

GSK-3 β and *BDNF* genes may not be associated with venlafaxine treatment response in Chinese of Han ethnicity

This article was published in the following Dove Medical Press journal:
Neuropsychiatric Disease and Treatment

Qianqian Sun^{1,2}
Fan Yuan^{1,2}
Decheng Ren^{1,2}
Gaini Ma^{1,2}
Fengping Yang^{1,3}
Xi Wu^{1,3}
Lin He^{1,3}
Guang He^{1,2}

¹Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders (Ministry of Education), Shanghai Jiao Tong University, Shanghai 200030, P.R. China; ²Shanghai Key Laboratory of Psychotic Disorders, Shanghai Institute of Mental Health, Shanghai Jiao Tong University, Shanghai 200030, P.R. China; ³Institute for Nutritional Sciences, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, P.R. China

Purpose: Venlafaxine is one of the commonly prescribed antidepressants for major depressive disorder (MDD). Accumulated evidence revealed the involvement of glutamatergic system in the pathophysiology of MDD and antidepressant treatment.

Methods: We recruited 193 MDD patients who have been taking venlafaxine for 6 weeks, and investigated whether single nucleotide polymorphisms (SNPs) in *GSK-3 β* and *BDNF* were associated with treatment response. Nine SNPs were selected randomly depending on association studies. Efficacy of treatment was determined by 17-item Hamilton Rating Scale. Allele and genotype frequencies were compared between responders and nonresponders.

Results: After adjusting the false discovery rate, no significant difference was observed between response and nonresponse groups in allele or genotype distributions after venlafaxine treatment for 6 weeks.

Conclusion: Our results indicated that genetic variants in the *GSK-3 β* and *BDNF* may not be associated with treatment response in MDD patients treated with venlafaxine.

Keywords: association, *GSK-3 β* , *BDNF*, major depressive disorder, venlafaxine

Introduction

Major depressive disorder (MDD) is a common, debilitating psychiatric disorder.¹ Venlafaxine, as a serotonin and norepinephrine reuptake inhibitor, is one of the major prescribed medications for MDD.² Previous studies implicate glutamate system genes, the glycogen synthase kinase-3 β (*GSK-3 β*) and brain-derived neurotrophic factor (*BDNF*), are involved in both pathophysiology of MDD and antidepressant treatment.³ Furthermore, *BDNF* gene promotes the growth of neurons in vitro mediated by *GSK-3 β* .⁴ However, pharmacogenetic studies of *GSK-3 β* and *BDNF* genes with antidepressant response are controversial in the literature.⁵⁻⁸ Therefore, we attempted to investigate whether *GSK-3 β* and *BDNF* gene polymorphisms are associated with venlafaxine treatment in the Han population.

For pharmacogenetics association study, 193 MDD patients in Chinese Han population (aged 18–65 years, no blood relationship) were recruited. All subjects recruited were of Han Chinese origin. Participants were first-onset patients. They did not receive any antidepressant treatment for at least 2 weeks and had no electroconvulsive therapy. Efficacy of treatment was determined by 17-item Hamilton Rating Scale, and all MDD patients had a minimum baseline Hamilton Rating Scale for Depression (HAM-D) score of 18 points. Clinical interviews were performed by board-certified and experienced psychiatrists. The study was approved by the Ethics Committee of the Human Genetics Center in Shanghai and conducted

Correspondence: Lin He; Guang He
Bio-X Institutes, Shanghai Jiao Tong
University, 1954 Huashan Road, Shanghai
200030, P.R. China
Tel/fax +86 0 21 6282 2491
Email helin@sjtu.edu.com;
heguang@sjtu.edu.cn

in accordance with the Declaration of Helsinki. All subjects signed the informed consent form.

All MDD patients received a continuous antidepressant treatment for >6 weeks. A total venlafaxine dose of 75–375 mg/day was used based on patients' conditions. Patients were evaluated at the end of weeks 1, 2, 4, and 6. Patients who have >50% reduction of HAMD score were assigned to response group, and <50% were assigned to nonresponse group at the end of week 6.⁹ Other psychotropic medications were not allowed during the study except an eligible dose of benzodiazepine for insomnia at bedtime.

