Research Paper

Brain-derived Neurotrophic Factor's Val66Met and C270T Polymorphisms Influence Citalopram/ Escitalopram Response in Chinese Patients with Major Depressive Disorder

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The aim of this study was to investigate the association between two brain-derived neurotrophic factor polymorphisms (Val66Met and C270T) and response to citalopram/escitalopram treatment. Chinese patients who met diagnostic and Statistical Manual of Mental Disorders criteria for major depressive disorder (n=180) were prescribed citalopram/escitalopram for 6 weeks. Depression severity was evaluated using the 17-item Hamilton rating scale for depression at baseline and week 2, 4, and 6 of treatment. The expression quantitative trait loci analysis was performed to investigate the functional effect of Val66Met and C270T on brain-derived neurotrophic factor expression in the brain and blood. A significant difference was found in genotype (χ^2=6.979, p=0.031, correction p=0.062) but not allele (p>0.05) frequencies of Val66Met between responders and non-responders. Homozygous GG showed a higher response than other two genotypes (χ^2=5.218, p=0.022, correction p=0.044). In addition, the C allele and CC genotype of C270T were significantly related to higher remission over 6 weeks among females (C/T, p=0.027, correction p=0.054; CC/TT, p=0.023, correction p=0.046) and first-episode major depressive disorder patients (C/T, p=0.023, correction p=0.046; CC/TT, χ^2= 6.870, p=0.009, correction p=0.018). Further expression quantitative trait loci analysis showed that Val66Met and C270T have functional effect on brain-derived neurotrophic factor expression in the brain. Brain-derived neurotrophic factor Val66Met and C270T polymorphisms were associated with therapeutic response to citalopram/escitalopram in Chinese major depressive disorder patients.

Key words: Brain-derived neurotrophic factor, Val66Met, C270T, polymorphism, depression, antidepressant

Antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenergic reuptake inhibitors, noradrenergic and specific serotonergic antidepressants are a primary treatment for major depression disorder (MDD). However, only about two thirds of MDD patients achieve remission after undergoing up to several cycles of antidepressant treatment, with one-third of patients showing no response[1]. Genetic variations are thought to contribute to the variable responses to antidepressants[2], which was also supported by a genome-wide association study[3]. As such, identifying single nucleotide polymorphisms (SNPs) associated with treatment resistance can potentially predict patient treatment outcome.

Brain-derived neurotrophic factor (BDNF) is a neurotrophin associated with response to antidepressants in MDD[4]. It is widely expressed in the brain, especially in the hippocampus and cortex[5]. Not only can BDNF promote differentiation and survival in peripheral and central neurons, but also regulate brain maturation, synaptic plasticity, and axon outgrowth[6]. Evidence from animal models[7], neuronal cultures[8], and clinical[9,10] and post-mortem[11] studies have

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shown that BDNF expression is dysregulated in MDD patients, which can be reversed by antidepressant treatment. It is believed that BDNF interacts with the 5-hydroxytryptamine neurotransmitter system to modulate the response to antidepressants[12,13].

The BDNF gene, with 11 exons and located on chromosome 11p31, is a vital candidate for the mechanism of action of antidepressants[14]. Val66Met (rs6265, G>A) is a most frequently investigated polymorphism of BDNF and the G to A exchange leads to the valine-to-methionine change at position 66. Evidence has shown that this polymorphism is implicated in activity-dependent secretion[15], blood levels of BDNF[16] and antidepressant response[17]. Citalopram and escitalopram are widely prescribed SSRIs, highly efficacious to treat depression[18]. However, the relationship between Val66Met and citalopram/escitalopram response is inconsistent. For example, two findings showed Met allele carriers of Val66Met responded better to citalopram and escitalopram[19,20]; whereas, another study found no association between Val66Met and treatment response to escitalopram[21]. Thus, whether Val66Met is associated with citalopram/escitalopram response hasn't been confirmed yet.

