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Associations of serotonin receptor gene HTR3A, HTR3B, and HTR3A haplotypes with bipolar disorder in Chinese patients

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ABSTRACT. Single nucleotide polymorphisms (SNPs) in HTR3A and HTR3B have been reported to be associated with bipolar disorder in European and Japanese populations. We explored the roles of 21 tag SNPs in HTR3A and HTR3B in susceptibility to bipolar disorder in a Chinese cohort. Twenty-one Tag SNPs were genotyped in a study consisting of 130 patients with bipolar disorder, who visited Shandong Mental Health Center between June 2013 and May 2014, and 109 healthy individuals as controls. All of the tag SNPs were genotyped using Sequenom MassArray matrix-assisted laser desorption/ionization time of flight spectrometry. Plink 1.07, Haploview 4.2, and SPSS 20.0 were used for the analysis of the genotypes and the associations of the haplotypes with bipolar disorder. Association analyses of tag

SNPs detected significant associations with the A allele in HTR3A rs1176719 (P = 0.030) and the C allele in HTR3A rs1176713 (P = 0.048). Haplotype-based association analyses indicated a statistically significant (P = 0.035) five-SNP haplotype (rs1062613:C, rs11604247:C, rs1176722:G, rs2276302:A, rs1176719:G) of linkage disequilibrium in block 3. Analysis of our small Chinese sample revealed a significant association of HTR3A with bipolar disorder, but yielded no evidence of an association between HTR3B and bipolar disorder. Furthermore, evidence for an association was found for a haplotype of HTR3A. Studies with larger Chinese samples are needed to verify our findings.

Key words: HTR3A; HTR3B; Bipolar disorder; Haplotype; Single nucleotide polymorphism

INTRODUCTION

Bipolar disorder (BPD) is a severe psychiatric disorder that affects up to 4% of the adult population worldwide and is characterized by recurrent episodes of depression and mania or hypomania (Fornaro et al., 2016). BPD is classified into bipolar disorder type I and bipolar disorder type II according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnostic criteria (Altinay et al., 2016). Several studies analyzing genetic linkages and candidate genes, and genome-wide association studies (GWAS) have presented evidence of important genetic etiology in BPD (Bauer and Pfennig, 2005; Merikangas et al., 2007).

Serotonin imbalance may be one of the pathogenic mechanisms underlying BPD. Serotonin 3 receptors (5-HT3s) are unique ligand-gated channel receptors associated with learning, memory, and emotion (Barnes and Sharp, 1999). These receptors are composed of five subunits (Tee et al., 2010): serotonin receptor 3A (HTR3A), serotonin receptor 3B (HTR3B), serotonin receptor 3C (HTR3C), serotonin receptor 3D (HTR3D), and serotonin receptor 3E (HTR3E) (Cederholm et al., 2009). The genes for HTR3A and HTR3B exist in close proximity to each other on chromosome 11q23.2 (Maricq et al., 1991). HTR3A and HTR3B have been cloned in mice for use in an experimental model (Barker et al., 2013). HTR3C, HTR3D, and HTR3E have been established in mammalian experimental models other than rodents (Holbrook et al., 2009; Karnovsky et al., 2003; Niesler et al., 2003). Recent genetic association studies have highlighted the significance of serotonin receptors 3A and 3B in psychiatric conditions, such as schizophrenia, BPD, alcohol dependence, and depression. 5-HT3 receptors have been shown to be associated with BPD in European and Japanese populations. A Japanese study has revealed that SNPs in HTR3B are associated with depression in female patients based on linkage disequilibrium (LD) (Yamada et al., 2006). Hammer et al. (2012) have confirmed rs1062613, rs1176744, and rs3831455 in the HTR3A and HTR3B genes, and the HTR3B variant rs1176744 as predisposing factors for BPD (Tencomnao et al., 2010; Tee et al., 2010). Niesler et al. (2001)'s findings suggest that c.178C>T (Pro16Ser) is an allele responsible for susceptibility to BPD. Seneviratne et al. (2013) and Johnson et al. (2013) demonstrated that Caucasian or European American subjects carrying one or more specific alleles of the HTR3A and HTR3B genes have significant differences in their responses to ondansetron vs. placebo in terms of drinking (Barker et al., 2013; Tang et al., 2013). Additionally, the interactions of these

variants significantly affected alcohol dependency (Weber et al., 2011; Johnson et al., 2013; Seneviratne et al., 2013). However, consistently susceptible gene factors associated with BPD were not found. Significant associations with overlapping haplotypes were not found in other studies.

