Adv Ther (2017) 34:713–724
DOI 10.1007/s12325-017-0482-2

ORIGINAL RESEARCH

The Impact of a Single Nucleotide Polymorphism in *SIGMAR1* on Depressive Symptoms in Major Depressive Disorder and Bipolar Disorder

Laura Mandelli · Sheng-Min Wang · Changsu Han · Soo-Jung Lee · Ashwin A. Patkar · Prakash S. Masand · Chi-Un Pae · Alessandro Serretti

Received: November 20, 2016 / Published online: January 31, 2017

ABSTRACT

Introduction: Ample evidence suggested a role of sigma-1 receptor in affective disorders since the interaction of numerous antidepressants with sigma receptors was discovered. A recent study on Japanese subjects found a genetic variant within the encoding gene *SIGMAR1* (rs1800866A>C) associated with major depressive disorder (MDD). We aimed to evaluate the same polymorphism in both MDD and bipolar disorder (BD) as well as its relationship to response to treatment with antidepressants and mood stabilizers.

Methods: A total of 238 MDD patients treated for an acute episode of depression, 132 BD patients in treatment with mood stabilizers for a manic or mixed episode, and 324 controls were genotyped for rs1800866. At discharge, response to treatments was evaluated in MDD and BD patients by the Hamilton Rating Scale for Depression (HRSD) and the Young Mania Rating Score (YMRS), respectively.

Results: In our Korean sample, allele frequencies were different from those reported in other Asian and non-Asian populations. The CC genotype was associated with BD and, as a trend, with MDD. No significant effect was observed on response to antidepressants in MDD or mood stabilizers in BD, although the CC genotype was more frequent among BD patients experiencing a mixed episode.

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L. Mandelli · A. Serretti
Department of Biomedical and NeuroMotor Sciences, Institute of Psychiatry, University of Bologna, Bologna, Italy

S.-M. Wang · S.-J. Lee · C.-U. Pae (✉)
Department of Psychiatry, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea
e-mail: pae@catholic.ac.kr

S.-M. Wang
International Health Care Center, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea

C. Han
Department of Psychiatry, Korea University, College of Medicine, Seoul, Republic of Korea

A. A. Patkar · C.-U. Pae
Department of Psychiatry and Behavioural Sciences, Duke University Medical Center, Durham, NC, USA

P. S. Masand
Global Medical Education, New York, NY, USA

P. S. Masand
Academic Medicine Education Institute, Duke-NUS Medical School, Singapore, Singapore

Conclusion: The present findings are the first to propose the putative role of genetic variants within *SIGMAR1* and sigma-1 receptor in BD. Sigma-1 receptor can modulate a number of central neurotransmitter systems as well as some other signaling pathways (e.g., neurotrophin and growth factor signaling) which are seemingly involved in BD and other mood disorders.

Keywords: Antidepressants; Bipolar disorder; Major depressive disorder; Mood stabilizers; Psychiatry; Sigma-1 receptor; *SIGMAR1*

INTRODUCTION

Sigma-1 receptors have been implicated in many neuropsychiatric disorders including drug addiction, schizophrenia, depression, anxiety disorders, neurodegenerative disorders, HIV-related neurocognitive impairment, and pain disorders [1]. Sigma-1 receptors are located in the specialized endoplasmatic reticulum (ER) membrane directly apposing mitochondria (mitochondria-associated ER membrane) [2, 3], but their localization can be very dynamic: they can translocate to other areas of the cell [4, 5] where they can interact with a plethora of membrane targets such as voltage-gated ion channels, glutamate and gamma-aminobutyric acid (GABA) ionotropic receptors, muscarinic and nicotinic acetylcholine receptors, dopamine D_1 receptor, and intracellular targets [5, 6]. Sigma-1 receptors have been reported to affect overall neuronal excitability through inhibition of Na^+ and K^+ currents and facilitation or inhibition of voltage-gated Ca^{2+} channels [1]. Furthermore, sigma-1 receptors have the potential to modulate *N*-methyl-D-aspartate receptor (NMDAR, a glutamate receptor) transmission [7, 8] and influence the glutamatergic system and excitatory neurotransmission [1].

Although a precise mechanism of functional response to sigma-1 receptor is still uncertain, it has been accepted that it can modulate a number of central neurotransmitter systems including glutamate/NMDA, serotonergic, dopaminergic, noradrenergic routes, and other signaling pathways (e.g., neurotrophin and growth factor signaling) which are related to brain function and involved in neuropsychiatric disorders [9]. Upregulation of sigma-1 receptor exerts a potent neuroprotective effect by ameliorating the so-called ER stress [5, 10, 11]. The ER stress is a condition characterized by an accumulation of unfolded proteins caused by oxidative stress, ischemic insults, disturbances in calcium homeostasis, and enhanced expression of normal and/or folding-defective proteins [12, 13]. Accumulating evidence suggests a role of ER stress and misfolded proteins in pathophysiology of major depressive disorder (MDD) [5, 11], and a high level of ER stress proteins has been observed in temporal cortex of depressed patients [14]. Upregulation of sigma-1 receptor not only ameliorates ER stress but also results in secretion of brain-derived neurotrophic factors (BDNF) by potentiating conversion of precursor proBDNF to mature BDNF [11, 15, 16]. Evidence also suggested that sigma-1 receptor greatly potentiates nerve-growth factor (NGF)-induced neurite outgrowth [17]. Sigma-1 receptor is also stimulated by endogenous neuroactive steroids, dehydroepiandrosterone (DHEA). Moriguchi et al. [18] reported that sigma-1 receptor stimulation by DHEA in hippocampal dentate gyrus ameliorates depressive-like behaviors in olfactory bulbectomized mice by enhancing neurogenesis via activation of the protein kinase B (Akt)/glycogen synthase kinase-3 beta (GSK-3β)/β-catenin pathway.

Much evidence has linked sigma receptor and mood disorders ever since the interaction of numerous antidepressants with sigma receptors was first discovered. In particular, fluvoxamine is a potent agonist of sigma-1 receptor [19]. In mice, expression of sigma-1 receptor decreased after chronic dexamethasone infusion, and this decrease was normalized after fluvoxamine treatment [20]. In a study with a small sample of 12 late-life MDD patients [21], mean plasma sigma-1 receptor concentration was increased significantly following 8 weeks of antidepressant treatment. However, no significant correlation was found between changes in plasma sigma-1 receptor concentration and clinical response to 8 weeks of antidepressant treatment. Evidence for involvement of sigma-1

receptor in mood disorders also came from the observation that sigma-1 receptor knockout mice showed increased immobility (a depressive-like phenotype) in a forced swimming test and agonists of the sigma-1 receptor exerted antidepressant effects in animal models [22–26].

Genetic heterogeneity may alter expression and functionality of sigma-1 receptor, with significant results on neuronal excitability and plasticity. The gene coding for sigma-1 receptor is located on chromosome 9 (9p13.3), and it spans about 7 kb and contains four exons [27]. Two single nucleotide polymorphisms (SNPs) within sigma-1 receptor (*SIGMAR1*) (rs1799729 and rs1800866) were reported to be possibly functional [27, 28]. In particular, rs1800866 is contained in a substitution from glutamine (CAG) to proline (CCG) that may perturb appropriate regulation of sigma-1 receptor transportation from ER to plasma membrane [28]. In humans, genome-wide association studies reported that there are no associations among genes encoding for SIGMAR1, MDD [29, 30], and clinical response to treatment with citalopram [31, 32]. However, a recent study performed on an Asian population consisting of Japanese patients with MDD treated with fluvoxamine or sertraline found that rs1800866 in *SIGMAR1* is associated with pathophysiology of MDD but not with response to fluvoxamine or sertraline [33]. In line with this result, our review of current literature showed that sigma receptor-mediated events could modulate activity of certain conventional antiepileptic drugs and antidepressants implemented for treatment of BD [34] and MDD [35]. However, we were not able to find any studies suggesting relationship among SNPs and particularly bipolar disorder (BD) as well as investigations on correlation between SNPs with treatment response for BD.

Even in the most recent and extensive review of the field of antidepressant pharmacogenetics, there is no mention of the potential role and relevant impact of *SIGMAR1* on mood disorders [36]. A number of markers in relation to the development of mood disorders and response to antidepressants have been extensively tested at multiple levels including genetic, epigenetic, gene expression, and protein. However, only few pharmacogenetic markers (i.e., FKBP5 in signaling transduction, SLC6A4, ABCB1, and HTR2A in neurotransmission, and CYP450 isoenzymes in drug metabolism) have been addressed for their clinical utility in terms of diagnosis and treatment of mood disorders [36]. In addition, pharmacogenetic tests are neither advised to include and combine different types of biomarkers nor suggested to target specific subpopulations of MDD with heterogeneous clinical features and clinical dimensions of mood disorders [36].

Given the lack of sufficient data about role of *SIGMAR1* in MDD and BD, we investigated the role of a candidate SNP within *SIGMAR1* (rs1800866) in a Korean sample of subjects affected by MDD ($n = 242$) and BD ($n = 132$) as compared to healthy controls ($n = 324$). We also tested the potential influence of rs1800866 on antidepressant treatments in MDD patients during an acute depressive episode and mood stabilizers in BD patients during an acute manic/mixed episode.

METHODS

Subjects

Patients were consecutively collected among patients admitted to the psychiatric unit of the Department of Psychiatry, Catholic University of Korea College of Medicine, Seoul, Korea. Inclusion criteria were represented by age between 18 and 80 years, current episode of depression for MDD patients, current episode of mania/mixed episode for BD patients, monotherapy with venlafaxine or paroxetine in MDD patients, monotherapy with lithium, valproate, or carbamazepine in BD patients. Exclusion criteria were represented by current or recent substance abuse, severe or unstable medical condition that may impair evaluations, neurological disorders, non-Asian ethnicity, treatments other than those specified above with the exception of antianxiety drugs, poor understanding or fluency of Korean language, mental retardation. Healthy subjects who underwent the same assessment as psychiatric patients were included as a control

group. The controls were aged between 18 and 80 years, of Asian ethnicity with a good understanding and fluency of Korean language, did not have current or recent substance abuse, severe or unstable medical conditions, neurological disorders, mental retardation, and they were not receiving treatment with psychotropic drugs with the exception of sedative/hypnotic drugs.

Clinical and sociodemographic data were collected by means of interviews or revision of the clinical charts. Diagnoses of MDD, current depressive episode, and BD or current manic/mixed episode were made according to the Diagnostic and Statistical Manual of mental disorders IV, text revised (DSM-IV-TR) criteria by the structured clinical interview for DSM-IV (SCID-I) [37]. Symptoms severity was evaluated by the Hamilton Rating Scale for Depression (HRSD) [38] in both MDD and BD patients, and the Young Mania Rating Scale (YMRS) [39] in BD patients only. All the patients were evaluated for symptoms severity at admission and discharge. Evaluations were performed by trained interviewers blind to genetic data.

