Progress in Neuropsychopharmacology & Biological Psychiatry 107 (2021) 110227

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Association between genetic variants of the norepinephrine transporter gene (*SLC6A2*) and bipolar I disorder

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ARTICLE INFO

Keywords:
Bipolar I disorder
SLC6A2
NET
Manic symptom
Psychotic symptom

ABSTRACT

We aimed to investigate the associations between genetic variants of the norepinephrine transporter gene (*NET*, also known as *SLC6A2*) and diagnosis of bipolar I disorder. In addition, we examined the relationship between the genetic variants and manic and psychotic symptoms in patients with bipolar I disorder. The three SNPs rs28386840, rs2242446, and rs5569 were genotyped in 326 patients: patients with bipolar I disorder ($n = 160$) and a control group ($n = 166$). Subsequently, multivariate logistic regression analysis adjusting for age and sex was conducted to identify independent influences of the SNPs on diagnosis of bipolar I disorder. A possible association between manic and psychotic symptoms and variants of *SLC6A2* was also investigated in patients with bipolar I disorder. The rs28836840 SNP in the 5'-UTR of *SLC6A2* was significantly associated with bipolar I disorder and with severity of manic and psychotic symptoms in this disorder. Individuals carrying a T allele in the rs28836840 SNP were likely to have a lower risk of bipolar I disorder or lower severity of manic and psychotic symptoms in patients with bipolar I disorder (bipolar I disorder diagnosis: OR = 0.643, 95% Cl = 0.468–0.883, $p = 0.006$; manic symptoms: $\beta = -2.457$, 95% Cl = −4.674 ~ −0.239, $p = 0.031$; psychotic symptoms: $\beta = -2.501$, 95% Cl = −4.700 ~ −0.301, $p = 0.027$). For the rs2242446 and rs5569 SNPs, there were no significant differences between patients with bipolar I disorder and those without. Our results revealed associations of the rs28386840 SNP with bipolar I disorder diagnosis and with severity of manic and psychotic symptoms. However, the findings reported here require replication in larger samples and various ethnic groups.

1. Introduction

Bipolar disorder affects approximately 1% of the world's population irrespective of nationality, ethnic origin, or socioeconomic status and represents one of the leading causes of disability, resulting in cognitive and functional impairment and increased mortality, particularly death by suicide (Grande et al., 2016). Although the pathogenesis of bipolar disorders is not clearly understood, there is mounting evidence of genetic factors affecting bipolar disorder susceptibility. The lifetime risks for bipolar disorder to relatives of an affected proband are 0.5–1.5% for unrelated members of the general population, 5–10% for first-degree relatives, and 40–70% for monozygotic co-twins (Craddock and Jones, 1999). Heritability estimates from twin studies are high: 89% in a hospital study of 67 twin pairs in the UK and 93% in a population study of 19,124 same-sex twin pairs in Finland (McGuffin et al., 2003; Kieseppä et al., 2004). There have been a lot of genome-wide association studies (GWAS) about the etiology of bipolar disorder (Craddock and Sklar, 2013; Prata et al., 2019; Stahl et al., 2019). However, most studies have only included European and Northern American populations, and few GWAS have been performed in Asian populations (Chen et al., 2013; Ikeda et al., 2018). In addition, although it has been proposed that there is a strong genetic component of bipolar disorder, complex genetic

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https://doi.org/10.1016/j.pnpbp.2020.110227
Received 12 August 2020; Received in revised form 11 December 2020; Accepted 15 December 2020
Available online 17 December 2020

architecture and phenotypic heterogeneity may contribute to the inconsistency of genome-wide significant findings within and across bipolar disorder GWAS (Stahl et al., 2019). In such a complex model, temperament influenced by environmental stimuli can play a crucial role on a genetic basis and also may determine the use of a polypharmacy (De Berardis et al., 2020; Fornaro et al., 2016; Iasevoli et al., 2013).

Norepinephrine (NE) is one of the neurotransmitters implicated in the pathogenesis of bipolar disorders. Several studies have reported that 3-methoxy-4-hydroxylphenyglycol (MHPG), a major metabolite of norepinephrine, was increased in the cerebrospinal fluid (CSF), plasma, and urinary monoamines of those with bipolar disorder (Shopsin et al., 1973; Swann et al., 1983, 1987). In addition, the severity of manic symptoms was significantly correlated with the MHPG level in CSF (Swann et al., 1983, 1987). In manic patients, treatment with lithium was associated with decreased level of CSF MHPG (Shopsin et al., 1973; Swann et al., 1987; Wilk et al., 1972). Furthermore, compared to patients with unipolar depression, bipolar patients showed lower level of urinary MHPG in the depressed state (Muscettola et al., 1984; Schatzberg et al., 1989; Schildkraut et al., 1978). These results show that complicated dysregulation of the NE system can have a crucial role in the pathophysiology of bipolar disorders.

