Scientific Research Publishing

Health, 2022, 14, 910-920
https://www.scirp.org/journal/health
ISSN Online: 1949-5005
ISSN Print: 1949-4998

Correlation of BDNF Gene Polymorphism and Psychological Nursing Intervention in Patients with Recurrent Spontaneous Abortion

Haiyan Lin[1], Chenyun Xu[2*]

[1]The Fourth People's Hospital of Haikou, Haikou, China
[2]Hainan General Hospital, Haikou, China
Email: *g2002m@163.com

How to cite this paper: Lin, H.Y. and Xu, C.Y. (2022) Correlation of BDNF Gene Polymorphism and Psychological Nursing Intervention in Patients with Recurrent Spontaneous Abortion. *Health*, **14**, 910-920.
https://doi.org/10.4236/health.2022.148064

Received: July 25, 2022
Accepted: August 19, 2022
Published: August 22, 2022

Abstract

Objective: To investigate the correlation between recurrent spontaneous abortion patients and brain derived neurotrophic factor BDNF gene polymorphism and the mechanism of BDNF and recurrent spontaneous abortion under stress state in order to provide theoretical basis for nursing psychological intervention of patients with recurrent abortion. **Methods:** Medical coping Questionnaire (MCMO) and post-traumatic stress Diagnostic Scale (POST-traumatic stress Scale) were adopted Dissorder (PTSD) (PCL-c) scale was used to diagnose the psychological stress of recurrent spontaneous abortion in our hospital, and the BDNF gene polymorphism and the correlation factors of METHYLation in BDNF promoter region were studied in 30 cases (control group) and normal control group. **Results:** The MCMQ score of the case group and the control group was significantly lower than that of the conventional group ($P < 0.05$), and the scores of "avoidance and submission" were higher than that of the conventional group, with statistical significance ($P < 0.05$). The distribution of BDNF gene g-712A genotype was significantly different between the case group and the control group. **Conclusion:** There are significant differences in PTSD between the case group and the control group, which are related to methylation in the PROMOTER region of BDNF and SNP g-712A of BDNF gene. AG patients in the case group are more susceptible to anxiety and depression, and GG PTSD is more severe in the case group. BDNF promoter methylation and G-712A were independent risk factors for PTSD in the case group.

Keywords

Recurrent Spontaneous Abortion, BDNF, Psychological, Care to Do

1. Introduction

The probability of one abortion in pregnancy is 15% - 20%, and 1% - 5% of pregnant women have recurrent spontaneous abortion (RSA) [1], among which 40% - 55% RSA has no definite cause at present [2]. Pregnancy itself is a complex psychological process, there are many factors to form the source of stress, which results in highly maternal stress state, causing many psychological barriers but at present the causes and treatment of repetitive abortion research mainly from the Angle of biology [3], this special group of patients with repetitive abortion the psychosocial characteristics and their influence on abortion, There are few studies at home and abroad, and they are not systematic and comprehensive [4]. This study explored the relationship between psychological stress and BDNF (rs6265) gene polymorphism in patients with unexplained habitual abortion and scientific psychological nursing intervention, systematically explored the psychosomatic symptoms, psychosocial influencing factors and genetic factors of patients with recurrent spontaneous abortion [5] [6]. From the perspective of psychology and genetics, the pathogenesis of unexplained habitual abortion high-risk groups was studied [7] [8] [9] [10], in order to provide a theoretical basis for the psychological nursing intervention of patients with habitual abortion, and to find out the method of individualized prevention and treatment of unexplained habitual abortion.

2. Data and Methods

2.1. Cases

Thirty patients with recurrent spontaneous abortion who visited the department of gynecology of the fourth people's hospital of haikou from l to August 2021 were selected aged between 30 and 38. The inclusion criteria were: 1) two or more consecutive spontaneous abortions without a history of live birth; 2) No restrictions on age or occupation, primary school education or above; 3) Patients with serious physical diseases and mental disorders were excluded.

2.2. In the Control Group

Thirty healthy women were selected aged between 30 and 38. The inclusion criteria were: 1) they had children and had no history of abortion, stillbirth or stillbirth; 2) General demographic data such as age, occupation and education level were matched with case group; 3) except those suffering from serious physical diseases, mental disorders and serious mental frustration within the past 1 year.

