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Research Article

The Association between Brain-Derived Neurotrophic Factor Gene Polymorphisms and Suicidal Behavior in Major Depression

Mira Choo, Yong Ku Kim*, Jung A Hwang, Heon Jeong Lee and Seung Hyun Kim

Department of Psychiatry, Korea University, Korea

***Corresponding author:** Yong Ku Kim, Department of psychiatry, University of Korea, College of Medicine, 152-703, Gojan 1-dong, Danwon-gu, Ansan, Gyeonggi-Do, Republic of Korea, Tel: 8231 412 5140; Fax: 8231 412 5144; Email: younku@korea.ac.kr

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Abstract

Objectives: Previous studies have suggested that genetic factors affect suicidal behavior in major depression. In particular, Brain-Derived Neurotrophic Factor (BDNF) genes have received much attention because of a possible association between such genes and suicidal behavior in major depression. In this study, we aimed to investigate associations between two BDNFSNPs (196G/A, 11757G/C) and suicidal behavior in major depression.

Method: Participants were 120 Major Depressive Disorder (MDD) patients attempting suicidal behavior, 117 non-suicidal MDD patients and 180 healthy controls. The genotype and allele frequencies of each group were analyzed using chi-squared statistics. Frequencies and haplotype reconstructions were calculated using SNP Analyzer 2.0.

Results: No significant associations were found between genotype distributions or allele frequencies of the two tested polymorphisms (196 G/A, 11757G/C) among suicidal MDD patients, non-suicidal MDD patients and controls. In the haplotype study, there was also no significant difference in haplotype analysis between suicidal MDD patients and non-suicidal MDD patients. However, the BDNF 196A–11757C haplotype combinations and196G–11757C haplotype combination were significantly lower in the suicidal MDD group and non-suicidal MDD group compared to healthy controls.

Conclusion: We did not find any relation between the tested BDNF genes and suicidal behavior in MDD. However, this study is significant in that this is the first haplotype study that tried to identify the associations between BDNF SNPs and suicidal behavior in a Korean population. Future research should be conducted with larger sample size sand more genetic markers, taking ethnicity into consideration.

Keywords: Suicide; Major depressive disorder; Brain-derived neurotrophic factor; Single nucleotide polymorphism; Gene

Abbreviations

BDNF: Brain-Derived Neurotrophic Factor; MDD: Major Depressive Disorder; SNP: Single Nucleotide Polymorphism

Introduction

Suicide is a prominent problem because it causes a high socioeconomic burden and significant disruption in interpersonal relationships and within the family [1,2]. Worldwide, the yearly suicide rate is approximately 16 per 100,000 people, which represents a substantial increase of 45% over the past 45 years; suicide is a major cause of death throughout the world [3]. Despite the devastating effects of depression and suicide on public health, there is still a dearth of knowledge regarding the underlying mechanisms of their pathogenesis.

It has been proposed that depression and suicide results from an inability of the brain to make appropriate adaptive synaptic responses to environmental stimuli. And the maladaptive response is regarded as the result of impaired synaptic/structural plasticity [4,5]. Neurotrophins provide a set of signals for survival and development of neurons in the central nervous system. Thus, it has been suggested that a pathological alteration of the neurotrophic factor system may lead to defects in neural maintenance and regeneration, reduce neural plasticity and eventually impair an individual's ability to adapt to crisis situations [6]. Among a variety of neurotrophins, Brain-Derived Neurotrophic Factor (BDNF), along with its receptors, TrkB and $p75^{NTR}$, has gained broad attention as a functional candidate gene in various mental disorders. The BDNF gene lies on the reverse strand of chromosome 11p13 and encodes a precursor peptide, pro-BDNF. In addition, BDNF is one of the most abundant neurotrophins in the brain [7]. It is believed that BDNF plays a crucial role in brain plasticity and neuronal development [5,7,8].

To date, a number of studies have suggested a possible role of BDNF in suicidal behavior. In human postmortem brain studies, mRNA and expression levels of BDNF in certain brain areas in suicide completers were significantly reduced [9-11]. These reductions in BDNF expression and protein levels appear to be especially prevalent

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in the prefrontal cortex and hippocampus [8]. Interestingly, the decrease in BDNF levels has been found in individuals who have committed suicide regardless of their underlying psychiatric diagnosis [9,11]. We noted the fact that suicidal victims with many psychiatric disorders such as bipolar disorder, schizoaffective disorder and substance use disorder and Major Depressive Disorder (MDD) also have decreased expression of BDNF and its related receptors.

