Pharmacological Reports 70 (2018) 55–59

Contents lists available at ScienceDirect

Pharmacological Reports

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

Original article

Val66Met functional polymorphism and serum protein level of brain-derived neurotrophic factor (BDNF) in acute episode of schizophrenia and depression

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A R T I C L E I N F O

Article history:
Received 8 May 2017
Received in revised form 4 July 2017
Accepted 7 August 2017
Available online 12 August 2017

Keywords:
Brain-derived neurotrophic factor (BDNF)
Val66Met functional polymorphism
Serum BDNF level
Depression
Schizophrenia

A B S T R A C T

Background: Brain-derived neurotrophic factor (BDNF) influences neuron differentiation during development as well as the synaptic plasticity and neuron survival in adulthood. BDNF has been implicated in the pathogenesis of schizophrenia and depression. Val66Met polymorphism and BDNF serum level are potential biomarkers in neuropsychiatric disorders. The aim of this study was to determine the effect of BDNF gene Val66Met functional polymorphism on serum BDNF concentration in patients with schizophrenia, during depression episode and in healthy control group.
Methods: 183 participants were recruited (61 patients with depressive episode, 56 females with schizophrenia, 66 healthy controls) from Polish population. Serum BDNF levels were measured using ELISA method. Val66Met polymorphism was genotyped using PCR- RFLP method.
Results: Serum BDNF levels were not associated with Val66Met polymorphism in either of the groups. A significant increase of BDNF level in schizophrenia ($p = 0.0005$) and depression ($p = 0.026$) comparing to the control group has been observed.
Conclusions: Our results suggest that the functional Val66Met BDNF polymorphism is not associated with BDNF serum levels, which is in line with previous findings. Replication studies on larger groups are needed.
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Introduction

Serious mental illnesses are major contributors to the global burden and represent a significant problem for public health [1]. Psychiatric disorders are very heterogeneous diseases with genetic and environmental components. Neurotrophic factors have been implicated in neuropsychiatric disorders, including schizophrenia and depression [2–4].

Brain-derived neurotrophic factor (BDNF) is a neurotrophin widely expressed in human brain. It is essential in the regulation of growth, differentiation, and survival of neurons in brain development. BDNF controls the development of dopaminergic, serotonergic, GABA-ergic and glutamatergic neurons [5,6] and exerts a significant effect on neurogenesis and neuroplasticity [7]. BDNF is mostly found in the hippocampus and cerebral cortex [8] – parts of the brain which control cognition, mood, and emotion. Abnormalities of synaptic plasticity induced by impaired BDNF expression may cause anatomical and functional disturbances [9–11]. On this basis, BDNF has been implicated in the pathophysiology of neurological and psychiatric disorders.

BDNF gene is located on chromosome 11p13 [12] and contains multiple alternative exons and one exon coding the pro-BDNF protein. Promoters of BDNF gene are regulated in a developmental, tissue-specific and activity-dependent manner [13]. Previous studies show that transport and local synthesis of BDNF in dendrites could regulate BDNF function [14].

Functional single nucleotide polymorphism 196 G > A in the 5'pro-region of the BDNF gene results in a valine to methionine

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http://dx.doi.org/10.1016/j.pharep.2017.08.002
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substitution at amino acid position 66. Polymorphism is located in the pro-region of BDNF protein, which interacts with trafficking protein sortilin. This interaction is necessary for the efficient sorting of BDNF. Met allele decreases interaction between BDNF and sortilin, causing deficits in trafficking and secretion of Met-BDNF. Met allele may also influence intercellular trafficking and secretion of BDNF by forming homo- and heterodimers that are less efficiently sorted and secreted from neurons [14]. This causes accumulation of BDNF protein in neurons and deficits in the synapses [15]. A most recent meta-analysis, conducted in neuropsychiatric disorders, comprising 1965 patients, suggests that there is no association between the Val66Met polymorphism and hippocampal volumes [16].

Association studies on functional Val66Met polymorphism of BDNF gene are widely carried out in psychiatric disorders with inconsistent results. Recent meta-analyses conducted on large patients' cohorts show a lack of association of Val66Met polymorphism with schizophrenia and mood disorders [17–21].

Animal studies show that brain and serum BDNF levels are positively correlated [22]. Based on the research findings indicating that Val66Met polymorphism may influence BDNF secretion in neurons and that BDNF protein is transported across the blood-brain barrier [23], it is reasonable to study BDNF protein levels in serum and plasma and to seek for an association between the functional polymorphism and circulating BDNF concentration. In this study, we have analyzed the association between BDNF Val66Met polymorphism and serum BDNF levels in patients with schizophrenia, depression and control group. We have also investigated the effect of the Val66Met polymorphism on serum BDNF levels in the Polish population.

Material and methods

183 participants were enrolled in the study: 61 patients with depression episode (42 females, mean age 39.6 years; SD 10.8 and 19 males, mean age 38.6 years, SD 15.3), 56 females diagnosed with schizophrenia (mean age 32.5, SD 9.7) and 66 healthy controls (45 females, mean age 39.6, SD 14 and 21 males, mean age 39 years, SD 13.3). Long-term treated patients were recruited during the acute episode on the admission to the psychiatry ward. A subgroup of 29 drug-naïve female outpatients with first depression episode was recruited in the mental health clinic. The diagnosis was made according to DSMIV and ICD10 criteria using Structured Clinical Interview for DSM-IV (SCID) [24]. All patients were evaluated for lifetime psychiatric symptomatology using the Operational Criteria for Psychotic Illness (OPCRIT) [25]. Positive and Negative Syndrome Scale (PANSS) [26] and 17-item Hamilton Depression Rating Scale (HDRS) [27] were used to assess the severity of schizophrenia and depression (respectively). The diagnosis was confirmed by two experienced psychiatrists. The sex- and age-matched control group consists of healthy volunteers recruited from the same geographical region of Poland. Exclusion criteria were: chronic or acute somatic or neurological diseases, increased CRP level (C-reactive protein). All subjects were of Caucasian origin and they were native Polish population. All participants gave written informed consent before participating in the study and their anonymity was preserved. The study was performed in accordance with the ethical standards established in the Declaration of Helsinki and was approved by the local medical ethics committee. Demographical and clinical characteristics of the groups are presented in Table 1.

10 ml of venous blood was withdrawn between 7.30 and 9.30 a.m., after an overnight fast, into anticoagulant-free tubes. After 1 h incubation, serum was separated by centrifugation, aliquoted and stored at −70 °C until further analysis. Blood for DNA isolation was withdrawn into EDTA tubes. Genomic DNA was extracted using the salting out method [28].

The single nucleotide polymorphism Val66Met (rs6265) in the BDNF gene was genotyped by the PCR-RFLP method. A 197-base pairs fragment of the BDNF gene was amplified by polymerase chain reaction (PCR) with a primer pair designed with Primer3 programme [27]. The primers had the following sequence: F: 5'ACT CTG GAG AGC GTG AAT GG 3'; R: 5' AGA AGA GGA GGC TCC AAA GG 3'. A 20 μl of amplification mixture contained: 150–300 ng of genomic DNA, 0.3 mM of each primer, 0.17 mM of each dNTP, 1.5 mM MgCl2, 75 mM Tris-HCl, 20 mM (NH4)2SO4, 0.01% Tween 20 and 0.4 U of Taq DNA polymerase (MBI Fermentas). Cycling conditions consisted of: an initial denaturation at 95 °C for 2 min; 35 cycles of 94 °C for 30 s, 60 °C for 30 s, 72 °C for 30 s; and final elongation at 72 °C for 5 min. PCR reaction was performed in PTC-200 (MJ Research) thermal cycler. A volume of 6.5 ml of each PCR product was then digested overnight in a total volume of 10 ml at 37 °C with 0.7 U of Eco72I restriction endonuclease (MBI Fermentas). Digestion products were then separated on 2.5% basica LE agarose gel (Prona, Spain) with the voltage set at 90 V and visualized by ethidium bromide staining. Band sizes were compared with pUC19DNA/MspI DNA ladder (MBI Fermentas). The uncut product size was 197 bp (allele A, Val). Allele G comprised the cut bands of 124 and 73 bp. Visualization of the RFLP analysis is presented in Fig. 1.