This study has been approved and supervised by the Ethics Committee of our hospital. All subjects in this study have obtained informed consent and signed informed consent by themselves and their family members.

2.3. PTSD Diagnostic Scale

The PTSD Checklist-Civilian Version (PCL-c) [11] [12] [13] [14] was developed by the Behavioral Science Branch of the Post-Traumatic Stress Disorder Re-

search Center in November 1994 according to DSM-W. Pcl-c combined with the dSM-IV 17-item self-report Scale for PTSD symptoms. Respondents rated each item on a scale of one (not quite) to five ("very") to indicate how much they had been bothered by that particular symptom in the past month, with a total score of 17 - 85. Therefore, the PCL-c scale is a very good diagnostic tool. In the United States, THE PCL-c scale is used to evaluate the diagnosis of PTSD symptoms, the effect of intervention and treatment of PTSD, and the prognosis of PTSD. According to the unified diagnostic criteria (DSM-IV, DSM-V, AND PTSD), the patients with PTSD with habitual abortion were diagnosed by 2 psychiatrists with intermediate professional title and above with clinical experience [15] [16] [17] [18] [19].

2.4. Medical Response Questionnaire

MedicaI Coping Modes Questionnai Re (MCMO) was developed by Feifel H *et al.*, which is suitable for evaluating patients' medical Coping styles. The scale divides coping styles into 20 items, including three coping styles of "facing", "avoiding" and "yielding", which are in line with the basic coping styles that people tend to adopt when facing stressful events.

2.5. Gene Polymorphism Detection

After admission, 5 ml of fasting blood was taken from the anterior elbow vein of all subjects in the morning, and 2 ml of the blood was slowly injected into the anticoagulant tube containing heparin along the tube wall, and immediately frozen at −70˚C. Genomic DNA was extracted by centrifuge column method using whole blood genomic DNA extraction Kit (OMEGA, USA), and the concentration and purity tests met the requirements of PCR amplification.

2.6. Methylation Detection

Genomic DNA was extracted using TIANamp Blood DNA Kit whole Blood Genomic DNA Extraction Kit (Tiangen, Beijing, China) and stored at −80˚C for future use. Methylation of BDNF promoter region was determined by MS-HRM (Methylation-Sensitive High Resolution Melting) method. Strictly follow the instructions of the kit (QIAGEN methylation Kit) and conduct the blood genome DNA sulfite test. After the reaction, the product was purified and recycled using the kit's own centrifugal column, and stored at −20˚C for future use. Ms-hrm primers (**Table 1**) are designed and synthesized by Shanghai Sangong Bioengineering Company and carried out on rotor-Gene 6000 (Corbett, Sydney, Australia). Each sample is in duplicate, and each run includes 100%, 50%, 10%. And 3% methylated and completely unmethylated standard substances were used to detect the methylation level of samples. 20 μL reaction system consists of 1 × PCR buffer, 1.5 to 3.0 mM MgCl2200 μMdNTP mixture, 200 - 400 nM forward and reverse primers, 1 × SYTO9 embedded dye (Thermo Fisher Scientific, Waltham, MA, USA), 0.5 U Hotstar Taq polymerase and 10 ng bisulphite conversion of DNA.

Table 1. Promoter primer sequences.

gene	primer
BDNF	F: 5'-CCCTGGAACGGAACTCTTCT-3'
	R: 5'-ATTGCATGGCGGAGGTAATA-3'

2.7. T-Test Was Used for Comparison between the Two Groups

One-way ANOVA was used for comparisons between multiple groups, and Tukey's Multiple post test was used for pairwise comparisons after ANOVA analysis. The count data were compared using Fisher's exact test. P was a two-sided test, and $P < 0.05$ was considered statistically significant. Odds rarios (Odds rarios) and 95% confidence intervals (95% confidence intervals) were calculated by nonlinear logistic regression analysis. The χ^2 test was used to test the existence of Hardy-Weinberg equilibrium of genotype distribution.

3. Results

3.1. Medical Response Questionnaire

Psychological stressors, facing difficulties, different coping styles will have different effects on the psychological stress response of patients. MCMQ includes three subscales: face, avoid and yield, which has good reliability and validity, and can be applied to the clinical research of psychological stress in Chinese patients.

The "face" score of the MCMQ score comparison study group was significantly lower than that of the conventional group ($P < 0.05$), and the "avoidance and yield" scores were higher than that of the conventional group, with statistically significant differences between the two groups ($P < 0.05$) (Table 2).

3.2. Gene Polymorphism Detection

All subjects received 5 to 10 ml of pre-elbow venous blood, anticoagulated with 0.5 mol/LEDTA (ethylenediamine tetraacetic acid) l mL, and immediately sent to the Central Laboratory of Hainan Hospital Affiliated to Hainan Medical College for −20˚C freezing. Genomic DNA was extracted by centrifugation column method with whole blood genomic DNA extraction kit (OMEGA, USA), and the concentration and purity test met the requirements of PCR amplification. Primer Premier5.0 Primer design software was used to design BDNF gene primers. The primers were synthesized by Shanghai Shenggong Bioengineering Technology Service Co., LTD. (Table 3). The design and synthesis of the primers were provided by Kingdomain Biological Co., LTD. The BDNF ELISA kit was operated according to the instructions. PCR kit was purchased from Shanghai Jerui Bioengineering Co., LTD. The PCR products were sent to Shanghai Shenggong Bioengineering Technology Service Co., LTD for sequencing.

3.3. Genotyping of BDNF Gene G11757C and RS6265 Polymorphisms

After the PCR amplification product of G11757C site of BDNF gene was di-

gested by Eco47 I enzyme, there were wild homozygous genotype GG (201 bp), mutant heterozygous genotype GC (201 bp, 157 bp and 44 bp) and mutant homozygous genotype CC (157 bp and 44 bp) (Figure 1(a)). After the PCR amplification product of rs6265 site of BDNF gene was cut by Eco72 I enzyme, there were mutant homozygous genotype AA (206 bp), mutant heterozygous genotype GA (206 bp, 137 bp and 69 bp) and wild homozygous genotype GG (137 bp and 69 bp) (Figure 1(b)).

3.4. Comparison of Genotype rs6265 and G-712A of BDNF Gene between the Case Group and the Control Group

There was no statistical difference in the distribution of rs6265 genotype of BDNF gene between the case group and the control group, while there was a significant difference in the distribution of G-712A genotype between the case group and the control group (Table 4).

Table 2. Comparison of MCMQ score between the two groups $(\bar{x} \pm s)$.

group	number	In the face	avoid	yield
Case group	30	13.39 ± 1.29	22.36 ± 1.31	16.15 ± 1.84
The control group	30	19.87 ± 3.66	14.49 ± 3.11	9.15 ± 3.08
T		16.700	23.321	19.511
P		<0.05	<0.05	<0.05

Table 3. PCR primer sequences.

SNP		Sequence
G11757C	Forward:	5'-ACCTGCCTGTGAGAAGCC-3'
	Reverse:	5'-CCACCAGAAAGCTCAATCFF-3'
rs6265	Forward:	5'-CTGGAGAGC6T6AATGGGCC-3'
	Reverse:	5'-TCCAGCAGAAAGAGAAGAGAGGC-3'

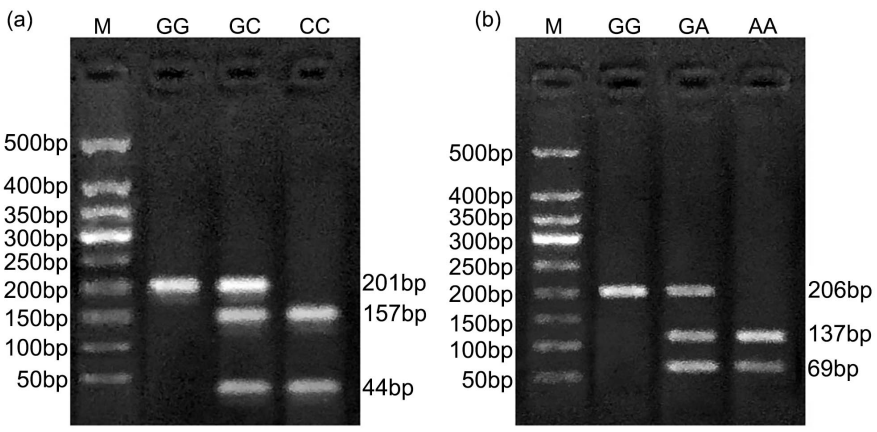

Figure 1. G11757C (a) and RS6265 (b) of BDNF gene.