We attempted to identify a susceptibility gene for BPD using 21 SNPs in HTR3A and HTR3B in Han Chinese patients. HTR3A and HTR3B SNPs were genotyped in order to obtain the haplotypes of the two serotonin receptors to investigate associations with BPD.

MATERIAL AND METHODS

Subjects

Samples were collected from 130 patients with BPD, including 68 patients with BPD type I and 62 patients with BPD type II visiting Shandong Mental Health Center in China between June 2013 and May 2014. Samples from 109 healthy individuals who were matched to the patients in terms of age, gender, and years of education were also obtained. Informed consent was obtained from all of the subjects prior to the study. The study was approved by the Ethical Committee board of Shandong University.

Inclusion and exclusion criteria for the patients were as follows: 1) all of the patients were diagnosed with bipolar disorder according to DSM-IV diagnostic criteria and were surveyed using the Structured Interview for DSM-IV. 2) Patients with serious somatic or neurological diseases and other acute or unstable medical conditions were excluded. Those with alcohol abuse and those undergoing addiction counseling were excluded. 3) None of the patients enrolled in the study had a history of alcohol or drug abuse. The healthy subjects enrolled at the same time were volunteers from Ji'nan, Shandong Province. These subjects had no serious somatic or neurological diseases or a history of alcohol or drug abuse.

DNA extraction and PCR amplification

A total of 5 mL peripheral fasting heparinized blood were collected from each subject. A QiaAMP Blood Mini Kit (Qiagen, Germany) was used to extract DNA and 200 μL peripheral whole blood sample according to the manufacturer's protocol. A NanoDrop ND-2000 (PEQLab Biotechnologie GmbH, Erlangen, Germany) was used to assess DNA concentration (10 ng/μL-20 ng/μL) and purity (260/280 ratio = 1.8-2.0) before PCR amplification. Ten nanograms of DNA for the target genes HTR3A and HTR3B (primers designed by AssayDesigner3.1) were amplified.

Selection of tag SNPs and genotyping

All of the tag SNPs were selected from the National Center for Biotechnology Information (NCBI) dbSNP build 138 (http://www.ncbi. nlm.nih.gov/snp/) and the HapMap Project release for Han Chinese in Beijing, China. The selection criteria for the tag SNPs were $r^2 > 0.8$ and MAF > 0.1 (minor allele frequency). The tag SNPs examined in a 100-kb region revealed 10 polymorphisms in HTR3A and 11 polymorphisms in HTR3B (see Table 1). The extended products were genotyped using a Sequenom Mass Array platform for MALDI-TOF spectrometry.

Table 1. Tag SNPs and minor allele frequency (MAF).

Gene	Tag SNP	Size (bp)	Allele		MAF
HTR3A	rs10789980	113,970,281	G	A	0.3734
	rs1062613	113,975,284	T	C	0.1113
	rs11604247	113,976,182	T	C	0.1155
	rs1176722	113,977,752	A	G	0.1155
	rs2276302	113,979,418	G	A	0.1181
	rs1176719	113,981,465	A	G	0.2458
	rs10160548	113,985,959	G	T	0.3347
	rs1176713	113,989,703	C	T	0.2353
	rs1182457	113,991,027	T	C	0.1151
	rs897685	113,993,387	G	A	0.1029
HTR3B	rs10789970	113,903,224	C	T	0.4097
	rs3758987	113,904,553	G	A	0.1757
	rs3831455	113,904,828	G	T	0.1610
	rs4938056	113,915,817	C	T	0.4208
	rs12421126	113,916,487	C	T	0.2302
	rs1176746	113,931,879	T	C	0.3809
	rs1176744	113,932,306	G	T	0.1646
	rs2276305	113,932,382	A	G	0.2479
	rs3782025	113,936,885	C	T	0.3846
	rs1672717	113,942,011	C	T	0.4038
	rs12795805	113,946,958	C	T	0.1639