ELISA analyses were performed with DuoSet ELISA Development Kit (R&D Systems kat. No DY248) according to manufacturer's instructions with minor modifications: plates were blocked for 3 h in reagent diluent (1% Bovine Serum Albumin (BSA)/ Phosphate Buffered Saline (PBS)). Plates were incubated with 100 μl of samples overnight at 4 °C with shaking. All samples and standards were run in duplicates. All plates were run within one week, on the same kit lot# by the same experienced operator. Standard curves ranged from 1000 to 15.6 pg/ml. Intra-assay and inter-assay variability was <5% coefficient of variation (CV) and <10% CV (accordingly).

Table 1
Demograpical and clinical characteristic of the studied group.

	schizophrenia	depression		control	
	females	males	females	males	females
n	56	19	42	21	45
age (mean ± SD)	32.5 ± 9.7	38.6 ± 15.3	39.6 ± 10.8	39 ± 13.3	39.6 ± 14
age of onset (mean ± SD)	22.85 ± 4.83	25.09 ± 7.91	32.84 ± 10.38		
drug free (n)	19		29		
PANSS (mean ± SD)	89.58 ± 12.58	na	na		
PANSS P (mean ± SD)	21.02 ± 3.73	na	na		
PANSS N (mean ± SD)	26.34 ± 5.83	na	na		
PANSS G (mean ± SD)	42.2 ± 6.45	na	na		
HDRS (mean ± SD)	na		25.04 ± 6.93		

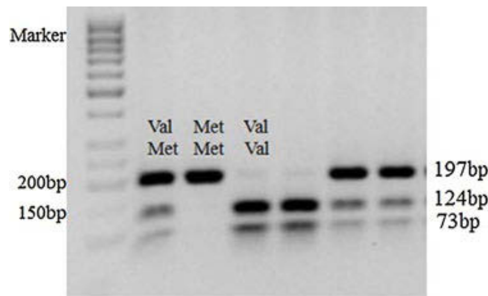

Fig. 1. PCR-RFLP analysis of BDNF Val66Met (rs6265) polymorphism.

CRP was measured by an immunoturbidimetry method on Beckmann Coulter AU 680 biochemistry analyzer.

Statistical analysis

The association study was performed using $\chi 2$ test and Fisher's exact test. Normality of the BDNF serum level variables was tested using Lillefors and Shapiro-Wilk tests. Association of genotypes (Val/Val *vs.* Val/Met + Met/Met), sex and diagnosis with serum BDNF protein levels, as the dependent variable, was performed using analysis of variance (ANOVA), Kruskal-Wallis rank test or Mann-Whitney *U* test. *Post-hoc* power calculation was accomplished in G*Power with the following settings: ANOVA or Wilcoxon-Mann-Whitney test, two-tails, logistic distribution. The significance level was set at 0.05.

Data were analyzed using STATISTICA v12 software, GraphPad QuickCalcs, (https://www.graphpad.com/quickcalcs/contingency2/), G*Power [29], and Hardy-Weinberg equilibrium calculator (http://www.oege.org/software/hwe-mr-calc.shtml).

Results

Val66Met polymorphism

Genotype distribution was in Hardy-Weinberg equilibrium for each group. No association of BDNF Val66Met polymorphism was observed for genotypes (sch *vs.* con $p = 0.79$; bp *vs.* con $p = 0.74$; sch + bp *vs.* con $p = 0.82$) or alleles (sch *vs.* con $p = 0.57$; bp *vs.* con $p = 0.51$; sch + bp *vs.* con $p = 0.86$). Results of the association analysis are presented in Table 2.

BDNF serum concentration

Mean BDNF serum concentration was: 28.85 ng/ml (SD = 11.57) in schizophrenia patients, 24.96 ng/ml in bipolar patients (SD 7.03) and 22.03 ng/ml (SD 6.76) in healthy controls. There were no statistical differences between subgroups with depression episode (inpatients 24.97 ng/ml, SD 8.79; outpatients 24.89 ng/ml, SD 5.16). Subgroups were combined for further analysis. BDNF serum concentrations were normally distributed in studied groups ($p > 0.2$).

