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# Val66Met polymorphism and serum brain-derived neurotrophic factor concentration in depressed patients

Zhang X, Wang X, Sha W, Zhou H, Zhang Y. Val66Met polymorphism and serum brain-derived neurotrophic factor concentration in depressed patients.

**Objective:** Accumulating evidence has suggested a pathophysiological role for brain-derived neurotrophic factor (BDNF) in major depressive disorder (MDD). The present study evaluated serum levels of BDNF and explored whether Val66Met BDNF gene polymorphism is correlated with changes in circulating BDNF levels in patients with MDD and control subjects.
**Methods:** Subjects were 76 patients with MDD and 50 controls. Diagnosis of MDD was determined by the use of a structured clinical interview according to Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) criteria. The concentrations of BDNF were measured by using the enzyme-linked immunosorbent assay. The Val66Met BDNF gene polymorphism was examined by the polymerase chain reaction technique.
**Results:** Serum BDNF was significantly lower in MDD patients than in normal control subjects ($p < 0.001$). There were no significant differences either in allele or genotype in the Val66Met polymorphism between the MDD and control groups. Moreover, genotype did not significantly correlate with the BDNF serum levels in the MDD or control groups.
**Conclusions:** Our study suggests that there is a decrease in serum BDNF levels in untreated MDD patients. However, serum BDNF levels were not associated with the Val66Met polymorphism.

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## Introduction

Brain-derived neurotrophic factor (BDNF) is a nerve growth factor which is abundant in the brain and periphery. BDNF is widely expressed throughout the brain and plays a major role in neuronal plasticity, survival and development (1). Much evidence suggests BDNF as a candidate molecule involved in the neurobiological and behavioural changes associated with major depressive disorder (MDD) (2). In animal models, forced swimming and chronic immobilisation stress decrease expression of BDNF mRNA (3,4), which can lead to neuronal atrophy in the hippocampus and other brain structures (5). Several neuroimaging studies revealed that the hippocampus undergoes selective volume reduction in the MDD patients (6). Infusion of BDNF itself into rat brain can produce an antidepressant-like effect by ameliorating learned helplessness (7). In addition, antidepressant drug and chronic electroconvulsive treatments increase the expression of BDNF and neurogenesis in the adult rat brain (8). Consistent with animal studies, increased BDNF expression in hippocampal tissue was found in antidepressant-treated subjects compared with untreated subjects (9) and decreased levels of BDNF mRNA and protein were observed in hippocampus and frontal cortex of suicide victims, most of them diagnosed with MDD (10). In addition, circulating levels of BDNF are reported to be lower in untreated depressed patients (11), while antidepressant medications appear to normalise this alteration (12). A meta-analysis found that serum BDNF levels are abnormally low in patients suffering from MDD and that the BDNF levels are elevated following a course of antidepressant treatment (13).

The BDNF gene val66met polymorphism has been associated with MDD, bipolar disorder and schizophrenia, but replication attempts have often provided inconclusive results (14,15). Although two recent studies found that the Val66met variant influences circulating levels of BDNF (16,17), the role of this genetic factor has been inconsistent. Indeed, several studies showed that the Val66met polymorphism was unrelated to the concentration of BDNF in serum, plasma or whole blood (18–20). The aim of this study was to further explore whether the Val66met polymorphism is correlated with the serum concentration of BDNF in MDD and whether serum BDNF concentrations are altered in drug-free patients with MDD compared to healthy control subjects.