Several clinical studies have examined BDNF levels in the serum or plasma of patients with MDD and patients with suicide attempt. In studies of serum BDNF levels including our research group, it has been reported that serum BDNF levels are significantly lower in both suicide attempters and MDD patients than in healthy controls [12-14]. Lee et al [14] and Kim et al [13] investigated plasma BDNF levels among suicidal MDD patients, non-suicidal MDD patients and healthy controls. In these two studies, it has been found that plasma BDNF levels in MDD patients with suicidal behavior are the lowest significantly among the three groups. Other studies similarly have found that plasma or platelet BDNF levels are decreased in suicidal depressive patients [14-17]. Furthermore, in a Japanese population study [18], the BDNF 196G/A polymorphism was not related to the development of MDD but was significantly associated with suicidal behavior in MDD. These findings provide evidence suggesting that modulation of BDNF in suicide is independent of underlying depression.

Therefore, we hypothesized that the BDNF polymorphism might contribute to suicidal behavior. Neurobiological vulnerability to suicide might be independent of underlying MDD. Two previously analyzed BDNF gene Single Nucleotide Polymorphisms (SNPs) were used in our study: 196 G/A (val66met, rs6265) in exon XIIIA and 11757G/C (rs16917204) in the 3' UTR of the BDNF gene. The aim of the present study is to investigate associations between the two BDNF polymorphisms (196 G/A, 11757 G/) and suicidal behavior in MDD. We investigated the differences in genotype and allele frequencies of these two SNPs among suicidal MDD patients, non-suicidal MDD patients and healthy controls. We also investigated genetic sequence association using haplotype analysis.

Material and Methods

Subjects and assessments

To evaluate the exclusive effect of BDNF polymorphisms on suicidal behavior, we distinguished the suicidal MDD group from the non-suicidal MDD group. The suicidal MDD group initially consisted of 186 patients admitted to the emergency room at Korea University Medical Center's Ansan Hospital from Mar 2004 to Mar 2009. Initial psychiatric interviews were performed within 24 hours after admission to the emergency room by trained psychiatrists using the Structured Clinical Interview for DSM-IV Axis I disorder (SCID-1) and Hamilton's Depression Rating Scale (HDRS) [19,20]. Thirty-seven suicidal patients were excluded because they had psychiatric conditions other than depression. In addition, 29patients diagnosed with Axis II disorders such as a personality disorder were also excluded. Of the 186 suicidal psychiatric patients, 120 suicidal patients who met DSM-IV criteria for MDD were included in this study. All suicidal MDD patients had an HDRS score over 18.

Suicidal behavior includes a wide spectrum of behaviors, such as completed suicides, high-lethality suicide attempts, and low-lethality suicide attempts [5]. In our study, we defined a suicide attempt as self-harm with at least some intent to end one's life. Two types of interviewer-rated suicidal scales were implemented for patients from the emergency room to evaluate the lethality of the suicidal attempt: the Lethality Suicide Attempt Rating Scale-updated (LSARS-II) [21] and the Risk-Rescue Rating (RRR) [22]. The LSARS-II uses an 11-point scale; a higher score indicates higher lethality (0="death is an impossible result" to 10="death is almost certain"). The RRR scale consists of five risk factors and five rescue factors. As described by the developers, total scores are calculated as follows: (risk rating scores/ (risk rating + rescue rating scores)) *100.

Two control groups were established for our study. The first group consisted of hospitalized, non-suicidal depressed patients. There were 164depressedinpatients without previous history of suicide attempts or a familial history of suicide. Depressed inpatients were evaluated independently by trained psychiatrists using the SCID-1 and HDRS [19,20]. Patients who were diagnosed with another Axis I disorder or Axis II disorder were excluded. Finally, a total of 117 MDD patients were included in this study. All non-suicidal MDD patients had HDRS scores over 18, the same as the suicidal MDD group.

The healthy control group consisted of randomly selected individuals who visited Korea University Ansan Hospital for regular health checkups. Subjects who had any personal or familial psychiatric history or a psychotropic medication history were excluded. Healthy controls were gender-matched to patient groups. A total of 180 healthy controls were included in this study. All patients and controls were biologically unrelated native Koreans. Written informed consent was obtained from all subjects. The study protocol was approved by the Ethics Committee of Korea University.

DNA analysis

DNA was extracted from blood leukocytes by using a commercial DNA extract kit, Wizard Genomic DNA purification kit (Promega, USA). To genotype the 196G/ASNP in the BDNF gene, a polymerase chain reaction was performed with the forward primer 5'- GAG GCT TGA CAT TGG CT-3' and the reverse primer 5'- CGT GTA CAA GTC TGC GTC CT -3'. The amplification mixture contained 0.5ul of 100-ng/ul DNA, 2.5ul of 10x Taq buffer, 0.5ul of 10mM dNTP mixture, 1ul of primers, 19.375ul of distilled water, and 0.125ul of Taq DNA polymerase (Sol Gent, Korea). Samples were amplified using a Thermo cycler (Verity 96-well thermal cycler, Applied Biosystems) for 35 cycles. After an initial 10 min at 95°C, each cycle consisted of 30 sec at 94°C, 30 sec at 62°C, and 30 sec at 72°C. After a final 5min at 72°C, the reaction was terminated at 4°C. The amplified DNA was digested with the restriction enzyme NIaIII (New England Bio labs), which cuts at the 196A site, and the product was electrophoresis in 3% agarose gels and stained with ethidium bromide. Homozygous genotypes were identified by the presence of 113bp bands (G/G) or bands of 75, 38bp (A/A). The heterozygous genotype had 3 bands: 113, 75, and 38bp (C/G).

To genotype the 11757G/CSNP, polymerase chain reaction was implemented using the forward primer 5'- GAG GCT TGA CAT TGG CT-3' and the reverse primer 5'- CGT GTA CAA GTC TGC GTC CT -3'. The amplification mixture contained 0.5ul of 100-ng/ ul DNA, 2.5ul of 10x Taq buffer, 0.5ul of 10mM dNTP mixture,

Table 1: Demographic characteristics of patients and control subjects
[1]significant for MDD with suicide vs. healthy controls (P<0.01) and MDD without suicide vs. healthy controls (P <0.01)
[2]Not significant for MDD with suicide vs. MDD without suicide (P=0.723)
[3]significant for MDD with suicide vs. MDD without suicide (P <0.01)
[4]Not significant for MDD with suicide vs. MDD without suicide (P=0.839)

	MDD with suicide attempts (n = 120)	MDD without suicide attempts (n = 117)	Healthy controls (n = 180)
Age[1]	41.93(SD 16.695)	40.70(SD 14.959)	34.01(SD 8.315)
Sex, female	81(67.5%)	87(74.4%)	125(69.4%)
Education (years)[1]	10.87	10.86	13.41
Age of onset (years)[2]	37.2	37.1	-
Number of previous depressive episodes	1.333	1.470	-
Family history of MDD (%)[3]	5.8	13.4	-
Family history of suicide attempts (%)[3]	6.7	1.4	-
HDRS[4]	23.184	23.79	-
LSARS-II	4.529(SD 2.1)	-	.-
RRR	38.90(SD 13.1)	-	.-

MDD: Major Depressive Disorder; HDRS: Hamilton Depression Rating Scale; LSARS-II: Lethality Suicide Attempt Rating Scale-updated (LSARS-II); RRR: Risk-Rescue Rating; SD: Standard Deviation.

1ul of primers, 19.375ul of distilled water, and 0.125ul of Taq DNA polymerase (Sol Gent, Korea). Samples were amplified using a Thermo cycler (Verity 96-well thermal cycler, Applied Biosystems) for 35 cycles. After an initial 10min at 95°C, each cycle consisted of 30sec at 94°C, 30sec at 62°C, and 30 sec at 72°C. After a final 5min at 72°C, the reaction was terminated at 4°C. The amplified DNA was digested with the restriction enzyme NIaIII (New England Bio labs), which cuts at the 196A site and the product was electrophoreses in 3% agarose gels and stained with ethidium bromide. Homozygous genotypes were identified by the presence of 113bp bands (G/G), or bands of 75, 38bp (A/A). The heterozygous genotype had 3 bands: 113, 75, 38bp (C/G).

