Journal of Affective Disorders 136 (2012) 833–840

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Serotonergic and BDNF genes and risk of depression after stroke

Jae-Min Kim *, Robert Stewart, Kyung-Yeol Bae, Sung-Wan Kim, Hee-Ju Kang, Il-Seon Shin, Joon-Tae Kim, Man-Seok Park, Myung-Kyu Kim, Sung-Woo Park, Young-Hoon Kim, Jong-Keun Kim, Ki-Hyun Cho, Jin-Sang Yoon

Department of Psychiatry, Chonnam National University Medical School, Gwangju 501-757, Republic of Korea
Department of Neurology, Chonnam National University Medical School, Gwangju 501-757, Republic of Korea
Department of Pharmacology, Chonnam National University Medical School, Gwangju 501-757, Republic of Korea
King's College London (Institute of Psychiatry), Section of Epidemiology, London SE5 8AF, UK
Department of Neuropsychiatry, School of Medicine, Haeundae Paik Hospital, Paik Institute for Clinical Research & FIRST research group, Inje University, Busan 612-030, Republic of Korea

ARTICLE INFO

Article history:
Received 20 July 2011
Received in revised form 24 September 2011
Accepted 24 September 2011
Available online 20 October 2011

Keywords:
Stroke
Depression
Brain-derived neurotrophic factor
Serotonin transporter
Serotonin receptor
Genetic association study

ABSTRACT

Background: Polymorphisms of serotonin transporter (5-HTT) and brain-derived neurotrophic factor (BDNF) have been investigated as candidate genes for post-stroke depression (PSD). Serotonin 2a receptor (5-HTR2a) genes have not been yet investigated in PSD. This study aimed to investigate whether the 5-HTT, 5-HTR2a, and BDNF genes are associated with PSD independently and/or interactively in a Korean sample with high prevalence of risk alleles.
Methods: In 276 stroke cases, depression was diagnosed using DSM-IV at 2 weeks after stroke, further classified to major PSD (N = 29), all (major plus minor) PSD (N = 77), and control (N = 199) groups. Associations between PSD and 5-HTTLPR, STin2 VNTR, 5-HTR2a 1438A/G, 5-HTR2a 102T/C, and BDNF val66met genotypes were estimated using logistic regression models, and gene–gene interactions were investigated using the generalized multifactor dimensionality reduction method.
Results: 5-HTR2a 1438 A/A genotype was associated with major PSD, while 5-HTTLPR s/s and BDNF met/met genotypes were associated with all PSD. There was a significant interaction between 5-HTR2a 1438A/G and BDNF val66met polymorphisms for major PSD and a borderline significant interaction between 5-HTTLPR and BDNF val66met polymorphisms for all PSD.
Conclusions: In a large cohort, we found evidence for serotonin and BDNF polymorphisms as susceptibility factors and gene–gene interactions between these systems for depression at 2 weeks post-stroke.

1. Introduction

Depression is common after stroke and has adverse effects on the course and prognosis of disease (Hackett et al., 2005; Robinson, 2003). Both psychosocial and biological factors are important in the etiology of post-stroke depression (PSD) (Spalletta et al., 2006; Whyte and Mulsant, 2002), and recently genetic predispositions have been suggested. The serotonin transporter (5-HTT) gene, located on chromosome 17q11.1–17q12, has received particular attention. The most frequently studied variant is a biallelic polymorphism in the 5-HTT gene linked promoter region (5-HTTLPR) with short (*s*) and long (*l*) alleles based on the presence or absence of a 43-base pair insertion/deletion polymorphism. The *s* allele reduces the transcriptional activity of the 5-HTT gene promoter resulting in decreased 5-HTT expression (Heils et al., 1995), and therefore has been hypothesized to be a risk factor for depression (Anguelova et al., 2003). Ramasubbu et al. (2006) reported that the 5-HTTLPR *s* allele was associated with PSD in a sample

* Corresponding author at: Department of Psychiatry, Chonnam National University Medical School, 5 Hak-dong, Dong-Ku, Gwangju 501-746, Republic of Korea. Tel.: +82 62 220 6143; fax: +82 62 225 2351.
E-mail address: jmkim@chonnam.ac.kr (J.-M. Kim).

0165-0327/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jad.2011.09.029

of 26 stroke patients with DSM-IV major depression and 25 non-depressed stroke patients, the first genetic study of PSD to our knowledge. Kohen et al. (2008) replicated this finding with a larger sample of 75 depressive and 75 non-depressive stroke patients categorized by the Geriatric Depression Scale 10/11 cutoff. Another common variant in 5-HTT gene is a triallelic polymorphism located in intron 2 and corresponding to 9-, 10-, or 12-variable tandem repeat units of 17-base pair (STin2 VNTR). The 9- and 12-repeat alleles (STin2.9 and STin2.12, respectively) have been shown to enhance transcription of 5-HTT compared with the 10-repeat allele (STin2.10) (Lovejoy et al., 2003), and have been found to be associated with affective disorders (Battersby et al., 1996; Jarrett et al., 2007). Kohen et al. (2008) found that participants with STin2 *9/12* or *12/12* genotype had higher risk of PSD compared with STin2 *10/10* genotype carriers, although Ramasubbu et al. (2008) found no such associations. As well as this 5-HTT polymorphism, the serotonin 2a receptor (5-HTR2a) gene, located on chromosome 13q14–q21, has also received attention. Two polymorphisms have been reported within this gene: a 1438A/G polymorphism in the promoter region, and an M*sp*I polymorphic site at position 102T/C. The 5-HTR2a 1438A/G *A* allele has been found to be associated with mood disorder and depressive mood (Bonnier et al., 2002; Enoch et al., 1999); and the 5-HTR2a 102T/*CC* allele has been found to be associated with major depressive disorder or suicidal ideation (Du et al., 2000; Zhang et al., 1997). However, these 5-HTR2a polymorphisms have not been investigated yet in the context of PSD.

Another more recent candidate for depression and PSD is the brain-derived neurotrophic factor (BDNF) gene. This is located on chromosome 11p14.1 and has several polymorphic markers. These include the single nucleotide polymorphism (SNP) at nucleotide 196G/A, which results in an amino acid substitution (valine to methionine) at codon 66 (val66met) of the proBDNF molecule. This SNP affects intracellular processing and secretion of BDNF, and the *met* allele is associated with reduced activity-dependent secretion of BDNF (Egan et al., 2003). Previously, we have reported a significantly stronger association between incident stroke and depression in the presence of the *met* allele in a 2 year prospective study with 500 community elders (Kim et al., 2008). However, this hypothesis has not been tested in a clinical case–control design so far.

