



The rs6265 Polymorphism of the BDNF Gene Is Related to Higher-Lethality Suicide Attempts in the Korean Population

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Objective Since the risk of suicide cannot be predicted by clinical symptoms alone, and suicide is known to have a genetic component, the discovery of genetic markers that can predict the lethality of suicide attempts is a clinically important topic. There have been many studies aiming to determine whether the rs6265 polymorphism of the BDNF gene is associated with suicidality; however, the results have been mixed, and there have been few studies investigating the relationship between this polymorphism and suicide attempt lethality.

Methods We assessed suicide lethality in 258 individuals who had attempted suicide using the relative risk ratio (RRR) scale and by genotyping the rs6265 polymorphism of the BDNF gene.

Results The RRR score for suicide attempts was higher in subjects with Met/Val and Val/Val genotypes than in that with a Met/Met genotype ($p=0.015$). The RRR score for suicide attempts was also higher in Val allele carriers (Met/Val+Val/Val) than in Met/Met homozygotes ($p=0.006$).

Conclusion This study demonstrates the possibility that the rs6265 polymorphism of the BDNF gene could be used as a genetic marker to predict the lethality of suicide attempts, but more replication studies are needed for the application of this result in clinical practice.

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Key Words Suicide attempt, Lethality, Brain derived neurotrophic factor, Gene, rs6265.

INTRODUCTION

Suicide is one of the most serious health and social problems and is a worldwide phenomenon. According to statistics from 2017, the suicide rate in South Korea was 24.3 per 100,000 individuals.¹ Although South Korea is a country with a declining suicide rate, its rate is still one of the highest among the Organization for Economic Cooperation and Development countries. Since the most important prevention is the early detection of groups at high risk for suicide, many studies and efforts to find high-risk groups have been steadily carried out, and many ge-

netic studies have been conducted to identify candidate genes for suicidal behavior. Many studies on genetic associations have suggested that several genes, such as those encoding serotonin receptors and transporters, tryptophan hydroxylase, and brain-derived neurotrophic factors (BDNFs), are related to suicidal behavior; however, these findings have not been consistently replicated.²

BDNF is a neurotrophic factor involved in the development and maintenance of neural cells³ and is important for cell survival and apoptosis in neural cells.⁴ Substantial evidence has shown that the BDNF gene has a connection with the genetic etiology of psychiatric disorders and suicidal behavior.⁵ Post-mortem studies have shown reduced BDNF expression in suicide victims,⁶ and major depressive disorder patients who attempted suicide have shown decreased plasma levels of BDNF.⁷ BDNF is encoded by the BDNF gene located on chromosome 11,⁸ and most genetic association studies between this gene and suicidal behavior were performed for the rs6265 polymorphism, which is also known as the Val66Met or G196A poly-

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morphism.⁹ The results of the association between the rs6265 single nucleotide polymorphism (SNP) and suicidal behavior are not conclusive, since both negative associations and positive

associations have been reported (Table 1).^{5,8-29} Recently, Gonzalez-Castro et al.⁹ conducted a meta-analysis to evaluate the association between the rs6265 polymorphism and suicidal be-

Table 1. Previous genetic studies investigating the association between rs6265 and suicide behavior

