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Neurotrophic Tyrosine Kinase Receptor Type 2 (NTRK2) Gene Associated with Treatment Response to Mood Stabilizers in Patients with Bipolar I Disorder

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Abstract

There is increasing evidence supporting the relationship between bipolar disorder (BP) and neurotrophin. The present study investigated the relationship between neurotrophic tyrosine kinase receptor type 2 (NTRK2) gene polymorphisms and bipolar I disorder (BP I) susceptibility and treatment response to mood stabilizers (lithium or valproate). Two-hundred eighty-four patients who met the DSM-IV criteria for BP I and 295 matched healthy controls were enrolled into this study. TaqMan® SNP genotyping assays were applied to genotype three NTRK2 gene polymorphisms (rs2769605, rs1565445, rs1387923). Our study showed a significant allelic association between NTRK2 gene polymorphism rs2769605 and treatment response to mood stabilizers in BP I patients (t=−2.53, P=0.01). However, no significant association between NTRK2 gene polymorphisms and BP I susceptibility was observed after correcting for multiple comparisons. The results suggest that the NTRK2 gene polymorphism likely plays an essential role in treatment response to mood stabilizers in Han Chinese BP I patients.

Keywords

Bipolar disorder; Brain-derived neurotrophic factor (BDNF); Neurotrophic tyrosine kinase receptor type 2 (NTRK2); Polymorphism; Association

Introduction

Bipolar disorder (BP) is a common, debilitating mental illness characterized by recurrent depressive and manic episodes. These episodes can impose significant financial and psychological burdens on societies, families, and individuals with this illness (Xu et al. 2010). Therefore, effective treatments for acute depressive and manic episodes and prevention of depression and/or mania relapses are essential. Pharmacological agents are a key component of the treatment of BP (Gao and Calabrese 2005). However, the mechanism of currently available pharmacological agents remains unclear. One of the main reasons for the unknown mechanism of current pharmacological treatments is due to lack of the knowledge on the pathophysiology of BP.

Family and epidemiological studies have demonstrated a strong genetic contribution to the risk for BP (Smoller and Finn 2003), suggesting that studying the gene(s) in patients with BP may help researchers and clinicians not only understand the pathophysiology of BP but

also the mechanism of pharmacological treatments. However, specific genes for BP have yet to be identified (Farmer et al. 2007; Hayden and Nurnberger 2006). As with other complex disorders, the difficulty of identifying BP-specific gene(s) stems from the etiological heterogeneity of BP and small phenotypic effect resulting from individual genetic variants (Kremeyer et al. 2006).

The neurotrophic tyrosine kinase receptor type 2 (NTRK2, alternative name tyrosine kinase receptor B, TRKB) is a specific receptor for neurotrophin brain-derived neurotrophic factor (BDNF). NTRK2 is an essential modulator of neural differentiation and cell survival and abundantly expressed in specific regions of human brain such as prefrontal cortex (Luberg et al. 2010). Recently, there is increasing evidence supporting that the impairment of neural plasticity is involved in the etiology and pharmacology of BD (Einat and Manji 2006; Zarate et al. 2006). More importantly, there are reports that the signal transduction BDNF/NTRK2 pathway might be involved in the pathogenesis of BP and the therapeutic mechanism of lithium in the treatment of BP (Hashimoto et al. 2004; Shaltiel et al. 2007).

Several single nucleotide polymorphisms (SNPs) in the NTRK2 gene have been studied in BP. However, their roles in BP including treatment response to lithium were inconsistent. SNP, rs2769605 in NTRK2 gene, was reported to be strongly associated with BP in an African-American population in a genome-wide association study (Smith et al. 2009). SNPs, rs1387923 and rs1565445, were significantly associated with lithium response in Caucasian individuals with BP (Bremer et al. 2007). However, a study in a Polish population found no association between lithium response and SNPs, rs1187326, rs1187327, and rs2289656 (Dmitrzak-Weglarz et al. 2008; Rybakowski et al. 2012). To further investigate the role of NTRK2 gene polymorphisms in BP susceptibility and treatment response to mood stabilizers, we performed an association study in a Han Chinese population.

Materials and Methods

Subjects

The Ethical Committee of Shanghai Mental Health Center reviewed and approved the study protocol. Written informed consent was obtained from each subject before any study-related procedures were performed. Males and females from 16 to 65 years old who met DSM-IV criteria for bipolar I disorder (BP I) (N=284) were enrolled. There were 127 males and 157 females. The mean age was 34.41±13.56 years. The mean age of first episode was 26.03±9.61 years. In addition, 295 age- and gender-matched healthy controls were included (134 males and 161 females). The mean age for the controls was 33.83±10.39 years. All subjects were Han Chinese in origin.

All BP I patients were recruited from those who were admitted to the Division of Mood Disorders at Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, from November 2006 to October 2010. Clinical diagnosis was made by two psychiatrists, one attending psychiatrist and one chief psychiatrist. Each patient was independently interviewed. Only patients diagnosed with the same axis I disorders by the two psychiatrists were recruited. The diagnose(s) were further confirmed with an Extensive Clinical Interview and a Structured Clinical Interview for DSM-IVAxis I Disorders, Patient Version (SCID-P) (First et al. 1997) by a research psychiatrist. The Extensive Clinical Interview contains items to assess demographics, mental status, suicidal severity, and other variables of interest. Controls were recruited from students and staff members at the Shanghai Mental Health Center and interviewed with SCID-P by a research psychiatrist. Subjects with any psychiatric disorder and chronic physical disease were excluded.

Treatment Response Assessment

Treatment response was retrospectively determined among the patients who were first treated with lithium or valproate monotherapy during previous hospitalization(s). This process was completed by a trained research assistant through reviewing medical record(s) and using a scale described previously (Grof et al. 2002). The scale including subscales A and B was developed specifically for retrospective evaluation of long-term treatment response in BP patients. Using this scale, researcher(s) can quantify the degree of improvement in the course of a treatment.

Subscale A is a composite measure of the change in frequency and severity of mood symptoms. Subscale A score is weighted by five factors which make up subscale B. The subscale B can assist researcher(s) to determine the probability that observed improvement is the result of a treatment rather than a spontaneous improvement or an effect of additional medication(s). A total score of this scale is obtained by subtracting a B score from an A score. A patient with a total score of 7 or higher was defined as a full responder. A patient with a total score of 5 or higher was considered as a responder, which corresponds to an approximately 50 % or better improvement in the course of a treatment (Garnham et al. 2007).

SNP Selection and Genotyping

Since an association of SNP, rs276960, with BP susceptibility (Smith et al. 2009) and SPNs, rs1387923 and rs1565445, with response to mood stabilizers (Bremer et al. 2007) have been reported, in this study, these three SNPs in NTRK2 gene were selected. Genomic DNA was extracted from peripheral blood according to standard laboratory procedures (Blood Genomic DNA Extraction Kit, Tiangen, Beijing). Genotyping was performed with TaqMan genotyping assay on an ABI PRISM 7900 Sequence Detection System (Applied Biosystems, Foster City, CA). Primers and probes were purchased from Applied Biosystems. All genotypes were independently confirmed by two researchers. If any discrepancy or ambiguous genotype occurred, a resolution was to repeat genotyping. Ten percent of the samples were randomly chosen to duplicate genotyping, and no genotype error was found.

Statistical Analyses

The χ^2 test for goodness of fit was used to check for Hardy–Weinberg equilibrium in genotype distributions in patients and controls. For the case–control genetic comparisons, differences in the genotype and allele distributions between patients and controls were examined using Pearson's χ^2 test. The response scores among different genotype groups were compared with *t* test. All statistical analyses were carried out by using the SPSS V. 17.0 software program (SPSS, Inc., Chicago, IL, USA). Bonferroni's adjustment was used for multiple comparisons. The adjusted *P* value for significance was set at 0.05/3=0.017.

Results

Association Analysis of NTRK2 Polymorphisms with BP I Susceptibility

The distributions of genotypes of NTRK2 gene polymorphisms in patients and healthy controls were consistent with Hardy–Weinberg equilibrium ($P>0.05$). The frequencies of genotypes are shown in Table 1.

For SNP rs2769605, the allele or genotype frequencies of BP I patients did not significantly differ from the controls (genotype-wise: $\chi^2=2.36$, $df=2$, $P>0.05$; allele-wise: $\chi^2= 0.21$, $df=1$, $P>0.05$). For SNP rs1565445, the allele or genotype frequencies of BP I patients also did not significantly differ from the controls (genotype $\chi^2=0.39$, $df=2$, $P>0.05$; allele $\chi^2=0.31$, $df=1$, $P>0.05$).

For SNP rs1387923, the genotype frequency of BP I patients did not significantly differ from the controls (χ^2=4.12, *df*=2, *P*>0.05), but the allele frequency of BP I patients was nominally significantly different from the controls (χ^2=4.49, *df*=1, *P*=0.03). The T allele was significantly associated with increased risk for BP I disorder with an OR of 1.33 (95 % CI 1.02 to 1.74). However, this association did not remain significant after Bonferroni correction for multiple comparisons.