The bioavailability of NE is regulated mainly by the norepinephrine transporter (NET) (Bönisch and Brüss, 2006). The NET functions via reuptake of NE released from presynaptic vesicles in a Na/Cl channel-dependent manner (Uhl and Johnson, 1994). Therefore, considering that NET can play an important role in central nervous monoaminergic homeostasis, genetic variations in NET can affect noradrenergic signals. The gene that encodes NET is *SLC6A2*, which is located on chromosome 16q12.2, consists of 15 exons, and includes approximately 300 single-nucleotide polymorphisms (SNPs) (Brüss et al., 1993). SNPs are located in promotor regions of *SLC6A2* and regulate transcriptional activity via modulation of DNA binding affinity (Zill et al., 2002). Meanwhile, according to the Stöber et al. (1996) study that systemically screened the whole coding region of the *SLC6A2* gene, SNP rs5569, located on exon 9, had high heterozygosity compared to other markers. Meta-analysis studies revealed that rs5569 is associated with methylphenidate efficacy in ADHD and risk of major depressive disorder (Myer et al., 2018; Rui et al., 2018). However, there have been no studies to identify whether the rs5569 SNP is related to bipolar disorder or related psychiatric symptoms.

Based on the aforementioned findings, the present study investigated the associations between genetic variants of *SLC6A2* and bipolar I disorder in a Korean sample, genotyping three SNPs of the *SLC6A2* gene: rs28386840 in the 5'-UTR, rs2242446 in the promoter, and rs5569 in exon 9. Additionally, we identified whether these genetic variants were associated with severity of manic and psychotic symptoms in patients with bipolar I disorder.

2. Materials and methods

2.1. Subjects

Participants of this study were 160 Korean psychiatric patients with bipolar I disorder who were admitted for hospitalization at Korea University Ansan Hospital, Ansan, Korea. They were recruited consecutively from 2006 to 2011. Each patient was assessed by a psychiatrist using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-4th Edition (DSM-IV) Axis I disorder (SCID-I) on the first day of hospitalization, and all subjects met the criteria of DSM-IV for bipolar I disorder. Participants who had been diagnosed with other psychiatric disorders including depressive disorders, psychotic disorders, anxiety disorders, substance use disorders, and cognitive disorders were excluded.

Information regarding age of onset, number of admissions, and duration of illness were collected through reviews of medical records and interviews with family members. Severity of manic and psychotic symptoms was assessed using the Young Mania Rating Scale (YMRS) and the Brief Psychiatric Rating Scale (BPRS). The YMRS is an 11-item scale that assesses the intensity of manic symptoms based on a clinical interview with the patient and takes into account the subjective comments of the patient and the clinician's own observations, with higher scores indicating more severe mania symptoms (Young et al., 1978). BPRS is used to assess psychiatric symptoms such as depression, anxiety, hallucinations, and unusual behaviors in psychotic disorders. This scale of seven points (0–6) measures a total of 18 items (Bech et al., 1988). The YMRS and BPRS were assessed on the first day of hospitalization. Patients who did not cooperate in the initial interview were assessed until the next day of hospitalization.

The normal control group comprised 166 persons who visited the health screening center of Korea University Ansan Hospital. Individuals who reported having experienced any of the following were excluded: scored 10 or higher on the Beck depressive inventory (BDI) or above 40 on the State-Trait Anxiety Inventory (STAI) or had a psychiatric disorder, a family history of psychiatric disorders, and/or history of psychiatric medication use.

Written informed consent was obtained from all participants, and this study's protocol was approved by the Institutional Review Board of Korea University Ansan Hospital (2005AS0008).

2.2. DNA extraction and genotyping

DNA was extracted from blood leukocytes using a commercial DNA extraction kit, Wizard Genomic DNA purification kit (Promega, USA). The three SNPs were genotyped by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) methods according to the protocol originally described in previous studies.

For rs2242446, 5′-CCA TTT GGG GCA GGC GAA AGT-3′ was used as the forward primer and 5′-CGC TGA CGG GAC GCA GGG TTC CCA GCC AAG-3′ was used as the reverse primer. For rs28386840, 5′-CCT GGG GCT CTG TTA GC-3′ was used as the forward primer and 5′-CCT GGA AGC AAT CGT TGG GG-3′ was used as the reverse primer. For rs5569, 5′-TTG ACT TTA TTG AAA TGC GGC-3′ was used as the forward primer and 5′-TCC AGG GAG ACC CTA ATT CC-3′ was used as the reverse primer. The amplification mixture contained 0.5ul of 100 ng/ul DNA, 2.5ul of 10× Taq buffer, 0.5ul of 10 mM dNTP mixture, 1ul primers, 19.375ul distilled water, and 0.125ul Taq DNA polymerase (SolGent, Korea). Samples were amplified using a thermocycler (GeneAmp PCR system2700, Applied Biosystems, Foster City, CA, USA). Initial denaturation at 95 °C for 5 min was followed by 35 (rs2242446) or 36 (rs28386840 and rs5569) cycles of 30s at 95 °C, 30s at 60 °C, and 30s at 72 °C. After a final 10 min at 72 °C, the reaction was terminated at 4 °C. The amplified DNA was digested with the restriction enzyme *Sty*I (New England Biolabs) for rs2242446, BsrsI (New England Biolabs) for rs28386840, and *Sau*96I (New England Biolabs) for rs5569. The product was electrophoresed in 3% agarose gel and stained with ethidium bromide. The homozygous and heterozygous genotypes were identified by band size.

2.3. Statistical analysis

Demographic variables between bipolar disorder patients and healthy controls were compared using chi-square test for dichotomous variables and *t*-test for continuous variables using SPSS 21.0 for Windows (IBM Corp., Armonk, NY, USA).

Deviations from Hardy–Weinberg equilibrium (HWE) were tested with the chi-square (χ^2) test at each SNP locus separately for cases and controls using PLINK v1.9 (http://www.cog-genomics.org/plink/1.9/). Association analyses between the genetic variants of *SLC6A2* and bipolar I disorder were conducted using PLINK 1.9. A multiple logistic regression model was used with additive genetic effects to identify independent influences of *SLC6A2* SNPs on development of bipolar I

disorder. In addition, linear regression models were used with additive genetic effects to determine whether the genetic variants were associated with severity of manic or general psychiatric symptoms in patients with bipolar I disorder. All multivariate regression models were performed after adjusting for age and sex. All *p*-values were adjusted for multiple testing correction in association analyses for bipolar I disorder (Bonferroni *q*-value <0.05).

3. Results

3.1. Clinical characteristics

The present study comprised 160 patients with bipolar I disorder and 166 normal controls. The mean ages of the two groups were significantly different (bipolar I disorders: mean = 34.24, SD = 11.42; normal controls: mean = 34.79, SD = 8.82, $p = 0.040$). The sex distribution of the two groups was not significantly different ($\chi^2 = 0.25$, $p = 0.617$). The male to female ratio was 0.72 (67/93) in the bipolar disorder group and 0.64 (64/103) in the normal control group. In bipolar I disorder patients, the mean age of onset was 29.71 years. The mean number of admissions and duration of illness were 3.06 times and 19.86 months, respectively. The mean baseline YMRS and BPRS scores were 31.13 and 23.74, respectively (Table 1).

3.2. Genotype distribution of the SLC6A2 SNPs

The distribution of genotypes among patients with bipolar I disorder and controls is presented in Table 2. The observed genotype frequencies for each SNP in *SLC6A2* did not differ from those expected from Hardy-Weinberg equilibrium in patients with bipolar I disorder or in controls ($p > 0.05$, χ^2 test) (Table 2).

3.3. Association between SLC6A2 SNPs and bipolar I disorder

The minor allele frequencies of rs28386840, rs2242446, and rs5569 are shown in Table 2. The frequencies of the variants were similar to those of East Asians in the 1000 Genomes Project (Consortium, 2015). Associations between bipolar I disorder and SLC6A2 SNPs, controlling for age and sex, are shown in Table 3. In the multivariate logistic regression analysis, the rs28836840 SNP was significantly associated with bipolar I disorder. Individuals carrying a T allele were likely to have a lower risk of bipolar I disorder (OR = 0.643, 95% Cl = 0.468–0.883, $p = 0.006$, $q = 0.018$). However, we found no association of either rs2242446 or rs5569 with bipolar I disorder.

3.4. Multivariate regression analysis of influence of the rs28386840 on severity of manic and psychotic symptoms in bipolar I disorder patients

We conducted linear regression analysis to examine the association between variants of the rs28386840 and severity of manic and psychotic symptoms in bipolar I disorder patients. In multivariate linear regression, rs28836840 was associated with both severity of manic and psychotic symptoms (Table 4). The T allele showed a negative association with severity of manic and psychotic symptoms, respectively (manic symptoms: $\beta = -2.457$, 95% Cl = −4.674 ~ −0.239, $p = 0.031$; psychotic symptoms: $\beta = -2.501$, 95% Cl = −4.700 ~ −0.301, $p = 0.027$, respectively).

Table 1
Demographic data of the participants.

	Bipolar disorder (N = 160)	Healthy controls (N = 166)
	Mean ± SD or n (%)	Mean ± SD or n (%)
Age (years)	34.24 ± 11.42	34.81 ± 8.82
Sex (female)	93 (58.13)	101 (60.84)
Age of onset (years)	29.71 ± 10.39	–
Number of admissions	3.06 ± 2.61	–
Duration of illness (month)	19.86 ± 7.79	–
Baseline YMRS	31.13 ± 10.00	–
Baseline BPRS	23.74 ± 9.92	–

YMRS: Young Mania Rating Scale; BPRS: Brief Psychiatric Rating Scale.

3.5. Multivariate regression analysis of influence of allele type on other phenotypes in bipolar I disorder patients

There was no SNP that influenced age of onset (rs28836840, $p = 0.430$; rs2242446, $p = 0.713$; rs5569, $p = 0.937$), number of admissions (rs28836840, $p = 0.527$; rs2242446, $p = 0.397$; rs5569, $p = 0.918$), or duration of illness (rs28836840, $p = 0.264$; rs2242446, $p = 0.408$; rs5569, $p = 0.293$).

4. Discussion

The current study investigated whether three SNPs (rs28386840, rs2242446, and rs5569) of the *SLC6A2* gene confer susceptibility to bipolar I disorder and influence severity of manic or psychiatric symptoms in bipolar I disorder patients. The rs28836840 SNP was significantly associated with diagnosis of bipolar I disorder. Individuals with the T allele are likely to have a lower risk of bipolar I disorder compared to those without. In addition, bipolar I disorder patients with the T allele likely have reduced severity of manic or psychotic symptoms.

Regarding the functional mechanisms of rs28386840, a previous study reported that the T allele significantly decreased the *SLC6A2* gene promoter function, which results in lowered noradrenergic neurotransmission (Kim et al., 2006). Swann et al. (2013) investigated the association between norepinephrine and impulsivity using yohimbine, which increases norepinephrine release by blocking alpha-noradrenergic receptors. Yohimbine increased plasma MHPG and VMA levels, which increased impulsive errors, response bias and accelerated reaction times. Kurita et al. (2014) reported a significant positive correlation between severity of manic symptoms (YMRS scores) and plasma level of MHPG. In addition, plasma level of MHPG was reduced throughout the manic status, response, and remission stages. Based on these reports, the effects of the rs28386840 SNP, which decreases noradrenergic neurotransmission, may function as a protective factor in bipolar I disorder and a peripheral biomarker consistently indicating progression of symptoms from the manic state to the remission state in bipolar I disorder.

We observed consistent associations of rs28386840 with bipolar I disorder, manic symptoms, and psychotic symptoms. In terms of psychotic symptoms, a review study suggested that elevated NE signaling plays a particularly prominent role in the paranoid subtype of schizophrenia (Fitzgerald, 2014). In addition, a range of evidence suggests functional overlap between schizophrenia and bipolar disorder: 1) they run together in families and may share various alleles, 2) existence of schizoaffective disorder further suggests overlapping factors in the two diseases, 3) they share symptomatology such as paranoia, hallucinations, and delusions, and 4) they have overlapping drug treatments (Fitzgerald, 2014). Based on these findings, the rs28386840 SNP may represent a shared etiological genetic component between manic and psychotic symptoms in bipolar I disorders.

Previous studies have reported that rs2242446 SNPs were not causally related to bipolar disorder in Caucasian and Han Chinese populations, which is consistent with the results of our study (Chang et al., 2007; Leszczynska-Rodziewicz et al., 2002). Although the results of aforementioned studies were consistent with our study, there were several considerations. A recent meta-analysis study has revealed that rs2242446 and rs5569 are not susceptibility factors for major depressive disorder (MDD) (Zhao et al., 2013). However, stratified analysis by ethnicity indicated that variants of rs5569 SNPs were associated with increased risk of MDD among Asians but not among Caucasians (Rui et al., 2018). In addition, Kim et al. (2014) reported that rs2242446 was

Table 2
Genotype distributions of the genetic variants of *SLC6A2* in patients with bipolar disorder (BPD) and without BPD (controls).

SNP	Location	Alleles (Major/Minor)	BPD (n = 160)				Control (n = 166)			
			Genotype n (%)			HWE p-value	Genotype n (%)			HWE p-value[a]
rs28386840	5'-UTR	A/T	AA 58 (36.3%)	AT 76 (47.5%)	TT 26 (16.3%)	0.871	AA 39 (23.5%)	AT 86 (51.8%)	TT 41 (24.7%)	0.756
rs2242446	Promoter	T/C	TT 70 (43.8%)	TC 78 (48.8%)	CC 12 (7.5%)	0.147	TT 67 (40.4%)	TC 78 (47.0%)	CC 21 (12.7%)	0.868
rs5569	Exon	G/A	GG 69 (43.1%)	GA 78 (48.8%)	AA 13 (8.1%)	0.207	GG 85 (51.2%)	GA 69 (41.6%)	AA 12 (7.2%)	0.847

[a] p-value from χ^2 test.

Table 3
Associations of *SLC6A2* SNPs with bipolar I disorder (BPD).

SNP	Effect allele	Allele frequency[a]	Allele count[a] (%)		OR[b] [95% CI]	p-value	q-value[c]
			BPD (N = 160)	Control (N = 163)			
rs28386840	T	0.454	128 (40.0%)	168 (50.6%)	0.643 [0.468–0.883]	0.006	0.018
rs2242446	C	0.341	102 (31.9%)	120 (36.1%)	0.808 [0.576–1.133]	0.217	0.651
rs5569	A	0.302	104 (32.5%)	93 (28.0%)	1.257 [0.887–1.782]	0.199	0.597

[a] Frequency and count of effect alleles.
[b] Adjusted for age and sex.
[c] Corrected p-value for multiple testing using Bonferroni method.

Table 4
Associations of the rs28386840 SNPs with manic and psychotic symptoms in a sample of 160 bipolar I disorder patients.

	Effect allele	β[a] (SE)	95% CI	p-value
Manic symptoms	T	−2.457 (1.131)	−4.674 - -0.239	0.031
Psychotic symptoms	T	−2.501 (1.122)	−4.700 - -0.301	0.027

[a] Adjusted for age and sex.

associated with suicidality in patients with MDD. Therefore, further studies are needed to consider various ethnicities and various psychiatric symptoms rather than specific diagnoses.

Our study has several limitations that should be considered. First, the small sample size of this study may be insufficient to fully detect the association between genetic variants of *SLC6A2* and bipolar I disorder (3.5% for an alpha threshold of 0.017). However, even though our sample was relatively small, it was accurately selected to increase the predictive power of our results. Second, this study examined only three of many variants in the *SLC6A2* gene. Future studies should shed light on the role of other genetic variants in bipolar disorders. Third, this study included only a Korean population; therefore, further replication studies with larger samples containing different ethnicities are needed. Fourth, we did not exclude patients with intellectual disability. When intellectual disability coexists in patients with bipolar disorders, the severity of manic and psychotic symptoms may be worse. Further studies should consider intellectual disability as an exclusion criterion.

5. Conclusion

To summarize, this study investigated associations between three specific *SLC6A2* variants, bipolar I disorder, and severity of manic and psychotic symptoms. We established associations of rs28386840 with bipolar I disorder diagnosis and severity of manic and psychotic symptoms. However, the findings reported here require replication in larger samples with various ethnic groups.

Authors contribution

Yong-Ku Kim designed the study and managed all procedure of this study and prepared manuscript. Sang-Won Jeon, Younjung Lee, and Se Young Kim recruited the subjects and received the informed consent. Sang-Won Jeon conducted the interview using SCID. Sun-Young Kim and Han-Na Kim designed the study and undertook the statistical analysis. Sun-Young Kim and Han-Na Kim wrote the original manuscript. Sang Won Jeon, Weon-Jeong Lim, Soo In Kim, Se Young Kim and Yong-Ku Kim revised the article and contributed to the final version of the manuscript.

Ethical statement

The authors declare that all experiments on human subjects were conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the Korea University University, and all participants provided their informed consents.

Declaration of Competing Interest

The authors declare no conflict of interest to report.

Acknowledgements

The paper is supported by Korea University (K1700531).

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