An analysis of variance (ANOVA) has shown that the dependent variable "BDNF concentration" was not significantly affected by the factor "genotype" (Val/Val *vs.* Val/Met + Met/Met) (F = 0.4028; d.f. = 1; $p = 0.526$) or "sex" (F = 0.0972, d.f. = 1; $p = 0.755$). Levene's test for equality of variances has revealed that variance including factor "diagnosis" was not homogenous. We have observed significant differences in BDNF levels between schizophrenia and control group ($p = 0.0005$) as well as depression and control group ($p = 0.026$). Statistically significant results have also been found when comparing healthy control group with combined schizophrenia and depression group ($p = 0.001$) (Fig. 2). BDNF level was higher in schizophrenia and depression than in healthy controls. There were no statistically significant differences in BDNF serum levels between schizophrenia and depression group ($p = 0.063$). *Post-hoc* achieved power for ANOVA analyses was 8%. The power of a Mann-Whitney *U* test ranged from 61 to 98% (Table 3).

Discussion

The lack of association of Val66Met polymorphism with schizophrenia and depression in our group is in line with other studies conducted among the Polish population [30,31]. In our study, we have found no correlation between Val66Met functional polymorphism and serum BDNF protein levels. Serum BDNF levels of patients either with schizophrenia or depression were significantly higher than in control subjects.

Studies on Val66Met polymorphism and serum BDNF level conducted on healthy groups are inconsistent, possibly due to the ethnical differences. Several studies show a lack of correlation between Val66Met polymorphism and serum BDNF levels [32–34] and decreased BDNF concentration in Val homozygote subjects of Caucasian origin [35,36]. An investigation conducted on a community-based sample from Sardinia (n = 2054) as well as a meta-analysis of 13 studies report no association of Val66Met polymorphism with serum BDNF levels [37]. Bus et al. found interactions between sex, genotype and BDNF levels in a population-based cohort of 548 healthy volunteers. Male Met carriers had higher BDNF levels, while no effect of the Val66Met polymorphism on BDNF level was found in females [38].

Most studies on Val66Met polymorphism and serum BDNF levels are conducted in affective disorders, with inconsistent results. In the study on large (n = 1435) group with Major Depressive Disorder (MDD), BDNF Met allele was associated with reduced serum BDNF levels and childhood abuse [39]. No correlation between BDNF Val66Met polymorphism and BDNF serum concentrations was observed in healthy group and bipolar patients, also including the severity of disease [40]. Terracino et al. found no significant differences between BDNF plasma levels and functional polymorphism, also after controlling for age, sex, education, ethnicity, BMI, smoking status and antidepressant use [41]. Studies on Japanese patients also do not show a correlation between Val66Met polymorphism and serum BDNF levels as well as a response to selective serotonin reuptake inhibitors [42]. In a study conducted by Ozan et al. on drug-free

Table 2
Brain-Derived Neurotrophic Factor (BDNF) Val66Met genotype and allele distribution in the studied groups: control (CON), schizophrenia (SCH), depression (DEP).

	CON					DEP + SCH					DEP					SCH				
	genotypes			alleles		genotypes			alleles		genotypes			alleles		genotypes			alleles	
	VV	VM	MM	V	M	VV	VM	MM	V	M	VV	VM	MM	V	M	VV	VM	MM	V	M
n	47	17	2	111	21	78	35	4	191	43	40	18	3	98	24	38	17	1	93	19
(%)	(71.2)	(25.75)	(3.3)	(84.1)	(15.9)	(66.7)	(29.9)	(3.4)	(81.6)	(18.4)	(65.6)	(29.5)	(4.9)	(80.3)	(19.7)	(67.8)	(30.4)	(1.8)	(83)	(17)
p						p = 0.82			p = 0.57		p = 0.74			p = 0.51		p = 0.8			p = 0.86	

p values – comparing to the control group.

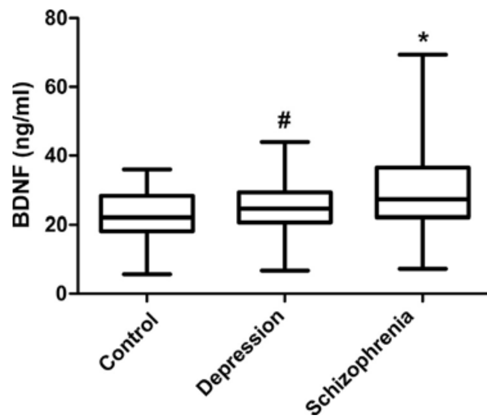

Fig. 2. BDNF serum concentration in schizophrenia, depression and control group. # depression *vs.* controls $p = 0.026$; * schizophrenia *vs.* controls $p = 0.0005$.

patients with MDD and healthy controls, a significantly lower serum BDNF level in Met-carriers subjects (patients and controls), regardless of health status was reported [43]. Other studies also did not find any correlations between Val66Met genotype and serum [44–46] or plasma [47] BDNF levels.