Statistical analysis

The presence of the Hardy-Weinberg equilibrium was tested using a chi-squared test for goodness of fit. Differences in clinical variables were examined using-tests. The genotype and allele frequencies of the three groups were analyzed using chi-squared statistics and Fisher's exact test using SPSS version 21.0. Frequencies and haplotype reconstructions were calculated using SNP Analyzer 2.0. The level of statistical significance was set at p-value< 0.05.

Results and Discussion

Demographics of the subjects

A total of 417subjects (120 MDD patients with a suicide attempt, 117 MDD patients without a suicide attempt, and 180healthy controls) were enrolled in the study. We analyzed the demographic factors using independent two sample t-test. There were significant difference in the age and education years between the suicidal and healthy controls and between non-suicidal groups and healthy controls (Table 1). There was no significant difference in HDRS scores between the suicidal and non-suicidal groups. (P value =0.839).

Genotype and allele frequencies of the two polymorphisms in suicidal MDD patients, non-suicidal MDD patients, and healthy controls (Table 2-1, Table 2-2)

The distributions of the BDNF 196G/A and 11757G/C polymorphisms in suicidal MDD patients, non-suicidal MDD patients and controls were in agreement with the Hardy-Weinberg equilibrium. The Hardy-Weinberg equilibrium of the two candidate SNPs were as follows: BDNF 196G/A (suicidal MDD patients, χ^2=0.023, df=1, *p*=0.880; non-suicidal MDD patients, χ2=0.027, df=1, *p*=0.869; healthy controls, χ2=1.079, df=1, *p*=0.299) and 11757G/C (suicidal MDD patients, χ2=0.099, df=1, *p*=0.753; non-suicidal MDD patients, χ2=0.027, df=1, *p*=0.869; healthy controls, χ2=1.385, df=1, *p*=0.239).

No differences in either genotype distributions or allele frequencies of BDNF 196G/A and 11757G/C polymorphism were observed among these three groups (Table 2-1). There were no significant differences in the genotype and allele frequencies between healthy controls and either MDD group (suicidal and non-suicidal), and between both MDD groups. (Tables 2-1 and 2-2).

Exploratory analysis between BDNF polymorphisms and lethality in patients with suicidal MDD (Table 3)

There were no significant differences in LSARS-II and RRR scores in 196 G/A SNP and 11757 G/C SNP.

Haplotype analysis of BDNF 196 G/Aand 11757G/C polymorphisms among suicidal MDD patients, non-suicidal MDD patients, and healthy controls (Table 4-1, Table 4-2, Table 4-3)

For the haplotype study, two SNPs (BDNF 196 G/A, 11757G/C) were analyzed using the SNP Analyzer program. The following haplotype combinations were obtained: GC, AC, AG and GC. The haplotype frequencies and statistics are presented in Tables 4-1 to 4-3. There was no significant difference in haplotype analysis between the suicidal MDD patient group and the non-suicidal MDD patient group (Table 4-1). However, in the haplotype analysis with suicidal MDD patients and healthy controls, there were significant differences with regard to BDNF 196 A– 11757 C haplotype combinations and the 196 G – 11757 C haplotype combination (Table 4-2). Similarly, in the haplotype analysis between the non-suicidal MDD group and healthy controls, significant differences were observed. BDNF 196 A–

Table 2: Genotype and allele frequencies of study participants.
All statistics were calculated based on comparisons among the three groups. (MDD patients with suicide, MDD patients without suicide, and healthy controls).