Genomic DNA extraction was carried out according to standard procedures with phenol/chloroform purification. Five single nucleotide polymorphisms (SNPs) (intron: rs4624596, rs182839, rs334533, and rs16830730; promoter: rs11925868) in *GSK-3 β* and four SNPs (downstream: rs925946; 3' UTR: rs7124442; exon: rs6265; promoter: rs908867) in *BDNF* gene based on the literature^{10,11} and the NCBI dbSNP database (<http://www.ncbi.nlm.nih.gov/SNP>). Genotyping of all SNPs was performed by a matrix-assisted laser desorption/ionization time-of-flight mass spectrometer using the MassARRAY[®] Analyzer 4 platform (Sequenom, San Diego, CA, USA).

Demographic differences between responders and nonresponders were calculated by the Student's *t*-test (age, age of onset, body mass index, and HAMD score) or Pearson's chi-squared test (gender, marital status, education, and family history). The SPSS Statistics Version 22 and R software (Lucent Technologies, Morris Plains, NJ, USA) were used to carry out the above analyses. Interrater reliability was evaluated by Kappa coefficients (Kappa value =0.85).¹² The online software SHEsis (<http://202.120.31.177/myanalysis.php>)¹³ and R (version 3.2.2) were used to analyze allelic and genotypic distributions. HaploView version 4.2 was used to estimate linkage disequilibrium of all pairs of SNPs with *D'*, which is the standard measurement.¹⁴ Hardy–Weinberg equilibrium (HWE) was calculated by using SHEsis. For all analyses, *P*-values were shown as two-tailed, and *P*<0.05 was considered statistically significant.

In our study, 175 MDD patients completed the 6-week venlafaxine treatment, in which 146 (83%) patients were responders and the remaining 29 (27%) participants who gave no response at the end of week 6 were termed as nonresponders. The endpoint values for responders and nonresponders of HAMD were 16.24±5.49 and 6.04±3.57, respectively. We found no significant difference between responders and nonresponders in age, BMI, number of episodes, HAMD baseline score, family history,

marital status, education years, and gender except for 6-week HAMD score (*P*<0.05). Thus, it is reasonable to conclude that no systematic differences can potentially affect clinical outcomes between the responders and nonresponders.

None of the SNPs showed significantly deviated HWE (*P*<0.05). Genotypes of response group vs nonresponse group were distributed as follows: rs4624596 C/T 84:12, T/T 35:7, C/C 27:10; rs182839 A/A 129:25, G/G 1:0, A/G 16:4; rs334533 A/A 39:13, G/G 26:4, A/G 81:12; rs11925868 C/C 122:25, C/A 23:4, A/A 1:0; rs16830730 G/G 53:9, A/A 33:7, A/G 60:13; rs925946 G/G 135:27, T/G 11:2; rs7124442 T/T 131:25, C/T 14:4, C/C 1:0; rs6265 G/G 34:6, A/A 41:5 A/G 71:18; rs908867 G/G 140:27, A/G 6:2. There is no significant difference observed between response and nonresponse groups in allele or genotype distributions (*P*>0.05), which is shown in Table S1. We also calculated *D'* and *r*² for all combinations of the four SNPs (data not shown). The haplotype distributions showed no significant association between all combinations of these SNPs with antidepressant efficacy in MDD patients.

The association between polymorphism rs6265 of *BDNF* gene and antidepressant treatment outcome has always been inconsistent.¹⁵ The polymorphism has been proven to be not associated with venlafaxine treatment response in our generalized anxiety disorder population.¹⁶ Our result indicated that the polymorphism was negative in MDD samples. Additionally, the other three common SNPs in *BDNF* gene and *GSK-3 β* gene were not associated with venlafaxine treatment in our Chinese MDD patients. However, there are some limitations in our study. Replicated studies with larger sample sizes and more common or rare variants are necessary to verify this association. A placebo control would offer a convincing estimation of the response rate and validate the association between the gene and venlafaxine treatment. Whereas, we did not use it due to high suicide rate in MDD patients. Furthermore, the phenotype of venlafaxine responses can be revealed with detailed genotypes.¹⁷ Despite these, the current study may shed new light on predicting venlafaxine responses in MDD treatment.

