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The impact of glycogen synthase kinase 3β gene on psychotic mania in bipolar disorder patients

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ABSTRACT

Objective: The aim of this study was to examine the relationships between glycogen synthase 3β gene polymorphisms and bipolar I disorder, manic in a Korean sample.
Methods: Patients with bipolar disorder (n = 118) and a control group (n = 158) were assessed by genotyping for GSK3β single nucleotide polymorphisms (SNPs) −1727A/T and −50C/T. The patients were divided into two groups according to the presence of psychotic symptoms (psychotic mania, n = 92; non-psychotic mania, n = 26) and also divided based on gender and age of onset. The severity of symptoms was measured using the Young Mania Rating Scale (YMRS) and the Brief Psychiatric Rating Scale (BPRS).
Results: There were no significant differences in the genotype distributions or allelic frequencies of GSK3β polymorphisms and gender between patients with bipolar disorder and a normal control group. According to haplotype analysis, there was no association between these two groups. However, analysis of the age of onset of bipolar disorder revealed significant differences in genotype and allele distributions among the patients. Patients who were homozygous for the wild-type variant (TT) had an older age of onset than carriers of the mutant allele (A/A: 27.4 ± 9.1; A/T: 30.1 ± 11.8; T/T: 42.3 ± 19.9; p = 0.034). We detected differences in allele frequencies of the GSK3β −1727A/T polymorphism between the psychotic mania group and the non-psychotic mania group.
Conclusion: This study suggests that GSK3β polymorphisms are not associated with bipolar disorder. However, the GSK3β SNP −1727A/T is associated with age of onset and presence of psychotic symptoms in bipolar disorder.

1. Introduction

Although the lifetime prevalence of bipolar disorder is approximately 1%, the morbidity rate among relatives of patients with bipolar disorder is 5–10% (Smoller and Finn, 2003). Therefore, it has been proposed that there is a stronger genetic component of bipolar disorder than other mood disorders; however genes associated with the disorder have not been identified.

Lithium and valproic acid are representative mood stabilizers used to treat acute-phase and maintenance-phase bipolar disorders. Although the mechanism of lithium has not yet been fully identified, (Klein and Melton (1996) suggested that lithium was effective in the treatment of bipolar disorder through direct inhibition of glycogen synthase kinase 3β (GSK3β). Valproic acid not only hinders GSK-3 directly, like lithium, but also suppresses it indirectly through phosphorylation of serine-9 of the protein (Chen et al., 1999; De Sarno et al., 2002; Grimes and Jope, 2001a; Kim et al., 2005). Therefore, results demonstrating that medications used for effective treatment of acute-phase and maintenance-phase bipolar disorders commonly suppress GSK3β imply that GSK3β plays a key role in the therapeutic action for bipolar disorder. The GSK3β gene contains single nucleotide polymorphisms (SNP), which are found most frequently at −1727A/T and −50C/T positions relative to the transcriptional start site and upstream of the coding sequence. Functional studies are required to evaluate these findings, because there is no obvious consensus sequence in the predicted promoter region for known transcription factor binding sites (Russ et al., 2002).

GSK3β is a serine/threonine kinase found in the cell cytoplasm, and activation of this kinase regulates the activity of substrates via the addition of phosphoric acid to either a serine or threonine residue of the substrate (Jope and Roh, 2006). GSK3β is important in three signaling pathways: the Wnt signaling pathway, the MAP kinase pathway, and

Abbreviations: GSK3β, Glycogen Synthase Kinase 3-beta; YMRS, Young Mania Rating Scale; BPRS, Brief Psychiatric Rating Scale; SNP, Single Nucleotide Polymorphism; DSM-IV, diagnosis criteria of Diagnostic and Statistical Manual of Mental Disorders-IV; SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorder; DNA, deoxyribonucleic acid; PCR, polymerase chain reaction; HTR, haplotype trend regression.

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the phosphatidylinositol-3 kinase pathway. Through these pathways, GSK-3 is known to control functions such as metabolism, gene expression, neuroplasticity, cell survival and death, neurogenesis and circadian rhythms in neurons (Grimes and Jope, 2001b).