The percentage change of the HDRS and YMRS scores from baseline to discharge was calculated by means of the formula $100 - (D/B \times 100)$, where D stands for discharge score and B for baseline score. Response was defined as a $\geq$50% symptoms reduction from baseline to discharge. Remission was defined as a YMRS score $\leq$12 and HAMD score $\leq$7 at discharge, respectively. Drug dosage equivalents were calculated according to the Columbia Antidepressant History Form (ATHF) [40, 41]. For antidepressants, dosage equivalents were calculated as follow: (1) paroxetine <10 mg/day or venlafaxine <75 mg/day, (2) paroxetine 10–19 mg/day or venlafaxine 75–149 mg/day, (3) paroxetine 20–39 mg/day or venlafaxine 150–224 mg/day, (4) paroxetine $\geq$40 mg/day or venlafaxine $\geq$225 mg/day. For mood stabilizers, dosage equivalents were calculated as follow: (1) lithium or valproate <600 mg/day, or carbamazepine <200 mg/day, (2) lithium or valproate 600–899 mg/day or carbamazepine 200–399 mg/day, (3) lithium or valproate $\geq$900 mg/day or carbamazepine $\geq$400 mg/day.

Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. All the patients were informed in detail about the aims and the procedures of the study and they signed an informed consent prior to inclusion into the study. The protocol and the informed consent were approved by the local ethical committee (approval number HC10TISI0031).

Statistical Analysis

All the statistical analyses were performed by the Statistica software [42]. Descriptive statistics were based on calculation of mean, standard deviation, and percentages.

For linear analyses we used the correlation analysis, the Student t test, and the one-way or repeated analysis of variance (ANOVA). To control for potential confounders and to test interactive effects we employed the linear or binary logistic regression analysis.

Although we performed a large number of tests, given the preliminary nature of the study we chose to maintain a threshold of $p < 0.05$ for significant associations, in order to detect small but potentially interesting effects that may deserve attention in further studies. With this parameter value, we had a sufficient power of 0.80 to detect small effect sizes of $w = 0.12$ in case–control associations with three genotypes.

Genetic Analysis

Genomic DNA was extracted from blood and quantified using standard methods [43]. A high-throughput genotyping method using a pyrosequencer (Biotage, Uppsala, Sweden) was used for genotyping the one rs1800866 *SIGMAR1* SNP. Polymerase chain reaction primers and sequencing primers (Bioneer, Daejeon, Korea) used for the pyrosequencing assay were designed using the Pyrosequencing Assay Design Software v1 (Biotage).

RESULTS

Healthy controls were 177 women (54.6%) and 147 men (45.4%), aged 45.4 ± 13.1 years. Healthy controls were not different from MDD patients in terms of sex and age, while BD patients comprised more men ($\chi^2 = 16.06$ $p < 0.001$) and were younger ($t = 6.23$ $p < 0.001$). Clinical and demographic variables of MDD and BD patients are reported in Table 1.

Genotypes for rs1800866 were in Hardy–Weinberg equilibrium ($p = 0.72$). According to the International HapMap project (http://www.hapmap.org), in Asians (Chinese population), the common variant for rs1800866 is the A allele (≈0.78), while in this Korean sample we found the opposite C allele having a higher frequency (0.65) than that of the A allele (0.35).

Genotypes for rs1800866 were not differentially stratified across healthy controls or MDD and BD patients (Table 2). However, BD patients showed a trend of association with the CC genotype when compared to controls ($\chi^2 = 5.76$, $p = 0.056$). Comparing CC homozygous with A allele carriers, the CC genotype was significantly associated with BD ($\chi^2 = 5.45$, $df = 0.019$, OR = 0.58 95% CI 0.38–0.87). Controlling for sex and age, the effect remained significant ($B = 0.26$, $p = 0.018$). Though not significantly, the CC genotype was also more represented among MDD (43.3%) than in controls (37.4%) ($p = 0.16$, OR = 0.45 95% CI 0.32–0.64) and, overall, mood disorder patients taken together were significantly more CC homozygous than controls ($\chi^2 = 4.63$, $p = 0.031$, OR = 0.50 95% CI 0.37–0.67, controlling for sex and age: $B = 0.17$, $p = 0.024$).