First author, year	Nation or ethnicity	Number of subjects (Suicidal/Nonsuicidal)	Diagnosis	Results
Asian				
Hwang et al., 2006 ¹⁴	Taiwan	107 (22/85)	Depression	No association
Iga et al., 2007 ¹⁵	Japan	154 (23/131)	Depression	Met allele was related to suicidal behavior
Huang and Lee, 2007 ¹³	Taiwan	132 (16/116)	Schizophrenia	Met/Met genotype was associated with suicide history
Kim et al., 2008 ¹⁶	Korea	169 (43/126)	Bipolar disorder	Higher risk of suicidal attempt in subjects with Met/Met genotype
Ratta-Apha et al., 2013 ²¹	Japan	674 (300/374) [‡]	Not available	No association
Wang et al., 2015 ²⁷	China	730 (365/365)	Not available	No association overall. However, Val/Val genotype is related to suicide attempt in elderly individuals
Xia et al., 2018 ²⁸	China	825 (123/702)	Schizophrenia	Association between Val allele and suicide attempt
Gonzalez-Castro et al., 2017 ⁹	Asia meta-analysis	6 studies	Various diagnoses	Increased suicide attempts in subjects with Val/Val genotype
Kim and Kim, 2018 ¹⁷	Korea	157 (25/132)	Schizophrenia	Suicide attempt is higher in subjects with Met allele
Choi et al., 2018 ¹¹	Korea	212 (69/143)	Mood disorders	No association
Non-Asian				
Vincze et al., 2008 ²⁶	Switzerland, France	127 (30/97) [†]	Bipolar disorder	Increased frequency of violent suicidal attempt in subjects with Val allele
Sarchiapone et al., 2008 ²²	Italy	170 (97/73)	Depression	Increased risk of suicidal behavior in Met carriers
Zarrilli et al., 2009 ⁸	Slovenia	512 (262/250)	Not available	No association
Schenkel et al., 2010 ²³	Brazil	120 (81/39) [*]	Major depressive disorder	Met allele is related to high lethality in suicide attempts
Spalletta et al., 2010 ²⁵	Italy	119 (33/86)	Schizophrenia	No association
Neves et al., 2011 ¹⁹	Brazil	160 (74/86)	Bipolar I disorder	No association
Pregelj et al., 2011 ²⁰	Slovenia	560 (359/201) [‡]	Not available	Increased frequency of female suicide victims who are Met carriers
Chojnicka et al., 2012 ¹²	Poland	1,066 (517/549) [‡]	Depression, schizophrenia, and other or unknown	No association
Nedic et al., 2013 ¹⁸	Croatia	691 (112/579)	Alcohol dependence	No association
Sears et al., 2013 ⁵	New Zealand	565	Bipolar disorder	No association
Zai et al., 2015 ²⁹	Canada	187 (55/132)	Schizophrenia	No association
Antypa et al., 2016 ¹⁰	Belgium	238 (97/141)	Mood disorders	No association
Schosser et al., 2017 ²⁴	Multicenter in Europe	250	Major depressive disorder	No association
Gonzalez-Castro et al., 2017 ⁹	Caucasian meta-analysis	8 studies	Various diagnoses	Increased suicide attempts in subjects with Met/Met genotype

*high-lethality suicide attempters/low-lethality suicide attempters, [†]violent suicide attempters/non-violent suicide attempters, [‡]suicide victims/control

havior, and they found no evidence of an association between the rs6265 polymorphism and suicidal behavior. However, subgroup analysis has shown increased suicidal risk in the Met/Met genotype group in Caucasian populations and increased suicidal risk in the Val/Val genotype group in Asian populations.⁹

Four genetic association studies between the rs6265 polymorphism and suicidality have been reported in Koreans.^{11,16,17,30} The association between rs6265 SNP and bipolar disorder was not significant in a study of Korean bipolar disorder patients, but the association between suicide attempt and this SNP was significant in this sample, indicating that participants with the Met/Met genotype showed a 4.9-fold higher risk of suicide attempt than those with the Val/Val genotype.¹⁶ In a study conducted in Korean schizophrenia patients, a higher frequency of suicide attempts in subjects with the Met allele was reported.¹⁷ However, Choi et al.¹¹ reported no association between rs6265 and suicide attempts in patients with mood disorder. A study of older adults aged 65 years or older showed no association between suicidal ideation and the rs6265 polymorphism and deviation from Hardy-Weinberg equilibrium.³⁰ Thus, to date, no consistent conclusions can be drawn from association studies between the rs6265 SNP and suicidal behavior in Koreans.

There have been many genetic association studies between rs6265 and suicide, but few studies have compared the lethality of suicide attempts among rs6265 genotypes. A suicide attempt is a dangerous act with the intent to die, but there is a wide range of lethality among suicidal behaviors. Therefore, the relationship between the lethality of suicidal behavior and the rs6265 SNP is of clinical significance. This study was conducted to investigate the relationship between the rs6265 polymorphism and the lethality of suicide attempts in Koreans.