Acknowledgments

We appreciate the contribution of the members participating in this study. This work was supported by the National Key Research and Development Program (2016YFC0906400, 2016YFC1307000, and 2016YFC0905000), the National Nature Science Foundation of China (81421061 and 81361120389), the Shanghai Key Laboratory of Psychotic Disorders (13dz2260500), the National Nature Science

Foundation of China (81121001, 31171237, 81421061, 81571503, and 81300556), the Shanghai Municipal Commission of Science and Technology Program (09DJ1400601), the Shanghai Leading Academic Discipline Project (B205), and Overseas Students Science and Technology Activities Project merit funding. We would like to thank Ruixue Yuan, Yan Bi, Jiaxin Hu, Yuhao Zhu, Zhenming Guo, Fei Xu, Weibo Niu, Lu Wang, Xingwang Li, and Tao Yu for supporting this work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Agrawal A, Nelson EC, Bucholz KK, et al. Major depressive disorder, suicidal thoughts and behaviours, and cannabis involvement in discordant twins: a retrospective cohort study. *Lancet Psychiatry*. 2017;4(9):706–714.
2. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*. 2018;391(10128):1357–1366.
3. Duman RS, Aghajanian GK. Neurobiology of rapid acting antidepressants: role of BDNF and GSK-3 β . *Neuropsychopharmacology*. 2014;39(1):233.
4. Yang JW, Ru J, Ma W, et al. BDNF promotes the growth of human neurons through crosstalk with the Wnt/ β -catenin signaling pathway via GSK-3 β . *Neuropeptides*. 2015;54:35–46.
5. Chi MH, Chang HH, Lee SY, et al. Brain derived neurotrophic factor gene polymorphism (Val66Met) and short-term antidepressant response in major depressive disorder. *J Affect Disord*. 2010;126(3):430–435.
6. Lin E, Chen PS, Huang LC, Hsu SY. Association study of a brain-derived neurotrophic-factor polymorphism and short-term antidepressant response in major depressive disorders. *Pharmacogenomics Pers Med*. 2008;1:1–6.
7. Tsai SJ, Liou YJ, Hong CJ, Yu YW, Chen TJ. Glycogen synthase kinase-3beta gene is associated with antidepressant treatment response in Chinese major depressive disorder. *Pharmacogenomics J*. 2008;8(6):384–390.
8. Ren Z, Yan P, Zhu L, et al. Dihydropyridinone exerts a rapid antidepressant-like effect in association with enhancement of BDNF expression and inhibition of neuroinflammation. *Psychopharmacology*. 2018;235(1):233–244.
9. Chuang HY, Chang YH, Cheng LY, et al. Venlafaxine, paroxetine and milnacipran for major depressive disorder: a pragmatic 24-week study. *Chin J Physiol*. 2014;57(5):265–270.
10. Kocabas NA, Antonijevic I, Faghel C, et al. Brain-derived neurotrophic factor gene polymorphisms: influence on treatment response phenotypes of major depressive disorder. *Int Clin Psychopharmacol*. 2011;26(1):1–10.
11. Czira ME, Wersching H, Baune BT, Berger K. Brain-derived neurotrophic factor gene polymorphisms, neurotransmitter levels, and depressive symptoms in an elderly population. *Age*. 2012;34(6):1529–1541.
12. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
13. Shi YY, He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. *Cell Res*. 2005;15(2):97–98.
14. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics*. 2005;21(2):263–265.
15. Andre K, Kampman O, Viikki M, et al. BDNF and NRG1 polymorphisms and temperament in selective serotonin reuptake inhibitor-treated patients with major depression. *Acta Neuropsychiatr*. 2018;30(3):168–174.
16. Narasimhan S, Aquino TD, Hodge R, Rickels K, Lohoff FW. Association analysis between the Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene and treatment response to venlafaxine XR in generalized anxiety disorder. *Neurosci Lett*. 2011;503(3):200–202.
17. Wong ML, Dong C, Flores DL, et al. Clinical outcomes and genome-wide association for a brain methylation site in an antidepressant pharmacogenetics study in Mexican Americans. *Am J Psychiatry*. 2014;171(12):1297–1309.