Linkage disequilibrium has been found between 5-HTTLPR and STin2 VNTR (Wendland et al., 2006), and between 5-HTR2a 1438A/G and 102T/C polymorphisms (Ono et al., 2001), and there is evidence that serotonin and BDNF systems may be linked at multiple intracellular and intercellular levels (Duman et al., 1997). Therefore, addressing potential gene–gene interactions may be helpful in elucidating the pathogenesis of PSD. This study aimed to investigate whether the 5-HTT, 5-HTR2a, and BDNF genes are associated with PSD independently and/or interactively in a sample of Korean stroke patients.

2. Methods

2.1. Study outline

This analysis was carried out as a component of a larger parent study, which seeks to investigate mental disorders in stroke survivors using a naturalistic prospective design. Participants were consecutively recruited from all patients with recent ischemic stroke hospitalized within the Department of Neurology of Chonnam National University Hospital, Gwangju, South Korea. Assessments are made at 2 weeks and 1 year post-stroke to investigate both acute and chronic outcomes. The recruitment period for the initial 2 week assessment was from 2006 to 2009 and only the 2 week data are considered in the analyses described here.

2.2. Participants

All patients with acute stroke hospitalized at the study site were approached regarding participation. Inclusion criteria were: i) confirmed ischemic stroke by brain magnetic resonance imaging (MRI), or computed tomography (CT) if MRI was contraindicated; ii) ability to complete the necessary investigations and questionnaires; and iii) capacity to understand the objective of the study and provide informed consent. Exclusion criteria were: i) severe physical illnesses which were life-threatening or interfering with the recovery from stroke; ii) communication difficulties due to dysphasia or dysarthria precluding informed consent and questionnaire completion; iii) any of the following comorbid neuropsychiatric conditions: dementia, Parkinson's disease, brain tumor, epilepsy, psychoses, alcohol and substance dependence; iv) severe physical illnesses limiting movement prior to stroke; and v) Mini-Mental State Examination (Folstein et al., 1975) score of <16. All participants gave written informed consent and the study was approved by the Chonnam National University Hospital Institutional Review Board.

2.3. Demographic and clinical characteristics

Age, gender, year of education, and previous histories of depression and stroke were recorded according to information obtained from the participant or their caregiver, as appropriate. Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS) (Kasner et al., 1999). All participants underwent brain MRI or CT imaging. Stroke location by hemisphere was divided into left, right, and bilateral with further sub-division into anterior, posterior, and both.

2.4. Diagnoses of PSD

The diagnoses of major and minor depressive disorders after stroke were determined by applying DSM-IV diagnostic criteria using the Mini International Neuropsychiatric Interview (MINI), a structured diagnostic psychiatric interview for DSM-IV (Sheehan et al., 1988) giving rise to major or minor depression categories. According to these criteria, patients were diagnosed as having major depression if they had at least one core symptom (i.e., depressed mood or loss of interest) and at least four other symptoms of depression. A diagnosis of minor depression was made if patients had at least one core symptom and at least two but less than five symptoms in total. PSD diagnoses were re-categorized into all PSD (major/minor depression) and major PSD. The MINI has been formally translated and standardized in Korean (Yoo et al., 2006).

2.5. Genotyping

Blood samples for genotyping were obtained in a subsample who agreed to this. DNA was extracted from venous blood using standard procedures. Polymerase chain reaction (PCR) and the PCR-based restriction fragment length polymorphism assays were performed (Table 1). The amplification conditions were pre-denaturation at 95 °C for 5 min, followed by 30 or 40 cycles consisting of denaturation at 95 °C for 35 s, 55 °C or 62 °C for 35 s and 72 °C for 35 s, and post-elongation at 72 °C for 5 min, with a final maintenance step at 4 °C, as required for each polymorphism. For 5-HTTLPR polymorphism, the genotypes were categorized as '*s*/*s*', '*s*/*l*', and '*l*/*l*'. For STin2 VNTR polymorphism, the *9* allele was extremely rare (present in only one participant), and therefore the genotypes were categorized as '*10*/*12*' and '*9* or *12*/*12*'. For 5-HTR2a 1438A/G polymorphism, the genotypes were categorized as '*G*/*G*', '*G*/*A*', and '*A*/*A*'. For 5-HTR2a 102T/C polymorphism, the genotypes were categorized as '*C*/*C*', '*C*/*T*', and '*T*/*T*'. For the BDNF *val*66*met* polymorphism, the genotypes were categorized as '*val*/*val*', '*val*/*met*', and '*met*/*met*'.

2.6. Statistical analyses

The two dependent variables were all PSD and major PSD. Demographic and clinical characteristics were compared between no PSD and all PSD, and between no PSD and major PSD using t-tests, χ^2 tests, or Fisher's exact tests as appropriate. Genotype distributions and allele frequencies for the five polymorphisms were compared between no PSD and all PSD, and between no PSD and major PSD using χ^2 tests, or Fisher's exact tests as appropriate. Tests for Hardy–Weinberg equilibrium and linkage dysequilibrium were made using Haploview v.4.2 program. Odds ratios (ORs) for all and major PSD outcomes by genotype were estimated using logistic regression models after adjustment for potential covariates. Finally, gene–gene interactions were investigated using generalized multifactor dimensionality reduction (GMDR) methods, which have been described in detail previously (Lou et al., 2007). The n-dimensional space formed by a given set of SNPs was reduced to a single dimension to analyze n-way interactions. Score based statistics were calculated using maximum-likelihood estimates to classify multifactor cells into two different groups (either high or low risk). This was carried out for all possible 2-locus to 5-locus combinations of SNPs, and the combination with the lowest misclassification error was selected. The GMDR software provides several output parameters including cross-validation consistency, testing balance accuracy, and p-values to assess interactions for each selected combination. The cross-validation consistency value measures the degree of consistency with which the selected combination is identified as the best model among all possibilities considered. The testing balance accuracy measures the degree to which the interaction accurately predicts case vs. control status with scores between 0.5 (indicating the model predicts no better than chance) and 1.0 (indicating perfect prediction). Permutation testing obtains empirical p-values of prediction accuracy as a benchmark based on 1000 shuffles. Potential covariates of PSD were included in the gene–gene interaction analyses. Logistic regression tests were performed additionally to confirm the results from the GMDR analyses. Finally, potential gene by stroke location interactions were investigated using logistic regression. Statistical analyses were carried out using SPSS 13.0 and GMDR software.