Table 4. Comparison of genotype and allele frequency distribution of RS6265 and G-712A loci of BDNF gene between the case group and the control group (N %).

SNP	The control group (n = 30)	Case group (n = 30)	*P*	OR (95% CI)
rs6265				
AA	32 (22.70)	33 (20.12)	Ref.	
AG	68 (48.23)	83 (50.61)	0.6557	1.184 (0.6633 - 2.110)
GG	41 (29.07)	48 (29.27)	0.7452	1.135 (0.5970 - 2.164)
A	132 (46.81)	149 (45.43)	Ref.	
G	150 (53.19)	179 (54.57)	0.7451	1.057 (0.7686 - 1.454)
G-712A				
AA	52 (36.88)	33 (20.12)	Ref.	
AG	65 (46.10)	75 (45.73)	0.0390	1.818 (1.062 - 3.200)
GG	24 (17.02)	56 (34.15)	**0.000**	3.677 (1.959 - 6.881)
A	169 (59.93)	141 (42.99)	Ref.	
G	113 (40.07)	187 (57.01)	**0.000**	1.983 (1.436 - 2.722)

Fisher's exact test, N = 305; OR: odds ratio, CI: confidence interval.

3.5. Genotype and Allele Frequency Distribution among Groups

There was no significant difference in genotype and allele frequency distribution of BDNF gene G11757C between the case group and the PTSD group, and between the case group and the control group (all P > 0.05). There was no significant difference in genotype and allele distribution of RS6265 locus between the case group and the control group (all P > 0.05). The genotype and allele frequency distribution of RS6265 locus in the case +PTSD group were significantly different from those in the case group: compared with GG genotype, Case group (GA + AA) genotype may increase the risk of PTSD (OR = 2.790, 95%CI = 1.400 - 5.560, P = 0.003), (OR = 3.477, 95%CI = 1.576 - 7.671, P = 0.002). Carrying the A allele was also associated with an increased risk of PTSD in the case group compared with the G allele (OR = 1.747, 95%CI = 1.217 - 2.508, P = 0.002) (Table 5 and Table 6).

4. Discussion

BDNF has been found to be associated with several neuropsychiatric diseases in studies [20]. According to previous studies, BDNF may help relieve fear of PTSD patients through BDNF signaling and serve as a potential target for PTSD treatment outcomes [21]. The aim of this study was to investigate the effect of BDNF gene polymorphism on patients with recurrent spontaneous abortion. Our results suggest that the GG genotype of BDNF RS6265 polymorphism may be a protective factor for PTSD in patients with recurrent spontaneous abortion.

Table 5. Haplotype analysis of BDNF gene G11757C and RS6265 loci in case group [n (%)].

haplotype	The control group	Case group	χ^2	P	OR (95% CI)
GG	81.67 (0.280)	80.92 (0.266)	0.137	0.711	1.071 (0.746 - 1.535)
GA	67.33 (0.231)	83.08 (0.273)	1.441	0.230	0.797 (0.550 - 1.155)
CG	83.33 (0.285)	73.08 (0.240)	1.556	0.22	1.262 (0.875 - 1.819)
CA	59.67 (0.204)	66.92 (0.220)	0.221	0.638	0.910 (0.614 - 1.348)

Note: OR: Odds Ratio; 95% CI: 95% confidence intervals.

Table 6. Haplotype analysis of BDNF gene G11757C and RS6265 loci in case group and PTSD group [n (%)].

haplotype	Case group	Case group +PTSD group	χ^2	P	OR (95% CI)
GG	51.66 (0.253)	88.66 (0.304)	1.505	0.220	0.778 (0.520 - 1.163)
GA	61.34 (0.301)	60.34 (0.207)	5.741	0.017	1.651 (1.093 - 2.493)
CG	35.34 (0.173)	76.33 (0.261)	5.452	0.021	0.592 (0.379 - 0.926)
CA	55.66 (0.273)	66.67 (0.228)	1.282	0.258	1.268 (0.840 - 1.914)

Note: OR: Odds Ratio; 95% CI: 95% confidence intervals.