The C270T polymorphism (rs56164415, C>T) is located in the 5' untranslated region of BDNF and may affect transcription efficiency and protein expression[22]. C270T has been linked to increased susceptibility to schizophrenia[23], Parkinson's disease[24], and autism[25]. Huuhka *et al*. found no association between C270T polymorphism and response to electroconvulsive therapy (ECT) in Caucasians; however, the CC genotype of C270T predicted good response in psychotic and late onset subtypes of depression[26]. To date, there have been no studies investigating the association between C270T and response to antidepressant drug treatment. Therefore, the purpose of this study was to explore the association between C270T and Val66Met of the BDNF gene and response to citalopram/escitalopram in Chinese population with MDD.

MATERIALS AND METHODS

Subjects:

Unrelated Chinese patients (n=180) with MDD were recruited at the Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, China. For pharmacogenetic analyses, only patients with a treatment cycle of at least 4 w from baseline were included (n=147). All patients were assessed by trained psychiatrists using the structured clinical interview for DSM-IV Axis I disorders. The inclusion criteria were as follows: 1) age between 18 and 65 y; 2) at least moderately severe depression and a total score on the 17-item Hamilton rating scale for depression (HAMD-17) of 18 or higher; 3) physical, laboratory, and electrocardiogram examinations showing no other clinically significant abnormalities. Exclusion criteria were as follows: 1) patients with bipolar, psychotic, or anxiety disorder, mental retardation, or disease related to alcohol or drug abuse; 2) patients with neurological or any other general disorders; 3) patients who were pregnant or breastfeeding; 4) at serious risk of suicide or with drug allergies; 5) patients taking monoamine oxidase inhibitors within the 4-w period prior to the start of the study. Patients were provided written, informed consent for their participation in the study. The ethics committee of Shanghai Mental Health Center and Huashan hospital (Shanghai, China) approved the protocol.

Treatment:

A total of 147 patients were treated with citalopram (n=58) and escitalopram (n=89) for 6 w. Drugs were given as monotherapy in patients. All patients had a medication washout for a minimum of 5 half-lives of all current psychotropic medications. Patients were treated with citalopram at a dose of 20 mg/d and escitalopram at a dose of 10 mg/d for the first 2 w. Psychiatrists adjusted the dosage according to the improvement of symptoms; if these had improved at w 2, then patients continued taking the initial dose of these drugs, but the dose was doubled for patients who showed no response to the drugs or exacerbation of depressive symptoms. Dosage modification was not allowed after 4 w. No other medications including antipsychotics, anxiolytics, or other antidepressants were allowed during the study, except for medication to treat insomnia (no more than 1 w) such as zolpidem, zopiclone, or clonazepam.

Clinical assessment:

Clinical symptoms were evaluated at baseline (w 0) and at w 2, 4, and 6 with the HAMD-17, Hamilton anxiety rating scale, and the Clinical Global Impression scale. Responders were defined as patients exhibiting a decrease in HAMD-17 total scores of at least 50 % at the end of w 6, and remitters were defined as those with scores less than 8. Patients who did not satisfy

these criteria were defined as non-responders and non-remitters, respectively.

DNA sequencing:

Genomic DNA from peripheral blood samples was phenol-chloroform extracted and purified. Genetic variations in the BDNF gene were genotyped by DNA sequencing. Fragments containing polymorphisms were amplified with the following forward and reverse primer sets: Val66Met, 5'-GAGTGATGACCATCCTTTTCCT-3' and 5'-CCTCATGGACATGTTTGCAG-3'; and C270T, 5'-ATTCCTGCAAAGGACCATGT-3' and 5'-TGTGGCCCATCTGATTGTAA-3'. PCR products were sequenced using a BigDye Terminator v1.1 Cycle Sequencing kit (Applied Biosystem) in a 5-µl reaction consisting of 1 µl purified PCR product (10 ng/µl), 0.5 µl of 2.5×BigDye, 0.15 µl of 5×BigDye buffer, 1 µl primer (3.2 pmol/µl), and 2.35 µl of sterilized deionized water. Reactions were run on an ABI 3730 sequencer (Applied Biosystems, Foster City, CA, USA). Twenty samples were randomly selected for duplicate detection to verify and quality of the results.

eQTLs datasets:

In order to explore the functional effects of Val66Met and C270T on the expression of the BDNF gene across different brain regions, a gene expression analyses was conducted using data from the BRAINEA (http://braineac.org). This dataset includes 10 brain regions from 134 neuropathologically normal individuals of European descent[27]. In addition, blood eQTL browser (https://molgenis58.target.rug.nl/bloodeqtlbrowser/) was used to understand the effects of these two SNPs on the expression of the BDNF in whole blood[28]. This resource contains the results of an eQTL meta-analysis from 5311 peripheral blood samples from 7 studies.