Statistical analysis

The variances in the genotypes, haplotypes, and alleles at each locus in the study and control groups were analyzed using the Pearson chi-square test or Fisher exact test to discover SNPs associated with the disease. Hardy-Weinberg equilibrium exact test and MAF were performed using Plink 1.07 (Purcell et al., 2007). Quantitative analyses, such as *t*-tests and chi-square tests, were performed using the SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA). Disease association analysis was performed using Haploview version 4.2 (Barrett et al., 2005). The "TCC" genotype of rs3831455 was replaced by "T" and "DEL" was replaced by "G" per the requirements of Haploview 4.2 for genotyping. "D" was used to measure the LDs of the loci. The global permutation test was based on the null hypothesis that all odds ratios (ORs) of haplotypes were equal and that the P value was corrected after 10,000 permutations. P values < 0.05 were considered to be statistically significant and were used to establish associations.

RESULTS

Association analyses of tag SNPs

All of the subjects in the patient and control groups were genotyped at a call rate of >97% for every tag SNP that did not violate Hardy-Weinberg equilibrium. A complete list of the individual variants is presented in Table 2. The "A" allele in HTR3A, rs1176719 ($P = 0.030$) and the "C" allele in rs1176713 ($P = 0.048$) were significantly associated with BPD. The pathogenic ORs for these alleles were 1.605 [95% confidence interval (CI) = 1.044-2.468] and 1.472 (95%CI = 1.054-2.473), respectively. The allelic frequencies of

the other tag SNPs in the patient and control samples were not found to be significantly associated with BPD (P > 0.05).

Table 2. Association analysis of tag SNPs.

Tag SNP	Minor allele	Allele frequency		P	OR	95%CI	
		Case	Control			L95	U95
HTR3A							
rs10789980	G	0.387	0.358	0.516	1.132	0.778	1.645
rs1062613	T	0.121	0.101	0.487	1.227	0.688	2.190
rs11604247	T	0.133	0.097	0.230	1.422	0.798	2.532
rs1176722	A	0.129	0.096	0.266	1.388	0.777	2.479
rs2276302	G	0.133	0.101	0.284	1.364	0.772	2.412
rs1176719	A	0.285	0.199	*0.030*	1.605	1.044	2.468
rs10160548	G	0.359	0.307	0.232	1.264	0.861	1.857
rs1176713	C	0.416	0.324	*0.048*	1.472	1.054	2.473
rs1182457	T	0.125	0.101	0.411	1.273	0.716	2.263
rs897685	G	0.094	0.106	0.645	0.868	0.475	1.586
HTR3B							
rs10789970	C	0.394	0.431	0.419	0.860	0.595	1.241
rs3758987	G	0.184	0.161	0.509	1.176	0.727	1.901
rs3831455	DEL.TCC	0.15	0.170	0.634	0.887	0.543	1.450
rs4938056	C	0.410	0.445	0.445	0.867	0.602	1.250
rs12421126	C	0.244	0.211	0.429	1.202	0.762	1.896
rs1176746	T	0.364	0.404	0.378	0.845	0.582	1.228
rs1176744	G	0.181	0.142	0.254	1.334	0.812	2.192
rs2276305	A	0.242	0.243	0.981	0.995	0.653	1.516
rs3782025	C	0.369	0.406	0.407	0.854	0.587	1.241
rs1672717	C	0.391	0.427	0.427	0.862	0.597	1.244
rs12795805	C	0.184	0.138	0.176	1.410	0.856	2.320

Haplotype-based association analysis

LD statistics for HTR3A and HTR3B were determined using Haploview 4.2 (Gabriel et al., 2002). Haplotype blocks were used to measure LD. Samples from patients with BPD exhibited substantial LD amongst themselves (Figure 1). Sixteen of 21 polymorphism sites were in the highest disequilibrium state and exerted strong effects on susceptibility to BPD. We detected two LD blocks each within HTR3A and HTR3B. As shown in Figure 1, the number and the color of the square indicates D' (100X) and the gray square denotes D' = 1. The gradient colors demonstrate the strengths of the LDs of the tag SNPs.

In HTR3B, LD block 1 was formed by two tag SNPs (rs10789970 and rs3758987). The frequencies of none of the three haplotypes (TA, TC, and TG) were significantly different (P > 0.05) between the patient group and the healthy control group. Six tag SNPs (rs12421126, rs1176746, rs1176744, rs22763 05, rs3782025, and rs1672717) formed LD block 2 and encompassed five haplotypes. None of these haplotypes was significantly associated with BPD (P > 0.05). rs3831455, rs4938056, and rs12795805 did not form a haplotype.

In HTR3A, the LD block 3 haplotype was formed by five tag SNPs (rs1062613:C, rs11604247:C, rs1176722:G, rs2276302:A, and rs1176719:G), which had nominally significantly different frequencies in the two groups (P value = 0.035). The other four haplotypes were not significantly associated with BPD (P > 0.05). Three tag SNPs (rs10160548, rs1176713, and rs1182457) formed LD block 4. None of the four haplotypes detected in block 4 were significantly associated with BPD (P > 0.05). rs10789970 and rs897685 did not form any haplotypes within HTR3A (Figure 1 and Table 3).

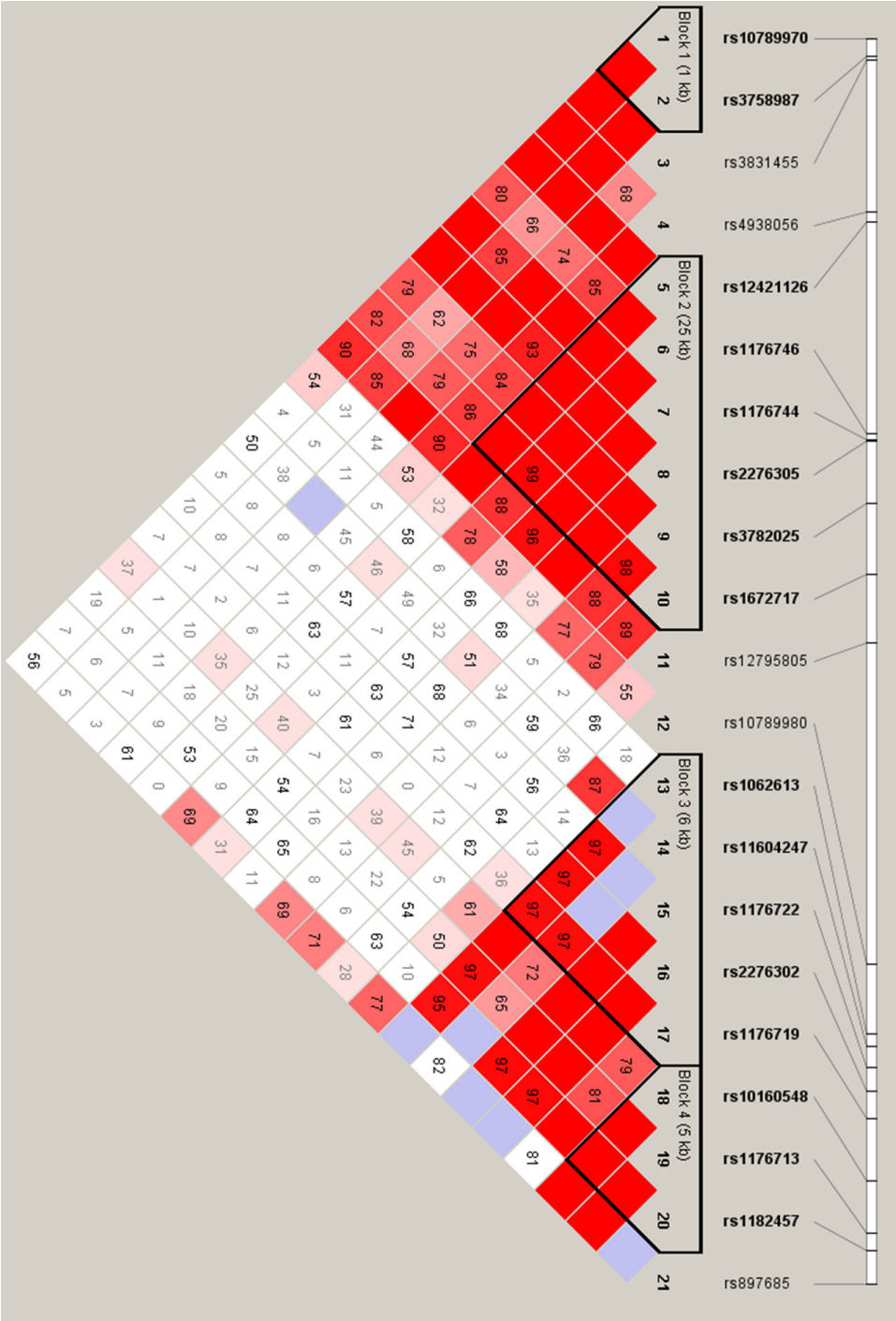

Figure 1. Linkage disequilibrium plot of HTR3A and HTR3B.

Table 3. Associations of haplotypes with BPD.

Block	Haplotype	Allele frequency		Chi square	P value
		Case	Control		
Block 1	TA	0.422	0.407	0.120	0.729
	CA	0.391	0.430	0.711	0.399
	TG	0.186	0.164	0.412	0.521
Block 2	TTTGCC	0.360	0.404	0.937	0.333
	CCTATT	0.240	0.228	0.094	0.759
	TCTGTT	0.178	0.188	0.075	0.784
	TCGGTT	0.182	0.142	1.378	0.240
	TCTGTC	0.027	0.018	0.398	0.528
Block 3	CCGAG	0.709	0.793	4.436	*0.035*
	CTGAA	0.124	0.092	1.273	0.259
	TCAGA	0.120	0.096	0.689	0.406
	CCGAA	0.027	0.009	2.020	0.155
Block 4	TTC	0.640	0.695	1.667	0.197
	GCC	0.140	0.095	2.197	0.138
	GCT	0.128	0.100	0.908	0.341
	GTC	0.093	0.109	0.339	0.560

DISCUSSION

We examined the roles of HTR3A and HTR3B in susceptibility to BPD in the Han Chinese population. Our findings support the 5-hydroxytryptamine hypothesis in the pathogenesis of BPD. Our study demonstrated that tag SNPs in HTR3A (rs1176719 and rs1176713) were significantly associated with BPD at the allelic, genotypic, and haplotype levels ($P < 0.05$). The haplotype CCGAG in LD block 3 was especially associated with BPD. In addition, the sixteen polymorphisms with the highest disequilibria were associated with maximum susceptibility to BPD, indicating that HTR3A and HTR3B may play significant roles in susceptibility to BPD. rs1176713 is a synonymous SNP located on exon 8 of HTR3A and can alter its expression level. rs1176719, located in intron 8 of HTR3A may be related to the regulation of gene expression.

Interestingly, a European study and Niesler et al. (2001)'s findings confirm that the c.178C>T (p.Pro16Ser) variant in HTR3A may represent a functional variability and affect BPD susceptibility. However, we were unable to replicate this finding in our study. sr1176744 and rs3831455 in HTR3B have been shown to associate with BPD in European populations but not in Han Chinese populations.

The present study had several limitations. The small sample size of the Han Chinese from North China accounts for a diverse genetic background based on regional and ethnic factors that may affect the onset of BPD. Many genes associated with BPD risk were detected using a candidate gene approach. Examples of these genes include those coding for monoamine oxidase (MAOA), dopamine transporter (DAT), serotonin transporter (5-HTT), 5-HT2A receptors, catechol-O-methyltransferase, brain-derived neurotrophic factor, Neuregulin 1, and disrupted-in-schizophrenia 1 (Neves et al., 2008; Perlis et al., 2008; Serretti and Mandelli, 2008; Barnett and Smoller, 2009; Ferreira et al., 2009). This necessitates a multiple gene blasting approach for more in-depth research into BPD. Furthermore, the use of GWAS as a key approach has been successful in candidate gene studies. However, a critical factor is whether GWAS can be used in different populations to better understand the associations between genotypes and BPD. Thus, additional studies and a much larger sample size incorporating

patients from other ethnic populations are required for the validation of our results. Hitherto, gene association analyses of BPD have not been successfully replicated. This situation is also common in other studies involving complex diseases. Meanwhile, large meta-analyses can be used to evaluate relevance and effectiveness. The current study primarily focuses on HTR3A and HTR3B at the DNA level and serves as a starting point for launching further genetic investigations centered on RNA and protein expressions of the two receptors associated with BPD. This is the first study to investigate the associations of HTR3A and HTR3B with BPD in a Han Chinese population. A strong link between HTR3A and BPD susceptibility is now established.

Conflicts of interest

The authors declare no conflict of interest.

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