First, we found that the MMSE score of patients with recurrent spontaneous abortion was significantly lower than that of the control group, and the level of BDNF in patients with recurrent spontaneous abortion was positively correlated with the neurocognitive function of PTSD. As previous studies have found, patients with recurrent spontaneous abortion perform less well in neurocognitive function than healthy controls [22]. BDNF has been reported to be involved in higher neurocognitive function as well as mental disorders, including depression [23]. There is evidence that BDNF can play a role in neurocognitive function through its expression, secretion and action [24]. In addition, the expression level of BDNF is also inhibited in depression and bipolar disorder [25]. The BDNF-TrKB pathway produces a ligand receptor system for synaptic plasticity and has been implicated in PTSD in fear states and inhibitory learning, and BDNF can be directly associated with PTSD through peripheral plasma and serum studies [26].

An important finding of our results was that GA + AA allele of RS6265 BDNF polymorphism caused lower MMSE scores, in contrast to GG allele and GG genotype of RS6265 BDNF polymorphism, and may be a potential contributing factor to the increased risk of recurrent spontaneous abortion. MMSE is a short examination designed to test mental state, and a lower MMSE score means poorer neurocognitive performance [27]. It has been reported that a variant of the BDNF allele may mediate anxiety disorders characterized by learning cues that suggest safety and risk [28]. In addition, BDNF variants can alter hippocampal neurocognitive function by mediating intracellular transport and actiity-dependent BDNF release (e.g. Rs6265) [29]. Met66 variants can affect the pro-

cessing of BDNF peptides, and also affect the release of BDNF peptides when neurons are activated [30]. According to previous studies, BDNF Val66Met (RS6265) carriers of (A/A or G/A) genotype showed A significantly larger hypo perfusion hippocampus compared with G/G genotype carriers, suggesting that G/G genotype carriers showed moderated neurocognitive function, which is consistent with our results [31]. In addition, RS6265 is associated with methamphetamine-induced psychosis, and its GG genotype shows low frequency in this psychosis, which can reduce the occurrence of this psychosis in the Thai population [32].

Our results also suggest that haplotype GA of BDNF G-712A and RS6265 may increase the risk of PTSD in patients with recurrent spontaneous abortion, while haplotype gene CG may reduce this risk. Previous findings suggest that individuals with a certain type of BDNF haplotype may overcome functional deficits because they are likely to benefit from corresponding therapeutic interventions that help restore neuronal plasticity [30]. Rs6265 and G-712A are considered to be two common SNPs in THE BDNF gene, and are believed to be clinically relevant to schizophrenia and depression [33]. G-712a polymorphism may affect the volume of white matter and gray matter in cerebellar hemispheres, and BDNF gene variation was found to be related to brain morphology [34]. Consistent with our results, BDNF gene polymorphisms including G-712A may be the cause of Alzheimer's disease-related depression [35]. In addition, in a similar study, C-C-G-G haplotype was considered to be the most common non-high-risk C-C-G-G haplotype in g-712A and RS6265 of BDNF gene [36].

After psychological intervention nursing, the psychological stress score of patients with recurrent spontaneous abortion was significantly improved, and the distribution of G-712A locus genotype was significantly different between the case group and the control group. It has an important influence on post-traumatic stress disorder in patients with recurrent spontaneous abortion. At the same time, it also shows that psychological intervention nursing can relieve the stress emotional distress of patients with recurrent spontaneous abortion.

5. Conclusion

Therefore, this study found that BDNF gene polymorphism was associated with PTSD, and GG genotype at rs6265 was a protective factor for PTSD in patients with recurrent spontaneous abortion. These findings may provide a new target for the prevention and treatment of PTSD. However, it is not clear why different haplotypes of BDNF G-712A and RS6265 polymorphism have opposite effects on PTSD. Therefore, further research on BDNF gene polymorphism in recurrent spontaneous abortion and the genetic mechanism of psychological intervention nursing is needed in the future.

Foundation Project

Hainan Health Commission Science and Technology Project (No. 20A200187).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Southwick, S.M. and Charney, D.S. (2012) The Science of Resilience: Implications for the Prevention and Treatment of Depression. *Science*, **338**, 79-82. https://doi.org/10.1126/science.1222942

[2] Pitman, R.K., Rasmusson, A.M., Koenen, K.C., Shin, L.M., Orr, S.P., Gilbertson, M.W., Milad, M.R. and Liberzon, I. (2012) Biological Studies of Post-Traumatic Stress Disorder. *Nature Reviews Neuroscience*, **13**, 769-787. https://doi.org/10.1038/nrn3339

[3] Holbrook, T.L., Galarneau, M.R., Dye, J.L., Quinn, K. and Dougherty, A.L. (2010) Morphine Use after Combat Injury in Iraq and Post-Traumatic Stress Disorder. *The New England Journal of Medicine*, **362**, 110-117. https://doi.org/10.1056/NEJMoa0903326

[4] McNally, R.J. (2006) Cognitive Abnormalities in Post-Traumatic Stress Disorder. *Trends in Cognitive Sciences*, **10**, 271-277. https://doi.org/10.1016/j.tics.2006.04.007

[5] Steenkamp, M.M., Litz, B.T., Hoge, C.W. and Marmar, C.R. (2015) Psychotherapy for Military-Related PTSD: A Review of Randomized Clinical Trials. *JAMA*, **314**, 489-500. https://doi.org/10.1001/jama.2015.8370

[6] Bryant, R.A., Ekasawin, S., Chakrabhand, S., Suwanmitri, S., Duangchun, O. and Chantaluckwong, T. (2011) A Randomized Controlled Effectiveness Trial of Cognitive Behavior Therapy for Post-Traumatic Stress Disorder in Terrorist-Affected People in Thailand. *World Psychiatry*, **10**, 205-209. https://doi.org/10.1002/j.2051-5545.2011.tb00058.x

[7] Nagahara, A.H. and Tuszynski, M.H. (2011) Potential Therapeutic Uses of BDNF in Neurological and Psychiatric Disorders. *Nature Reviews Drug Discovery*, **10**, 209-219. https://doi.org/10.1038/nrd3366

[8] Autry, A.E. and Monteggia, L.M. (2012) Brain-Derived Neurotrophic Factor and Neuropsychiatric Disorders. *Pharmacological Reviews*, **64**, 238-258. https://doi.org/10.1124/pr.111.005108

[9] Han, E.J., Kim, Y.K., Hwang, J.A., Kim, S.H., Lee, H.J., Yoon, H.K. and Na, K.S. (2015) Evidence for Association between the Brain-Derived Neurotrophic Factor Gene and Panic Disorder: A Novel Haplotype Analysis. *Psychiatry Investigation*, **12**, 112-117. https://doi.org/10.4306/pi.2015.12.1.112

[10] Huang, Y.W., Ruiz, C.R., Eyler, E.C., Lin, K. and Meffert, M.K. (2012) Dual Regulation of miRNA Biogenesis Generates Target Specificity in Neurotrophin-Induced Protein Synthesis. *Cell*, **148**, 933-946. https://doi.org/10.1016/j.cell.2012.01.036

[11] Karayannis, T., Au, E., Patel, J.C., Kruglikov, I., Markx, S., Delorme, R., *et al.* (2014) Cntnap4 Differentially Contributes to GABAergic and Dopaminergic Synaptic Transmission. *Nature*, **511**, 236-240. https://doi.org/10.1038/nature13248

[12] Bruenig, D., Lurie, J., Morris, C.P., Harvey, W., Lawford, B., Young, R.M. and Voisey, J. (2016) A Case-Control Study and Meta-Analysis Reveal BDNF Val66Met Is a Possible Risk Factor for PTSD. *Neural Plasticity*, **2016**, Article ID: 6979435. https://doi.org/10.1155/2016/6979435

[13] Carrard, A., Salzmann, A., Perroud, N., Gafner, J., Malafosse, A. and Karege, F. (2011) Genetic Association of the Phosphoinositide-3 Kinase in Schizophrenia and Bipolar Disorder and Interaction with a BDNF Gene Polymorphism. *Brain and Be-*

havior, **1**, 119-124. https://doi.org/10.1002/brb3.23

[14] Chen, Z.Y., Jing, D., Bath, K.G., Ieraci, A., Khan, T., Siao, C.J., *et al.* (2006) Genetic Variant BDNF (Val66Met) Polymorphism Alters Anxiety-Related Behavior. *Science*, **314**, 140-143. https://doi.org/10.1126/science.1129663

[15] Zhang, L., Benedek, D.M., Fullerton, C.S., Forsten, R.D., Naifeh, J.A., Li, X.X., *et al.* (2014) PTSD Risk Is Associated with BDNF Val66Met and BDNF Overexpression. *Molecular Psychiatry*, **19**, 8-10. https://doi.org/10.1038/mp.2012.180

[16] Vauthey, J.N., Lauwers, G.Y., Esnaola, N.F., Do, K.A., Belghiti, J., Mirza, N., *et al.* (2002) Simplified Staging for Hepatocellular Carcinoma. *Journal of Clinical Oncology*, **20**, 1527-1536. https://doi.org/10.1200/JCO.2002.20.6.1527

[17] Kilpatrick, D.G., Resnick, H.S., Milanak, M.E., Miller, M.W., Keyes, K.M. and Friedman, M.J. (2013) National Estimates of Exposure to Traumatic Events and PTSD Prevalence Using DSM-IV and DSM-5 Criteria. *Journal of Traumatic Stress*, **26**, 537-547. https://doi.org/10.1002/jts.21848

[18] Kilpatrick, D.G. (2013) The DSM-5 Got PTSD Right: Comment on Friedman (2013). *Journal of Traumatic Stress*, **26**, 563-566. https://doi.org/10.1002/jts.21844

[19] Dick, J.P., Guiloff, R.J., Stewart, A., Blackstock, J., Bielawska, C., Paul, E.A. and Marsden, C.D. (1984) Mini-Mental State Examination in Neurological Patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **47**, 496-499. https://doi.org/10.1136/jnnp.47.5.496

[20] 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. and 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*, **141**, 387-393. https://doi.org/10.1002/ajmg.b.30332

[21] Andero, R. and Ressler, K.J. (2012) Fear Extinction and BDNF: Translating Animal Models of PTSD to the Clinic. *Genes Brain and Behavior*, **11**, 503-512. https://doi.org/10.1111/j.1601-183X.2012.00801.x

[22] Cohen, B.E., Neylan, T.C., Yaffe, K., Samuelson, K.W., Li, Y. and Barnes, D.E. (2013) Posttraumatic Stress Disorder and Cognitive Function: Findings from the Mind Your Heart Study. *Journal of Clinical Psychiatry*, **74**, 1063-1070. https://doi.org/10.4088/JCP.12m08291

[23] Yano, H., Ninan, I., Zhang, H., Milner, T.A., Arancio, O. and Chao, M.V. (2006) BDNF-Mediated Neurotransmission Relies upon a Myosin VI Motor Complex. *Nature Neuroscience*, **9**, 1009-1018. https://doi.org/10.1038/nn1730

[24] Park, H. and Poo, M.M. (2013) Neurotrophin Regulation of Neural Circuit Development and Function. *Nature Reviews Neuroscience*, **14**, 7-23. https://doi.org/10.1038/nrn3379

[25] Grassi-Oliveira, R., Stein, L.M., Lopes, R.P., Teixeira, A.L. and Bauer, M.E. (2008) Low Plasma Brain-Derived Neurotrophic Factor and Childhood Physical Neglect Are Associated with Verbal Memory Impairment in Major Depression—A Preliminary Report. *Biological Psychiatry*, **64**, 281-285. https://doi.org/10.1016/j.biopsych.2008.02.023

[26] Mahan, A.L. and Ressler, K.J. (2012) Fear Conditioning, Synaptic Plasticity and the Amygdala: Implications for Posttraumatic Stress Disorder. *Trends in Neurosciences*, **35**, 24-35. https://doi.org/10.1016/j.tins.2011.06.007

[27] Saczynski, J.S., Marcantonio, E.R., Quach, L., Fong, T.G., Gross, A., Inouye, S.K.

and Jones, R.N. (2012) Cognitive Trajectories after Postoperative Delirium. *The New England Journal of Medicine*, **367**, 30-39. https://doi.org/10.1056/NEJMoa1112923

[28] Soliman, F., Glatt, C.E., Bath, K.G., Levita, L., Jones, R.M., Pattwell, S.S., *et al.* (2010) A Genetic Variant BDNF Polymorphism Alters Extinction Learning in Both Mouse and Human. *Science*, **327**, 863-866. https://doi.org/10.1126/science.1181886

[29] Zhai, J., Yu, Q., Chen, M., Gao, Y., Zhang, Q., Li, J., *et al.* (2013) Association of the Brain-Derived Neurotrophic Factor Gene G196A rs6265 Polymorphisms and the Cognitive Function and Clinical Symptoms of Schizophrenia. *International Journal of Clinical and Experimental Pathology*, **6**, 1617-1623.

[30] Jiang, X., Xu, K., Hoberman, J., Tian, F., Marko, A.J., Waheed, J.F., Harris, C.R., Marini, A.M., Enoch, M.A. and Lipsky, R.H. (2005) BDNF Variation and Mood Disorders: A Novel Functional Promoter Polymorphism and Val66Met Are Associated with Anxiety but Have Opposing Effects. *Neuropsychopharmacology*, **30**, 1353-1361. https://doi.org/10.1038/sj.npp.1300703

[31] Borroni, B., Bianchi, M., Premi, E., Alberici, A., Archetti, S., Paghera, B., Cerini, C., Papetti, A. and Padovani, A. (2012) The Brain-Derived Neurotrophic Factor Val66Met Polymorphism Is Associated with Reduced Hippocampus Perfusion in Frontotemporal Lobar Degeneration. *Journal of Alzheimer's Disease*, **31**, 243-251. https://doi.org/10.3233/JAD-2012-120226

[32] Iamjan, S.A., Thanoi, S., Watiktinkorn, P., Nudmamud-Thanoi, S. and Reynolds, G.P. (2015) BDNF (Val66Met) Genetic Polymorphism Is Associated with Vulnerability for Methamphetamine Dependence. *Pharmacogenomics*, **16**, 1541-1545. https://doi.org/10.2217/pgs.15.96

[33] Wang, C.K., Xu, M.S., Ross, C., Lo, R., Procyshyn, R.M., Vila-Rodriguez, F., White, R.F., Honer, W.G. and Barr, A.M. (2015) Development of a Cost-Efficient Novel Method for Rapid, Concurrent Genotyping of Five Common Single Nucleotide Polymorphisms of the Brain Derived Neurotrophic Factor (BDNF) Gene by Tetra-Primer Amplification Refractory Mutation System. *International Journal of Methods in Psychiatric Research*, **24**, 235-244. https://doi.org/10.1002/mpr.1475

[34] Agartz, I., Sedvall, G.C., Terenius, L., Kulle, B., Frigessi, A., Hall, H. and Jonsson, E.G. (2006) BDNF Gene Variants and Brain Morphology in Schizophrenia. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, **141**, 513-523. https://doi.org/10.1002/ajmg.b.30338

[35] Zhang, L., Fang, Y., Zeng, Z., Lian, Y., Wei, J., Zhu, H., Jia, Y., Zhao, X. and Xu, Y. (2011) BDNF Gene Polymorphisms Are Associated with Alzheimer's Disease-Related Depression and Antidepressant Response. *Journal of Alzheimer's Disease*, **26**, 523-530. https://doi.org/10.3233/JAD-2011-110113

[36] Borroni, B., Grassi, M., Archetti, S., Costanzi, C., Bianchi, M., Caimi, L., Caltagirone, C., Di Luca, M. and Padovani, A. (2009) BDNF Genetic Variations Increase the Risk of Alzheimer's Disease-Related Depression. *Journal of Alzheimer's Disease*, **18**, 867-875. https://doi.org/10.3233/JAD-2009-1191