## Materials and methods

From the cohort of psychiatric inpatients admitted to the Department of Psychiatry of Yangzhou Wu Tai Shan Hospital in China between January 2006 and March 2007, 76 Chinese Han depressive patients between 20 and 65 years of age were recruited. Diagnosis of MDD was determined by the use of a structured clinical interview according to Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) criteria (21,22); they had no history of other psychiatric disorders or physical/neurological diseases. None of the patients had a history of a manic or hypomanic episodes or a first-degree relative with bipolar disorder. The diagnosis was reached independently by at least two senior psychiatrists. All patients scored 18 or higher on the 21-item Hamilton Depression Rating Scale (HDRS-21), which was used for assessment of symptom severity (23). They were either medication-naive or medication-free for at least 4 weeks. For these patients BDNF values were obtained from serum samples collected on the day before antidepressant initiation. Fifty healthy subjects (22 males and 28 females) were studied as control subjects. Control subjects were not on medication and had no history, or first-degree family history, of mental disorders, neurological diseases or drug abuse. Age, gender and education years were matched between the MDD patients and the normal controls. The study was approved by the local Institutional Ethics Committee. Written informed consent was obtained after a full written and verbal explanation of the study. None of the subjects were regular drinkers or smoker.

Following an overnight fast, serum samples from the patients and healthy controls were collected between 8:00 and 9:00 and stored at −80 °C until used for assay. The concentrations of BDNF were measured with the enzyme-linked immunosorbent assay (Emax Immunoassay System kit; Promega, Madison, WI, USA) according to the manufacturer's instructions. The samples were diluted 1:2 with block and sample 1× buffer. All samples were tested in triplicate and the mean was calculated. The intra- and inter-assay coefficients of variation were <4 and <5%, respectively. Genomic DNA was extracted from 300 µl ethylene diamine tetra acetic acid-anticoagulated venous blood using Puregene DNA Purification kit (Gentra, Minneapolis, MN, USA) according to the manufacturer's recommendation. Polymerase chain reaction was performed with the sense primer 5′-ACT CTG GAG AGC GTG AAT-3′ and the antisense primer 5′-ATA CTG TCA CAC ACG CTC-3′. The amplified DNA was digested with the *Nla*III restriction enzyme (New England Biolabs, Beverly, MA, USA), which cuts at the 196A site and the product was electrophoresed in 2% agarose gels and stained with ethidium bromide. Restriction enzyme digestion results in a 243 bp product (66Val) or 168 and 75 bp products (66Met).

The chi-squared goodness-of-fit test was used to test the distribution of genotypes and allele frequencies for deviations from Hardy–Weinberg equilibrium in patients and normal control samples. Chi-squared or Fisher's exact test was performed on categorical data and study groups were compared for continuous variables by a two-tailed *t*-test or Mann–Whitney *U* test. Analysis of covariance was performed to compare BDNF serum concentrations between genotype groups, using age and gender as covariates. The relationship between the serum BDNF and clinical variables was examined using Pearson's correlation coefficient. Statistical significance is indicated by *p* values less than 0.05. All statistical analyses were performed using SPSS (version 10.0 for Microsoft Windows, SPSS Inc., Chicago, IL, USA).

## Results

Table 1 shows the demographic and clinical characteristics of both the MDD and control groups. The

Table 1. Demographic features, HDRS scores and BDNF serum concentrations of the groups

| | Major depression ($n = 76$) | Control ($n = 50$) | *p* |
|---|---|---|---|
| Age (years) | 45.1 ± 14.7 | 43.4± 13.4 | 0.519 |
| Gender | | | |
| Male | 34 (44.7%) | 22 (44.0%) | 0.935 |
| Female | 42 (55.3%) | 28 (56.0%) | |
| Age at onset (SD), years | 36.6 ± 13.1 | | |
| Duration of illness (SD), years | 8.3 ± 9.3 | | |
| HDRS (SD) | 28.6 ± 7.9 | | |
| BDNF(SD), ng/ml | 24.7 ± 12.7 | 36.6 ± 16.4 | 0.0001* |

*Mann–Whitney *U* test.