In patients with chronic schizophrenia there was no association of Val66Met polymorphism with serum BDNF levels, although decreased BDNF concentration and the effect of genotype on weight gain in males during antipsychotic treatment has been observed [48]. The decrease of BDNF levels in Met-carriers has been observed in Armenian [49] and Greek patients with schizophrenia [50]. No effect of the Val66Met polymorphism on serum BDNF levels has been found in other studies [47,51,52].

Met66 allele frequency varies in different populations, from being absent in Sub-Saharan Africans, and reaching up to 72% in Asian populations. [53]. Val66Met polymorphism is considered to be connected with production and secretion of BDNF protein [15], however, when comparing the studies on Caucasian and Asian populations, most results show no differences in BDNF serum levels as well as no impact of Val66Met polymorphism on BDNF serum levels.

Research results on BDNF levels in schizophrenia are ambiguous. Our finding of elevated serum BDNF levels in schizophrenia patients is in line with several reports [54–57], whereas most studies show decreased BDNF serum levels in schizophrenia and depression. Meta-analyses conducted in schizophrenia confirm reduced serum and plasma BDNF concentrations [58,59]. The recently published paper includes a total of 41 studies and more than 7000 participants. Lower BDNF levels, compared to controls, are observed in first-episode schizophrenia and have been shown to attenuate illness progression. Decreased BDNF does not correlate with the severity of positive and negative symptoms. BDNF concentrations increase in a time-dependent manner with treatment (regardless of the presence or absence of treatment response), irrespective of the antipsychotic dose. Such effect is observed only in studies that measured BDNF in plasma; in serum, such relation was not observed [59].

Serum and plasma BDNF levels are widely studied in affective disorders. Recent meta-analyses show lower BDNF concentrations in depression and manic state. BDNF levels increase in euthymia after successful pharmacological treatment and are comparable to that in healthy controls [60–62]. Interestingly, in the latest meta-analysis comprising almost 4000 participants, longer duration of the illness was correlated with higher BDNF levels in bipolar disorder patients [62].

The lack of association between the Val66Met functional polymorphism and serum BDNF levels in our study is in line with most of the reported findings and could be related to relatively small sample size or heterogeneity of the studied group. BDNF expression may be regulated by many factors, including the pharmacological treatment, thus the significant increase of serum BDNF levels in chronically medicated schizophrenic patients could be a consequence of long-term antipsychotic treatment, duration of the illness or genetic background. Further studies on larger and more homogenous groups in Polish population are warranted, considering BDNF in the context of a potential biomarker in psychiatric disorders.

Table 3
Comparison of BDNF serum levels in subgroups divided according to genotype, sex and diagnosis.

	schizophrenia	depression	control
BDNF (ng/ml) (mean ± SD)	28.85 ± 11.57	24.96 ± 7.03	22.03 ± 6.76
One-way ANOVA			
	F-statistic	*p*	power
BDNF level *vs.* genotype	0.289	0.591	8,30%
BDNF level *vs.* sex	2.856	0.092	39%
Mann-Whitney *U* test			
	Z-statistic	*p*	power
sch *vs.* con	−3.419	0.0005	98%
dep *vs.* con	−2.222	0.026	70%
sch *vs.* dep	−1.858	0.063	61%
sch + dep *vs.* con	−3.327	0.001	91%

Limitations

Relatively small sample size. Low power of the Val66Met polymorphism association with serum protein levels. Heterogeneity of the studied groups.

Declaration of interest

All authors declare no conflict of interest.

Acknowledgements

This work was supported by Polish Ministry of Science and Higher Education grant no NN402243635 and funding of Poznan University of Medical Sciences number 502-01-0221964403168.

We want to thank to Anna Leszczynska-Rodziewicz.