Response to Antidepressant Response in Patients Affected by Major Depressive Disorder (MDD)

From intake to discharge, HDRS scores decreased significantly ($t = 20.40$, $df = 237$, $p < 0.001$). Controlling for sex, age, and medication dose equivalents, the type of administered drug (paroxetine or venlafaxine) did not impact on improvement of depressive

Table 1 Demographic and clinical data of major depressive disorder (MDD) and bipolar disorder (BD) patients

	MDD (n = 238) *N* (%)	**BD (n = 132)** *N* (%)
Female	149 (62.6)	45 (34.1)
Positive FH of psychiatric disorders	193 (100.0)	35 (94.6)
Missing	45	95
Suicide history	53 (22.4)	22 (19.8)
Missing	1	21
	Mean (SD)	**Mean (SD)**
Age	43.6 (14.8)	37.2 (11.9)
Missing	1	1
Age at onset	39.7 (13.7)	26.7 (8.7)
Missing	1	10
Illness duration	3.9 (5.3)	11.9 (9.9)
Missing	1	11

MDD major depressive disorder, *BD* bipolar disorder, *FH* family history

Table 2 rs1800866 genotypes stratified for cases and controls

	CC		CA		AA		X^2; p
Controls	121	37.4%	164	50.6%	39	12.0%	6.43; 0.17
MDD	103	43.3%	105	44.1%	30	12.6%	
BD	65	49.2%	52	39.4%	15	11.4%	

MDD major depressive disorder, *BD* bipolar disorder

Table 3 Clinical features of patients with MDD stratified for rs1800866 genotypes

	CC		CA		AA		F; p
	$N = 103$		$N = 105$		$N = 30$		
	N/mean	(%/SD)	N/mean	(%/SD)	N/mean	(%/SD)	
Baseline HRSD	23.7	(7.4)	22.4	(7.2)	21.6	(7.2)	1.36; 0.26
Discharge HRSD	14.8	(7.2)	12.7	(6.2)	13.2	(5.6)	2.58; 0.08*
Response (% from baseline)	36.9	(25.9)	42.1	(24.7)	37.0	(22.8)	1.27; 0.28
Responders	35	38.9%	47	52.2%	8	8.9%	4.43; 0.11
Remitters	25	41.0%	29	47.5%	7	11.5%	0.40; 0.82
Type of AD							
Paroxetine	67	40.6%	76	46.1%	22	13,3%	1.57; 0.46
Venlafaxine	36	49.3%	29	39.7%	8	11.0%	
AD doses							
Paroxetine	21.2	(9.2)	20.5	(9.3)	18.8	(10.7)	0.49; 0.61
Venlafaxine	157.5	(25.4)	154.0	(21.3)	168.8	(34.7)	1.08; 0.35
Drug dose equivalents	2.0	(0.5)	1.9	(0.5)	1.9	(0.6)	0.62; 0.54

MDD major depressive disorder, *AD* antidepressant, *HRSD* Hamilton Rating Scale for Depression
* $p < 0.05$

symptoms ($p = 0.16$). Clinical data of MDD, stratified for rs1800866 genotypes, are reported in Table 3. Genotypes were not associated with response or remission after antidepressant treatment, though CC homozygotes showed a trend for higher scores at discharge. Comparing CC homozygotes with A allele carriers and controlling for age and sex, the trend was maintained ($B = 0.05$, $p = 0.057$).

Response to Mood Stabilizers

Manic symptoms severity significantly decreased during treatment ($t = 16.22$, $df = 131$, $p < 0.001$). Sex, age, and rs1800866 did not influence the course of symptoms ($p = 0.94$). Controlling for sex, age, and medication dose equivalents, the type of administered drug (lithium, carbamazepine, or valproate) did not impact on improvement of depressive symptoms ($p = 0.16$). Antianxiety drugs and their dose equivalents did not impact on response and remission either. Clinical data of BD, stratified for rs1800866 genotypes, are reported in Table 4. Genotypes were not associated with response or remission after treatment. However, CC homozygotes had more severe depressive symptoms at baseline and they were more likely to meet diagnosis for a mixed episode.

Table 4 Clinical features of patients with BD stratified for rs1800866 genotypes

	CC		CA		AA		*F*	*p*
	N = 65		*N* = 52		*N* = 15			
	Mean	SD	Mean	SD	Mean	SD		
Drug dose equivalents	1002.2	372.7	1107.0	309.1	1028.6	535.5	0.90	0.41
Baseline YMRS	32.9	10.1	33.6	7.9	33.9	8.9	0.12	0.89
YMRS at discharge	19.6	6.1	19.9	4.0	20.1	5.5	0.09	0.92
Baseline HRSD	8.7	4.2	7.3	3.5	4.7	3.5	7.15	0.001
HRSD at discharge	3.3	2.7	2.8	2.3	2.1	2.0	1.55	0.22
	N	%	*N*	%	*N*	%	X^2	*p*
Mixed episode	39	58.2	25	37.3	3	4.5	8.45	0.015
Treatment								
Carbamazepine	2	50.0	1	25.0	1	25.0	1.66	0.80
Lithium	18	43.9	19	46.3	4	9.8		
Valproate	25	44.6	22	39.3	9	16.1		
Responders	17	51.5	13	39.4	3	9.1	0.26	0.88
Remitters	7	70.0	1	10	2	20	4.74	0.09

MDD major depressive disorder, *BD* bipolar disorder, *AD* antidepressant, *HRSD* Hamilton Rating Scale for Depression, *YMRS* Young Mania Rating Scale

DISCUSSION

Despite existing evidence of sigma-1 receptor being a target of commonly used antidepressants [19], its involvement in depressive-like behaviors in animals (e.g., see [18]) and in the regulation of systems involved in the pathophysiology of depressive disorders [1, 9, 14, 16, 17], only few and inconsistent human studies have tested the role of *SIGMAR1* gene in mood disorders and its relationship with treatment responsiveness. As mentioned, large genome-wide association studies reported no association among *SIGMAR1*, MDD [29, 30], and clinical response to treatment with citalopram [31, 32]. However, two recent studies reported that antidepressant treatments are associated with increased plasma levels of sigma-1 receptors in MDD patients [21] and SNP rs1800866 was associated with MDD in a sample of Japanese subjects [33], although neither of these studies found a relationship with therapeutic response. To the best of our knowledge, no study investigated *SIGMAR1* in BD. Therefore, we aimed to (1) replicate the association between rs1800866 within *SIGMAR1* and MDD [33] and test the association with response to other antidepressant treatments; (2) test the association with BD and therapeutic response to mood stabilizers.

First, contrary to our expectation, in our Korean population, the minor allele C for rs1800866 was more frequent than the major allele A (minor allele frequency, MAF ≈64.8). According to the International HapMap project (http://hapmap.ncbi.nlm.nih.gov), MAF is of about 0.10 in Caucasians and 0.22 in the Asian Japanese population.

Second, the CC genotype was associated with BD and, to a lower extent, with MDD. While Kishi et al. reported that there is an association between the AA genotype and MDD

[33], we found an opposite relationship between rs1800866 genotypes and mood disorders. Nevertheless, this finding may go along with the different frequency of the rs1800866 alleles in the two populations. Genetic variants present different frequencies in different populations and they may have opposite effects on a phenotype, probably because of different linkage disequilibrium with another causal mutation, the so-called flip-flop effect [44]. In our sample, MDD patients showed only a trend of association with the CC genotype. However, Kishi and colleagues found an association between the CC genotype with MDD small in effect size ($p = 0.02$, OR = 0.56) in a larger sample of 466 MDD patients and 516 controls. The sample size of our study was relatively small, with 238 MDD and 324 controls, which may have prevented us from detecting significant smaller effect size.

