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Evidence for Association between the Brain-Derived Neurotrophic Factor Gene and Panic Disorder: A Novel Haplotype Analysis

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Objective Panic disorder (PD) is a common psychiatric disorder with a complex etiology, and several studies have suggested that it has a genetic component. Brain-derived neurotrophic factor (BDNF) is the most abundant of the neurotrophins in the brain and is recognized for its important role in the survival, differentiation and growth of neurons. Several lines of research have suggested possible associations between the BDNF gene and PD. In this study, we investigated the BDNF 196G/A (rs6265), 11757G/C (rs16917204), and 270C/T (rs56164415) single nucleotide polymorphisms (SNPs) in order to determine an association with PD. We also identified the genetic sequence associations with PD via haplotype analysis.

Methods Participants in this study included 136 PD patients and 263 healthy controls. Male and female subjects were analyzed separately. The genotype and allele frequencies of the PD patients and controls were analyzed using χ^2 statistics. Frequencies and haplotype reconstructions were calculated using the SNP analyzer 2.0.

Results We found no significant statistical differences in the genotype distributions or allele frequencies of the three tested polymorphisms between the PD and control groups. In addition, no differences were found between PD patients and the controls in either male or female subgroups. However, we found that, the frequency of the G-C haplotype for 196G/A and 11757G/C was significantly higher in PD patients than in the controls.

Conclusion Our result suggest that patients with the G-C haplotype for 196G/A and 11757G/C may be more susceptible to the development of PD. Further studies are needed to replicate the associations that we observed. **Psychiatry Investig 2015;12(1):112-117**

Key Words Panic disorder, Brain-derived neurotrophic factor, Polymorphism.

INTRODUCTION

Panic disorder (PD) is an anxiety disorder characterized by recurrent, unexpected panic attacks, one or more of which is accompanied by worry about future attacks or their implications, or by a change in behavior related to the attacks.

Several studies have suggested a genetic component to PD. Family and twin studies indicate a genetic influence on PD, with heritability estimated at more than 40%.[1,2] Multiple genetic linkage studies have indicated that chromosomal regions 13q, 14q, 22q, 4q31-34, and most likely 9q31, are associated with PD.[3] However, the genes involved and the specific roles of genetic variations in patients with PD remain unknown.

There has been a gradual emergence of research conceming into the underlying biological factors of PD. Brain-derived neurotrophic factor (BDNF) is a polypeptide encoded by a gene located on chromosome 11p13.[4] BDNF is the most abundant of the neurotrophins in the brain, and is recognized for its important role in the survival, differentiation and growth of neurons.[5-7] BDNF is also crucially involved in activity-dependent neuronal plasticity.[8] BDNF levels increased significantly after treatment in antidepressant responders, and BDNF may play

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a critical role in the pathophysiology of major depression and antidepressant treatment.[9,10] Several lines of research have suggested associations between BDNF genes and PD. In an animal study, BDNF conditional mutant mice were found to be hyperactive after exposure to stressors and had higher levels of anxiety when evaluated in a light/dark exploration test.[11] In another study, antidepressants were observed to suppress panic attacks, and chronic administration of antidepressants increased BDNF expression in the rat cerebral cortex.[12] Several papers have reported that the 196G/A (rs6265) single nucleotide polymorphism (SNP) of the BDNF gene in the coding region of exon XIIIA is related to decreased hippocampal volume and hippocampus-medicated memory performance in humans.[13-15] Based on these findings, it is reasonable to consider BDNF as a possible candidate gene involved in the pathophysiology of PD.

We hypothesized that the BDNF gene contributes to susceptibility to PD. The aim of the present study was to detect a possible association between three BDNF gene polymorphisms and PD. The three analyzed BDNF gene SNPs were: 196G/A (val66met, rs6265) in exon XIIIA, 11757G/C (rs16917204) in the 3' UTR of the BDNF gene, and 270C/T (rs56164415) in a non-coding region of exon V.

Three previous studies have been published on the associations between PD and the 196G/A (rs6265) and, 270C/T (rs56164415) SNPs of the BDNF gene,[16-18] though they detected no significant associations. However, no studies have been conducted on the association between PD and the BDNF gene through evaluation of the related haplotypes. In this study, we not only investigated the differences in genotype and allele frequencies between PD patients and controls, but also identified the genetic sequence association with PD via haplotype analysis. In previous studies, linkage disequilibrium analysis identified strong linkages between BDNF gene polymorphisms 196G/A (rs6265), 11757G/C (rs16917204), and 270C/T (rs56164415).[19,20] Furthermore, we aim to detect possible differences between male and female subgroups and examine the association of BDNF gene polymorphisms with PD in agoraphobia and non-agoraphobia subgroups. The identification of positive associations will help to establish the pathogenesis of PD.