Association Analysis of NTRK2 Polymorphisms with Treatment Response

For SNP rs2769605, the response scores differed significantly between different genotype carriers (G/G genotype and allele A carriers) in BP I patients (*t*=−2.53, *P*=0.01) even after Bonferroni correction for multiple comparisons. The scores of treatment response to lithium or valproate in allele A carriers were significantly higher than the scores of those with genotype G/G. For SNPs rs1565445 and rs1387923, the response scores did not differ significantly between different genotype carriers in BP I patients (*t*= −0.74, *P*=0.46; *t*=0.26, *P*=0.80) (Table 2).

Discussion

To the best of our knowledge, this is the first study to investigate the association between polymorphisms in NTRK2 gene and susceptibility to BP, and treatment response to mood stabilizers, respectively, in a Han Chinese population. We found that, compared to healthy controls, there was no significant association between NTRK2 gene polymorphisms and BP I susceptibility after correcting for multiple comparisons. However, among the patients with BP I disorder, the rs2769605 polymorphism was significantly associated with treatment response to lithium or valproate. Meanwhile, the G/G homozygous carriers had the lowest treatment response scores, suggesting that the G/G genotype may be a risk factor for poor response to lithium or valproate.

The finding of no significant association between BP I and rs2769605 is somewhat consistent with a previous study (Smith et al. 2009), in which there was a significant association between the NTRK2 gene rs2769605 polymorphism and BP susceptibility in an American population of African ancestry, but not in an American population of European ancestry. These data suggest that the association between bipolar susceptibility and rs2769605 may depend on ethnic origins. Since there was significant difference in the T allele frequency of rs1387923 between patients with BP I disorder and the controls before adjusting for multiple comparisons, large sample studies are needed to investigate the relationship between rs1387923, especially T allele, and bipolar susceptibility.

The NTRK2 gene rs1387923 polymorphism was reported to be associated with lithium response in a Caucasian population, but the interaction between rs1387923 and lithium response depended upon clinical phenotype (euphoric/dysphoric mania) and comorbidity (post-traumatic stress disorder and a history of suicidal ideation) (Bremer et al. 2007). Our data did not show any significant association between rs1387923 and rs1565445 polymorphisms and treatment response to mood stabilizers. In contrast, we found that the rs2769605 polymorphism in NTRK2 gene was significantly associated with mood stabilizer treatment response in BP I patients. The discrepancies between our findings and previous observations can be due to many factors such as different ethnic backgrounds, ascertainment of diagnosis, phenotype definition, control selection, limited power (due to their small sample sizes), and/or possible confounding by population substructure (Fan and Sklar 2008; Petryshen et al. 2010). Moreover, the interaction (s) between genetic polymorphisms and environment factors such as stressful life events and enhanced stress response in the pathogenesis of BP and/or response to treatment could not be ignored (Hosang et al. 2010; Vinberg et al. 2009).

The mechanisms of NTRK2 gene polymorphisms in the pathogenesis and pharmacology of BP need to be further clarified. Postmortem studies have shown abnormalities of morphometry and NTRK2 (TrkB) protein expression in the hippocampus of patients with BP (Dunham et al. 2009; Thompson Ray et al. 2011). TrkB mRNA level revealed a significant decrease in layer II of the hippocampal entorhinal cortex in BP patients (Thompson Ray et al. 2011), but in another study, no change in TrkB density was seen in any diagnosis including schizophrenia, bipolar disorder, and major depressive disorder (Dunham et al. 2009). One possible reason for this discrepancy might be due to group differences in TrkB isoforms that could not be revealed by selected TrkB antibody (Dunham et al. 2009). However, decreases in TrkB density were observed in subjects who carried the minor allele of NTRK2 SNPs rs1187323 and rs1187326 (main effect of genotype). Reductions in TrkB density were seen in every subregion of the hippocampus (molecular layer, granule cell layer, stratum oriens, pyramidal layer, and stratum radiatum) (Dunham et al. 2009). These observations imply that NTRK2 gene polymorphisms could affect protein expression and hippocampus function. More recently, an in vivo study showed that NTRK2 gene polymorphism rs11140714 could impact white matter connections and gray matter volume in patients with major depressive disorder (Murphy et al. 2012).