We found that the rs1800866 was significantly associated with BD. To the best of our knowledge, no previous study investigated *SIGMAR1* gene in BD. Evidence showed the involvement of sigma-1 receptor in schizophrenia, and a recent meta-analysis of the literature found that rs1800866 was associated with schizophrenia in Japanese populations [45, 46]. Since sigma-1 receptor directly or indirectly regulates signal transduction, ER stress, cellular redox, and cellular survival and synaptogenesis, and some of their ligands exert antidepressants and neuroprotective actions [11], they may also be involved in BD. We found that the CC genotype was associated with more severe depressive symptoms at baseline in BD patients having a mixed episode. Thus, the CC genotype may not only predispose development of BD but may also be involved in development of more complicated illness such as co-occurrence of manic and depressive symptoms, which are often more resistant to monotherapy with mood stabilizers [47]. Accordingly, patients with a diagnosis of mixed episode showed a poorer response to mood stabilizers ($\chi^2 = 4.94$, $p = 0.026$) than those who showed either manic or depressive episodes. We believe that further investigation is needed with regard to this interesting yet still elusive finding.

No evidence of involvement of sigma-1 receptor in the response to either antidepressants or mood stabilizers agents was noted, with the exception of a non-significant trend for slightly higher depressive symptoms in CC allele carriers at the end of follow-up. Except for the small trend pertaining to antidepressant response, our data are in line with the study by Kishy et al. [33] which showed that there is no association between CC allele carriers and treatment response in MDD patients who received fluvoxamine or sertraline. It is unclear from the published paper whether the authors analyzed clinical response in relation to the different agents, but it seems that rs1800866 influenced response to neither sertraline nor fluvoxamine. In our study, the specific medication did not have interactive effects with rs1800866 genotype either. These data are in contrast with other evidence supporting antidepressants interacting with sigma-1 receptor. However, antidepressants are known to have different levels of affinity for sigma-1 receptor, and some have no affinity at all. Fluvoxamine has the highest affinity for this receptor, followed by sertraline and fluoxetine. Citalopram and paroxetine seem to have a scarce or null affinity for sigma-1 receptor [19]. Venlafaxine is also known to have a very weak affinity for this receptor [48]. Therefore, with regard to both paroxetine and venlafaxine reserving poor affinity for sigma-1 receptor, the genetic variability for *SIGMAR1* may not influence the clinical heterogeneity of therapeutic response to these drugs. Future studies should be focused on more active ligands of sigma-1 receptor, such as fluvoxamine, fluoxetine, and sertraline.

Very limited evidence has reported an interaction between common mood stabilizers used or treatment of BD and sigma-1 receptor activity. To the best of our knowledge, sigma receptor-mediated events can modulate the activity of some conventional antiepileptic drugs. A sigma receptor ligand (3-PPP) has been reported to diminish protective activity of valproate, but not that of carbamazepine, against maximal electroshock [34], but a direct effect of antiepileptic drugs on sigma-1 receptor has not yet been proven. To date, there is no data

supporting a role of mood stabilizers in targeting or regulating sigma-1 receptor activity. In our study, we found no evidence for an involvement of the rs1800866 variants in response to mood stabilizers, but further studies both aimed at testing the role of *SIGMAR1* in disease risk and mood stabilizers efficacy are necessarily required.