METHODS

Subjects and assessments

Study participants included 136 patients diagnosed with PD (79 males, 57 females). All patients met the Diagnostic and Statistial Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for PD. Each patient was given a diagnostic assessment based on clinical interviews using the Structured Clinical Interview for DSM-IV (SCID).[21] Patients with comorbid mood disorder, any type of psychotic disorder (including schizophrenia), or other anxiety disorders were excluded. Concurrent agoraphobia was present in 70 (74.5%) of the included patients.

The normal control group consisted of 263 randomly selected healthy individuals (138 males, 125 females) who visited Korea University Ansan Hospital for regular health screenings. Subjects were excluded if they had any self-reported personal or familial psychiatric history, or a history of psychotropic medication. All patients and control subjects 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 using a commercial DNA extract kit (Wizard Genomic DNA Purification Kit, Promega, USA). In order to genotype the 196G/A (rs6265) SNP in the BDNF gene, polymerase chain reaction (PCR) was performed using the forward primer 5'-GAG GCT TGA CAT CAT TGG CT-3' and the reverse primer 5'-CGT GTA CAA GTC TGC GTC CT-3'. The amplification mixture contained 0.5u μL of 100ng/μL DNA, 2.5 μL of 10x Taq buffer, 0.5 μL of 10 mM dNTP mixture, 1 μL of primers, 19.375 μL of distilled water, and 0.125 μL of Taq DNA polymerase (SolGent, Korea). Samples were amplified using a thermocycler (Veriti 96-well thermal cycler, Applied Biosystems) for 35 cycles. After an initial 10min 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 5 min at 72°C, the reaction was terminated at 4°C. The amplified DNA was digested with the restriction enzyme NIaIII (New England Biolabs), which cuts at the 196A site, and the product was electrophoresed on 3% agarose gels and stained with ethidium bromide. Homozygous genotypes were identified by the presence of 113bp bands (G/G), or bands of 75 and, 38 bp (A/A). The heterozygous genotype had 3 bands: 113, 75, and 38bp (C/G).

In order to genotype the 11757G/C (rs16917204) SNP in the BDNF gene, PCR was performed using the forward primer 5'-CCT CCT GCA GCC ATT AGT-3' and the reverse primer 5'-AAT ACA AGT AGG ACC CTA GC-3'. Amplification was performed using the same methods described for the BDNF 196G/A SNP. The amplified DNA was digested with the restriction enzyme AvaII (New England Biolabs). Homozygous genotypes were identified by the presence of 65, 61, and 44 bp bands (C/C), or bands of 105 and 65 (G/G). The heterozygous genotype (C/G) had all four bands.

In order to genotype the 270C/T (rs56164415) SNP in the BDNF gene, the reaction mixture consisted of 0.5 μL of 100 ng/μL DNA, 2.5 μL of 10x Taq buffer, 0.5 μL of 10 mM dNTP

mixture, 1 μL of primers (forward primer: 5'-CAG AGG AGC CAG CCC GGT GCG-3', reverse primer 5'-CTC CTG CAC CAA GCC CCA TTC-3'), 9 μL of Band Doctor, 10.375 μL of distilled water, and 0.125 μL of Taq DNA polymerase (SolGent, Korea). The amplified DNA was digested with the restriction enzyme HinfI (New England Biolabs). Homozygous genotypes were identified by the presence of 127 and 78 bp bands (C/C), or bands of 127 and 63 (T/T). The heterozygous genotype (C/T) had all three bands.

Statistical analysis

The presence of Hardy-Weinberg equilibrium was tested by using a χ^2 test for goodness of fit. Differences in clinical variables were examined through t-tests. The genotype and allele frequencies of the PD patients and controls were analyzed using χ^2 statistics and Fisher's exact test using SPSS version 12.0. Frequencies and haplotype reconstructions were calculated using the SNP analyzer 2.0 (http://snp.istech21.com/snpanalyzer/2.0/). The level of statistical significance was set at $p<0.05$.

RESULTS

No significant difference was found in gender distribution between the PD patients (male:female=79:57) and healthy controls (male:female=138:125) ($\chi^2=1.140$, $p=0.286$). The mean age of PD patients was 40.6±9.6 years and the mean age of control group participants was 31.2±8.4 years. There was no significant difference in the mean age between the two groups ($t=10.046$, $p=0.052$).