Supplementary material

Neuropsychiatric Disease and Treatment downloaded from <https://www.dovepress.com/> by 3.235.236.13 on 15-May-2021
For personal use only.

Table S1 Genotype and allele distributions of GSK3 β and BDNF polymorphisms in response and nonresponse groups to venlafaxine

Gene	SNP ID	Allele frequency		OR (95% CI)	χ^2	P-value ^a	Genotype frequency		χ^2	P-value ^a	HWE
		C	T				C/T	T/T			
GSK3 β	rs4624596	Response	138 (0.472)	154 (0.527)	1.373 (0.779–2.419)	0.270	84 (0.575)	35 (0.239)	4.076	0.130	0.176
		Nonresponse	32 (0.551)	26 (0.448)			12 (0.413)	7 (0.241)			
	rs182839	Response	274 (0.938)	18 (0.061)	0.886 (0.288–2.723)	0.833	129 (0.883)	1 (0.006)	0.381	0.826	0.816
		Nonresponse	54 (0.931)	4 (0.068)			25 (0.862)	0 (0)			
rs334533	Response	159 (0.544)	133 (0.455)	1.589 (0.882–2.862)	0.120	39 (0.267)	26 (0.178)	3.804	0.149	0.359	
	Nonresponse	38 (0.655)	20 (0.344)			13 (0.448)	4 (0.137)				12 (0.413)
rs11925868	Response	267 (0.914)	25 (0.085)	1.264 (0.422–3.779)	0.674	122 (0.835)	23 (0.157)	0.279	0.869	0.997	
	Nonresponse	54 (0.931)	4 (0.068)			25 (0.862)	4 (0.137)				0 (0)
rs16830730	Response	166 (0.568)	126 (0.431)	0.871 (0.495–1.534)	0.633	53 (0.363)	33 (0.226)	0.295	0.862	0.145	
	Nonresponse	31 (0.534)	27 (0.465)			9 (0.31)	7 (0.241)				13 (0.448)
BDNF	rs925946	Response	281 (0.962)	11 (0.037)	1.096 (0.236–5.08)	0.906	135 (0.924)	11 (0.075)	0.014	0.904	0.897
		Nonresponse	56 (0.965)	2 (0.034)			27 (0.931)	2 (0.068)			
rs7124442	Response	276 (0.945)	16 (0.054)	0.782 (0.251–2.431)	0.671	131 (0.897)	14 (0.095)	0.647	0.723	0.668	
	Nonresponse	54 (0.931)	4 (0.068)			25 (0.862)	4 (0.137)				0 (0)
rs6265	Response	139 (0.476)	153 (0.523)	1.179 (0.671–2.072)	0.566	34 (0.232)	41 (0.28)	2.012	0.365	0.954	
	Nonresponse	30 (0.517)	28 (0.482)			6 (0.206)	5 (0.172)				18 (0.62)
rs908867	Response	286 (0.979)	6 (0.02)	0.587 (0.115–2.985)	0.516	140 (0.958)	6 (0.041)	0.430	0.511	0.959	
	Nonresponse	56 (0.965)	2 (0.034)			27 (0.931)	2 (0.068)				2 (0.068)

Note: ^aPearson's P-value.

Abbreviations: HWE, Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism.

Neuropsychiatric Disease and Treatment

Dovepress

Publish your work in this journal

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the 'PsycINFO' database and CAS,

and is the official journal of The International Neuropsychiatric Association (INA). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal>