 3    | C/A                    | .404                 | .435 (.N = 168)       | .423 (.N = 168)       | .347 (.N = 170)       |
|           |                    |            |                        |                      | .748 (.N = 226)       | .245 (.N = 106)       |                      |
| rs10194776 | 231688263          | Intron 2    | G/A                    | .392                 | .415 (.N = 164)       | .417 (.N = 168)       | .355 (.N = 172)       |
|           |                    |            |                        |                      | .659 (.N = 226)       | .208 (.N = 106)       |                      |
| rs16827801 | 231689021          | Intron 2    | G/A                    | .495                 | .440 (.N = 168)       | .518 (.N = 170)       | .529 (.N = 172)       |
|           |                    |            |                        |                      | .243 (.N = 226)       | .594 (.N = 106)       |                      |
| rs1549339  | 231691070          | Intron 2    | G/A                    | .399                 | .423 (.N = 168)       | .418 (.N = 170)       | .355 (.N = 172)       |
|           |                    |            |                        |                      | .717 (.N = 226)       | .387 (.N = 106)       |                      |
| rs17586428 | 231697099          | Intron 1    | G/A                    | .217                 | .178 (.N = 90)        | NA                    | .167 (.N = 90)        |
|           |                    |            |                        |                      | .025 (.N = 118)       |                       |                      |

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 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; 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. In this table, we used the coding of all alleles based on the coding system of the Illumina system.

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 Haplov4.2 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 r2 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–G–C–G (with a frequency of 39%) showed a significant inverse 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 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,
interaction between the serotonin and dopamine pathways associated with high BAS fun seeking. Among these significant

| Table 2 | Associations 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) |
| rs17619900       | G               | 2.18            | .0298| AA   | 12.43| (2.23)| 299 | AG  | 12.76| (2.13)| 165  | GG  | 13.57| (2.34)| 14  |
| rs6437000        | A               | 3.47            | .0006| AA   | 13.16| (2.19)| 166 | AC  | 12.25| (2.18)| 238  | CC  | 12.35| (2.04)| 74  |
| rs10194776       | A               | 3.08            | .0022| AA   | 13.11| (2.18)| 174 | AG  | 12.22| (2.21)| 233  | GG  | 12.46| (1.98)| 71  |
| rs16827801       | G               | 3.47            | .0006| AA   | 12.31| (1.93)| 120 | AC  | 12.37| (2.29)| 243  | GG  | 13.30| (2.14)| 115 |
| rs1549339        | A               | 3.69            | .0003| AA   | 13.18| (2.18)| 170 | AG  | 12.22| (2.18)| 235  | GG  | 12.34| (2.05)| 73  |
| rs17856428       | 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 3 | Associations between the major haplotypes of the HTR2B gene and BAS fun seeking. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Haplotype       | Frequency       | t               | p               | t               | p               | t               | p               |
| A–A–G–A         | .48             | 3.76            | .0002           | .12             | –0.57           | –.569           |
| C–G–A–G         | .39             | –2.33           | .0013           |                 |                 |                 |
| A–A–A–A         | .12             |                 |                 |                 |                 |                 |

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.

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 (Patti & Vanderschuren, 2008), whereas 5-HT2B 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 dopaminine 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 Finish 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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