The distributions of the BDNF 196G/A (rs6265), 11757G/C (rs16917204), and 270C/T (rs56164415) polymorphisms in PD patients and controls were in agreement with the Hardy-Weinberg equilibrium. The Hardy-Weinberg equilibria of the three candidate genes were as follows: BDNF 196G/A (rs6265) (PD, $\chi^2=0.6183$, df=1, $p=0.4317$; controls, $\chi^2=0.5107$, df=1, $p=0.4748$); BDNF 11757G/C (rs16917204) (PD, $\chi^2=2.9975$, df=1, $p=0.0834$; controls, $\chi^2=2.2959$, df=1, $p=0.1297$); and BDNF 270C/T (rs56164415) (PD, $\chi^2=0.0169$, df=1, $p=0.8965$; controls, $\chi^2=0.0010$, df=1, $p=0.9754$). There were no significant statistical differences in the genotype distributions or the allele frequencies of the three tested polymorphisms between the PD and control groups (Table 1, 2, and 3).

In order to test the hypothesis that BDNF SNPs have a gender dependent effect on susceptibility to PD, the genotype and allele frequencies of male patients, female patients, and controls were compared. There were no differences between PD patients and controls in either the male or female subgroups. Furthermore, no significant association was demonstrated between PD patients and controls in agoraphobia subgroups (Table 1, 2, and 3).

Because the frequency of the T allele of the BDNF 270C/T (rs56164415) polymorphism was much lower than that of the C allele in both PD patients and the controls, only two SNPs [BDNF 196G/A (rs6265) and 11757G/C (rs16917204)] were analyzed for the calculation of haplotype frequencies. The calculation of haplotype frequencies in the PD group, as compared with the controls, revealed a statistically significant difference with regard to the G-C haplotype combinations [OR=2.87; $p=0.0002$, $p^*=0.0009$ (p^* is the p value obtained after the Bonferroni correction)] (Table 4). The patient groups showed a significantly higher frequency of the G-C haplotype (for 196G/A and 11757G/C) as compared with the controls. The frequency changes were 12.2% in patients and 4.3% in controls. After the Bonferroni correction, the findings regard-

Table 1. Genotype and allele frequencies of BDNF 196G/A (rs6265) in panic disorder (PD) patients and controls

	Genotypes			χ^2	p	Allele frequencies		χ^2	p
	G/G	G/A	A/A			G	A		
PD patients	42	63	31	1.565	0.457	147	125	0.425	0.514
Controls	81	135	47			297	229		
Male PD patients	25	35	19	0.479	0.787	85	73	0.485	0.486
Male controls	48	62	28			158	118		
Female PD patients	17	28	12	1.562	0.458	62	52	0.047	0.829
Female controls	33	73	19			139	111		
Male controls	48	62	28	4.767	0.092	158	118	0.145	0.704
Female controls	33	73	19			139	111		
PD with agoraphobia	26	39	23	2.947	0.229	91	85	1.208	0.272
Controls	81	135	47			297	229		
PD without agoraphobia	16	24	8	0.131	0.937	56	40	0.116	0.734
Controls	81	135	47			297	229		

BDNF: brain-derived neurotrophic factor

ing the G-C haplotype remained significant.

DISCUSSION

PD is a common psychiatric disorder with a complex etiology that likely involves multiple genes in addition to nongenetic influences.[22-27] Many previous studies have identified associations between BDNF polymorphisms and psychiatric disorders. Associations have been found between the BDNF 196G/A (rs6265) polymorphism and chronic depression,[28] treatment response in patients with major depression,[29] and Alzheimer's disease,[30,31] although findings have not always been consistent. Additionally, the BDNF 11757G/C (rs16917204) polymorphism may be associated with Alzheimer's disease[19,32,33] and schizophrenia.[34] The last polymorphisms located in the 5'-untranslated lesion (UTR) BDNF 270C/T (rs56164415) are associated with Alzheimer's disease,[19] anorexia nervosa,[35] and treatment response in schizophrenia.[36]

This study found no genotype or allele distribution differences between PD patients and controls. These results are consistent with the results of previous studies. For example, Lam et al.[16] reported finding no differences in BDNF gene 196G/A (rs6265) polymorphisms between patient and control groups and no association between the polymorphism and PD with agoraphobia in a Chinese population. Shimizu et al.[18] similarly reported finding no significant differences in the frequencies of the genotypes or alleles of two BDNF SNPs [196G/A (rs6265), 270C/T (rs56164415)] between patients and controls in a Japa-

Table 2. Genotype and allele frequencies of BDNF 11757G/C (rs16917204) in panic disorder (PD) patients and controls

	Genotypes			χ^2	p	Allele frequencies		χ^2	p
	G/G	G/C	C/C			G	C		
PD patients	48	57	31	1.445	0.486	153	119	1.312	0.252
Controls	102	114	47			318	208		
Male PD patients	29	32	18	0.807	0.668	90	68	0.898	0.343
Male controls	59	52	27			170	106		
Female PD patients	19	25	13	1.283	0.526	63	51	0.498	0.48
Female controls	43	62	20			148	102		
Male controls	59	52	27	3.796	0.15	170	106	0.315	0.575
Female controls	43	62	20			148	102		
PD with agoraphobia	26	41	21	2.923	0.232	93	83	3.151	0.076
Controls	102	114	47			318	208		
PD without agoraphobia	22	16	10	1.674	0.433	60	36	0.142	0.706
Controls	102	114	47			318	208		

