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# Influence of *BDNF* Variants on Diagnosis and Response to Treatment in Patients with Major Depression, Bipolar Disorder and Schizophrenia

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**Key Words**
Brain-derived neurotrophic factor · BDNF · Major depression · Bipolar disorder · Schizophrenia

**Abstract**
***Aim:*** The present study aimed to explore whether some single nucleotide polymorphisms (SNPs) within the *BDNF* gene could be associated with major depression (MD), bipolar disorder (BD) and schizophrenia, and whether they could predict clinical outcomes in Korean inpatients treated with antidepressants, mood stabilizers and antipsychotics, respectively. ***Methods:*** One hundred and forty-five patients with MD, 132 patients with BD, 221 patients with schizophrenia and 170 psychiatrically healthy controls were genotyped for 5 *BDNF* SNPs (rs2030324, rs7103873, rs10835210, rs11030101 and rs6265). Baseline and final clinical measures – including the Montgomery-Asberg Depression Rating Scale, Young Mania Rating Scale and Positive and Negative Symptoms Scale for patients with MD, BD and schizophrenia, respectively – were recorded. ***Results:*** rs10835210 CA and rs11030101 AT genotype frequencies were higher in BD and schizophrenia patients than in healthy and MD subjects. No significant association was found with clinical improvement. ***Discussion:*** Our findings provide evidence of an association between BDNF and BD and schizophrenia. However, taking into account the several limitations of our study, including the moderately small sample size, further research is needed to draw more definitive conclusions.



## Introduction

Neurotrophins are putative factors involved in the development and maintenance of peripheral and central nervous system (CNS) functions [1], and whose disruption affects how neuronal networks are developed or maintained [2]. Alterations in neurotrophin levels have repeatedly been observed in patients with psychiatric disorders [3], and several psychotropic treatments have been found to regulate brain levels of neurotrophins [e.g. 4, 5]. Increasing evidence suggests that one neurotrophin in particular, brain-derived neurotrophic factor (BDNF), could be one of the key factors involved in the etiology and response to treatment of several psychiatric disorders [6–8].

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BDNF has survival-promoting actions on a variety of CNS neurons including hippocampal and cortical neurons [9, 10], as well as cholinergic [11], nigral dopaminergic [12] and serotonergic ones [13]. In fact, BDNF knockout mice exhibit enhanced hippocampal cell death as compared with wild-type animals [10]. Conversely, exogenous BDNF administration has been found to increase the survival of the hippocampal neurons lacking BDNF [10] and to protect against reductions in striatal dopamine content induced by neurotoxins in the mouse [14]. Furthermore, infusion of BDNF in the midbrain exerts a potent neurotrophic effect on serotonergic neurons [15] and infusion of BDNF into the forebrain is followed by a significant elevation of serotonin neuronal fiber density and protection of neurons from neurotoxic damage [16].

Several studies have reported alterations of BDNF expression in animal models of major depression (MD) and schizophrenia, which can be reverted by pharmacological treatment [6–8]. Similarly, in human studies, decreased BDNF levels which can be reverted by pharmacological treatment have repeatedly been observed in several psychiatric disorders including MD [17, 18], bipolar disorder (BD) [19, 20] and schizophrenia [21, 22].

Following such findings, increasing emphasis has been given to the role of several genetic variants within the BDNF gene (*BDNF*) mapping to chromosome 11p13, a region with potentially significant links to schizophrenia [23], concerning the etiology and response to treatment of such disorders. The most consistently investigated single nucleotide polymorphism (SNP) in *BDNF* is Val66Met, also known as G196A or rs6265. Several studies have suggested that rs6265 variants could be associated with MD in samples of different ethnicities [24–28], even though such findings have not been consistently replicated [29]. In addition, the same variant has also been involved in the response to selective serotonin reuptake inhibitors in MD patients of Asian ethnicity [30–32]. However, such findings were not replicated in Korean subjects treated with mirtazapine [33], nor in German patients treated with various antidepressants [34].

Pertaining to patients suffering from BD, the val66val allele of *BDNF* seems to be associated with an increased risk of BD as well as with early onset and rapid cycling, even though such an association was not consistently replicated in Asian populations [8]. In addition, a few studies have recently suggested that rs6265 variants could be involved in the response to lithium [35–37]. However, discrepant results have also been reported [38], and there is no complete consensus with regard to the specific variants involved [39]. Also, there is some evidence to suggest that rs6265 variants could be associated with a diagnosis of schizophrenia [40] and related traits [41], but not in response to antipsychotic treatments [42]. However such findings have not been replicated and negative results have consistently been reported as well [43].

Of note, several other SNPs within BDNF have been investigated in association with psychiatric disorders and patient response to the treatments mentioned above. However, inconsistent results have frequently been observed. As an example, rs2030324 has been explored in association with both MD [26, 44] and schizophrenia [40], as well as with the response to some psychotropic medications such as lithium [35]. However, no association was observed between such SNPs and outcomes of interest. In a further study, rs10835210 was associated with the response to escitalopram in patients with MD [45] but the same SNP was not associated with MD in an independent study [44], and there is a lack of empirical evidence concerning a possible role of such SNPs in other psychiatric disorders. Also, a recent study has observed an association between MD and 5 further SNPs within *BDNF* (rs12273539, rs11030103, rs28722151, rs41282918 and rs11030101) [26], and other studies have suggested possible associations between further SNPs and MD [24], BD [46, 47] and schizophrenia [48, 49]. Note, however, that such observations, mainly derived from studies with small sample sizes, fall short of replications and should therefore be considered with caution.