The GSK3β gene is located on 3q13.3–21.1, and a previous study by Bailer et al. found that a potential gene related to bipolar disorder was also located on chromosome 3q. Therefore, it has been hypothesized that the GSK3β gene has a high possibility of being related to bipolar disorder (Bailer et al., 2002; Hansen et al., 1997). Many researchers have studied this possible relationship, but these studies have showed conflicting results. Lesort et al. (1999) reported autopsy data indicating that there were no differences in the amount and the activity of GSK3β protein compared to normal brain tissue in bipolar patients, and Nishiguchi et al. (2006) reported that the frequencies of the −1727A/T and −50T/C mutations of GSK-3β were not significantly different between bipolar patients and normal persons. However, Scassellati et al. (2007) suggested that GSK3β gene is unlikely to have a major effect on the genetic susceptibility to bipolar disorder, even when gender and age at onset of the disorder are taken into account. Benedetti et al. (2004) revealed that no association was detected between GSK3β −50T/C SNP and the presence of bipolar disorder, and GSK3β −50T/C homozygotes for the wild-type variant (T/T) displayed an earlier age at onset than did carriers of the mutant allele. Interestingly, Szczepankiewicz et al. (2006) found that a correlation between the C allele of −50C/T and T/C genotypes was observed in female patients with bipolar disorder type 2 but not in males. In a previous study, we examined the relationship between −1727A/T and −50C/T polymorphisms of GSK3β with mood disorders in 258 Korean patients with schizophrenia and bipolar disorder, and observed that the distributions of GSK3β gene polymorphisms and allelic frequencies were not significantly different between the patient group and a control group (Lee et al., 2006). Further research on the relationship between GSK3β and bipolar disorder in the Korean population is needed to elucidate the contradictory results found by these previous studies. The present study investigated the relationship between GSK3β and bipolar disorder in a Korean sample, and determined whether a connection between GSK3β and psychotic symptoms could be assessed using clinical characteristics such as age of onset and haplotype.

2. Subjects and methods

2.1. Subjects

The subjects of this study were 118 Korean psychiatric patients with bipolar disorder type 1 who were admitted for hospitalization at Korea University Ansan Hospital, Ansan, Korea through the outpatient clinic or emergency center. All subjects met the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) for bipolar disorder (APA, 1994). Each patient was assessed by a psychiatrist using the Structured Clinical Interview for DSM-IV Axis I Disorder (SCID-I) on the first day of hospitalization, and patients who did not cooperate in initial interviews were evaluated within three days of hospitalization (First et al., 1998). Exclusion criteria included other psychiatric disorders based on DSM-IV definitions, such as schizophrenia, alcohol abuse, substance abuse and personality disorders, organic brain disease and physical disease. Data regarding age of onset, duration, and numbers of illness episode were collected through reviews of medical histories and interviews with family members. The normal control group included 158 persons who visited the health promotion center of Korea University Ansan Hospital and volunteers who participated in this study. Individuals with psychiatric or family histories of psychiatric disease, and/or histories of taking psychiatric medications, were excluded from the control group. All study participants gave informed consent for participation. We assessed the severity of manic symptoms using the Young Mania Rating Scale (YMRS; Young et al., 1978) and psychotic symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS; 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 within three days of hospitalization. The presence of psychotic symptoms was evaluated by the existence of auditory hallucinations or delusions based on DSM-IV criteria and assessed via interviews with patients and reviews of medical records. This study was approved by the Institutional Review Board of Korea University Ansan Hospital.

2.2. Genotyping

DNA was extracted from blood leukocytes using the Wizard Genomic DNA purification kit (Promega, USA). Polymerase chain reaction (PCR) was performed to genotype the 1727A/T SNP of the GSK-3β gene with the forward primer 5′-TCA CAC AAA AAT CCA ATT TTG T-3′ and the reverse primer 5′-ACA GTG AGG TAT GGC TAC GTC A-3′. The amplification mixture contained 1 μl of 100 ng/μl DNA, 2.5 μl of 10× Ex Taq buffer, 2 μl of 2.5 mM Ex dNTP mixture, 1 μl primer, 18.375 μl distilled water, and 0.125 μl Taq polymerase (TaKaRa, Japan). Samples were amplified using a Thermocycler (GeneAmp PCR system 2700, Applied Biosystems, Foster City, CA, USA) for 36 cycles. After an initial 5 min at 95 °C, each cycle consisted of 45 s at 95 °C, 45 s at 54 °C, and 45 s 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 MseI (New England Biolabs), which targets the -1727A site, and the product

Table 1
Demographic characteristics of patients and normal control subjects.

Characteristic	Normal controls (N = 158)		Patients with psychotic features (N = 92)		Patients without psychotic features (N = 26)		Analysis	
	Mean ± SD		Mean ± SD		Mean ± SD		t	p
Age (years)	35.6 ± 8.6		33.8 ± 10.9		34.4 ± 12.5		0.06	0.81[a]
Age of onset (years)			28.4 ± 10.2		29.0 ± 11.5		0.04	0.84[b]
Number of episodes			2.5 ± 3.0		2.6 ± 2.2		0.03	0.87[b]
Years of education (years)	13.7 ± 2.2		12.4 ± 2.9		12.9 ± 1.6		0.54	0.46[b]
Duration of illness (month)			63.0 ± 84.4		100.0 ± 144.3		1.53	0.22[b]
Baseline YMRS			33.3 ± 10.3		30.4 ± 12.5		1.31	0.25[b]
Baseline BPRS			21.3 ± 9.3		16.1 ± 8.3		5.73	0.019*,[b]
	N	%	N	%	N	%	χ^2(df = 2)	p
Female (sex)	96	58.9	51	76.1	16	23.9	0.31	0.58[a]

SD: standard deviation, YMRS: Young Mania Rating Scale, BPRS: Brief Psychiatric Rating Scale.
[a] *t*-test between normal controls and patients with bipolar disorder.
[b] t-test between patients with psychotic features and patients without psychotic features.
* $p<0.05$.