A number of limitations should be considered. The overall samples size was clearly limited for genetic studies, but it had a sufficient statistical power to detect significant small effects. We performed a large number of tests comparing not only cases and controls but also analyzing genotypes in association with remission and response to antidepressants, mood stabilizers, and other clinical variables. Thus, the multiple comparisons may have increased the risk to detect false positive findings which are very common in candidate gene studies. If we considered a correction for multiple testing, e.g., two case–control analyses and two tests on response to antidepressants and to antimanic agents, we would have to consider a significance level of at least 0.0125 (Bonferroni correction: 0.05/4 tests), leading to loss of a number of interesting results in the present study. To the best of our knowledge, this the first study which specifically focused on a genetic variant within *SIGMAR1* in both MDD and BD as well as response to antidepressants and mood stabilizers. Thus, we decided not to correct for multiple testing in order to maximize the possibility of obtaining data so that the data may be further investigated in future studies pertaining to larger and independent samples or different ethnic groups. In addition, correction of multiple comparisons may also create some caveats as proposed by a number of researchers: loss of valuable intriguing findings, hindering the advance of the research, reduction of sample power, production of publication bias, increase of type II error; on the other hand, simple description of types of significance test and the reason why could be a practical and alternative way to deal with multiple comparisons [49, 50]. Further, MDD and BD share only a part of the genetic liability.

In the present study only one SNP was considered. The *SIGMAR1* gene spans about 7 kb and contains four exons and several polymorphic regions which could potentially modulate the biologic activity. However the rs1800866 polymorphism is most widely investigated in the literature, mostly in Asians (Japanese especially), with evidence of it being functional [27, 28]. Since we were unable to detect studies on *SIGMAR1* in the Korean population, and only few other validated polymorphisms in the promoter, coding exon, and 3′UTR regions with a minor allele frequency (MAF) >0.05 are reported, we decided to focus specifically on this variant only.

The BD sample was composed of patients having a manic or mixed episode only, as we were specifically interested in response to antimanic agents. We did not collect information regarding previous episodes, and it may be possible that the included BD patients represent a subgroup of subjects suffering from frequent manic/mixed episodes. Having no such information, the association between *SIGMAR1* and BD may not be the same as in other more heterogeneous samples. On the other hand, the inclusion of patients with concurrent depressive symptoms allowed us to detect an association between *SIGMAR1* and more severe depressive symptoms in manic patients as discussed above.

As previously stated, we were specifically interested in response to antidepressants and mood stabilizers, so we included patients only under monotherapy with the exception of antianxiety drugs. In addition, only patients under monotherapy with specific drugs were included (i.e., venlafaxine or paroxetine in MDD and lithium or valproate or carbamazepine in BD). On the one hand, this strict selection of drugs may represent a point of strength of the study (i.e., decrease bias from various treatment regimens); on the other hand, we cannot generalize the findings obtained on response to other antidepressants and mood stabilizers. This is especially important in the case of antidepressants, as they have different affinity for sigma-1 receptors.

CONCLUSION

In our Korean sample, we found a different distribution of alleles for rs1800866 (higher frequency of minor allele C than major allele A) when compared to other Asian (Japanese and Chinese) and Caucasian populations. In partial agreement with a previous study [33], this polymorphism showed a trend of association with MDD, but the CC genotype was especially more frequent in BD subjects than in controls, and the same genotype was more frequent among patients experiencing a mixed episode. To the best of our knowledge, this is the first report suggesting a role for sigma-1 receptor and the encoding gene in BD. No influence of the rs1800866 was observed in treatment response either with antidepressants in MDD or to mood stabilizers in mixed/manic BD patients. Nevertheless, given previous evidence of some antidepressants as agonists of sigma-1 receptor, further studies on antidepressants with high affinity for this receptor should be performed. The role of sigma-1 receptor in BD and potential interaction with mood stabilizer agents also deserve further investigation.

ACKNOWLEDGEMENTS

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (Grant Number : HC15C1405).

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Disclosures. Laura Mandelli, Sheng-Min Wang, Changsu Han, Soo-Jung Lee, Ashwin A. Patkar, Prakash S. Masand, Chi-Un Pae, and Alessandro Serretti declare no personal, financial, commercial, or academic conflicts of interest.

Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. All the patients were informed in detail about the aims and the procedures of the study and they signed an informed consent prior to inclusion into the study. The protocol and the informed consent were approved by the local ethical committee (approval number HC10TISI0031).

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request. All authors presented no conflicts of interest to disclose.

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