References

[1] Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 2013;382:1575–86.
[2] Ansorge MS, Hen R, Gingrich JA. Neurodevelopmental origins of depressive disorders. Curr Opin Pharmacol 2007;7:8–17.
[3] Lima-Ojeda JM, Rupprecht R, Baghai TC. Neurobiology of depression: a neurodevelopmental approach. World J Biol Psychiatry 2017;1–33.
[4] Shoval G, Weizman A. The possible role of neurotrophins in the pathogenesis and therapy of schizophrenia. Eur Neuropsychopharmacol 2005;15:319–29.
[5] Angelucci F, Brene S, Mathe AA. BDNF in schizophrenia, depression and corresponding animal models. Mol Psychiatry 2005;10:345–52.
[6] Mattson MP. Glutamate and neurotrophic factors in neuronal plasticity and disease. Ann N Y Acad Sci 2008;1144:97–112.
[7] Numakawa T, Suzuki S, Kumamaru E, Adachi N, Richards M, Kunugi H. BDNF function and intracellular signaling in neurons. Histol Histopathol 2010;25:237–58.
[8] Wetmore C, Ernfors P, Persson H, Olson L. Localization of brain-derived neurotrophic factor mRNA to neurons in the brain by in situ hybridization. Exp Neurol 1990;109:141–52.
[9] Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry 2006;59:1116–27.