3. Results

3.1. Recruitment

A total of 363 eligible stroke patients were recruited. The mean (SD) interview time point from stroke was 12.3 (3.0) days. Of these 276 (76.0%) agreed to provide blood samples for genotyping, and formed the study sample for the present analyses. There were no significant differences between participants and non-participants with respect to any demographic and clinical characteristics (all p-values>0.15). Of the 276 participants, major depression was diagnosed in 29 (10.5%), minor depression in 48 (17.4%), and 77 (27.9%) were categorized as having any PSD.

3.2. Demographic and clinical characteristics by PSD

In the analyzed sample, the mean (SD; range) age was 64.3 (9.5; 35–87) years; 59.4% (N = 164) were male; the mean (SD) duration of education was 8.5 (5.0) years; previous depression was reported in 15 participants (5.4%); previous stroke was reported in 27 participants (9.8%); and the mean (SD) NIHSS score was 3.5 (3.2). Stroke laterality was left hemisphere in

Table 1
Polymerase chain reaction (PCR) methods for allele detection.

Polymorphism	Forward (F) and reverse (R) primer	Restriction enzyme	PCR product and allele
5-HTTLPR	F: 5′-GGCGTTGCCGCTCTGAATGC-3′	–	44 bp 14 copy of a repetitive sequence: *s*
	R: 5′-GAGGGACTGAGCTGGACAACCAC-3′		44 bp 16, 18, 20 and 22 copies of a repetitive sequence: *l*
STin2 VNTR	F: 5′-GTCAGTATCACAGGCTGCGAG-3′	–	17 bp 9 copy of a repetitive sequence: *9*
	R: 5′-TGTTCCTAGTCTTACGCCAGTGG-3′		17 bp 10 copy of a repetitive sequence: *10*
			17 bp 12 copy of a repetitive sequence: *12*
5-HTR2a 1438A/G	F: 5′-ACTGCGAAACCAACTTATTTCC-3′	MSpI	232 and 120 bp: 1438*G*
	R: 5′-CTTGTGCAGATTCCCATTAAGG-3′		352 bp: 1438*A*
5-HTR2a 102T/C	F: 5′-TCTGCTACAAGTTCTGGCTTC-3′	HpaII	342 bp: 102*T*
	R: 5′-CTGCAGCTTTTTCTCTAGGGG-3′		215 and 126 bp: 102*C*
BDNF val66met	F: 5′-GGTGAGAAGAGTGATGACCA-3′	BbrPI	490 and 208 bp: 66*val*
	R: 5′-GCCAGCCAATTCTCTTTTG-3′		698 bp: 66*met*

5-HTTLPR: serotonin transporter gene linked promoter region; STin2 VNTR: serotonin transporter intron 2 variable number tandem repeat; 5-HTR2a: serotonin 2a receptor; BDNF: brain-derived neurotrophic factor.

Table 2
Sample characteristics by post-stroke depression (PSD) status.

	No PSD (N = 199)	All PSD (N = 77)	Major PSD (N = 29)	p-value[a]	p-value[b]
Age, mean (SD) years	63.5 (9.4)	66.5 (9.5)	64.6 (10.3)	0.018	0.555
Gender, N (%) male	121 (60.8)	43 (55.8)	16 (55.2)	0.452	0.563
Education, mean (SD) year	8.7 (5.0)	8.0 (5.1)	7.5 (4.9)	0.270	0.220
Previous depression, N (%)	6 (3.0)	9 (11.7)	3 (10.3)	0.004	0.092
Previous stroke, N (%)	15 (7.5)	12 (15.6)	5 (17.2)	0.044	0.084
NIHSS, mean (SD) score	3.2 (3.2)	4.2 (3.2)	4.8 (3.6)	0.002	0.016
Stroke hemisphere, N (%)					
Left	85 (42.7)	41 (53.2)	10 (34.5)	0.288	0.679
Right	104 (52.3)	33 (42.9)	17 (58.6)		
Bilateral	10 (5.0)	3 (3.9)	2 (6.9)		
Stroke location, N (%)					
Anterior	104 (52.3)	55 (71.4)	24 (82.8)	0.013	0.008
Posterior	71 (35.7)	15 (19.5)	4 (13.8)		
Both	24 (12.1)	7 (9.1)	1 (3.4)		

NIHSS: National Institutes of Health Stroke Scale.
[a]p-value for all PSD versus no PSD.
[b]p-value for major PSD versus no PSD using χ^2, Fisher's exact or t-tests, as appropriate.

126 (45.7%), right hemisphere in 137 (49.6%), and bilateral in 13 (4.7%); and stroke location was anterior in 159 (57.6%), posterior in 86 (31.2%), and both in 31 (11.2%). These characteristics are compared by PSD status in Table 2. Compared to those without PSD, the combined case groups were significantly older, more likely to have previous histories of stroke and/or depression, had higher NIHSS scores, and were more likely to have an anterior stroke location. The major PSD group had higher NIHSS scores and more frequently had experienced anterior stroke location compared to those with no depression.

3.3. Genotype distribution and allele frequency

No deviation from the Hardy–Weinberg equilibrium was observed for any genotype ($\chi^2 = 3.03$, 1.97, 2.83, 0.00, and 3.74 for 5-HTTLPR, STin2 VNTR, 5-HTR2a 1438 A/G, 5-HTR2a 102T/C, and BDNF val66met respectively; all p-values > 0.05). Genotype distributions and allele frequencies are compared by PSD status in Table 3. Cases with any depression had significantly higher 5-HTTLPR *s* allele, 5-HTR2a 1438 *A* allele, and BDNF *met* allele frequencies compared to controls with no depression. The major depression group had significantly higher 5-HTR2a 1438 *A* allele and BDNF *met* allele frequencies compared to controls. If Bonferroni corrections were applied, considering multiple comparisons, the strength of these associations remained significant between major PSD and 5-HTR2a 1438 *A* allele, with borderline significance for the other combinations.