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Table 2. The Val66met polymorphism and BDNF serum concentrations according to the genotype in MDD patients and controls

| | Allele frequency | | Genotype distribution | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Val | Met | Val/Val | | Val/Met | | Met/Met | |
| Group | Frequency | Frequency | *n* | Frequency | *n* | Frequency | *n* | Frequency |
| Patients | 0.49 | 0.51 | 17 | 0.22 | 40 | 0.53 | 19 | 0.25 |
| Controls | 0.52 | 0.48 | 13 | 0.26 | 26 | 0.52 | 11 | 0.22 |
| BDNF (ng/ml) | | | | | | | | |
| Patients | | | | 21.7 ± 12.1 | | 26.9 ± 12.7 | | 22.8 ± 13.0 |
| Controls | | | | 31.2 ± 10.0 | | 38.9 ± 18.2 | | 37.5 ± 18.0 |

concentrations of serum BDNF were significantly lower in the patients with MDD (mean = 24.7 ± 12.7 ng/ml, $p < 0.001$) compared with the control subjects (mean = 36.6 ± 16.4 ng/ml). No significant correlation was found between serum BDNF and age in MDD patients ($r = 0.196$, $p = 0.089$) or controls ($r = 0.045$, $p = 0.756$). Moreover, there was no significant difference in the serum BDNF levels between males and females (MDD patients: male = 34, 22.02 ± 11.7 ng/ml vs. female = 42, 26.9 ± 13.1 ng/ml, $p = 0.098$; control group: male = 22, 38.5 ± 17.9 ng/ml vs. female = 28, 35.1 ± 15.3 ng/ml, $p = 0.48$). Neither age at onset ($r = 0.067$, $p = 0.576$) nor duration of MDD ($r = 0.168$, $p = 0.148$) correlated significantly with serum BDNF in patients. No significant correlation was observed between BDNF and HDRS scores ($r = -0.063$, $p = 0.586$) in MDD patients. The HDRS has been shown to be multi-dimensional which has only some items to assess the severity of depression (24). Maier and Philipp (25) have developed a subscale that assess the severity of depression includes items of depressed mood, guilt, work/interests, psychomotor retardation, anxiety and general somatic symptoms. There was no significant correlation between the serum BDNF and HDRS item 1 (depressed mood: $r = 0.023$, $p = 0.842$), item 2 (guilt: $r = 0.058$, $p = 0.62$), item 7 (work/interests: $r = -0.152$, $p = 0.189$), item 8 (psychomotor retardation: $r = -0.116$, $p = 0.316$), item 10 (anxiety: $r = 0.102$, $p = 0.379$) and items 13 (general somatic symptoms: $r = -0.122$, $p = 0.293$). The serum BDNF levels in patients with a family history of mood disorders ($n = 15$, 25.6 ± 12.5 ng/ml) did not differ from those in patients without such a history ($n = 61$, 24.5 ± 12.8 ng/ml; $p = 0.761$).

Allele frequencies and genotype distributions of the subjects for the Val66Met in the BDNF gene were shown in Table 2. The genotypic distributions in MDD ($\chi^2 = 0.227$, $df = 2$, $p = 0.893$) and control groups ($\chi^2 = 0.084$, $df = 2$, $p = 0.959$) were consistent with the Hardy–Weinberg equilibrium. There were no significant differences in the distribution of the allele frequencies and genotype between the MDD patients and controls ($\chi^2 = 0.265$, $df = 1$, $p = 0.607$; $\chi^2 = 0.283$, $df = 2$, $p = 0.868$, respectively). The BDNF serum concentrations were not significantly different between the genotypes of Val66met polymorphism in MDD patients and controls.

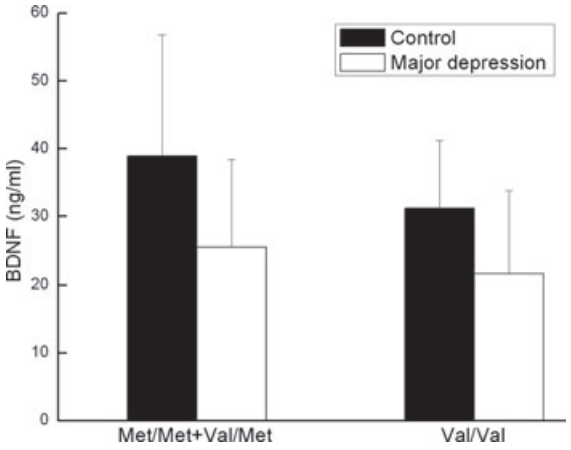


*Fig. 1.* Val66Met polymorphism and BDNF serum concentrations in major depression disorder patients and control subjects.