[10] Lang UE, Hellweg R, Gallinat J. BDNF serum concentrations in healthy volunteers are associated with depression-related personality traits. Neuropsychopharmacology 2004;29:795–8.
[11] Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biol Psychiatry 2008;64:527–32.
[12] Maisonpierre PC, Le Beau MM, Espinosa 3rd R, Ip NY, Belluscio L, de la Monte SM, et al. Human and rat brain-derived neurotrophic factor and neurotrophin-3: gene structures, distributions, and chromosomal localizations. Genomics 1991;10:558–68.
[13] Aid T, Kazantseva A, Piirsoo M, Palm K, Timmusk T. Mouse and rat BDNF gene structure and expression revisited. J Neurosci Res 2007;85:525–35.
[14] Chen ZY, Bath K, McEwen B, Hempstead B, Lee F. Impact of genetic variant BDNF (Val66Met) on brain structure and function. Novartis Found Symp 2008;289:180–8 discussion 8–95.
[15] Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 2003;112:257–69.
[16] Harrisberger F, Smieskova R, Schmidt A, Lenz C, Walter A, Wittfeld K, et al. BDNF Val66Met polymorphism and hippocampal volume in neuropsychiatric disorders: a systematic review and meta-analysis. Neurosci Biobehav Rev 2015;55:107–18.
[17] Kheirollahi M, Kazemi E, Ashouri S. Brain-derived neurotrophic factor gene Val66Met polymorphism and risk of schizophrenia: a meta-analysis of case-control studies. Cell Mol Neurobiol 2016;36:1–10.
[18] Zhao X, Huang Y, Chen K, Li D, Han C, Kan Q. The brain-derived neurotrophic factor Val66Met polymorphism is not associated with schizophrenia: an updated meta-analysis of 11,480 schizophrenia cases and 13,490 controls. Psychiatry Res 2015;225:217–20.
[19] Gyekis JP, Yu W, Dong S, Wang H, Qian J, Kota P, et al. No association of genetic variants in BDNF with major depression: a meta- and gene-based analysis. Am J Med Genet B Neuropsychiatr Genet 2013;162B:61–70.
[20] Li M, Chang H, Xiao X. BDNF Val66Met polymorphism and bipolar disorder in European populations: a risk association in case-control, family-based and GWAS studies. Neurosci Biobehav Rev 2016;68:218–33.
[21] Verhagen M, van der Meij A, van Deurzen PA, Janzing JG, Arias-Vasquez A, Buitelaar JK, et al. Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity. Mol Psychiatry 2010;15:260–71.
[22] Karege F, Schwald M, Cisse M. Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. Neurosci Lett 2002;328:261–4.
[23] Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 1998;37:1553–61.
[24] First MB, Spitzer RL, Gibbon M, Williams J. Structured Clinical Interview for DSM IV Axis I Disorders, Clinician Version (SCID-CV). 1996.
[25] McGuffin P, Farmer A, Harvey I. A polydiagnostic application of operational criteria in studies of psychotic illness: development and reliability of the OPCRIT system. Arch Gen Psychiatry 1991;48:764–70.
[26] Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–76.
[27] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
[28] Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 1988;16:1215.
[29] Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175–91.
[30] Pelka-Wysiecka J, Wronski M, Jasiewicz A, Grzywacz A, Tybura P, Kucharska-Mazur J, et al. BDNF rs 6265 polymorphism and COMT rs 4680 polymorphism in deficit schizophrenia in Polish sample. Pharmacol Rep 2013;65:1185–93.
[31] Grzywacz A, Samochowiec A, Ciechanowicz A, Samochowiec J. Family-based study of brain-derived neurotrophic factor (BDNF) gene polymorphism in alcohol dependence. Pharmacol Rep 2010;62:938–41.
[32] Trajkovska V, Marcussen AB, Vinberg M, Hartvig P, Aznar S, Knudsen GM. Measurements of brain-derived neurotrophic factor: methodological aspects and demographical data. Brain Res Bull 2007;73:143–9.
[33] Duncan LE, Hutchison KE, Carey G, Craighead WE. Variation in brain-derived neurotrophic factor (BDNF) gene is associated with symptoms of depression. J Affect Disord 2009;115:215–9.
[34] Luykx JJ, Boks MP, Breetvelt EJ, Aukes MF, Strengman E, da Pozzo E, et al. BDNF Val66Met homozygosity does not influence plasma BDNF levels in healthy human subjects. Prog Neuropsychopharmacol Biol Psychiatry 2013;43:185–7.
[35] Lang UE, Hellweg R, Sander T, Gallinat J. The Met allele of the BDNF Val66Met polymorphism is associated with increased BDNF serum concentrations. Mol Psychiatry 2009;14:120–2.
[36] Minelli A, Zanardini R, Bonvicini C, Sartori R, Pedrini L, Gennarelli M, et al. BDNF serum levels, but not BDNF Val66Met genotype, are correlated with personality traits in healthy subjects. Eur Arch Psychiatry Clin Neurosci 2011; 261(5):323–9.
[37] Terracciano A, Piras MG, Lobina M, Mulas A, Meirelles O, Sutin AR, et al. Genetics of serum BDNF: meta-analysis of the Val66Met and genome-wide association study. World J Biol Psychiatry 2013;14:583–9.
[38] Bus BA, Arias-Vasquez A, Franke B, Prickaerts J, de Graaf J, Voshaar RC. Increase in serum brain-derived neurotrophic factor in met allele carriers of the BDNF Val66Met polymorphism is specific to males. Neuropsychobiology 2012;65:183–7.
[39] Elzinga BM, Molendijk ML, Oude Voshaar RC, Bus BA, Prickaerts J, Spinhoven P, et al. The impact of childhood abuse and recent stress on serum brain-derived neurotrophic factor and the moderating role of BDNF Val66Met. Psychopharmacology (Berl) 2011;214:319–28.
[40] Tramontina J, Frey BN, Andreazza AC, Zandona M, Santin A, Kapczinski F. Val66met polymorphism and serum brain-derived neurotrophic factor levels in bipolar disorder. Mol Psychiatry 2007;12:230–1.
[41] Terracciano A, Martin B, Ansari D, Tanaka T, Ferrucci L, Maudsley S, et al. Plasma BDNF concentration, Val66Met genetic variant and depression-related personality traits. Genes Brain Behav 2010;9:512–8.
[42] Yoshimura R, Kishi T, Suzuki A, Umene-Nakano W, Ikenouchi-Sugita A, Hori H, et al. The brain-derived neurotrophic factor (BDNF) polymorphism Val66Met is associated with neither serum BDNF level nor response to selective serotonin reuptake inhibitors in depressed Japanese patients. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:1022–5.
[43] Ozan E, Okur H, Eker C, Eker OD, Gonul AS, Akarsu N. The effect of depression, BDNF gene val66met polymorphism and gender on serum BDNF levels. Brain Res Bull. 2010;81:61–5.
[44] Elfving B, Buttenschon HN, Foldager L, Poulsen PH, Andersen JH, Grynderup MB, et al. Depression, the Val66Met polymorphism, age, and gender influence the serum BDNF level. J Psychiatr Res 2012;46:1118–25.
[45] Kreinin A, Lisson S, Nesher E, Schneider J, Bergman J, Farhat K, et al. Blood BDNF level is gender specific in severe depression. PLoS One 2015;10:e0127643.
[46] Katsuki A, Yoshimura R, Kishi T, Hori H, Umene-Nakano W, Ikenouchi-Sugita A, et al. Serum levels of brain-derived neurotrophic factor (BDNF), BDNF gene Val66Met polymorphism, or plasma catecholamine metabolites, and response to mirtazapine in Japanese patients with major depressive disorder (MDD). CNS Spectr 2012;17:155–63.
[47] Chen SL, Lee SY, Chang YH, Chen SH, Chu CH, Wang TY, et al. The BDNF Val66Met polymorphism and plasma brain-derived neurotrophic factor levels in Han Chinese patients with bipolar disorder and schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2014;51:99–104.
[48] Zhang XY, Zhou DF, Wu GY, Cao LY, Tan YL, Haile CN, et al. BDNF levels and genotype are associated with antipsychotic-induced weight gain in patients with chronic schizophrenia. Neuropsychopharmacology 2008;33:2200–5.
[49] Zakharyan R, Boyajyan A. Brain-derived neurotrophic factor blood levels are decreased in schizophrenia patients and associate with rs6265 genotypes. Clin Biochem. 2014;47:1052–5.
[50] Sotiropoulou M, Mantas C, Bozidis P, Marselos M, Mavreas V, Hyphantis T, et al. BDNF serum concentrations in first psychotic episode drug-naive schizophrenic patients: associations with personality and BDNF Val66Met polymorphism. Life Sci 2013;92:305–10.
[51] Zhang XY, Chen DC, Xiu MH, Haile CN, Luo X, Xu K, et al. Cognitive and serum BDNF correlates of BDNF Val66Met gene polymorphism in patients with schizophrenia and normal controls. Hum Genet 2012;131:1187–95.
[52] Zhang XY, Zhang WF, Zhou DF, Chen da C, Xiu MH, Wu HR, et al. Brain-derived neurotrophic factor levels and its Val66Met gene polymorphism predict tardive dyskinesia treatment response to Ginkgo biloba. Biol Psychiatry 2012;72:700–6.
[53] Petryshen TL, Sabeti PC, Aldinger KA, Fry B, Fan JB, Schaffner SF, et al. Population genetic study of the brain-derived neurotrophic factor (BDNF) gene. Mol Psychiatry 2010;15:810–5.
[54] Gama CS, Andreazza AC, Kunz M, Berk M, Belmonte-de-Abreu PS, Kapczinski F. Serum levels of brain-derived neurotrophic factor in patients with schizophrenia and bipolar disorder. Neurosci Lett 2007;420:45–8.
[55] Reis HJ, Nicolato R, Barbosa IG, Teixeira do Prado PH, Romano-Silva MA, Teixeira AL. Increased serum levels of brain-derived neurotrophic factor in chronic institutionalized patients with schizophrenia. Neurosci Lett 2008;439:157–9.
[56] Guimaraes LR, Jacka FN, Gama CS, Berk M, Leitao-Azevedo CL, Belmonte de Abreu MG, et al. Serum levels of brain-derived neurotrophic factor in schizophrenia on a hypocaloric diet. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1595–8.
[57] Ajami A, Hosseini SH, Taghipour M, Khalilian A. Changes in serum levels of brain derived neurotrophic factor and nerve growth factor-beta in schizophrenic patients before and after treatment. Scand J Immunol 2014;80:36–42.
[58] Green MJ, Matheson SL, Shepherd A, Weickert CS, Carr VJ. Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. Mol Psychiatry 2011;16:960–72.
[59] Fernandes BS, Steiner J, Berk M, Molendijk ML, Gonzalez-Pinto A, Turck CW, et al. Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: meta-analysis and implications. Mol Psychiatry 2015;20:1108–19.
[60] Fernandes BS, Molendijk ML, Kohler CA, Soares JC, Leite CM, Machado-Vieira R, et al. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. BMC Med 2015;13:289.
[61] Fernandes BS, Berk M, Turck CW, Steiner J, Goncalves CA. Decreased peripheral brain-derived neurotrophic factor levels are a biomarker of disease activity in major psychiatric disorders: a comparative meta-analysis. Mol Psychiatry 2014;19:750–1.
[62] Munkholm K, Vinberg M, Kessing LV. Peripheral blood brain-derived neurotrophic factor in bipolar disorder: a comprehensive systematic review and meta-analysis. Mol Psychiatry 2016;21:216–28.