BDNF: brain-derived neurotrophic factor

Table 3. Genotype and allele frequencies of BDNF 270C/T (rs56164415) in panic disorder (PD) patients and controls

	Genotypes			χ^2	p	Allele frequencies		χ^2	p
	C/C	C/T	T/T			C	T		
PD patients	133	3	0	3.011	0.083	269	3	2.995	0.084
Controls	262	1	0			525	1		
Male PD patients	78	1	0	1.755	0.185	157	1	1.751	0.186
Male controls	138	0	0			276	0		
Female PD patients	55	2	0	1.772	0.183	112	2	1.757	0.185
Female controls	124	1	0			249	1		
Male controls	138	0	0	1.108	0.292	276	0	1.106	0.293
Female controls	124	1	0			249	1		
PD with agoraphobia	86	2	0	2.787	0.095	174	2	2.775	0.096
Controls	262	1	0			525	1		
PD without agoraphobia	47	1	0	1.843	0.175	95	1	1.837	0.175
Controls	262	1	0			525	1		

BDNF: brain-derived neurotrophic factor

Table 4. Haplotype analysis for BDNF SNPs in panic disorder patients and controls

SNP		Frequency (%)		OR	95% CI	p-value	p-value*
-196G/A (rs6265)	-11757G/C (rs16917204)	Patients	Controls				
G	G	41.82	52.11	0.694	0.157−0.932	0.015	0.06
A	C	31.53	35.2	0.896	0.658−1.221	0.488	(-)
A	G	14.43	8.34	1.702	1.059−2.736	0.027	0.107
G	C	12.22	4.35	2.87	1.604−5.136	0.0002	0.0009

*p-value after Bonferroni correction. BDNF: brain-derived neurotrophic factor

nese population. Otowa et al.[17] subsequently reported no significant association between three BDNF SNPs, including BDNF 196G/A (rs6265), and PD in a Japanese population.

PD is approximately twice as common in women as in men, with a 5% lifetime prevalence among women versus 2% among men.[37] A study including analyses stratified by gender revealed that female patients had lower levels of BDNF than female controls, and this result was stronger in female patients with anxiety disorders.[38] Therefore, we subdivided our PD and healthy control groups by gender. However, the hypothesis that BDNF SNPs have a gender-dependent effect on susceptibility to PD was not supported by our analysis. Furthermore, no association was observed between polymorphisms of BDNF genes and PD with agoraphobia.

Because the three BDNF polymorphisms analyzed in our study are linked, we calculated the haplotype frequencies, finding that the frequency of the G-C haplotype (for 196G/A and 11757G/C) is significantly higher in PD patients than in controls. Our results suggest that patients with the G-C haplotype (for 196G/A and 11757G/C) may be more susceptible to the development of PD.

There are some limitations to this study. First, the sample size was not sufficient to detect associations within the subgroups of PD. Our results showed that the frequency of the T allele portion of the BDNF 270C/T (rs56164415) polymorphism was much lower than that of the C allele portion in both PD patients and controls. This result is consistent with previous research in Japanese and Caucasian samples,[18,39-42] suggesting that such allele distributions might not have ethnic variability. The low frequency of the T allele may make the results prone to false positive errors, especially when small samples are analyzed. It is meaningful that our sample size is larger than those used in previous studies (Lam et al.[16]: 103 patients, 180 controls; Shimizu et al.[18]: 109 patients, 178 controls). In our haplotype analysis, the sample sizes of the GC allele subgroups (12% of patients, 4% of controls) were relatively small, and our hypothesis might be confirmed in a study using a larger sample. Second, our population consisted exclusively of Korean subjects, without ethnic diversity. Previous studies on genetic associations in PD also examined only Asian groups; therefore, research investigating diverse ethnic groups is needed. Third, we investigated only BDNF SNPs. In future research, association studies with multiple genes are needed to identify possible genetic interactions and the pathogenesis of PD. Further, clinical research should examine the possible relationships between genetic variations of BDNF and panic symptom severity or antidepressant treatment response. Moreover, studies identifying possible associations between the BDNF polymorphism and BDNF levels would be helpful in understanding the pathophysiology of PD.

PD is a complex and heterogeneous psychiatric condition. In addition to genetic factors, neurobiological and psychosocial factors may be involved in pathogenesis of PD, and these factors may interact with each other. An understanding of this heterogeneity will be facilitated by the continued development and application of genetic, neurobiological, neuroimaging, and cognitive-behavioral approaches, which can refine PD phenotypes and elucidate the genotypes associated with this disorder.

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