3.4. Individual effects of genotypes on PSD risks after adjustment

Associations between genotypes and PSD status adjusted for age, previous depression and stroke, NIHSS score, and stroke location are summarized in Table 4. The 5-HTTLPR *s/s* and the BDNF *met/met* genotypes were significantly associated with any depression, but only the 5-HTR2a 1438 *A/A* genotype was significantly associated with major depression. Although no other significant associations were found, the odds tended to be higher with increasing numbers of the hypothesized risk alleles.

3.5. Gene–gene interactions

The genotype distributions between the two 5-HTT genes and between the two 5-HTR genes were not independent. That is, strong linkage disequilibrium was observed between the 5-HTTLPR and STin2 VNTR polymorphisms ($D' = 0.522$, $r^2 = 0.252$, p-value < 0.001); and between the 5-HTR2a 1438 A/G and 5-HTR2a 102T/C polymorphisms ($D' = 0.807$, $r^2 = 0.345$, p-value < 0.001). GMDR analyses for adjusted 2- to

Table 3
Genotype and allele frequencies by post-stroke depression (PSD) status.

	No PSD (N = 199)	All PSD (N = 77)	Major PSD (N = 29)	p-value[a]	p-value[b]
5-HTTLPR					
l/l	24 (12.0)	3 (3.9)	2 (6.9)	0.036	0.296
l/s	75 (37.7)	24 (31.2)	8 (27.6)		
s/s	100 (50.3)	50 (64.9)	19 (65.5)		
l allele	123 (30.9)	30 (19.5)	12 (20.7)	0.011	0.134
s allele	292 (69.1)	124 (80.5)	48 (79.3)		
STin2 VNTR					
10/12	32 (16.1)	11 (14.3)	1 (3.4)	0.712	0.089
9 or *12/12*	167 (83.9)	66 (85.7)	28 (96.6)		
5-HTR2a 1438A/G					
G/G	61 (30.7)	17 (22.1)	4 (13.8)	0.119	0.005
G/A	91 (45.7)	33 (42.9)	10 (34.5)		
A/A	47 (23.6)	27 (35.1)	15 (51.7)		
G allele	213 (53.5)	67 (43.5)	18 (31.0)	0.045	0.002
A allele	185 (46.5)	87 (56.5)	40 (69.0)		
5-HTR2a 102T/C					
T/T	52 (26.1)	14 (18.2)	5 (17.2)	0.282	0.133
T/C	99 (49.7)	39 (50.6)	12 (41.4)		
C/C	48 (24.1)	24 (31.2)	12 (41.4)		
T allele	203 (51.0)	67 (43.5)	22 (37.9)	0.115	0.067
C allele	195 (49.0)	87 (56.5)	36 (62.1)		
BDNF val66met					
val/val	51 (25.6)	13 (16.9)	6 (20.7)	0.051	0.012
val/met	113 (56.8)	41 (53.2)	11 (37.9)		
met/met	35 (17.6)	23 (29.9)	12 (41.4)		
val allele	215 (54.0)	67 (43.5)	23 (39.7)	0.019	0.032
met allele	183 (46.0)	87 (56.5)	35 (60.3)		

5-HTTLPR: serotonin transporter gene linked promoter region; STin2 VNTR: serotonin transporter intron 2 variable number tandem repeat; 5-HTR2a: serotonin 2a receptor; BDNF: brain-derived neurotrophic factor.
[a]p-value for all PSD versus no PSD.
[b]p-value for major PSD versus no PSD using χ^2 or Fisher's exact tests as appropriate.

Table 4
Adjusted[a] associations of genotypes with post-stroke depression (PSD) status.

Polymorphism		All PSD		Major PSD	
		OR (95% CI)	p-value	OR (95% CI)	p-value
5-HTTLPR	*l/l*	Ref	0.024	Ref	0.148
	l/s	3.14 (0.80–12.3)		1.53 (0.28–8.38)	
	s/s	4.39 (1.16–16.5)		2.55 (0.52–12.5)	
STin2 VNTR	*10/12*	Ref	0.857	Ref	0.182
	9 or *12/12*	1.08 (0.49–2.38)		4.07 (0.52–31.9)	
5-HTR2a 1438A/G	*G/G*	Ref	0.147	Ref	0.003
	G/A	1.02 (0.50–2.09)		1.56 (0.45–5.42)	
	A/A	1.74 (0.81–3.75)		5.59 (1.62–19.3)	
5-HTR2a 102T/C	*T/T*	Ref	0.070	Ref	0.086
BDNF val66met	*T/C*	1.35 (0.65–2.83)		1.03 (0.33–3.23)	
	C/C	2.11 (0.93–4.79)		2.49 (0.77–8.06)	
	val/val	Ref	0.036	Ref	0.055
	val/met	1.37 (0.65–2.91)		0.94 (0.31–2.82)	
	met/met	2.45 (1.05–5.75)		2.79 (0.91–8.54)	

5-HTTLPR: serotonin transporter gene linked promoter region; STin2 VNTR: serotonin transporter intron 2 variable number tandem repeat; 5-HTR2a: serotonin 2a receptor; BDNF: brain-derived neurotrophic factor.
[a]Adjusted for age, previous depression, previous stroke, National Institutes of Health Stroke Scale score, and stroke location. p-value for logistic regression likelihood ratio test.

5-locus models are summarized in Table 5. There was a significant 2-locus model involving 5-HTR2a 1438 A/G and BDNF val66met polymorphisms for major PSD, and a borderline significant 2-locus model involving 5-HTTLPR and BDNF val66ment polymorphisms for any PSD. In a logistic regression analysis re-examining these interactive effects, the Wald statistic (on one degree of freedom) was 6.03 ($p = 0.033$) for a 5-HTR2a 1438 A/G × BDNF val66met interaction, and 3.17 ($p = 0.063$) for a 5-HTTLPR × BDNF val66ment interaction. No significant models were found for any other combinations.

3.6. Gene–stroke location interactions

The interactive effects of genes by stroke location on PSD status were investigated in logistic regression models but no significant interactions were found for any combinations. The Wald statistics (on one degree of freedom) were 0.03–2.73 (all $p > 0.1$) for the all PSD, and were 0.36–1.53 (all $p > 0.2$) for major PSD.