BDNF serum concentrations by genotypes in major depression disorder patients and control group were presented in Fig. 1. There were no significant differences in BDNF serum concentrations between the Met/Met + Val/Met and Val/Val genotype groups (MDD patients: $p = 0.199$; control group: $p = 0.472$). An analysis of covariance in all research subjects independent of the diagnostic status showed that the dependent variable BDNF serum concentrations were not significantly affected by the factor 'genotype' (Met/Met + Val/Met vs. Val/Val: $F = 2.172$, $df = 1$, $p = 0.143$), the covariate 'age' ($F = 1.199$, $df = 1$, $p = 0.276$) and 'gender' ($F = 0.189$, $df = 1$, $p = 0.665$).

## Discussion

The main findings of this study were that serum BDNF were significantly lower in the patients with MDD compared with the control subjects. We found no significant differences either in allele or genotype in the Val66Met polymorphism between the MDD and control groups. Moreover, genotype did not significantly correlate with the BDNF serum levels in the MDD or control groups.

Previous studies reported that serum or platelet BDNF levels were reduced in depressed patients (2,11,26), while antidepressant treatment appears to normalise this alteration (12,13). Two meta-analyses study showed a reduction of both BDNF serum and plasma levels in MDD (13,27); our finding was consisted with their reports. In addition, some studies report that serum BDNF levels are negatively



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correlated with the severity of depression (12,28). However, Lee et al. (29) reported that plasma BDNF levels had significant positive correlations with HDRS. Our findings show no significant correlation between HDRS score and serum BDNF. Moreover, we found no significant correlation between serum BDNF and HDRS items 1, 2, 7, 8, 10 and 13. Thus, we infer from our findings that serum BDNF levels are not significantly correlated with the severity of depression. We found no significant correlation between serum BDNF and age or gender. Neither age at onset nor duration of MDD correlated significantly with serum BDNF in patients. These results are consistent with other findings (13,26). A lot of determinants may affect the BDNF level. Bus et al. (30) identified eight independent determinants of serum BDNF levels, i.e. time of blood withdrawal, time of storage, food intake before sampling, urbanicity, age, sex, smoking status and drinking behavior. Huang et al. (31) found that there are significantly low serum BDNF protein levels in depressive patients than healthy controls in women, but not in men. Moreover, there were significantly increased changes in serum BDNF protein levels in women patients taking antidepressants during a period of 4 weeks. For the responders in women, there were significantly increased changes in serum BDNF protein levels, but not in men.

We found that the allele frequency of the Val66Met polymorphism in BDNF was not different between MDD and control groups. This negative result is also consistent with previous studies involving Asian populations (32,33). In contrast, an association has been reported between the BDNF Val66Met polymorphism and geriatric depression in a Chinese population (34). Zou et al. (35) detected a significant genetic association between the BDNF Val66Met polymorphism and treatment response in patients with MDD in their meta-analysis and Val/Met heterozygous patients have a better response rate in comparison with Val/Val homozygous patients, especially in the Asian population. Moreover, Kato and Serretti (36) found that the Met allele carriers have a favourable response to antidepressant treatment. However, Domschke et al. (37) did not find an association between genetic variation in BDNF and antidepressant treatment response or remission. A recent meta-analysis of the association of the BDNF Val66Met polymorphism with MDD investigated 2812 patients and 10 843 controls from 14 case–control studies (38), but did not detect any significant association. Verhagen et al. (38) found that the BDNF Val66Met polymorphism is of greater importance in the development of MDD in men than in women. Our results indicate a possible trend towards an interaction between gender and serum BDNF in MDD patients. (male = 34, 22.02 ± 11.7 ng/ml vs. female = 42, 26.9 ± 13.1 ng/ml, $p = 0.098$). Our failure to show significant association supports the conclusion that BDNF gene Val66Met polymorphism may not play a major role in MDD pathogenesis for our Chinese sample population.

The Val66Met polymorphism lies within the pro-BDNF sequence, which is cleaved post-transcriptionally. Although this polymorphism does not affect mature BDNF protein function, it has been shown to affect activity-dependent secretion of BDNF in cultured cells (39). A study by Egan et al. (40) showed that the Val/Met polymorphism at codon 66 in the BDNF affects intracellular distribution, packaging and release of the BDNF protein *in vitro*. Although it has been hypothesised that BDNF Val66Met genotype is associated with circulating levels of BDNF (16,17), the contribution of this genetic factor remains unclear. Others suggest that the Val66Met polymorphism influences only local activity-dependent secretion from neurons, whereas the constitutive secretion and average BDNF concentrations in brain and blood are unaffected by the genotype (41). In addition, other work has reported that the Val66Met polymorphism is unrelated to whole blood BDNF concentration (19) and is also unrelated to plasma or serum concentrations of BDNF (18,20,42). Our findings are consistent with the majority of these studies.

Some limitations of this study must be taken into consideration. First, the number of patients was small and it would therefore be unwise to generalise the results. We cannot rule out the association of other genetic polymorphisms in the BDNF gene with BDNF serum concentrations which would require further investigation and confirmation in larger samples and other ethnic populations.

## References


1. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 2001;**24**:677–736.
2. Brunoni AR, Lopes M, Fregni F. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. Int J Neuropsychopharmacol 2008;**11**:1169–1180.
3. Russo-Neustadt A, Ha T, Ramirez R, Kesslak JP. Physical activity-antidepressant treatment combination: impact on brain-derived neurotrophic factor and behavior in an animal model. Behav Brain Res 2001;**120**:87–95.
4. Smith MA, Makino S, Kvetnansky R, Post RM. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. J Neurosci 1995;**15**:1768–1777.




https://doi.org/10.1111/j.1601-5215.2011.00560.x Published online by Cambridge University Press

5. Schmidt HD, Duman RS. The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. Behav Pharmacol 2007;**18**:391–418.
6. Koolschijn PC, van Haren NE, Lensvelt-Mulders GJ, Hulshoff Pol HE, Kahn RS. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Hum Brain Mapp 2009;**30**:3719–3735.
7. Siuciak JA, Lewis DR, Wiegand SJ, Lindsay RM. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). Pharmacol Biochem Behav 1997;**56**:131–137.
8. Altar CA, Whitehead RE, Chen R, Wörtwein G, Madsen TM. Effects of electroconvulsive seizures and antidepressant drugs on brain-derived neurotrophic factor protein in rat brain. Biol Psychiatry 2003;**54**:703–709.
9. Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry 2001;**50**:60–265.
10. Dwivedi Y, Rizavi HS, Conley RR, Roberts RC, Tamminga CA, Pandey GN. Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. Arch Gen Psychiatry 2003;**60**:804–815.
11. Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G. Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry 2005;**57**:1068–1072.
12. Gonul AS, Akdeniz F, Taneli F, Donat O, Eker C, Vahip S. Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. Eur Arch Psychiatry Clin Neurosci 2005;**255**:381–386.
13. Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analysis and implications. Biol Psychiatry 2008;**64**:527–532.
14. Rybakowski JK. BDNF gene: functional Val66Met polymorphism in mood disorders and schizophrenia. Pharmacogenomics 2008;**9**:1589–1593.
15. Schumacher J, Jamra RA, Becker T et al. Evidence for a relationship between genetic variants at the brain-derived neurotrophic factor (BDNF) locus and major depression. Biol Psychiatry 2005;**58**:307–314.
16. 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**:120–122.
17. Ozan E, Okur H, Eker C, Eker OD, Gönül AS, Akarsu N. The effect of depression, BDNF gene val66met polymorphism and gender on serum BDNF levels. Brain Res Bull 2010;**81**:61–65.
18. Jiang H, Wang R, Liu Y, Zhang Y, Chen ZY. BDNF Val66Met polymorphism is associated with unstable angina. Clin Chim Acta 2009;**400**:3–7.
19. 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**:143–149.
20. 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**:230–231.
21. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edn. Washington, DC: American Psychiatric Association, 1994.
22. First MB, Spitzer RL, Gibbon M, Williams JB. Structured clinical interview for DSM-IV (SCID-I). New York: Biomedics Research Department, 1998.
23. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;**23**:56–62.
24. Bagby RM, Ryder AG, Schuller DR, Marshail MB. The Hamilton Depression Rating Scale: Has the Gold Standard become a lead weight? Am J Psychiatry 2004;**161**: 2163–2177.
25. Maier W, Philipp M. Improving the assessment of severity of depressive states: a reduction of the Hamilton Depression Scale. Pharmacopsychiatry 1985;**18**:114–115.
26. Lee BH, Kim YK. Reduced platelet BDNF level in patients with major depression. Prog Neuropsychopharmacol Biol Psychiatry 2009;**33**:849–853.
27. Bocchio-Chiavetto L, Bagnardi V, Zanardini R et al. Serum and plasma BDNF levels in major depression: a replication study and meta-analyses. World J Biol Psychiatry 2010;**11**:763–773.
28. Shimizu E, Hashimoto K, Okamura N et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry 2003;**54**:70–75.
29. Lee BH, Kim H, Park SH, Kim YK. Decreased plasma BDNF level in depressive patients. J Affect Disord 2007;**101**:239–244.
30. Bus BA, Molendijk ML, Penninx BJ et al. Determinants of serum brain-derived neurotrophic factor. Psychoneuroendocrinology 2011;**36**:228–239.
31. Huang TL, Lee CT, Liu YL. Serum brain-derived neurotrophic factor levels in patients with major depression: effects of antidepressants. J Psychiatr Res 2008;**42**:521–525.
32. Hong CJ, Huo SJ, Yen FC, Tung CL, Pan GM, Tsai SJ. Association study of a brain-derived neurotrophic-factor genetic polymorphism and mood disorders, age of onset and suicidal behavior. Neuropsychobiology 2003;**48**:186–189.
33. Tsai SJ, Cheng CY, Yu YW, Chen TJ, Hong CJ. Association study of a brain-derived neurotrophic-factor genetic polymorphism and major depressive disorders, symptomatology, and antidepressant response. Am J Med Genet B Neuropsychiatr Genet 2003;**123B**:19–22.
34. Hwang JP, Tsai SJ, Hong CJ, Yang CH, Lirng JF, Yang YM. The Val66Met polymorphism of the brain-derived neurotrophic-factor gene is associated with geriatric depression. Neurobiol Aging 2006;**27**:1834–1837.
35. Zou YF, Ye DQ, Feng XL, Su H, Pan FM, Liao FF. Meta-analysis of BDNF Val66Met polymorphism association with treatment response in patients with major depressive disorder. Eur Neuropsychopharmacol 2010;**20**: 535–544.
36. Kato M, Serretti A. Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. Mol Psychiatry 2010;**15**:473–500.
37. Domschke K, Lawford B, Laje G et al. Brain-derived neurotrophic factor (BDNF) gene: no major impact on antidepressant treatment response. Int J Neuropsychopharmacol 2010;**13**:93–101.
38. Verhagen M, van der Meij A, van Deurzen PA, Janzing JG, Arias-Vásquez A, Buitelaar JK, Franke B. Meta-analysis of the BDNF Val66Met polymorphism in




https://doi.org/10.1111/j.1601-5215.2011.00560.x Published online by Cambridge University Press

major depressive disorder: effects of gender and ethnicity. Mol Psychiatry 2010;**15**:260–271.
39. Chen ZY, Patel PD, Sant G, Meng CX, Teng KK, Hempstead BL, Lee FS. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. J Neurosci 2004;**24**:4401–4411.
40. Egan MF, Kojima M, Callicott JH et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 2003;**112**:257–269.
41. Chen ZY, Jing D, Bath KG et al. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science 2006;**314**:140–143.
42. Terracciano A, Martin B, Ansari D et al. Plasma BDNF concentration, Val66Met genetic variant and depression-related personality traits. Genes Brain Behav 2010;**9**: 512–518.



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