Statistical analysis:

Categorical variables of demographic data are presented as percent (%) frequency and were analyzed with the χ^2 test. Continuous variables of demographic data are expressed as mean±standard deviation and were evaluated with the Student's t test. Hardy-Weinberg equilibrium for genotype frequencies in patients was determined with the χ^2 test. Allele and genotype distributions for Val66Met and C270T were compared between remitters and non-remitters and between responders and non-responders with the χ^2 test. The haplotype analysis was performed on the SHEsis online software (http://analysis2.bio-x.cn/myAnalysis.php). The pharmacogenetic analysis of Val66Met and C270T variant effects on HAMD-17 total and change scores over the 6 w of antidepressant treatment was carried out with an overall repeated-measures analysis of variance (with genotype as the fixed factor and weeks as repeated measure). Age, gender, first episode or recurrence, recent episode (month), total course (month), BMI and drug categories were included as covariates. All statistical analyses were performed using SPSS v.19.0 software (SPSS Inc., Chicago, IL, USA). The level of statistical significance was assumed at $p<0.05$ (two-sided test). Bonferroni correction was performed by multiplying the p values by the number of SNPs.

RESULTS AND DISCUSSION

According to HAMD-17 scores at 6 w, 147 patients were divided into remitter (n=81, HAMD<8) and non-remitter (n=66, HAMD≥8) groups, and responder (n=123, decreased rate of HAMD-17≥50 %) and non-responder (n=24, decreased rate of HAMD-17< 50 %) groups. The demographic data are summarized in Table 1. There were no differences in age, duration of the current episode of depression, duration of illness, BMI, first/recurrent episode, and dosage of citalopram/escitalopram. There were no sex differences between remitters and non-remitters, but a difference was observed between responders and non-responders (p=0.047), with the former comprising mostly females.

The two SNPs were in Hardy-Weinberg equilibrium. The allele and genotype frequencies of the two polymorphisms are shown in Table 2. There was a significant association in genotype frequencies (χ^2=6.979, p=0.031, correction p=0.062) not in allele frequencies (p>0.05) of Val66Met between responders and non-responders. For further analysis, homozygous GG exhibited a higher response to genotypes with A (GA and AA; χ^2=5.218, p=0.022, correction p=0.044). There were no differences in allele or genotype frequencies of Val66Met between remitters and non-remitters. For C270T, there were no differences in allele and genotype frequencies between remitters and non-remitters or between responders and non-responders (p>0.05).

With frequencies >0.03 in our population, the two SNPs generated 4 common haplotypes with remission status and 3 haplotypes with response status. However, no haplotypes showed significant associations with remission and response status after antidepressant treatment in patients with MDD (all p>0.05).

TABLE 1: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

Characteristics	Overall (n=147)	Remitter (n=81)	Non-remitter (n=66)	p	Responder (n=123)	Non-responder (n=24)	p
Sex: male	59 (40.1 %)	28 (34.6 %)	31 (47.0 %)	0.127	45 (36.6 %)	14 (58.3 %)	0.047*
Female	88 (59.9 %)	53 (65.4 %)	35 (53.0 %)		78 (63.4 %)	10 (41.7 %)	
Age (year)	38.41±13.39	36.78±13.60	40.41±12.94	0.102	38.54±13.58	37.75±12.58	0.793
Duration of current episode (month)	5.97±8.75	6.35±9.29	5.49±8.08	0.552	5.99±9.14	5.83±6.57	0.936
Duration of illness (month)	47.21±72.88	49.88±66.60	43.93±80.32	0.624	44.10±61.08	63.13±116.66	0.243
BMI	22.21±2.98	21.83±2.72	22.68±3.23	0.083	22.12±2.88	22.68±3.45	0.402
First episode	63 (42.9 %)	34 (42.0 %)	29 (43.9 %)	0.811	53 (43.1 %)	10 (41.7 %)	0.897
Recurrence	84 (57.1 %)	47 (58.0 %)	37 (56.1 %)		70 (56.9 %)	14 (58.3 %)	
Dose (mg/day, 2-6 w)							
Citalopram		27.41±9.84	26.45±9.50	0.709	26.80±9.57	27.50±10.35	0.850
Escitalopram		14.81±5.04	14.57±5.05	0.825	15.07±5.03	13.13±4.79	0.162

*P<0.05, the difference is statistically significant

TABLE 2: THE GENOTYPE AND ALLELE ANALYSIS OF SNPs WITH RESPONSE AND REMISSION STATUS

	Genotype			x^2	p	Allele		x^2	p
Val66Met	GG	GA	AA			G	A		
Remitter (n=81)	20	49	12	1.549	0.461	89	73	1.214	0.271
Non-remitter (n=66)	12	40	14			64	68		
Response (n=123)	31	69	23	6.979	**0.031***	131	115	0.886	0.347
Non-response (n=24)	1	20	3			22	26		
C270T	CC		CT			C	T		
Remitter (n=81)	71		10	2.093	0.148	152	10	1.907	0.167
Non-remitter (n=66)	52		14			118	14		
Response (n=123)	102		21	0.064	0.801	225	21	0.058	0.809
Non-response (n=24)	21		3			45	3		

*P<0.05, the difference is statistically significant

For the subgroup analysis, the 147 patients were divided according to sex (male, n=59 and female, n=88). The results are shown in Table 3. Among females, the C allele and CC genotype of C270T were significantly related to higher remission over 6 w (C/T, p=0.027, correction p=0.054; CC/TT, p=0.023, correction p=0.046). A significant association for Val66Met genotypes in females but not in males was noted between responders and non-responders (χ^2=7.057, p=0.029, correction p=0.058), and females who were homozygous (GG+AA) showed a better response than those who were heterozygous (GA; p=0.040, correction p=0.080).

Patients were divided into first-episode (n=63) and recurrent-episode (n=84) groups according to the number of depression episodes (Table 3). The C-allele and CC genotype of C270T were related to higher remission over 6 w in first-episode patients (C/T, p=0.023, correction p=0.046; CC/TT, χ^2=6.870, p=0.009, correction p=0.018). Among recurrent-episode patients, a significant association was found across the three genotypes of Val66Met between responders and non-responders (χ^2=10.312, p=0.006, correction p=0.012), and recurrent patients who were homozygous (GG+AA) showed a better response than those who were heterozygous (GA; χ^2=7.277, p=0.007, correction p=0.014). There were no differences in other subgroups for Val66Met and C270T between remitters and non-remitters or between responders and non-responders.

There were no differences in HAMD-17 raw scores over 6 w across Val66Met genotypes (all p>0.05; fig. 1A). However, a trend in HAMD-17 change scores over 6 w was observed across Val66Met genotypes (GG>GA>AA; fig. 1B). In addition, there were no differences across C270T genotypes in raw or change HAMD-17 scores over time (p>0.05). In analyses stratified by gender and depression status, there were no differences in HAMD-17 total or change scores across genotypes of Val66Met and C270T (all p>0.05).

Using BRAINEAC data, we found that Val66Met genotypes differentially affect BDNF gene expression

within the frontal cortex (p=0.045, correction p=0.090) and the occipital cortex (p=0.016, correction p=0.032; fig. 2A). In these regions, individuals with the GG genotype show significantly lower expression of BDNF. In addition, it was also found that C270T genotypes differentially affect BDNF gene expression within the cerebellar cortex (p=0.041, correction p=0.082). Individuals with the GG genotype show significantly higher expression of BDNF than other two genotypes (AA+GA; fig. 2B). The Val66Met was also identified as eQTLs for BDNF (p=0.0014, correction p=0.0028) using blood eQTL browser, however, the Z-score of –3.21 indicated that the G allele was associated with higher BDNF expression in the blood opposite to what we found using BRAINEAC (fig. 2B). The C270T across BDNF was not cis-eQTLs in this database.

In this study, it was found that BDNF Val66Met and C270T polymorphisms were associated with the therapeutic response to citalopram/escitalopram in Chinese patients with MDD. To our knowledge, this is the first study to investigate the association between C270T and response to antidepressant drug treatment.

Val66Met is a functional non-synonymous single nucleotide polymorphism that has been extensively investigated in the context of various antidepressants,

TABLE 3: SUBGROUP ANALYSIS OF SNPs WITH RESPONSE AND REMISSION STATUS

		Val66Met					C270T			
		GG	GA	AA	x^2	p	CC	CT	x^2	p
Male (n=59)	remitters	8	18	2	2.744	0.254	21	7	0.273	0.601
	non-remitters	5	20	6			25	6		
	responders	12	27	6	2.880	0.237	34	11	-	0.713[a]
	non-responders	1	11	2			12	2		
Female (n=88)	remitters	12	31	10	0.239	0.887	50	3	-	**0.023***[,a]
	non-remitters	7	20	8			27	8		
	responders	19	42	17	7.057	**0.029***	68	10	-	1.000[a]
	non-responders	0	9	1			9	1		
First episode (n=63)	remitters	9	22	3	2.804	0.246	32	2	6.870	**0.009***
	non-remitters	6	16	7			20	9		
	responders	14	31	8	1.470	0.480	43	10	-	0.676[a]
	non-responders	1	7	2			9	1		
Recurrence (n=84)	remitters	11	27	9	0.717	0.699	39	8	0.195	0.659
	non-remitters	6	24	7			32	5		
	responders	17	38	15	10.312	**0.006***	59	11	-	1.000[a]
	non-responders	0	13	1			12	2		

[a]Fisher's exact test; *p<0.05, the difference is statistically significant

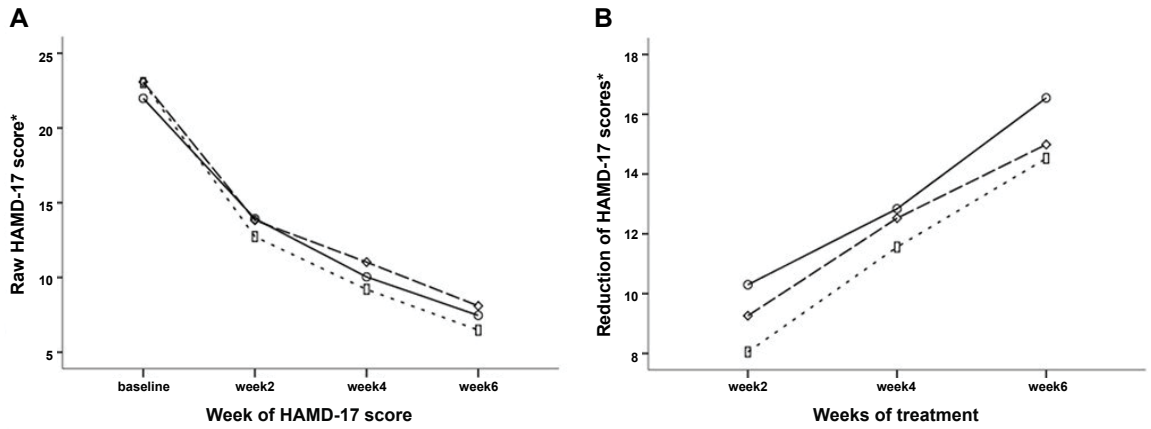

Fig. 1: Raw HAMD-17 scores and reduction scores for antidepressant treatment

Scores for antidepressant treatment across BDNF Val66Met genotypes in 147 patients with MDD at baseline and weeks 2, 4, and 6. '*' Adjusted for age, sex, first episode or recurrence, recent episode (month), total course (month), BMI, and drug type. A: Raw HAMD-17 scores across Val66Met genotypes, ——— AA, ---- GA, ···· GG. B: Reduction HAMD-17 scores across Val66Met genotypes; ···· AA, ---- GA, ——— GG

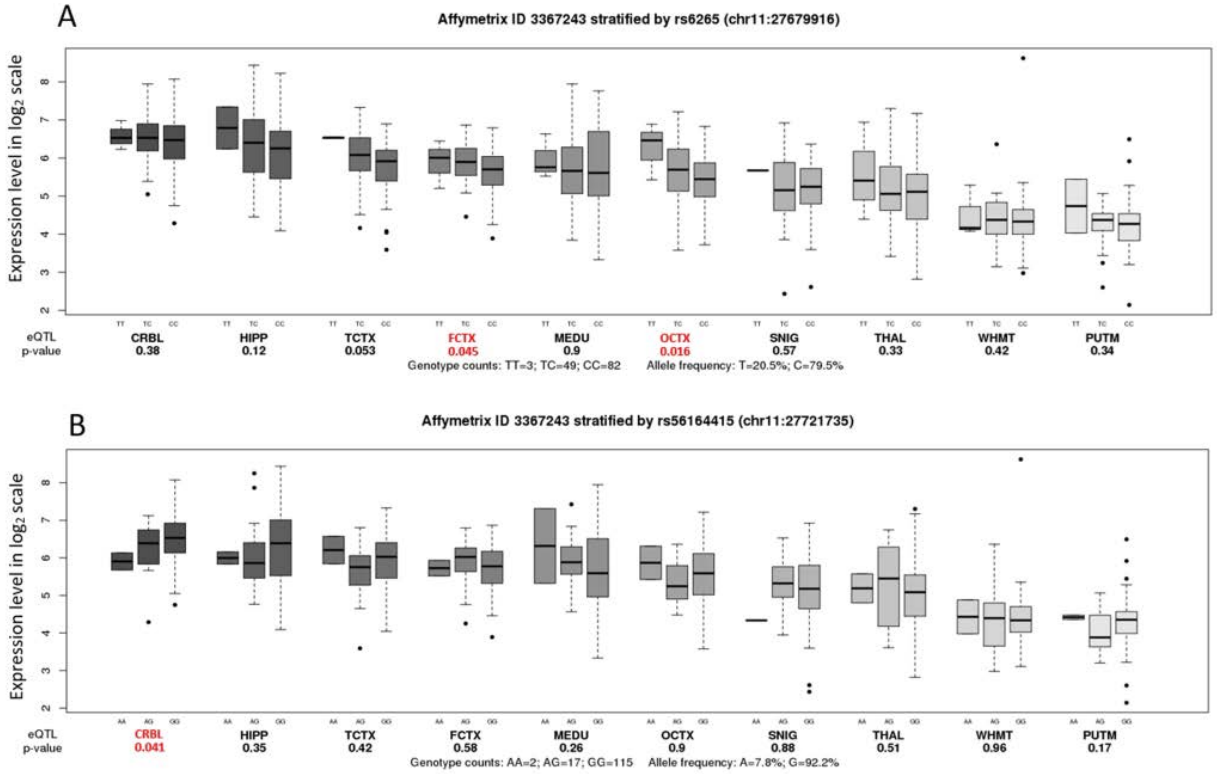

Fig. 2: Association of rs6265 (Val66Met) and rs56164415 (C270T) with BDNF mRNA expression levels in ten brain regions
A. Affymetrix ID 3367243 stratified by rs6265; B. Affymetrix ID 3367243 stratified by rs56164415. Data were extracted from the BRAINEAC database. CRBL- cerebellar cortex, HIPP- hippocampus, TCTX- temporal cortex, FCTX- frontal cortex, MEDU- the inferior olivary nucleus (sub dissected from the medulla), OCTX- occipital cortex, SNIG- substantia nigra, THAL- thalamus at the level of the lateral geniculate nucleus, WHMT- intralobular white matter and PUTM- putamen at the level of the anterior commissure

including fluoxetine[14], mirtazapine[16], and venlafaxine[29]. Several studies have examined the association between Val66Met with citalopram/escitalopram, but the results are inconsistent. An imaging study found that Met (A) allele carriers of BDNF Val66Met had lower fractional anisotropy values in the left uncinate fasciculus relative to Val/Val (GG) individuals, reflecting a lower percent change of depression severity after 8 w of treatment with citalopram or quetiapine XR[30]. Lanctôt *et al.* found GG homozygotes of the BDNF polymorphism showed a greater percent change of HAMD-17 scores in response to citalopram treatment[31]. In this study, it was found that patients who were homozygous GG carriers of Val66Met showed a positive association with response as compared to genotypes with A (GA and AA). Thus, the results of our study are consistent with these previous findings. In addition, clinical reports[32] and animal experiments[33] have shown that the Met/Met (AA) genotype was associated with worse response to fluoxetine, which is an SSRI like citalopram/escitalopram. These findings confirm that the GG genotype is linked to better response to citalopram/escitalopram.

Some studies found no association between Val66Met and response to antidepressant treatment or even the opposite trends. For instance, Choi *et al.* found M allele carriers responded better to citalopram treatment in a Korean population[20], which may indicate ethnic differences. Moreover, Alexopoulos *et al*. found depressed older Caucasian BDNF Met carriers had a higher remission rate than Val/Val (GG) homozygotes after 12 w of treatment with escitalopram[19]. Similarly, Kang *et al.* found patients carrying the Met allele (A) who were treated with escitalopram had a higher rate of remission than non-carriers[34]. The reasons for these different findings may be that the former study population consisted of geriatric depression patients, whereas the latter included MDD patients with acute coronary syndrome. In addition, another study has reported that polymorphisms of the BDNF gene are not associated with the response to escitalopram[21]; this may be due to the relatively small sample size in this study.

In the present investigation it was found that homozygous (GG+AA) of Val66Met showed a better response to citalopram/escitalopram than

those who were heterozygous (GA) among females and recurrent MDD patients. A meta-analysis has demonstrated that the BDNF gene influences MDD in a gender-specific way, and the level of gender differences in gene environment interaction, of sexual dimorphism of the hippocampus, or of gender-related differences in symptoms of depression may explain this phenomenon[35]. Other studies have showed that Val66Met polymorphism interacted with gender to influence the serum BDNF level[36], cortisol responses to mental stress[37], or bimanual motor control in healthy humans[38]. The reason why the Val66Met homozygous among females and recurrent MDD patients exhibited a better response to antidepressant than the heterozygous patients, need further exploration.

The association between C270T and antidepressant treatment response had not been previously reported. In our study, for the first time, we found that the C allele and CC genotypes of C270T were significantly associated with higher remission in females and in first-episode MDD patients. A previous study reported no relationship between C270T polymorphism and response to ECT in MDD patients, however, the CC genotype of C270T could predict good response within psychotic and late-onset depression subgroups[26]. It was consistent with our findings in a sense. In another study, Zhang *et al*. found no association between C270T genotypes and paroxetine treatment after 8 w in Alzheimer's disease-related depression, a possible explanation for such discrepancy was disease characteristics[39]. Moreover, the frequency of the T allele was quite low and the minor allele frequency was 0.03 for Chinese, indicating the possibility of type II error due to a lack of statistical power[40]. Thus, further studies were required to verify the results.

We found that the Val66Met was identified as eQTLs for BDNF in both of the brain and blood databases. The conclusions, however, are not consistent. The G allele was associated with higher BDNF expression in the blood opposite to what we found using BRAINEAC. Therefore, this SNP is cis-eQTLs for BDNF, but there appears to be tissue-specific directionality of associations with the SNP. In addition, we found individuals with the CC genotype of C270T show significantly higher expression of BDNF than do either those with the CT genotype or those with the TT genotype. These results may support that these two SNPs of BDNF may influence its expression.

There were several limitations to our study. First, the sample size didn't derive from calculation and was relatively small, especially for subgroup analyses, which limits the generalizability of the findings. Second, only Chinese participants were included into this study for ethnic homogeneity. Various frequencies of Val66Met and C270T polymorphisms in other ethnic populations should be taken into consideration when evaluating antidepressant efficacy. Third, several positive findings are modest and cannot survive after correction for multiple comparisons. Fourth, further studies were not performed to verify our findings. Thus, the datum is not replicated at any level of outcome and not graduated for the different genotypes, which makes it less clearly interpretable. Moreover, there were no available blood concentrations of citalopram/escitalopram in our study. Finally, some confounding factors were not considered in the study including dietary habits, lifestyle, social support, and economic conditions that may have influenced the response to antidepressant treatment.

In conclusion, the present study found that BDNF Val66Met and C270T polymorphisms were associated with the antidepressant treatment and may predict the response to citalopram/escitalopram in MDD patients in the Chinese population. These findings could help to devise a personalized treatment strategy prior to antidepressant treatment. Confirmation of these findings across other populations and exploration of the BDNF polymorphisms effect in pharmacogenetics may lead to novel strategies in the development of antidepressants.

Conflict of interest:

The authors declare no conflict of interest.

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