METHODS

Subjects

All participants (n=258) were suicide attempters, and they were enrolled in this study from emergency rooms at 5 university hospitals in Daegu-Gyeongbuk province. A suicide attempt was defined as a self-directed harmful behavior with some intent to die. Trained psychiatric residents interviewed suicide attempters after patients had recovered from a medically acute state, just before discharge from the hospital. The psychiatric residents evaluated and diagnosed the patients using a structured questionnaire about suicide and psychiatric diagnoses with reference to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision.³¹ A board-certified psychiatrist at each hospital confirmed the participants' psychiatric diagnoses based on a review of their medical records and case report form.

The Institutional Review Boards in the Kyungpook National University Hospital (approved number KNUH 2011-04-014-003) and four other university hospitals approved this study. All the participants and caregivers received written and verbal explanations regarding the study and provided written informed consent.

Genotyping

Three cubic centimeters of venous blood was collected from each participant, and genomic DNA was isolated from peripheral blood leukocytes using the Qiagen QIAamp Blood Kit (Qiagen, Valencia, CA, USA). The DNA concentration was determined using a NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, Wilmington, DE), and the purity of the DNA was assessed based on a 260/280 nm absorbance ratio from 1.7 to 2.1. The rs6265 polymorphism was genotyped using a previously described method,^{5,32} and all genotyping procedures were performed at D&P Biotech, Inc. (Daegu, Korea). The genotyping was performed by melting-curve analysis using fluorescence-labeled hybridization probes (LightCycler 480 Instrument, Roche Diagnostic GmbH, Mannheim, Germany).

Assessment of suicide attempt lethality and depression severity

The lethality of individual suicidal behaviors was evaluated using Weisman and Worden's risk-rescue rating (RRR) system.³³ According to the RRR system, lethality can be expressed as a ratio of five risk and five rescue factors, and the total risk and rescue point scores range from 1 to 5, respectively.³³ The RRR score is determined by the formula [risk score/(risk score+rescue score)] \times 100.³³ The severity of depression was evaluated by a psychiatrist using the validated Korean version of the Hamilton Depression Rating Scale (K-HDRS).³⁴ Impulsivity was evaluated using the validated Korean version of the Barratt Impulsiveness Scale II (BIS II).³⁵

Statistical analysis

Conformity with the Hardy-Weinberg equilibrium (HWE) was tested using the χ^2 test for goodness of fit. We used chi-squared tests or Fisher's exact test and analysis of variance to analyze categorical and normally distributed continuous variables, respectively. To analyze nonnormally distributed continuous variables, Kruskal-Wallis or Mann-Whitney tests were used. The cutoff for statistical significance was set at $p < 0.05$. Statistical Package for the Social Sciences for Windows ver. 23.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data.

RESULTS

Demographic and clinical characteristics of participants and their comparison among the three genotypes

The participants' demographic data, severity of depression, BIS total scores, clinical information (methods of suicide attempt, alcohol use at the time of a suicide attempt, current psychiatric treatment, and presence of medical illnesses which interfered with daily life), and principal psychiatric diagnosis as well as comparisons across the three genotypes are presented in Table 2. The participants were 43.3 ± 17.7 years old (mean \pm SD), and they comprised 109 (42.2%) males and 149 (57.8%) females (Table 2). The mean ages and sex ratio of the subjects, the proportion of psychiatric diagnoses, and the K-HDRS and BIS total scores did not differ among the three genotype groups (Table 2). The comparison of several clinical variables (methods of suicide attempt, alcohol use at the time of a suicide attempt,

presence of psychiatric treatment, and presence of medical illness) did not reveal statistically significant differences among the three genotype groups (Table 2). The genotype frequency in the participants did not deviate from the HWE for rs6265 ($\chi^2=0.167$, $p=0.682$).

Comparison of lethality of suicide attempts among the genotypes

A comparison of RRR score and the number of previous suicide attempts among the three genotype groups of rs6265 is presented in Table 3. The RRR score for suicide attempts was higher in subjects with Met/Val and Val/Val genotypes than in those with a Met/Met genotype ($\chi^2=8.36$, $p=0.015$) (Table 3). The RRR score for suicide attempts was also higher in participants who were Val allele carriers (Met/Val+Val/Val) than in Met/Met homozygotes ($Z=-2.75$, $p=0.006$) (Table 4). The number of previous suicide attempts did not differ among the three genotypes of rs6265 (Table 3).