Overall, such findings suggest that at least rs6265 and possibly other genetic variants in *BDNF* could play an important role in the etiology of several psychiatric disorders as well as in the response to some of their treatments, even though there is not yet complete consensus with regard to the specific variants involved. Significant differences across the studies in terms of psychiatric disorders, pharmacological treatments, psychometric assessments and ethnicities under investigation, as well as different criteria for defining remission and response, could partially explain why discrepant findings have sometimes been observed. In addition, so far there is only a little evidence concerning the association between several *BDNF* SNPs and the etiology and response to treatment of the psychiatric disorders mentioned above.

Accordingly, the present paper aims to investigate whether a set of SNPs within *BDNF* including rs6265 and other 4 SNPs which have received little attention so far (rs2030324, rs7103873, rs10835210, rs11030101) could be associated with MD, BD and schizophrenia, and to explore whether such variants could predict clinical outcome in patients suffering from MD, BD and schizophre-

**Table 1.** BDNF SNPs considered in this study

| SNP ID | Position | Distance | Alleles | Location | Amino acid change |
|---|---|---|---|---|---|
| rs2030324 | 27683491 (–5964) | 26,598 | T/C | promoter | none |
| rs7103873 | 27656893 (20635) | 4,407 | G/C | intron | none |
| rs10835210 | 27652486 (25042) | 15,166 | C/A | intron | none |
| rs11030101 | 27637320 (40208) | 828 | A/T | intron | none |
| rs6265 | 27636492 (41036) | | G/A | coding exon | 66 V/M |

Position refers to absolute chromosomal position, with the relative position to the start codon given in parenthesis. V = Valine; M = methionine. All data from www.snpper.chip.org.

nia naturalistically treated with antidepressants, mood stabilizers and antipsychotics, respectively. In addition, as a secondary outcome, we explored whether such variants could be associated with clinical and sociodemographic variables of our sample.

## Methods

*Subjects*

The sample under investigation in the present study comprised 145 inpatients suffering from MD, 132 inpatients with BD, and 221 inpatients with schizophrenia who were consecutively recruited at the Department of Psychiatry of the Catholic University of Korea College of Medicine, Seoul, Korea. As this study is a post hoc convenience analysis, the sample size was not determined a priori. Patients were eligible for inclusion if they had a documented clinical diagnosis of MD, BD or schizophrenia according to the DSM-IV criteria, as assessed by the Mini-International Neuropsychiatric Interview (MINI) [50]. The sample has been previously reported by our group investigating other genes.

There were not any particular restrictions with respect to treatments, concomitant comorbidities and first vs. following episodes of disease. However, patients were excluded if they currently had severe or unstable medical and neurological conditions, were being treated with a long-acting antipsychotic, had concomitant alcohol and substance abuse disorders, and if they were not of Korean ethnicity. The choice not to use excessively tight inclusion and exclusion criteria was motivated by the decision to include a sample of subjects that could be representative of the usual psychiatric inpatients in Korea. A further sample of 170 Korean psychiatrically healthy subjects – who underwent the same assessment as psychiatric patients to exclude possible psychiatric disorders and who were asked for the presence of any known psychiatric disorder in first- and second-degree relatives, and came from the same location as the psychiatric patients in the present study – was also included to compare genotype and allelic frequencies between the 4 populations of subjects under investigation.

All patients admitted to the hospital were assessed for the severity of illness at baseline and at discharge by means of psychometric questionnaires specific to each disorder under investigation. In more detail, MD severity was assessed by means of the Hamilton Rating Scale for Depression (HAM-D) [51], mania severity in patients with BD was assessed by means of the Young Mania Rating Scale (YMRS) [52], and schizophrenia severity was assessed by means of the Positive and Negative Symptoms Scale (PANSS) [53]. Scorers were trained with the specific instruments with good inter-rater reliability ($\kappa > 0.8$). Additionally, the following clinical and demographic variables were recorded: gender, age, clinical subtypes, age at onset, familiar history of psychiatric disorders, lifetime suicide attempts, duration of admission, drugs at discharge and concomitant anxiolytics. The study protocol was approved by the institutional review board (approval number HC10TISI0031). All patients (18–65 years old) provided written informed consent before participating in the study.

*Outcome Measures*

The main outcome measures of the present study were: (1) differences between genetic and allelic frequencies in patients with MD, BD and schizophrenia, as well as healthy control subjects, and (2) influences of the five SNPs under investigation on clinical improvement in the 3 groups of psychiatric patients mentioned above separately analyzed. Secondary outcomes of interest included the effects of SNPs on the clinical and demographic variables mentioned above, as well as on response and remission rates. Both continuous and categorical analyses were performed. In accordance with previous studies, response was defined a priori as a $\geq$50% reduction in symptoms from baseline to discharge [e.g. 54–56]. Remission was defined as a MADRS score $\leq$7 at discharge for patients with MD [54] and as a YMRS score $\leq$12 for patients with BD [57]. Unfortunately, it was not possible to determine remission rates for patients with schizophrenia, as current consensus-based operational criteria require data from 8 single items of the PANSS [58] (or the Brief Psychiatric Rating Scale [59]) that were not recorded in the present study.