4. Discussion

The principal findings of this genetic association study of depression in the acute period after stroke were that 5-HTTLPR *s/s* and BDNF *met/met* genotypes were independently associated with any depression, that 5-HTR2a 1438 *A/A* genotype was independently associated with major depression, and that 5-HTR2a 1438 A/G and BDNF val66met polymorphisms were interactively associated with major depression.

To our knowledge, this study, although limited in size is one of the largest to date on genes associated with depression following stroke, as well as being the first to report on associations between 5-HTR2a polymorphisms and PSD and the first to report on an interaction between serotonergic and BDNF genotypes for this outcome. It is also one of the first, to our knowledge, to investigate an East Asian sample. One of the strengths of our study was that depression was ascertained using a structured diagnostic interview. Based on DSM-IV, major PSD was found in 10.5% and minor PSD was found in 17.4% (all PSD 27.9%). These were comparable to, although

Table 5
Optimal gene–gene interaction models for post-stroke depression (PSD) according to the generalized multifactor dimensionality reduction method.[a]

Locus number	Best combination	Cross-validation consistency	Testing balance accuracy	p-value
All PSD				
2	5-HTTLPR, BDNF val66met	10/10	61.35	0.075
3	5-HTTLPR, STin2 VNTR, BDNF val66met	10/10	59.41	0.126
4	5-HTTLPR, STin2 VNTR, 5-HTR2a 1438A/G, BDNF val66met	10/10	57.15	0.341
5	5-HTTLPR, STin2 VNTR, 5-HTR2a 1438A/G, 5-HTR2a 102T/C, BDNF val66met	10/10	49.51	0.963
Major PSD				
2	5-HTR2a 1438A/G, BDNF val66met	9/10	64.35	0.036
3	5-HTTLPR, 5-HTR2a 1438A/G, BDNF val66met	10/10	60.15	0.139
4	5-HTTLPR, 5-HTR2a 1438A/G, 5-HTR2a 102T/C, BDNF val66met	10/10	54.14	0.775
5	5-HTTLPR, STin2 VNTR, 5-HTR2a 1438A/G, 5-HTR2a 102T/C, BDNF val66met	10/10	56.55	0.666

5-HTTLPR: serotonin transporter gene linked promoter region; STin2 VNTR: serotonin transporter intron 2 variable number tandem repeat; 5-HTR2a: serotonin 2a receptor; BDNF: brain-derived neurotrophic factor.
[a]Adjusted for age, previous depression, previous stroke, National Institutes of Health Stroke Scale score, and stroke location. p-value based on 1000 permutations.

slightly higher than findings from previous studies with similar designs, diagnostic criteria and time point since stroke, which have reported prevalences of 6% for major depression and 22% for all depression (Aben et al., 2003; Berg et al., 2001). Another strength was that depression and other variables were assessed at a similar time point (two weeks after stroke) in all participants. It has been reported that the etiology of depression may differ according to the time elapsed after stroke, with biological factors more important at an acute stage and psychosocial factors increasing in salience later on (Bhogal et al., 2004). The present study focused on the acute post-stroke period, and therefore reduced the risk of bias arising from heterogeneous time since stroke. A further advantage was that participants were consecutive patients with a recent stroke from the study hospital, unlike previous studies which have applied potentially more selective case–control designs (Kohen et al., 2008; Ramasubbu et al., 2006). This reduced the likelihood of selection bias and increases the potential generalizability. A limitation was that the sample size was limited for detecting associations with low frequency alleles, or gene–gene interactions, particularly for major PSD. Another potential limitation was that the SNP rs25531, located immediately upstream of 5-HTTLPR in 5-HTT gene and associated with the regulation of 5-HTT transcription (Wendland et al., 2006), was not assayed. However, the potentially relevant variant (*G*) of this SNP is known to extremely rare in Asian populations (Zhang et al., 2009). A further limitation was that genotyping was only possible in 76% of the total stroke patients in the parent study, although there were no significant differences in demographic and clinical characteristics between those with and without blood samples.

The role of the 5-HTTLPR *s* allele as a risk factor for depression has been controversial (Levinson, 2006). However, this allele has been associated with depression after stressful life events, replicated in various age groups (Caspi et al., 2003; Kendler et al., 2005; Kim et al., 2007), and linked to depression occurring in combination with medical diseases such as Parkinson's disease (Mossner et al., 2001), hip fracture (Lenze et al., 2005), coronary disease (Otte et al., 2007), and multisystem chronic ill-health (Kim et al., 2009), which are all potential environmental stressors. In line with these findings, the *s* allele has also been found to be significantly associated with depression after stroke in previous research (Kohen et al., 2008; Ramasubbu et al., 2006), as well as in our own study. The evaluation points for depression have differed between previous studies, being unclear in the report from one study (Ramasubbu et al., 2006), within 4 months after stroke in another (Kohen et al., 2008), and at 2 weeks in our study. These suggest that the 5-HTTLPR *s* allele might be associated with depression at various time points after stroke. This association may be explained by underlying relationships observed between 5-HTTLPR allele status, brain structures, and response to antidepressants. For example, depressed older *s* allele carriers with major depression were found to have lower caudate nucleus volume (Hickie et al., 2007), as well as both microstructural white matter abnormalities and a low remission rate when treated with an SSRI antidepressant than *l* homozygotes (Alexopoulos et al., 2009). The strength of the association did not reach significance for major PSD in our study which may reflect a lack of power. Previous findings of an association between STin2 VNTR polymorphism and PSD have been inconsistent with one study reporting a significant association between STin2 *9* or *12/12* genotype and PSD (Kohen et al., 2008), but another finding no such association (Ramasubbu et al., 2006). In our study we also found no significant association between STin2 VNTR polymorphism and PSD either before or after adjustment.

The serotonergic receptor system has also been implicated in the pathophysiology of mood disorders and in the action of antidepressants. 5-HTR2a polymorphisms have received particular attention but have not been investigated in relation to PSD. A novel finding of the present study was the significant association between the *A* allele of the 5-HTR2a 1438A/G polymorphism and major PSD. The 5-HTR2a 1438A/G *A* allele has been found to be associated with mood disorders and depressive mood (Bonnier et al., 2002; Enoch et al., 1999; Jansson et al., 2003) and our findings support this. With respect to the 5-HTR2a 102T/C polymorphism, the *C* allele was associated with both all PSD and major PSD at borderline significance levels in our study. In a meta-analysis, it was concluded that the 5-HTR2a 102T/*CC* allele was not directly associated with depressive disorders (Anguelova et al., 2003). However, it has been found to be significantly associated with particular traits related to depression such as suicidal ideation (Du et al., 2000; Zhang et al., 1997) and treatment responses (Minov et al., 2001; Serretti et al., 2000).