Table 2. Demographic and clinical variables of patients in the three rs6265 genotype groups

	Total (N=258)	Met/Met (N=57)	Met/Val (N=132)	Val/Val (N=69)	Statistics*	
Age (years old)	43.3 \pm 17.7	42.1 \pm 17.3	42.4 \pm 18.1	45.9 \pm 17.2	F=1.06	p=0.347
Sex (m/f)	109/149	22/35	56/76	31/38	$\chi^2=0.52$	p=0.773
Education (years)	11.0 \pm 3.9	10.8 \pm 4.0	11.1 \pm 3.9	11.0 \pm 3.9	F=0.10	p=0.903
K-HDRS	15.4 \pm 7.2	15.6 \pm 6.8	15.4 \pm 7.6	15.2 \pm 6.8	F=0.05	p=0.950
BIS-Total	56.4 \pm 9.7	55.4 \pm 8.9	56.1 \pm 10.2	57.6 \pm 9.3	F=0.77	p=0.463
Methods of suicide attempt (%)						
Ingestion of medications	125 (48.4)	31 (54.4)	61 (46.2)	33 (47.8)	$\chi^2=10.25$	p=0.567
Ingestion of pesticides or chemicals	79 (30.6)	15 (26.3)	42 (31.8)	22 (31.9)		
Hanging	12 (4.7)	5 (8.8)	4 (3.0)	3 (4.3)		
Jumping	4 (1.6)	0 (0)	3 (2.3)	1 (1.4)		
Inhalation	17 (6.6)	1 (1.8)	13 (9.8)	3 (4.3)		
Cutting	16 (6.2)	4 (7.0)	7 (5.3)	5 (7.2)		
Others	5 (1.9)	1 (1.8)	2 (1.5)	2 (2.9)		
Psychiatric diagnosis						
Depressive disorder	169	34 (59.6)	86 (65.2)	49 (71)	$\chi^2=8.57$	p=0.572
Bipolar disorder	26	8 (14)	14 (10.6)	4 (5.8)		
Psychotic disorder	21	3 (5.3)	13 (9.8)	5 (7.2)		
Anxiety disorder	1	0 (0)	1 (0.8)	0 (0)		
Adjustment disorder	31	9 (15.8)	12 (9.1)	10 (14.5)		
Other	10	3 (5.3)	6 (4.5)	1 (1.4)		
Alcohol use at the time of suicide attempt (%)	114 (44.4)	25 (43.9)	56 (42.7)	33 (47.8)	$\chi^2=0.48$	p=0.787
Under psychiatric treatment (%)	74 (28.8)	21 (36.8)	36 (27.3)	17 (25.0)	$\chi^2=2.43$	p=0.297
Use of psychotropic medication (%)	96 (37.2)	23 (40.4)	52 (39.4)	21 (30.4)	$\chi^2=1.87$	p=0.393
Presence of medical illness (%)	47 (18.3)	10 (17.5)	21 (15.9)	16 (23.5)	$\chi^2=1.77$	p=0.412

The values are the means \pm SD or number of participants (percentage). *analysis of variance, chi-squared test, or Fisher's exact test. K-HDRS: Korean version of the Hamilton Depression Rating Scale, BIS: Barratt Impulsiveness Scale

Table 3. Comparison of the relative risk ratio scores of current suicidal attempt and the number of previous suicidal attempts among the three rs6265 genotype groups

	Met/Met (N=57)	Met/Val (N=132)	Val/Val (N=69)	Statistics*	
Previous suicidal attempts	2.0±1.2	1.9±1.6	1.8±1.6	F=0.15	p=0.858
Relative risk ratio	27.9±12.0	33.9±13.4	32.1±13.3	$\chi^2=8.36$	p=0.015†

The values are the means±SD. *analysis of variance or Kruskal-Wallis test, †significance at p<0.05

Table 4. Comparison of the relative risk ratio score of suicide attempt between rs6265 Val carriers and Met/Met homozygotes

	Met/Val+Val/Val (N=201)	Met/Met (N=57)	Statistics*
Relative risk ratio	33.3±13.4	27.9±12.0	Z=-2.75, p=0.006†

The values are the means±SD. *Mann-Whitney test, †significance at p<0.05

DISCUSSION

The present study investigated the difference in the RRR of current suicide attempts among the rs6265 polymorphism genotypes of the BDNF gene. We identified more lethal suicide attempts in Val carriers (Val/Val+Met/Val) than Met/Met homozygotes of the rs6265 SNP. To the best of our knowledge, this is the first report to investigate the relationship between lethality of suicide and the rs6265 SNP in Asian and Korean populations.

The results from similar research topics have been reported in bipolar disorder patients in Switzerland and France²⁶ and in major depressive disorder patients in Brazil.²³ Violent (or lethal) suicide attempts (e.g., hanging, use of firearms or knives, and jumping from heights) were associated with the Val allele of the rs6265 SNP in the Swiss and French populations²⁶ and with the Met allele in the Brazilian population (Caucasian 75%).²³

There was no report of the relationship between the lethality of suicide and the rs6265 SNP in Asian or Korean populations prior to this study. Several studies in Asian populations have reported a higher risk of suicide attempt in subjects with the Met allele or a Met/Met genotype,^{13,15-17} although others have reported a significant association between the Val/Val genotype and risk of suicide^{27,28} or no association.^{11,14,21} Recently, Gonzalez-Castro et al.⁹ reported increased suicidal risk in the Val/Val genotype group in Asian populations by meta-analysis using data from six previous studies, and this result is partially in line with our research. The discrepancy between the results of the meta-analysis (higher risk in those with the Val/Val genotype) and the results in the majority of previous reports (higher risk in those with the Met allele or Met/Met genotype) might be explained by the fact that the primary goal of most previous studies is to study the association between psychiatric disorder with the rs6265 SNP and the number of suicide attempters is generally small.⁹ Studies on this topic performed in Korea do not show consistent results either,^{11,16,17,30} so further studies are needed.

A previous study reported different allele frequencies between Asian and European populations.²¹ These large inter-racial differences in the genotype frequency of the rs6265 polymorphism may have resulted in inconsistent results in previous studies due to genetic-ethnic dependency.^{9,36} According to race-specific data on allele frequency, the rs6265 allele frequency in the Korean population showed a relatively higher frequency of the Met allele than other races,³⁷ and the allele frequency (Met:Val=0.48:0.52) in our study was similar to the frequency in these data.

A limitation of this study was that there was no control group for suicide attempters, so we could not show a genetic association between rs6265 and suicide attempt. Because the study population was based on suicide attempters who visited the emergency room, it was difficult to establish a suitable control group. However, because interviews in this study were conducted in the emergency room after suicide attempt, our study has strength in that the information on the lethality, method, and motivation of the suicide attempt is relatively accurate compared to that in studies based on long-term recall. In addition, because suicidality was defined as an emergency room admission after an actual suicide attempt rather than suicidal ideation, we think that this research was performed using a clearer and more appropriate phenotype. Another limitation is that the Korean version of the RRR scale, a tool for evaluating the lethality of suicide attempts, has not been validated. However, since this scale consists of short words or phrases and is evaluated by the clinician, we did not believe that the scale was linguistically problematic. Indeed, a number of studies have used this scale in Korea.³⁸⁻⁴⁰

We hope that the relationship between the rs6265 polymorphism and the lethality of suicide attempts described in this study will be useful for predicting serious suicide risk in future clinical practice. However, to apply the results of this study to clinical practice, replication studies on more subjects, including healthy controls, are needed.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Seunghee Won. Data curation: Jong Hun Lee, Kwanghun Lee, Hee-Cheol Kim, Wan Seok Seo, Seunghee Won. Formal analysis: Seung-Gul Kang. Funding acquisition: Seunghee Won, Seung-Gul Kang. Investigation: Jong Hun Lee, Kwanghun Lee, Hee-Cheol Kim, Wan Seok Seo, Seunghee Won. Methodology: Seunghee Won. Project administration: Seunghee Won. Resources: Seunghee Won. Software: Seunghee Won. Supervision: Seunghee Won. Validation: Seunghee Won, Seung-Gul Kang. Visualization: Seunghee Won, Seung-Gul Kang. Writing—original draft: Seung-Gul Kang, Seunghee Won. Writing—review & editing: Seunghee Won.

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