Taken together, these data suggest that NTRK2 gene polymorphisms may play an important role in the pathogenesis of BP and its treatment response to mood stabilizers, although the current findings have been inconsistent. To reduce potential discrepancy, future studies with large sample size with the same definition of phenotypes and the same diagnostic and study procedures are essential. Our preliminary finding of the positive association between rs2769605 and treatment response to mood stabilizers suggests that patient's NTRK2 genotype profile may provide guidance for clinicians to select mood stabilizers and other pharmacological agents for bipolar patients in a way that maximizes efficacy and tolerability and minimizes side effect(s) in a socalled "personalized medicine" era (Zandi and Judy 2010). However, further adequately powered, well-designed pharmacogenetic studies in bipolar patients who are prospectively and sequentially treated with lithium, valproate, and other mood stabilizer are needed before any "personalized" treatment can be implemented.

Several limitations of this study should be considered. First, the findings should be considered preliminary due to a modest sample size. With the hypothesis of gene action only and log-additive inheritance mode, BP I prevalence rate in the population as 1 % and genetic relative risk (odd ratio) as 1.5, and the allele frequency identified in control subjects, in the current study, the sample powers to detect difference of an allele frequency between BP I patients and control subjects were 27 % for rs2769605, 35 % for rs1565445, and 32 % for rs1387923, respectively. Based on the identified difference in response scores between different genotypes for rs2769605, the statistical power in the current study was 0.55. Therefore, at least 135 patients per arm in a future study would be needed to detect a significant difference at α=0.02 with a power of 80 %. Clearly, it is feasible to conduct a larger sample study to support or refute our findings. Second, the treatment response to mood stabilizers in this study was retrospectively assessed, although we used a valid scale. Third, for treatment response, we only reviewed those patients who were first treated with lithium or valproate monotherapy (146/284). Therefore, the relationship between NTRK2 gene polymorphisms and response to antipsychotics or other mood stabilizers needs to be further investigated. Moreover, we did not compare the difference between NTRK2 gene polymorphisms and response to individual mood stabilizer such as lithium versus valproate.

In conclusion, we found that there was a significant association between the NTRK2 gene polymorphism rs2769605 and the treatment response to mood stabilizers in Chinese BP I patients. However, our results did not support a major role of NTRK2 gene polymorphisms in the susceptibility for BP I disorder in a Han Chinese population. Future comprehensive

sequencing analyses of the NTRK2 gene region in large well-characterized clinical samples are warranted to elucidate the role of this gene in treatment response to mood stabilizers in BP.

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Table 1

Genotype and allele distribution of NTRK2 polymorphisms in bipolar I disorder patients and controls

Group	*N*	Genotype			χ^2 value	*df*	*P* value	Allele		χ^2 value	*df*	*P* value	OR (95 % CI)
rs2769605		**G/G (%)**	**G/A (%)**	**A/A (%)**				**G (%)**	**A (%)**				
Patients	283	164 (58.0 %)	109 (38.5 %)	10 (3.5 %)	2.364	2	0.307	437 (77.2 %)	129 (22.8 %)	0.209	1	0.648	0.94 (0.71, 1.24)
Controls	293	181 (61.8 %)	97 (33.1 %)	15 (5.1 %)				459 (78.3 %)	127 (21.7 %)				
rs1565445		C/C	C/T	T/T				C	T				
Patients	281	40 (14.2 %)	119 (42.3 %)	122 (43.4 %)	0.394	2	0.821	199 (35.4 %)	363 (64.6 %)	0.308	1	0.579	0.93 (0.73, 1.19)
Controls	292	47 (16.1 %)	122 (41.8 %)	123 (42.1 %)				216 (37.0 %)	368 (63.0 %)				
rs1387923		T/T	T/C	C/C				T	C				
Patients	279	169 (60.6 %)	92 (33.0 %)	18 (6.5 %)	4.166	2	0.125	430 (77.1 %)	128 (22.9 %)	4.492	1	0.034	1.33 (1.02, 1.74)
Controls	292	155 (53.1 %)	108 (37.0 %)	29 (9.9 %)				418 (71.6 %)	166 (28.4 %)		1		

NTRK2 neurotrophic tyrosine kinase receptor type 2, *df* degrees of freedom, *OR* odds ratio, *CI* confidence interval

Table 2

Comparison of response scores between different genotypes of NTRK2 in bipolar I disorder patients

SNP	*N*	Mean	SD	*N*	Mean	SD	*t* value	*df*	*P* value
rs2769605		G/G			G/A + A/A				
	82	5.55	2.36	64	6.45	1.84	−2.53	144	0.013
rs1565445		T/T			C/T + C/C				
	70	5.82	2.16	76	6.09	2.23	−0.74	144	0.458
rs1387923		T/T			T/C + C/C				
	96	5.98	2.14	50	5.88	2.30	0.26	144	0.796

NTRK2 neurotrophic tyrosine kinase receptor type 2, *SNP* single nucleotide polymorphism, *SD* standard deviation, *df* degrees of freedom