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RAPID COMMUNICATION

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

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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]

[1]Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders (Ministry of Education), Shanghai Jiao Tong University, Shanghai 200030, P.R. China; [2]Shanghai Key Laboratory of Psychotic Disorders, Shanghai Institute of Mental Health, Shanghai Jiao Tong University, Shanghai 200030, P.R. China; [3]Institute 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-3β* 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-3β* and *BDNF* may not be associated with treatment response in MDD patients treated with venlafaxine.

Keywords: association, *GSK-3β*, *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-3β (*GSK-3β*) 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-3β*.[4] However, pharmacogenetic studies of *GSK-3β* and *BDNF* genes with antidepressant response are controversial in the literature.[5–8] Therefore, we attempted to investigate whether *GSK-3β* 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 (HAMD) 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

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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-3β* and four SNPs (downstream: rs925946; 3′ UTR: rs7124442; exon: rs6265; promoter: rs908867) in *BDNF* gene based on the literature10,11 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-3β* 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.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Genotype and allele distributions of *GSK3β* 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
GSK3β	rs4624596		C	T				C/T	T/T	C/C			
		Response	138 (0.472)	154 (0.527)	1.373 (0.779–2.419)	1.212	0.270	84 (0.575)	35 (0.239)	27 (0.184)	4.076	0.130	0.176
		Nonresponse	32 (0.551)	26 (0.448)				12 (0.413)	7 (0.241)	10 (0.344)			0.678
	rs182839		A	G				A/A	G/G	A/G			
		Response	274 (0.938)	18 (0.061)	0.886 (0.288–2.723)	0.044	0.833	129 (0.883)	1 (0.006)	16 (0.109)	0.381	0.826	0.816
		Nonresponse	54 (0.931)	4 (0.068)				25 (0.862)	0 (0)	4 (0.137)			0.923
	rs334533		A	G				A/A	G/G	A/G			
		Response	159 (0.544)	133 (0.455)	1.589 (0.882–2.862)	2.407	0.120	39 (0.267)	26 (0.178)	81 (0.554)	3.804	0.149	0.359
		Nonresponse	38 (0.655)	20 (0.344)				13 (0.448)	4 (0.137)	12 (0.413)			0.902
	rs11925868		C	A				C/C	C/A	A/A			
		Response	267 (0.914)	25 (0.085)	1.264 (0.422–3.779)	0.176	0.674	122 (0.835)	23 (0.157)	1 (0.006)	0.279	0.869	0.997
		Nonresponse	54 (0.931)	4 (0.068)				25 (0.862)	4 (0.137)	0 (0)			0.923
	rs16830730		G	A				G/G	A/A	A/G			
		Response	166 (0.568)	126 (0.431)	0.871 (0.495–1.534)	0.227	0.633	53 (0.363)	33 (0.226)	60 (0.41)	0.295	0.862	0.145
		Nonresponse	31 (0.534)	27 (0.465)				9 (0.31)	7 (0.241)	13 (0.448)			0.867
BDNF	rs925946		G	T				G/G		T/G			
		Response	281 (0.962)	11 (0.037)	1.096 (0.236–5.08)	0.013	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)			0.96
	rs7124442		T	C				T/T	C/T	C/C			
		Response	276 (0.945)	16 (0.054)	0.782 (0.251–2.431)	0.180	0.671	131 (0.897)	14 (0.095)	1 (0.006)	0.647	0.723	0.668
		Nonresponse	54 (0.931)	4 (0.068)				25 (0.862)	4 (0.137)	0 (0)			0.923
	rs6265		G	A				G/G	A/A	A/G			
		Response	139 (0.476)	153 (0.523)	1.179 (0.671–2.072)	0.329	0.566	34 (0.232)	41 (0.28)	71 (0.486)	2.012	0.365	0.954
		Nonresponse	30 (0.517)	28 (0.482)				6 (0.206)	5 (0.172)	18 (0.62)			0.425
	rs908867		G	A				G/G		A/G			
		Response	286 (0.979)	6 (0.02)	0.587 (0.115–2.985)	0.420	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)			0.960

Note: [a]Pearson's *P*-value.

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