*DNA Analysis*

The genetic SNPs included in the present study were chosen among those which were either previously investigated in association with MD, BD and schizophrenia and/or with response to pharmacological treatments of such diseases or with a reported prevalence of at least 5% for the variant allele among Asian populations (data from http://hapmap.ncbi.nlm.nih.gov/) and not previously investigated. Genomic DNA was extracted from blood by

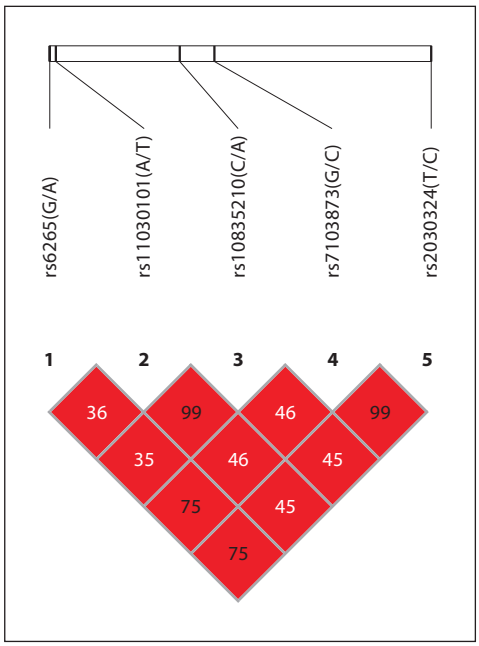


**Fig. 1.** LD and D′ for five SNPs within *BDNF*.

standard methods and quantified. High-throughput genotyping using a pyrosequencer (Biotage AB, Sweden) was utilized for genotyping the five SNPs (rs2030324, rs7103873, rs10835210, rs11030101 and rs6265) of *BDNF* under investigation (table 1). PCR primers (Bioneer, Daejeon, Korea) and sequencing primers (Bioneer) used for the pyrosequencing assay were designed by using the Pyrosequencing Assay Design Software v.1 (Biotage), and 1 primer of each primer set was biotinylated.

*Statistical Analysis*

Statistical analyses were performed using the Statistica package for Windows. Differences in the allelic and genetic frequencies between healthy subjects and patients with MD, BD and schizophrenia, as well as the effects of such variants on response and remission rates, were calculated using the $\chi^2$ statistic. Clinical improvements were investigated by means of repeated-measures ANOVA. In order to exclude possible confounding factors, we performed a correlation analysis among all variables under investigation versus the dependent ones. We then included variables that were significantly associated with any specific outcome of interest during following analyses as needed. Haploview 3.2 was used to generate a linkage disequilibrium (LD) map and to test for Hardy-Weinberg equilibrium (HWE) [60]. Tests for associations using multi-marker haplotypes were performed using the statistics environment 'R' (http://www.R-project.org), package 'haplo.score', to compare response and remission rates among different haplotypes. Permutations (n = 10,000) were performed to estimate the global significance of the results for all haplotypes analyses and to validate the expectation-maximization values. Further analyses were performed using Statistica.

All p values were 2-tailed. Statistical significance was calculated by means of the false discovery rate which allows for a correction of multiple testing without being as conservative as the Bonferroni correction [61]. Taking into account the strong LD between rs11030101 and rs10835210 as well as between rs7103873 and rs2030324, we only corrected for 3 SNPs, for disease conditions (n = 3) and main outcomes of interest (n = 2). The first time for which the inequality was reversed was 0.015. With these parameters we had a sufficient power (0.80) to detect a small-medium effect size (ω = 0.16) that, as an example, corresponded to an odds ratio of 1.94 between the 3 groups of patients and the group of controls and to detect medium to medium-large (d = 0.29, 0.31 and 0.24) effect sizes for patients with MD, BD and schizophrenia, respectively, carrying the AA genotype of rs11030101 as compared with those carrying the AT genotype [62]. Such effects sizes corresponded to the possibility of detecting final differences on MADRS, YMRS and PANSS scores of 4, 4 and 6.5 points, respectively.

## Results

*Sociodemographic Features of MD Patients and Controls*

Sociodemographic features, such as gender, age and further clinical and sociodemographic variables, are reported in table 2. For control subjects, only data on gender and age were collected. The groups did not differ with regard to gender ($\chi^2 = 6.66$, p = 0.11), whereas they differed with regard to age ($\chi^2 = 3.75$, p = 0.01). Patients with BD were significantly younger and patients with MD were significantly older than patients with schizophrenia and healthy controls.

*HWE and LD for rs2030324, rs7103873, rs10835210, rs11030101 and rs6265*

All 5 SNPs within *BDNF* were in HWE in the whole sample (rs2030324: p = 1, rs7103873: p = 0.58, rs10835210: p = 0.66, rs11030101: p = 0.41, rs6265: p = 0.36). Strong LD was observed among all SNPs, particularly between rs11030101 and rs10835210 as well as between rs7103873 and rs2030324 (fig. 1). Patients and healthy volunteers separately analyzed yielded similar results (data not shown). The only exceptions included rs10835210 and rs11030101, which were not in HWE in the samples of subjects with MD (p = 0.04 for both SNPs) or BD (p = 0.04 and 0.03, respectively).

*Differences between Genotype and Allele Frequencies in MD, BD, Schizophrenia Patients and Healthy Controls*

There were significant differences in the genotype frequencies of rs10835210, rs11030101 across different groups of subjects. Rs10835210 CA and the rs11030101 AT geno-

**Table 2.** Clinical and demographic characteristics of the sample

| | | MD (n = 145) | BD (n = 132) | Schizophrenia (n = 221) | Controls (n = 170) |
|---|---|---|---|---|---|
| Gender | males | 75 (52) | 87 (66) | 126 (57) | 105 (62) |
| | females | 70 (48) | 45 (34) | 95 (43) | 65 (38) |
| Age | | 41.37 ± 14.07 | 36.35 ± 11.60 | 38.01 ± 12.67 | 38.83 ± 12.80 |
| HAM-D | baseline | 28.20 ± 6.52 | | | |
| | discharge | 13.70 ± 8.01 | | | |
| YMRS | baseline | | 33.27 ± 9.09 | | |
| | discharge | | 19.80 ± 5.25 | | |
| PANSS total | baseline | | | 94.05 ± 13.75 | |
| | discharge | | | 76.63 ± 9.01 | |
| Clinical subtypes | MD/BD without PF | 105 | 73 (55) | not available | |
| | MD/BD with PF | 11 | 57 (43) | | |
| | dysthymia | 4 | – | | |
| | MD NOS | 5 | – | | |
| | missing values | 20 | 2 (2) | | |
| Age at onset, years | | 38.08 ± 13.29 | 26.58 ± 10.19 | 28.46 ± 10.98 | |
| Family history of psychiatric disorders | yes | 30 (21) | 42 (32) | 38 (17) | |
| | no | 92 (63) | 35 (26) | 183 (83) | |
| | missing values | 23 (16) | 55 (42) | 0 | |
| Suicide attempts | yes | 36 (25) | 22 (17) | 43 (19) | |
| | no | 92 (63) | 89 (67) | 178 (81) | |
| | missing values | 17 (12) | 21 (16) | 0 | |
| Duration of admission, days | | 32.31 ± 20.55 | 33.66 ± 21.07 | 37.64 ± 16.75 | |
| Drug | paroxetine | 35 (24) | | | |
| | venlafaxine | 21 (14) | | | |
| | fluoxetine | 40 (27) | | | |
| | mirtazapine | 23 (16) | | | |
| | lithium | | 41 (31) | | |
| | valproate | | 56 (42) | | |
| | lamotrigine | | 5 (4) | | |
| | risperidone | | | 78 (34) | |
| | olanzapine | | | 54 (24) | |
| | quetiapine | | | 13 (6) | |
| | amisulpride | | | 32 (15) | |
| | other | 3 (3) | – | 6 (4) | |
| | missing values | 23 (16) | 30 (23) | 38 (17) | |
| Concomitant anxiolytics | alprazolam | 30 (21) | 5 (4) | 22 (10) | |
| | lorazepam | 73 (50) | 82 (62) | 198 (90) | |
| | clonazepam | 3 (2) | 3 (3) | 0 | |
| | BuSpar | 4 (3) | 7 (5) | 0 | |
| | none | 35 (24) | 35 (26) | 0 | |

Figures represent numbers with percentages in parentheses or means ± SD. PF = Psychotic features; NOS = not otherwise specified.

**Table 3.** Allelic and genotype frequencies in subjects with MD, BD, schizophrenia, healthy control subjects and in the general Asian population

| MD | BD | Schizophrenia | Healthy subjects | General population | $\chi^2$ | p value |
|---|---|---|---|---|---|---|
| *Allele frequencies* | | | | | | |
| rs2030324 | | | | | | |
| T: 158 (55%) | T: 133 (50%) | T: 211 (48%) | T: 163 (48%) | T: 45% | 3.80 | 0.28 |
| C: 132 (45%) | C: 131 (50%) | C: 231 (52%) | C: 177 (52%) | C: 55% | | |
| rs7103873 | | | | | | |
| G: 158 (55%) | G: 133 (50%) | G: 211 (48%) | G: 162 (48%) | G: 45% | 3.95 | 0.26 |
| C: 132 (45%) | C: 131 (50%) | C: 231 (52%) | C: 178 (52%) | C: 55% | | |
| rs10835210 | | | | | | |
| C: 208 (72%) | C: 178 (67%) | C: 291 (66%) | C: 226 (66%) | C: 63% | 3.08 | 0.37 |
| A: 82 (28%) | A: 86 (33%) | A: 151 (34%) | A: 114 (34%) | A: 37% | | |
| rs11030101 | | | | | | |
| A: 208 (72%) | A: 179 (68%) | A: 292 (66%) | A: 226 (66%) | A: 60% | 2.92 | 0.40 |
| T: 82 (28%) | T: 85 (32%) | T: 150 (34%) | T: 114 (34%) | T: 40% | | |
| rs6265 | | | | | | |
| G: 152 (52%) | G: 150 (57%) | G: 260 (59%) | G: 197 (58%) | G: 63% | 3.19 | 0.36 |
| A: 138 (48%) | A: 114 (42%) | A: 182 (41%) | A: 143 (42%) | A: 37% | | |
| *Genotype frequencies* | | | | | | |
| rs2030324 | | | | | | |
| T/T: 42 (29%) | T/T: 30 (23%) | T/T: 49 (22%) | T/T: 38 (22%) | T/T: 21% | | |
| T/C: 74 (51%) | T/C: 73 (55%) | T/C: 113 (51%) | T/C: 87 (51%) | T/C: 49% | 4.69 | 0.58 |
| C/C: 29 (20%) | C/C: 29 (22%) | C/C: 59 (27%) | C/C: 45 (27%) | C/C: 30% | | |
| rs7103873 | | | | | | |
| G/G: 42 (29%) | G/G: 30 (23%) | G/G: 49 (22%) | G/G: 38 (22%) | G/G: 21% | | |
| G/C: 75 (51%) | G/C: 73 (55%) | G/C: 113 (51%) | G/C: 86 (51%) | G/C: 49% | 4.92 | 0.55 |
| C/C: 29 (20%) | C/C: 29 (22%) | C/C: 59 (27%) | C/C: 46 (28%) | C/C: 30% | | |
| rs10835210 | | | | | | |
| C/C: 80 (55%) | C/C: 54 (41%) | C/C: 93 (42%) | C/C: 81 (48%) | C/C: 41% | | |
| C/A: 48 (33%) | C/A: 70 (53%) | C/A: 105 (48%) | C/A: 64 (37%) | C/A: 43% | 18.01 | 0.006 |
| A/A: 17 (12%) | A/A: 8 (6%) | A/A: 23 (10%) | A/A: 25 (15%) | A/A: 16% | | |
| rs11030101 | | | | | | |
| A/A: 80 (55%) | A/A: 55 (42%) | A/A: 94 (43%) | A/A: 81 (48%) | A/A: 47% | | |
| A/T: 48 (33%) | A/T: 69 (52%) | A/T: 104 (47%) | A/T: 64 (37%) | A/T: 37% | 16.99 | 0.009 |
| T/T: 17 (12%) | T/T: 8 (6%) | T/T: 23 (10%) | T/T: 25 (15%) | T/T: 16% | | |
| G/G: 40 (27%) | G/G: 40 (30%) | G/G: 77 (35%) | G/G: 58 (34%) | G/G: 45% | | |
| G/A: 72 (50%) | G/A: 70 (53%) | G/A: 106 (48%) | G/A: 81 (48%) | G/A: 37% | 4.19 | 0.65 |
| A/A: 33 (23%) | A/A: 22 (17%) | A/A: 38 (17%) | A/A: 31 (18%) | A/A: 18% | | |

The $\chi^2$ statistics refer to subjects with MD, BD, schizophrenia and healthy controls. Data from the general population have been retrieved from international databases (http://snpper.chip.org).

type frequencies were more represented in subjects with BD and schizophrenia as compared with healthy controls and particularly with MD subjects (table 3). There were no further significant differences between genotype and allele frequencies in patients with MD, BD and schizophrenia and in healthy controls (table 3; all p values >0.015). Furthermore, there were no differences in haplotype frequencies across samples.

*BDNF rs2030324, rs7103873, rs10835210, rs11030101 and rs6265 and Clinical Improvement*

We did not observe any significant association between the 5 genotypes, alleles and haplotypes under investigation and clinical improvement (all p values >0.015).

**Table 4.** Main clinical characteristics of patients according to genotype

| | | Females | Suicide attempts | Concomitant anxiolytics | Familial history of psychiatric disorders | Age years | Age at onset years | Duration of admission days | Baseline HAM-D scores | Baseline YMRS scores | Baseline total PANSS scores |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *MD* | | | | | | | | | | | |
| rs2030324 | T/T | 21 (50) | 10 (26) | 31 (74) | 9 (26) | 42.42 ± 16.15 | 39.54 ± 13.08 | 33.11 ± 27.69 | 27.77 ± 5.65 | | |
| | T/C | 37 (50) | 20 (31) | 55 (74) | 17 (25) | 41.40 ± 14.35 | 38.16 ± 14.28 | 32.62 ± 18.15 | 28.25 ± 6.55 | – | |
| | C/C | 12 (41) | 6 (24) | 24 (83) | 4 (14) | 39.16 ± 14.12 | 34.08 ± 12.53 | 32.95 ± 18.82 | 26.16 ± 6.31 | | – |
| rs7103873 | G/G | 21 (50) | 10 (26) | 31 (74) | 9 (26) | 42.42 ± 16.15 | 39.54 ± 13.08 | 33.11 ± 27.69 | 27.77 ± 5.65 | | |
| | G/C | 37 (50) | 20 (31) | 55 (74) | 17 (25) | 41.40 ± 14.35 | 38.16 ± 14.28 | 32.62 ± 18.15 | 28.25 ± 6.55 | – | |
| | C/C | 12 (41) | 6 (24) | 24 (83) | 4 (14) | 39.16 ± 14.12 | 34.08 ± 12.53 | 32.95 ± 18.82 | 26.16 ± 6.31 | | – |
| rs10835210 | C/C | 39 (48) | 19 (26) | 56 (70) | 43 (89) | 41.00 ± 15.08 | 38.63 ± 13.30 | 31.64 ± 22.56 | 28.36 ± 5.68 | | |
| | C/A | 22 (46) | 15 (37) | 40 (83) | 69 (86) | 41.17 ± 14.42 | 37.95 ± 14.57 | 35.57 ± 20.22 | 27.12 ± 7.11 | – | – |
| | A/A | 7 (41) | 2 (13) | 14 (82) | 16 (88) | 39.69 ± 15.33 | 32.69 ± 11.96 | 30.38 ± 19.04 | 26.00 ± 6.09 | | |
| rs11030101 | A/A | 39 (48) | 19 (26) | 56 (70) | 43 (89) | 41.00 ± 15.08 | 38.63 ± 13.30 | 31.64 ± 22.56 | 28.36 ± 5.68 | | |
| | A/T | 22 (46) | 15 (37) | 40 (83) | 69 (86) | 41.17 ± 14.42 | 37.95 ± 14.57 | 35.57 ± 20.22 | 27.12 ± 7.11 | – | – |
| | T/T | 7 (41) | 2 (13) | 14 (82) | 16 (88) | 39.69 ± 15.33 | 32.69 ± 11.96 | 30.38 ± 19.04 | 26.00 ± 6.09 | | |
| rs6265 | G/G | 19 (47) | 10 (29) | 25 (76) | 7 (21) | 37.78 ± 13.93 | 33.50 ± 12.63 | 31.15 ± 17.43 | 26.28 ± 6.17 | | |
| | G/A | 33 (46) | 16 (26) | 53 (74) | 14 (23) | 43.50 ± 14.04 | 40.00 ± 14.41 | 34.75 ± 25.56 | 28.43 ± 7.01 | – | – |
| | A/A | 18 (55) | 10 (28) | 32 (80) | 9 (24) | 40.57 ± 16.77 | 37.92 ± 12.22 | 30.78 ± 15.20 | 27.75 ± 4.23 | | |
| *BD* | | | | | | | | | | | |
| rs2030324 | T/T | 11 (37) | 6 (25) | 23 (77) | 8 (40) | 35.14 ± 11.51 | 25.32 ± 10.42 | 31.89 ± 16.73 | | 34.85 ± 8.82 | – |
| | T/C | 23 (32) | 8 (13) | 55 (75) | 21 (52) | 37.18 ± 12.24 | 25.91 ± 9.78 | 35.70 ± 24.84 | – | 31.35 ± 8.28 | |
| | C/C | 11 (40) | 8 (32) | 19 (65) | 13 (68) | 37.16 ± 11.51 | 29.70 ± 11.73 | 30.50 ± 14.99 | | 34.41 ± 8.94 | |
| rs7103873 | G/G | 11 (37) | 6 (25) | 23 (77) | 8 (40) | 35.14 ± 11.51 | 25.32 ± 10.42 | 31.89 ± 16.73 | | 34.85 ± 8.82 | – |
| | G/C | 23 (32) | 8 (13) | 55 (75) | 21 (52) | 37.18 ± 12.24 | 25.91 ± 9.78 | 35.70 ± 24.84 | – | 31.35 ± 8.28 | |
| | C/C | 11 (40) | 8 (32) | 19 (65) | 13 (68) | 37.16 ± 11.51 | 29.70 ± 11.73 | 30.50 ± 14.99 | | 34.41 ± 8.94 | |
| rs10835210 | C/C | 20 (37) | 9 (20) | 41 (78) | 15 (39) | 36.25 ± 10.81 | 26.15 ± 10.78 | 30.51 ± 17.12 | | 33.82 ± 8.99 | – |
| | C/A | 22 (31) | 12 (20) | 40 (70) | 24 (60) | 37.11 ± 13.16 | 26.87 ± 10.45 | 37.46 ± 24.85 | – | 31.88 ± 8.39 | |
| | A/A | 3 (37) | 1 (14) | 6 (75) | 3 (60) | 36.28 ± 9.25 | 27.42 ± 8.50 | 26.85 ± 10.94 | | 33.71 ± 8.26 | |
| rs11030101 | A/A | 20 (37) | 9 (20) | 41 (78) | 15 (39) | 36.25 ± 10.81 | 26.15 ± 10.78 | 30.51 ± 17.12 | | 33.82 ± 8.99 | – |
| | A/T | 22 (31) | 12 (20) | 40 (70) | 24 (60) | 37.11 ± 13.16 | 26.87 ± 10.45 | 37.46 ± 24.85 | – | 31.88 ± 8.39 | |
| | T/T | 3 (37) | 1 (14) | 6 (75) | 3 (60) | 36.28 ± 9.25 | 27.42 ± 8.50 | 26.85 ± 10.94 | | 33.71 ± 8.26 | |
| rs6265 | G/G | 17 (43) | 10 (28) | 28 (70) | 16 (71) | 40.00 ± 12.63 | 30.85 ± 10.88 | 33.64 ± 16.94 | | 39.56 ± 33.14 | – |
| | G/A | 20 (29) | 8 (14) | 53 (76) | 19 (44) | 35.62 ± 11.33 | 24.86 ± 9.65 | 33.75 ± 24.88 | – | 40.30 ± 32.29 | |
| | A/A | 8 (36) | 4 (22) | 16 (73) | 7 (44) | 34.05 ± 11.22 | 24.30 ± 10.11 | 33.25 ± 16.10 | | 40.78 ± 34.15 | |
| *Schizophrenia* | | | | | | | | | | | |
| rs2030324 | T/T | 24 (49) | 13 (27) | 49 (100) | 6 (12) | 39.00 ± 13.41 | 29.00 ± 11.40 | 37.97 ± 19.38 | | | 93.42 ± 15.76 |
| | T/C | 48 (43) | 20 (18) | 113 (100) | 21 (19) | 38.51 ± 12.72 | 28.50 ± 10.80 | 37.14 ± 16.21 | – | – | 93.89 ± 13.34 |
| | C/C | 23 (39) | 10 (17) | 59 (100) | 11 (19) | 37.55 ± 12.41 | 27.93 ± 11.13 | 38.06 ± 14.75 | | | 93.87 ± 11.85 |
| rs7103873 | G/G | 24 (49) | 13 (27) | 49 (100) | 6 (12) | 39.00 ± 13.41 | 29.00 ± 11.40 | 37.97 ± 19.38 | | | 93.42 ± 15.76 |
| | G/C | 48 (43) | 20 (18) | 113 (100) | 21 (19) | 38.51 ± 12.72 | 28.50 ± 10.80 | 37.14 ± 16.21 | – | – | 93.89 ± 13.34 |
| | C/C | 23 (39) | 10 (17) | 59 (100) | 11 (19) | 37.55 ± 12.41 | 27.93 ± 11.13 | 38.06 ± 14.75 | | | 93.87 ± 11.85 |
| rs10835210 | C/C | 48 (52) | 21 (23) | 93 (100) | 14 (15) | 38.29 ± 13.20 | 29.31 ± 11.20 | 37.27 ± 18.29 | | | 94.06 ± 15.33 |
| | C/A | 39 (37) | 17 (16) | 105 (100) | 19 (18) | 38.83 ± 12.61 | 28.11 ± 11.09 | 38.10 ± 15.24 | – | – | 93.79 ± 12.22 |
| | A/A | 48 (52) | 5 (22) | 23 (100) | 5 (22) | 36.52 ± 11.90 | 26.69 ± 9.70 | 36.43 ± 15.43 | | | 92.69 ± 11.52 |
| rs11030101 | A/A | 48 (52) | 21 (23) | 93 (100) | 14 (15) | 38.29 ± 13.20 | 29.31 ± 11.20 | 37.27 ± 18.29 | | | 94.06 ± 15.33 |
| | A/T | 39 (37) | 17 (16) | 105 (100) | 19 (18) | 38.83 ± 12.61 | 28.11 ± 11.09 | 38.10 ± 15.24 | – | – | 93.79 ± 12.22 |
| | T/T | 48 (52) | 5 (22) | 23 (100) | 5 (22) | 36.52 ± 11.90 | 26.69 ± 9.70 | 36.43 ± 15.43 | | | 92.69 ± 11.52 |
| rs6265 | G/G | 34 (44) | 13 (17) | 77 (100) | 15 (19) | 38.18 ± 12.11 | 28.32 ± 11.18 | 38.42 ± 14.85 | | | 93.59 ± 11.64 |
| | G/A | 44 (42) | 20 (19) | 106 (100) | 20 (19) | 38.24 ± 12.50 | 27.78 ± 9.70 | 36.55 ± 16.05 | – | – | 93.75 ± 15.04 |
| | A/A | 17 (45) | 10 (26) | 6 (16) | 3 (8) | 39.05 ± 14.85 | 30.56 ± 13.58 | 38.64 ± 20.83 | | | 94.29 ± 12.85 |

Data presented as n with percentage in parentheses, or means ± SD. Percentages refer to the number of cases for which information was available.

*BDNF rs2030324, rs7103873, rs10835210, rs11030101 and rs6265 and Response, Remission Rates and Further Clinical and Sociodemographic Variables*

An association was observed between rs6265 variants and age at onset in patients with BD. In more detail, patients carrying the AA and the AG genotype showed a lower age of onset as compared with those carrying the GG genotype ($F = 5.91$, d.f. = 1, 242, $p = 0.015$; table 4). Similarly, allele analysis showed that BD subjects carrying the A allele of rs6265 had a significantly lower age of onset as compared with those carrying the G allele. In accordance with such findings, the analysis of the rs10835210-rs11030101-rs6265 and of the rs11030101-rs6265 haplotypes showed a trend for an association between such haplotypes and age of onset in BD patients (global-stats = 8.69, d.f. = 3, $p = 0.03$, and global-stats = 7.44, d.f. = 2, $p = 0.02$, respectively). In particular, the C-A-A rs10835210-rs11030101-rs6265 as well as the rs11030101-rs6265 A-A haplotypes were associated with lower age at onset ($p = 0.012$ and 0.018, respectively) whereas the C-A-G rs10835210-rs11030101-rs6265 as well as the rs11030101-rs6265 A-G were associated with a higher age of onset ($p = 0.012$ for both analyses). Adding covariates to such analyses did not significantly influence the results. No further genotype, allele or haplotype analysis focusing on the 5, 4, 3 and 2 SNPs' haplotypes was significantly associated with any clinical or sociodemographic variable (all $p > 0.015$).

## Discussion

The present paper was aimed at exploring whether specific SNPs within *BDNF,* including rs2030324, rs7103873, rs10835210, rs11030101 and rs6265, could be associated with MD, BD and schizophrenia, and whether the same variants could predict clinical outcomes in such groups of patients treated with antidepressants, mood stabilizers and antipsychotics, respectively. In addition, we explored whether such variants could be associated with several clinical and sociodemographic variables in our sample.

First of all, our results suggest that the rs10835210 CA and the rs11030101 AT genotype frequencies were higher in subjects with BD and schizophrenia as compared with healthy control subjects and particularly with subjects with MD. The observation that such heterozygous genotypes rather than the homozygous genotypes were associated with specific disorders is consistent with negative findings of the allele analysis. Even though such markers do not alter the protein sequence, it is noteworthy that they could have functional relevance in the regulation of gene expression [63]. However, taking into account that such SNPs were not in HWE in the subsamples of patients with MD and BD, possibly because of the limited sample size of our sample or due to sampling errors, such results should be considered with extreme caution and further research is needed to achieve more definitive conclusions. Of note, in an early study, rs10835210 variants were not found to be associated with MD in an independent family-based study focusing on Chinese subjects [44]. Such a finding is consistent with the results of the present study, where the largest differences in rs10835210 variants were observed between BD and schizophrenia patients on the one hand and healthy controls and MD patients on the other. However, no significant difference was observed in rs10835210 genotype frequencies between MD patients and psychiatrically healthy subjects.

On the other hand, we did not find any association between rs6265 variants in healthy subjects and psychiatric patients. Even though several studies have suggested that rs6265 variants could be associated with MD in samples of different ethnicities [24–28], it is worth mentioning that a recent study and meta-analysis did not support the existence of an association between rs6265 and MD [29]. Furthermore, current preliminary evidence suggests that specific haplotypes including rs6265 rather than single-locus analyses could be associated with a diagnosis of schizophrenia [40] and that rs6265 is not associated with BD in Asian populations [8]. Overall, our findings suggesting no association between rs6265 and MD, BD and schizophrenia are consistent with the available literature on this topic.

Additionally, we did not find any significant association between the alleles, genotypes and haplotypes under investigation in the present study and the response to treatments. Previous studies reported an association between rs6265 variants and response to fluoxetine and citalopram in patients with MD of Asian ethnicity [30, 31]. However, such findings were not replicated in Korean subjects treated with mirtazapine [33] and in German patients treated with various antidepressants [34]. Taking into account the use of different antidepressants as well as the relatively small sample size of our study, further research in larger samples focusing on single rather than on miscellaneous antidepressants is needed to clarify whether the negative results observed in our study could be ascribed to our methodology or they could reflect a real lack of association between response to ADs and rs6265 in Korean subjects. Furthermore, there is limited

evidence focusing on the role of several *BDNF* SNPs, including those investigated in the present study, and the response to antidepressants, mood stabilizers and antipsychotics. However, consistent with the results of our study, available preliminary studies suggest that such SNPs are not significantly associated with response to psychotropic medications [35, 42, 45].

Finally, we observed a significant association between the rs6265 A allele as well as the AA and AG genotypes and a lower age of onset in patients with BD. Interestingly, previous studies have shown that the val allele of rs6265 (corresponding to A allele in our study) could be associated with BD in children and adolescents [8]. Even though in the present study the A allele was only associated with a slightly earlier onset of BD, it is noteworthy that the results of our study go in the same direction as those of earlier studies, and further research is needed to confirm such an association in larger samples. On the other hand, our results did not provide evidence concerning an association between SNPs under investigation in the present study and further clinical or sociodemographic variables, a result that substantially replicates those of earlier studies.

Before firm conclusions are drawn, however, several limitations affecting the present study should be carefully considered. First of all, candidate genetic studies (as the present one) are associated with a high likelihood of false-positive findings [64]. Accordingly, further replications in independent samples are needed to confirm our results. On the other hand, negative results observed in our study could be simply related to the lack of statistical power, which could obscure small effects exerted by single SNPs or to the possibility that SNPs under investigation in our study could be associated with a diagnosis of a psychiatric disorder or with response to treatments only when interacting with specific environmental cues. Indeed, such an issue is particularly concerning as the present study is a post hoc analysis and no a priori analysis was performed to establish the minimum sample size required to detect small genetic differences. In addition, in genetic studies, biological measures (usually defined as biomarkers) are increasingly used in order to have more pathophysiologically homogenous samples. As an example, a recent study showed that the risk of depression onset was associated with heightened morning salivary cortisol levels, which in turn was modulated by *BDNF* genes [65]. The weakness of not having defined 'more homogenous' samples of patients by using biomarkers may have contributed to the negative pharmacogenetic results.

A further concern is related to the use of several drugs with different mechanisms of action for each cohort of patients that do not allow one to draw definitive conclusions with regard to the influence of the SNPs under investigation upon specific drugs or classes of drugs. However, our decision to include patients treated with different drugs could have the advantage of being closer to 'real world' clinical practice. Additionally, our categorization of psychiatric disorder was based upon current DSM-IV criteria, as assessed by the MINI. However, with such an instrument there is neither the ability to rule out the possibility that patients with MD could switch in the future to a diagnosis of BD, nor to exclude a possible switch to schizoaffective disorder. Such issues are important for genetic studies, as shown by recent findings suggesting that BD and schizophrenia could share many important risk genes [66]. Also, the duration of hospitalization in the present study could be considered insufficient to ascertain a lack of response and remission, though this time frame is consistent with common clinical practice [67]. Furthermore, we asked healthy controls to report only known psychiatric disorders among first- and second-degree relatives, thereby limiting the possibility to detect whether sub-threshold or untreated psychiatric disorders among family members of healthy control subjects could exist. Finally, in the present study, we investigated only 5 SNPs that further tag another 11 SNPs (data from http://hapmap.ncbi.nlm.nih.gov/), even though *BDNF* includes 209 validated SNPs; as a consequence, we were able to cover approximately only 2.5% of the gene variance.

In conclusion, our study suggests that rs10835210 CA and rs11030101 AT genotypes could be associated with BD and schizophrenia, and that the A allele as well as the AA and AG genotypes of rs6265 could be associated with lower age of onset in BD patients as compared with the G allele and the GG genotype. However, taking into account the several limitations stated above, further research is needed to confirm and extend our results.


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