Previously, we have reported a significant association between the BDNF val66met *met* allele and incident PSD in a Korean community (Kim et al., 2008), and were here able to replicate this in a clinical post-stroke sample. The *met* allele has been associated with reduced activity-dependent secretion of BDNF (Egan et al., 2003), and because BDNF is the most abundant neurotrophin in the brain and has antidepressant neuroprotective effects (Manji et al., 2001), functional deficiency might increase a depressogenic impact of stroke. In addition, BDNF appears to have survival-promoting actions on a variety of CNS structures including hippocampal, cortical, cholinergic, dopaminergic and serotonergic neurons (Manji et al., 2001), and neuronal repair after stroke in brain regions associated with depression might therefore be more delayed in those with the *met* allele. In addition, relationships between BDNF *val/met* status, white matter abnormalities and response to antidepressants in late-life depression have been reported (Alexopoulos et al., 2010). However, the relationship between BDNF *val/met* status and PSD might be more complex than deficient neuroprotection related to inadequate transcription of BDNF. The effects of BDNF in the brain vary depending on the location in which it is expressed. For example, administration of BDNF in the ventral tegmentum has been found to be depressogenic in animals and blockade of BDNF action in the nucleus accumbens has an antidepressant-like effect (Eisch et al., 2003), while BDNF may have an antidepressant effect in the hippocampus (Manji et al., 2001). Therefore this finding requires further exploration and replication in other populations.

The GMDR approach was used to investigate potential gene–gene interactions for PSD. Our findings support evidence that the serotonin and BDNF systems are linked at micro- and macroscopic levels. For example, stress has been associated with reductions in both Raphe serotonin transporter mRNA and hippocampal BDNF mRNA (Vollmayr et al., 2000). We have previously reported a three-way gene–

gene–environment (5-HTTLPR, BDNF, and life stresses) interaction for depression in late-life in an East Asian population (Kim et al., 2007). Novel findings clearly require replication in other populations as with all genetic association studies, and it should be borne in mind that the present analysis was restricted to the acute stage of stroke. Further studies later after stroke are needed because the etiology of depression cannot be assumed to remain constant.

With respect to allele frequencies, there are known ethnic differences between East Asian and Caucasian populations. Our sample had higher 5-HTTLPR *s* allele, 72% compared to 43–44% in other settings (Collier et al., 1996; Kohen et al., 2008); for the STin2 VNTR *9* or *12/12* allele: 84% compared to 63–67% (Collier et al., 1996; Kohen et al., 2008); for the 5-HTR2a 1438A/G *A* allele: 49% compared to 38–41% (Bonnier et al., 2002; Enoch et al., 1999); and for the BDNF val66met *met* allele: 49% compared to 17–21% (Kaufman et al., 2006; Zhang et al., 2006). Taken together, the potential risk alleles for PSD (5-HTTLPR *s*, STin2 VNTR *9* or *12/12*, 5-HTR2a 1438A/G *A*, and BDNF val66met *met*) were relatively common in our sample as has been found in other East Asian studies (Kato et al., 2005; Kunugi et al., 1997, 2004; Ohara et al., 1998). These results may have public health relevance in East Asian populations in terms of the increased genetic vulnerability to PSD, and it is noteworthy that the prevalence of PSD of the present study was higher than findings from Western studies with similar designs (Aben et al., 2003; Berg et al., 2001).

Role of funding source

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2009-0087344). The Ministry of Education, Science and Technology had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. RS is funded by the NIHR Specialist Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King's College London.

Conflict of interest

The authors declare that we have no conflict of interest in relation to this study.

Acknowledgment

None.

References

Aben, I., Verhey, F., Strik, J., Lousberg, R., Lodder, J., Honig, A., 2003. A comparative study into the one year cumulative incidence of depression after stroke and myocardial infarction. Journal of Neurology, Neurosurgery, and Psychiatry 74 (5), 581–585.

Alexopoulos, G.S., Murphy, C.F., Gunning-Dixon, F.M., Glatt, C.E., Latoussakis, V., Kelly Jr., R.E., Kanellopoulos, D., Klimstra, S., Lim, K.O., Young, R.C., Hoptman, M.J., 2009. Serotonin transporter polymorphisms, microstructural white matter abnormalities and remission of geriatric depression. Journal of Affective Disorders 119 (1–3), 132–141.

Alexopoulos, G.S., Glatt, C.E., Hoptman, M.J., Kanellopoulos, D., Murphy, C.F., Kelly Jr., R.E., Morimoto, S.S., Lim, K.O., Gunning, F.M., 2010. BDNF Val66met polymorphism, white matter abnormalities and remission of geriatric depression. Journal of Affective Disorders 125 (1–3), 262–268.

Anguelova, M., Benkelfat, C., Turecki, G., 2003. A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: I. Affective disorders. Molecular Psychiatry 8 (6), 574–591.

Battersby, S., Ogilvie, A.D., Smith, C.A., Blackwood, D.H., Muir, W.J., Quinn, J.P., Fink, G., Goodwin, G.M., Harmar, A.J., 1996. Structure of variable number tandem repeat of the serotonin transporter gene and association with affective disorder. Psychiatric Genetics 6 (4), 177–181.

Berg, A., Palomaki, H., Lehtihalmes, M., Lonnqvist, J., Kaste, M., 2001. Poststroke depression in acute phase after stroke. Cerebrovascular Diseases 12 (1), 14–20.

Bhogal, S.K., Teasell, R., Foley, N., Speechley, M., 2004. Lesion location and poststroke depression. Systematic review of the methodological limitations in the literature. Stroke 35 (3), 794–802.

Bonnier, B., Gorwood, P., Hamon, M., Sarfati, Y., Boni, C., Hardy, B., 2002. Association of 5-HT(2A) receptor gene polymorphism with major affective disorder: the case of a subgroup of bipolar disorder with low suicide risk. Biological Psychiatry 51 (9), 762–765.

Caspi, A., Sugden, K., Moffitt, T.E., Talyor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301 (5631), 386–389.

Collier, D.A., Stober, G., Li, T., Heils, A., Catalano, M., Di Bella, D., Arranz, M.J., Murray, R.M., Vallada, H.P., Bengel, D., Müller, C.R., Roberts, G.W., Smeraldi, E., Kirov, G., Sham, P., Lesch, K.P., 1996. A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. Molecular Psychiatry 1 (6), 453–460.

Du, L., Bakish, D., Lapierre, Y.D., Ravindran, A.V., Hrdina, P.D., 2000. Association of polymorphism of serotonin 2A receptor gene with suicidal ideation in major depressive disorder. American Journal of Medical Genetics 96 (1), 56–60.

Duman, R.S., Heninger, G.R., Nestler, E.J., 1997. A molecular and cellular theory of depression. Archives of General Psychiatry 54 (7), 597–606.

Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., Weinberger, D.R., 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112 (2), 257–269.

Eisch, A.J., Bolanos, C.A., de Wit, J., Simonak, R.D., Pudiak, C.M., Barrot, M., Verhaagen, J., Nestler, E.J., 2003. Brain-derived neurotrophic factor in the ventral midbrain–nucleus accumbens pathway: a role in depression. Biological Psychiatry 54 (10), 994–1005.

Enoch, M.A., Goldman, D., Barnett, R., Sher, L., Mazzanti, C.M., Rosenthal, N.E., 1999. Association between seasonal affective disorder and the 5-HT2A promoter polymorphism, −1438G/A. Molecular Psychiatry 4 (1), 89–92.

Folstein, M.F., Fostein, S.E., McHugh, P.R., 1975. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 12 (3), 189–198.

Hackett, M.L., Yapa, C., Parag, V., Anderson, C.S., 2005. Frequency of depression after stroke: a systematic review of observational studies. Stroke 36 (6), 1330–1340.

Heils, A., Teufel, A., Petri, S., Seemann, M., Bengel, D., Balling, U., Riederer, P., Lesch, K.P., 1995. Functional promoter and polyadenylation site mapping of the human serotonin (5-HT) transporter gene. Journal of Neural Transmission. General Section 102 (3), 247–254.

Hickie, I.B., Naismith, S.L., Ward, P.B., Scott, E.M., Mitchell, P.B., Schofield, P.R., Scimone, A., Wilhelm, K., Parker, G., 2007. Serotonin transporter gene status predicts caudate nucleus but not amygdala or hippocampal volumes in older persons with major depression. Journal of Affective Disorders 98 (1–2), 137–142.

Jansson, M., Gatz, M., Berg, S., Johansson, B., Malmberg, B., McClearn, G.E., Schalling, M., Pedersen, N.L., 2003. Association between depressed mood in the elderly and a 5-HTR2A gene variant. American Journal of Medical Genetics 120B (1), 79–84.

Jarrett, M.E., Kohen, R., Cain, K.C., Burr, R.L., Poppe, A., Navaja, G.P., Heitkemper, M.M., 2007. Relationship of SERT polymorphisms to depressive and anxiety symptoms in irritable bowel syndrome. Biological Research for Nursing 9 (2), 161–169.

Kasner, S.E., Chalela, J.A., Luciano, J.M., Cucchiara, B.L., Raps, E.C., McGarvey, M.L., Conroy, M.B., Localio, R., 1999. Reliability and validity of estimating the NIH stroke scale score from medical records. Stroke 30 (8), 1534–1537.

Kato, M., Ikenaga, Y., Wakeno, M., Okugawa, G., Nobuhara, K., Fukuda, T., Fukuda, K., Azuma, J., Kinoshita, T., 2005. Controlled clinical comparison of paroxetine and fluvoxamine considering the serotonin transporter promoter polymorphism. International Clinical Psychopharmacology 20 (3), 151–156.

Kaufman, J., Yang, B.Z., Douglas-Palumberi, H., Grasso, D., Lipschitz, D., Houshyar, S., Krystal, J.H., Gelernter, J., 2006. Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. Biological Psychiatry 59 (8), 673–680.

Kendler, K.S., Kuhn, J.W., Vittum, J., Prescott, C.A., Riley, B., 2005. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression. Archives of General Psychiatry 62 (5), 529–535.

Kim, J.M., Stewart, R., Kim, S.W., Yang, S.J., Shin, I.S., Kim, Y.H., Yoon, J.S., 2007. Interactions between life stressors and susceptibility genes (5-

HTTLPR and BDNF) on depression in Korean elders. Biological Psychiatry 62 (5), 423–428.
Kim, J.M., Stewart, R., Kim, S.W., Yang, S.J., Shin, I.S., Kim, Y.H., Yoon, J.S., 2008. BDNF genotype potentially modifying the association between incident stroke and depression. Neurobiology of Aging 29 (5), 789–792.
Kim, J.M., Stewart, R., Kim, S.W., Yang, S.J., Shin, I.S., Yoon, J.S., 2009. Modification by two genes of associations between general somatic health and incident depressive syndrome in older people. Psychosomatic Medicine 71 (3), 286–291.
Kohen, R., Cain, K.C., Mitchell, P.H., Becker, K., Buzaitis, A., Millard, S.P., Navaja, G.P., Teri, L., Tirschwell, D., Veith, R., 2008. Association of serotonin transporter gene polymorphisms with poststroke depression. Archives of General Psychiatry 65 (11), 1296–1302.
Kunugi, H., Hattori, M., Kato, T., Tatsumi, M., Sakai, T., Sasaki, T., Hirose, T., Nanko, S., 1997. Serotonin transporter gene polymorphisms: ethnic difference and possible association with bipolar affective disorder. Molecular Psychiatry 2 (6), 457–462.
Kunugi, H., Iijima, Y., Tatsumi, M., Yoshida, M., Hashimoto, R., Kato, T., Sakamoto, K., Fukunaga, T., Inada, T., Suzuki, T., Iwata, N., Ozaki, N., Yamada, K., Yoshikawa, T., 2004. No association between the Val66Met polymorphism of the brain-derived neurotrophic factor gene and bipolar disorder in a Japanese population: a multicenter study. Biological Psychiatry 56 (5), 376–378.
Lenze, E.J., Munin, M.C., Ferrell, R.E., Pollock, B.G., Skidmore, E., Lotrich, F., Rogers, J.C., Quear, T., Houck, P., Reynolds III, C.F., 2005. Association of the serotonin transporter gene-linked polymorphic region (5-HTTLPR) genotype with depression in elderly persons after hip fracture. The American Journal of Geriatric Psychiatry 13 (5), 428–432.
Levinson, D.F., 2006. The genetics of depression: a review. Biological Psychiatry 60 (2), 84–92.
Lou, X.Y., Chen, G.B., Yan, L., Ma, J.Z., Zhu, J., Elston, R.C., Li, M.D., 2007. A generalized combinational approach for detecting gene-by-gene and gene-by-environment interactions with application to nicotine dependence. American Journal of Human Genetics 80 (6), 1125–1137.
Lovejoy, E.A., Scott, A.C., Fiskerstrand, C.E., Bubb, V.J., Quinn, J.P., 2003. The serotonin transporter intronic VNTR enhancer correlated with a predisposition to affective disorders has distinct regulatory elements within the domain based on the primary DNA sequence of the repeat unit. The European Journal of Neuroscience 17 (2), 417–420.
Manji, H.K., Drevets, W.C., Charney, D.S., 2001. The cellular neurobiology of depression. Nature Genetics 7 (5), 541–547.
Minov, C., Baghai, T.C., Schule, C., Zwanzger, P., Schwarz, M.J., Zill, P., Rupprecht, R., Bondy, B., 2001. Serotonin-2A-receptor and -transporter polymorphisms: lack of association in patients with major depression. Neuroscience Letters 303 (2), 119–122.
Mossner, R., Henneberg, A., Schmitt, A., Syagailo, Y.V., Grassle, M., Hennig, T., Simantov, R., Gerlach, M., Riederer, P., Lesch, K.P., 2001. Allelic variation of serotonin transporter expression is associated with depression in Parkinson's disease. Molecular Psychiatry 6 (3), 350–352.
Ohara, K., Nagai, M., Tsukamoto, T., Tani, K., Suzuki, Y., Ohara, K., 1998. 5-HT2A receptor gene promoter polymorphism −1438G/A and mood disorders. Neuroreport 9 (6), 1139–1141.
Ono, H., Shirakawa, O., Nishiguchi, N., Nishmura, A., Nushida, H., Ueno, Y., Maeda, K., 2001. Serotonin 2A receptor gene polymorphism is not associated with completed suicide. Journal of Psychiatric Research 35 (3), 173–176.
Otte, C., McCaffery, J., Ali, S., Whooley, M.A., 2007. Association of a serotonin transporter polymorphism (5-HTTLPR) with depression, perceived stress, and norepinephrine in patients with coronary disease: the Heart and Soul Study. The American Journal of Psychiatry 164 (9), 1379–1384.
Ramasubbu, R., Tobias, R., Buchan, A.M., Bech-Hansen, N.T., 2006. Serotonin transporter gene promoter region polymorphism associated with poststroke major depression. The Journal of Neuropsychiatry and Clinical Neurosciences 18 (1), 96–99.
Ramasubbu, R., Tobias, R., Bech-Hansen, N.T., 2008. Extended evaluation of serotonin transporter gene functional polymorphisms in subjects with poststroke depression. Canadian Journal of Psychiatry 53 (3), 197–200.
Robinson, R.G., 2003. Poststroke depression: prevalence, diagnosis, treatment, and disease progression. Biological Psychiatry 54 (3), 376–387.
Serretti, A., Lorenzi, C., Lilli, R., Smeraldi, E., 2000. Serotonin receptor 2A, 2C, 1A genes and response to lithium prophylaxis in mood disorders. Journal of Psychiatric Research 34 (2), 89–98.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1988. The mini-international neuropsychiatric interview (M.I.N.I):the development and validation of a structured diagnostic psychiatric interview for DSM-VI and ICD-10. The Journal of Clinical Psychiatry 59 (suppl.20), S22–S33.
Spalletta, G., Bossu, P., Ciaramella, A., Bria, P., Caltagirone, C., Robinson, R.G., 2006. The etiology of poststroke depression: a review of the literature and a new hypothesis involving inflammatory cytokines. Molecular Psychiatry 11 (11), 984–991.
Vollmayr, B., Keck, S., Henn, F.A., Schloss, P., 2000. Acute stress decreases serotonin transporter mRNA in the raphe pontis but not in other raphe nuclei of the rat. Neuroscience Letters 290 (2), 109–112.
Wendland, J.R., Martin, B.J., Kruse, M.R., Lesch, K.P., Murphy, D.L., 2006. Simultaneous genotyping of four functional loci of human SLC6A4, with a reappraisal of 5-HTTLPR and rs25531. Molecular Psychiatry 11 (3), 224–226.
Whyte, E.M., Mulsant, B.H., 2002. Post stroke depression: epidemiology, pathophysiology, and biological treatment. Biological Psychiatry 52 (3), 253–264.
Yoo, S.W., Kim, Y.S., Noh, J.S., Oh, K.S., Kim, C.H., Namkoong, K., Chae, J.H., Lee, G.C., Jeon, S.I., Min, K.J., Oh, D.J., Joo, E.J., Park, H.J., Choi, Y.H., Kim, S.J., 2006. Validity of Korean version of the Mini-International Neuropsychiatric Interview. Anxiety Mood 2 (1), 50–55.
Zhang, H.Y., Ishigaki, T., Tani, K., Chen, K., Shih, J.C., Miyasato, K., Ohara, K., Ohara, K., 1997. Serotonin-2A receptor gene polymorphism in mood disorders. Biological Psychiatry 41 (7), 768–773.
Zhang, H., Ozbay, F., Lappalainen, J., Kranzler, H.R., van Dyck, C.H., Charney, D.S., Price, L.H., Southwick, S., Yang, B.Z., Rasmussen, A., Gelernter, J., 2006. Brain derived neurotrophic factor (BDNF) gene variants and Alzheimer's disease, affective disorders, posttraumatic stress disorder, schizophrenia, and substance dependence. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics 141B (4), 387–393.
Zhang, J.L., Yang, J.F., Chan, P., 2009. No association between polymorphism of serotonin transporter gene and depression in Parkinson's disease in Chinese. Neuroscience Letters 455 (3), 155–158.