	MDD with suicide attempts (n = 120)		MDD without suicide attempts (n = 117)		Healthy controls (n = 180)		χ2	*p*-value
	n	%	n	%	n	%		
196G/A								
Genotype							0.635	0.959
G/G	37	30.0%	36	30.8%	51	28.3%		
G/A	60	50.8%	57	48.7%	96	53.3%		
A/A	23	19.2%	24	20.5%	33	18.3%		
Allele							0.068	0.967
G	134	55.8%	128	55.1%	198	55.0%		
A	106	44.2%	106	44.9%	162	45.0%		
11757G/C								
Genotype							2.664	0.616
G/G	36	30.0%	36	30.8%	68	37.8%		
G/C	61	50.8%	57	48.7%	79	81.7%		
C/C	23	19.2%	24	20.5%	33	18.3%		
Allele							1.763	0.414
G	132	55.4%	128	55.1%	214	59.7%		
C	108	44.6%	106	44.9%	146	40.3%		

MDD: Major Depressive Disorder.

Table 2-1: Genotype and allele frequency for 196G/A in suicidal MDD patients, non-suicidal MDD patients, and healthy controls.

	Genotype			χ2	*p*-value	Allele		χ2	*p*-value
	G/G	G/A	A/A			G	A		
Suicidal MDD	37	60	23	0.635	0.959	134	106	0.068	0.967
Non-suicidal MDD	36	57	24			128	106		
Controls	52	96	33			198	162		
Suicidal MDD	37	60	23	0.182	0.913	134	106	0.040	0.841
Controls	52	96	33			198	162		
Suicidal MDD	37	60	23	0.119	0.942	134	106	0.061	0.804
Non-suicidal MDD	36	57	24			128	106		
Non-suicidal MDD	36	57	24	0.612	0.736	128	106	0.005	0.943
Controls	52	96	33			198	162		

MDD: Major Depressive Disorder.

Table 2-2: Genotype and allele frequency for 11757G/C in suicidal MDD patients, non-suicidal MDD patients, and healthy controls.

	Genotype			χ2	*p*-value	Allele		χ2	*p*-value
	G/G	G/C	C/C			G	C		
Suicidal MDD	36	61	23	2.664	0.616	132	108	1.763	0.414
Non-suicidal MDD	36	57	24			128	106		
Controls	68	79	33			214	146		
Suicidal MDD	36	61	23	2.027	0.363	132	108	1.165	0.280
Controls	68	79	33			214	146		
Suicidal MDD	36	61	23	0.119	0.942	132	108	0.004	0.948
Non-suicidal MDD	36	57	24			128	106		
Non-suicidal MDD	36	57	24	1.531	0.465	128	106	1.306	0.253
Controls	68	79	33			214	146		

MDD: Major Depressive Disorder.

Table 3: Comparison of lethality scores according to genotype in patients with suicidal MDD.
There were no significant differences among genotypes in each of the BDNF SNP genes. All data are presented as mean.

	LSARS-II	RRR
196 G/A		
G/G	4.55	37.94
G/A	4.53	38.93
A/A	4.51	38.51
11757 G/C		
G/G	4.54	42.22
G/C	4.54	38.24
C/C	4.51	36.45

MDD: Major Depressive Disorder
LSARS-II: lethality Suicide Attempt Rating Scale-updated
RRR: Risk-Rescue Rating Scale

11757 C haplotype combinations and the 196 G – 11757 C haplotype combination were significantly lower in the suicidal MDD group and non-suicidal MDD groups compared to healthy controls. After Bonferroni corrections, the findings still remained significant.

Discussion

BDNF, one of the most abundant neurotrophic factors, is known for its important role in the maintenance, survival of neurons and synaptic plasticity. Several lines of evidence have suggested that BDNF is involved in depression. mRNA and protein expression of BDNF are decreased in depressive patients in postmortem studies. Furthermore, several studies have reported that antidepressant treatment up-regulates the expression of BDNF and results in increases of BDNF production [23,24]. This led to the proposal of the "neurotrophin hypothesis of depression" [25]. Thereafter, many studies focused on identifying candidate BDNF SNPs for depression and suicide. In 196G/A polymorphism, a substitution of valine to methionine at cod on 66 in the prod main impairs the sorting of BDNF [25]. Thus, 196G/A polymorphisms were suggested as candidate SNP which may affect serum/plasma BDNF level in depression and suicidal behavior. However, the results of case-control studies conflicted, with as many published reports in favor of the hypothesis [4,26,27]. And asthe opposition [28,29]. Several meta-analyses of these association studies [10,15,30,31] were also conducted and suggested that there were no associations between these genetic variants in BDNF and major depression.

At the same time, several studies were conducted to identify an association of BDNF polymorphism with suicide. Hong et al. and Hwang et al. investigated an association between BDNF 196G/A polymorphism and suicidal behavior in Chinese patients and reported negative results [27,28]. Of studies reporting positive associations, the results were inconsistent with each other. Iga et al [26] reported that the dose of the 66Met allele had significant effects on the presence of psychotic features, suicidal behavior, and family history within Japanese depressive patients. However, there were no differences in the genotype and allele frequencies among the patients and control subjects. Sarchiapone et al [32] investigated depressed patients who had (n=97) and had not (n=73) attempted suicide and reported that the BDNF Val66Met polymorphism variant (GA+AA) appeared to show a significantly increased risk of suicidal behavior. This was not confirmed in a postmortem study of relatively large suicidal patients (n=512) [33]. Similarly, Pregelj et al [34] genotyped 560 DNA samples from 359 suicide victims and 201 control subjects from a Caucasian population. They reported no association between the BDNF 196G/A polymorphism and all included suicide victims, while suggesting that Met/Met and Met/Val genotypes could be risk factors for violent suicide in female subjects.

In regard to the BDNF 11757 G/C SNP association studies, the number of studies is limited. And most of them reported no association with psychiatric disorders; alcohol dependency-related depression [35], heroin dependency [36], and ADHD [37]. Likewise, we found no genotype or allele distribution differences of BDNF 11757G/C SNP among suicidal MDD patients, non-suicidal MDD patients and healthy controls.

In our study, there were no significant associations between these two genotype distribution/allele frequencies and either the suicidal MDD group or non-suicidal MDD group or healthy controls. Our results concerning the association between the tested BDNF polymorphisms (196G/A, 11757G/C) and major depression are consistent with previous meta-analyses [10,15,31]. The results of genetic studies linking BDNF gene and suicidal behavior are conflicting. However, our findings are line with previous genetic case-control studies that reported no association between suicide and BDNF gene polymorphisms [27,28,33,34]. To confirm these results, studies with larger sample size sac counting for ethnicity are needed.

We observed a significant result from the SNP haplotype study of these two genetic variants. BDNF 196A–11757G and 196G–11757C haplotype combination frequencies were significantly lower in both suicidal MDD patients and non-suicidal MDD patients than in healthy controls. Our results suggest that subjects who have a 196A–11757G combination or a 196G–11757C combination may be less susceptible to the development of major depression or suicidal behavior. However,

Table 4-1: Haplotype analysis for BDNF SNPs in suicidal MDD patients group and non-suicidal MDD patients group.
[1]*p*-value after Bonferroni correction.
[2]Statistics were calculated based on a comparison between suicidal MDD patients and healthy controls.

Haplotype		Frequency (%)			Association model	Statistics				
196G/A	11757 G/C	S-MDD	NS- MDD	Total		OR	95% CI	*p*-value	*p*-value[1]	$\chi 2^2$
G	G	55.417	55.128	55.274	MUL	1.012	0.704-1.453	0.95	1	0.004
A	C	44.167	44.872	44.515	MUL	0.972	0.676-1.396	0.877	1	0.024
A	G	0	0	0	MUL	-	-	-	-	-
G	C	0.417	0	0.211	MUL	-	-	-	-	-

S-MDD: Suicidal Major Depressive Disorder; NS-MDD: Non-Suicidal Major Depressive Disorder; MUL: Multiplicative Model; OR: Odds Ratio; CI: Confidence Interval.

Table 4-2: Haplotype analysis for BDNF SNPs in suicidal MDD patients and healthy controls
[1]p-value after Bonferroni correction.
[2]Statistics were calculated based on a comparison between suicidal MDD patients and healthy controls.

Haplotype		Frequency (%)			Association model	Statistics				
196 G/A	11757G/C	S-MDD	Healthy controls	Total		OR	95% CI	*p*-value	*p*-value[1]	χ^2[2]
G	G	55.417	51.046	52.872	MUL	1.176	0.847-1.632	0.333	1	0.938
A	C	44.167	36.323	39.539	MUL	1.366	0.979-1.906	0.066	0.263	3.385
A	G	0	8.677	5.128	MUL	0	0-0	<0.01	<0.01	21.053
G	C	0.417	3.954	2.461	MUL	0.112	0.015-0.859	0.011	0.044	6.448

S-MDD: Suicidal Major Depressive Disorder; MUL: Multiplicative Model; OR: Odds Ratio; CI: Confidence Interval.

Table 4-3: Haplotype analysis for BDNF SNPs in non-suicidal MDD patients and healthy controls
[1]*p*-value after Bonferroni correction.
[2]Statistics were calculated based on a comparison between non-suicidal MDD patients and healthy controls.

Haplotype		Frequency (%)			Association model	Statistics				
196G/A	11757 G/C	NS- MDD	Healthy controls	Total		OR	95% CI	*p*-value	*p*-value[1]	χ^2[2]
G	G	55.128	51.046	52.743	MUL	1.162	0.835-1.617	0.372	1	0.796
A	C	44.872	36.323	39.780	MUL	1.406	1.006-1.966	0.046	0.184	3.982
A	G	0	8.677	5.169	MUL	0	0-0	<0.01	<0.01	20.537
G	C	0	3.954	2.308	MUL	0	0-0	<0.01	<0.01	8.639

NS-MDD: Non-Suicidal Major Depressive Disorder; MUL: Multiplicative Model; OR: Odds Ratio; CI: Confidence Interval.

because the frequencies of the 196A–11757C haplotype combination and the 196G–11757C haplotype combination were extremely small compared with those of other haplotype combinations, it should be interpreted with caution.

There are several limitations in the present study. First, as discussed earlier, the frequencies of the 196A–11757C haplotype combination and the 196G–11757C haplotype combination were relatively small compared to those of the 196G-11757G and 196A-11757C combination subgroups (GC haplotype subgroups, 0.417% of suicidal depressive patients, 0% of non-suicidal depressive patients, 3.954% of controls, total 1.618%; AG haplotype subgroups, 0% of suicidal depressive patients, 0% of non-suicidal depressive patients, 8.677% of controls, total 3.657%)(Tables 4-1 to 4-3). These extremely low frequencies can make the results prone to false positive errors, especially when analyzing small sample sizes. Second, our study sample was restricted to a Korean population. Because of an ethnic difference in the frequency of the BDNF gene polymorphism, this hinders the generalization of our results. Third, we investigated only two SNPs of the BDNF gene. It is not certain that the studied SNPs are the main factor for serum/plasma BDNF level. In the future, studies correlating BDNF polymorphism to BDNF level or gene expression is needed. Suicide is a complicated phenomenon that results from the interaction of several different factors, including genes, neurobiological changes and psychosocial factors [38]. Similarly, BDNF is influenced by many factors such as child trauma, stress, hormone, cholesterol metabolism, antidepressant treatment and other medical conditions. When selecting control group, we did not sufficiently consider cofounders which may affect serum/plasma level or gene expression of BDNF. Given the complexity of the etiology and pathophysiology of suicidal behavior, a combined or multimodal approach is necessary. Fourth, we had a small sample size in this study. Finally, our study did not distinguish suicide attempt from completed suicide nor account for suicidal severity/lethality. Because suicidal behavior includes a wide spectrum of behaviors including completed suicides, high-lethality suicide attempts, and low-lethality suicide attempts [5], future studies will need to examine the association of BDNF according to suicide lethality or depressive symptom severity

Conclusion

Identifying genetic risk factors of suicide will be helpful for the prevention and treatment of patients who might be at risk for suicide. Thus, it is important to find candidate genes and to determine the level of contribution of the specific gene. In our sample of suicidal MDD patients, we did not find any association between two BDNF polymorphisms (196G/A, 11757G/C) and suicidal behavior of MDD patients in terms of gene distribution and allele frequency. However, in the haplotype analysis, 196A–11757G and 196G–11757C combination frequencies were significantly lower in both suicidal MDD patients and non-suicidal MDD patients than in healthy controls. To our knowledge, this is the first haplotype study that tried to identify the associations between two BDNF SNPs and suicidal behavior in a Korean population. To confirm our results, future research should be conducted with larger sample sizes and larger genetic markers.

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