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GRIK4 and *GRM7* gene may be potential indicator of venlafaxine treatment reponses in Chinese of Han ethnicity

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Abstract

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

By using 193 MDD patients who have been taking venlafaxine for 6 weeks, we investigated whether single nucleotide polymorphisms (SNPs) in glutamate ionotropic receptor kainate type subunit 4 (*GRIK4*), glutamate ionotropic receptor AMPA type subunit 1 (*GRIA1*) and glutamate metabotropic receptor 7 (*GRM7*) were associated with treatment response. 14 SNPs were selected randomly depended on association studies. Efficacy of treatment was determined by 17-item of Hamilton Rating Scale. Allele and genotype frequencies were compared between responders and non-responders.

After adjusting by the false discovery rate (FDR), rs6589847 and rs56275759 in *GRIK4* and rs9870680 in *GRM7* showed associating with venlafaxine treatment response at week 6. (FDR: $P = .018$, $P = .042$, and $P = .040$, respectively).

Our results indicated that genetic variants in the *GRIK4* and *GRM7* may associate with the treatment response in MDD patients treated by venlafaxine.

Abbreviations: AIC = Akaike information criterion, FDR = false discovery rate, *GRIA1* = glutamate ionotropic receptor AMPA type subunit 1, *GRIK4* = glutamate ionotropic receptor kainate type subunit 4, *GRM7* = glutamate metabotropic receptor 7, GWAS = genome-wide association study, HAMD = Hamilton Rating Scale for Depression, LD = linkage disequilibrium, MDD = major depressive disorder, PCR = polymerase chain reaction, SNPs = single nucleotide polymorphisms, SNRIs = serotonin and norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitor, STAR*D = Treatment Alternatives to Relieve Depression.

Keywords: *GRIA1*, *GRIK4*, *GRM7*, major depressive disorder, response, venlafaxine

1. Introduction

Major depressive disorder (MDD), a common debilitating psychiatric disorder, affects 10% to 15% of population annually in global.[1–3] Antidepressants, classified by slightly different mechanisms of pharmacological actions, are most commonly prescribed agents for MDD.[4] According to the study, 30% to 40% of the patients still do not respond to the currently available antidepressants. Moreover, the balance among the efficacy, safety, and tolerability of those drugs are always far from ideal.

The serotonin and norepinephrine reuptake inhibitors (SNRIs) venlafaxine is one of the available first-line antidepressant medications in many countries.[5] Venlafaxine has sorts of

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advantages such as better tolerance and higher remission rate in MDD compared with selective serotonin reuptake inhibitor (SSRIs) and other antidepressants.[6] A systematic meta-analysis compared with 21 antidepressant drugs for MDD indicated that response and remission rates of venlafaxine are greater than other antidepressants (range of odds ratio [ORs] 1.19–1.96).[4] Although the efficacy of venlafaxine is certain, inconsistent pharmacogenetic studies have led to a renewed focus on the substantially genetic factors in the antidepressant response.[7,8]

Glutamate is a major excitatory neurotransmitter in the central nervous system. MDD patients always show aberrant glutamatergic neurotransmission. This is partially caused by the polymorphism in glutamate receptor genes.[9] Glutamate receptor genes are potential therapeutic targets for MDD, for instance, ketamine, an antagonist of the *N*-methyl-d-aspartate (NMDA) glutamate receptor (GluR), has rapid antidepressant efficacy in clinical application.[10,11] Previous studies indicated that venlafaxine can regulate the expression levels of NMDA receptor genes, such as *GRIN2B*, *GRIN2A,* and *GRIA3*. The upregulation of *GRIA3* gene by venlafaxine in MDD patients is accorded with the theory that SSRIs play a role in the glutamatergic-system.[12] In recent pharmacogenomics investigations, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) demonstrated several glutamate receptor genes (glutamate ionotropic receptor kainate type subunit 4 [*GRIK4]*, *GRIN2A,* and *GRIK1*) showed to associate with citalopram response.[13,14]*GRIA3* and *GRIK2* are associated with treatment-emergent suicidal ideation.[15,16] Otherwise, within up to 6 weeks of treatment with several types of antidepressants, *GRIK4* is not significantly associated with Caucasian MDD patients.[17] The contradictory results rekindled the importance between antidepressant treatment and glutamic system gene variants. However, there are a few pharmacogenetic studies on association of glutamate receptor and venlafaxine antidepressant response in the literature. Therefore, we hypothesized that genetic variants in glutamate receptor genes may influence the antidepressant response[18,19] and we carried out the association study between *GRIK4*, *GAR1A,* and *GMR7* and venlafaxine treatment response in MDD individuals.

2. Materials and methods

2.1. Subjects

The 193 unrelated individuals (aged 18–65 years old), fulfilled with DSM-V (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) criteria for MDD were recruited. The MDD patients had a minimum baseline Hamilton Rating Scale for Depression (HAMD) score at 18 points. Interrater reliability was evaluated by Kappa coefficients (Kappa value = 0.85).[20] 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 all subjects signed the informed consent form.

Participants were first-onset patients. They cannot receive any antidepressant treatment for at least 2 weeks and had no electroconvulsive therapy treatment. Patients with other axis I psychiatric disorders, such as schizophrenia, rapid cycling bipolar disorder, dementia, generalized anxiety disorder, obsessive-compulsive disorder, or substance abuse, and those with axis II disorders (including personality disorders), major medical/neurological disorders, or pregnancy were excluded. All the patients were of unrelated (no blood relationship) Chinese population of Han ethnicity.

2.2. Treatment and Data collection

We used 17-item HAMD to evaluate the severity of symptoms and medication efficacy. All MDD individuals received a 6-week continuous antidepressant treatment. A total dose of 75 to 375 mg per day of venlafaxine were used according to patients' conditions. Then the patients were evaluated at the beginning and later at week 1, 2, 4, and 6 of continuous treatment. Other psychotropic medications were not allowed during the study except an eligible dosage of benzodiazepine for insomnia at bedtime.

Two independent experienced psychiatrists performed the HAMD score and they were blind to patients' genotype. The responders were defined as a no less than 50% reduction of HAMD score at the end of week 6. The reduction of HAMD score less than 50% at the end of week-6 was defined as non-response group. It is reasonable to select the sixth week as the time point to calculate reduction rate since this duration of treatment is thought to be sufficient for an antidepressant drug to show its clinical efficacy.[21]

2.3. Genotyping

Genomic DNA was extracted from venous blood leukocytes using the phenol-chloroform method. Considering that the coverage of a gene and minor allele frequency should be above 0.03, glutamate ionotropic receptor AMPA type subunit 1 (*GRIA1)*, *GRIK4*, and glutamate metabotropic receptor 7 (*GRM7)* gene were selected on the literature[19,22–25] and the NCBI dbSNP database (http://www.ncbi.nlm.nih.gov/SNP) (Table 1). Genotyping of all single nucleotide polymorphisms (SNPs) was performed by a matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometer using the MassARRAY Analyzer 4 platform (Sequenom, CA). All primers were designed by the accompanying software Spectro designer. The polymerase chain reaction (PCRs) were carried out

Table 1

The 14 SNPs in the *GRIK4, GRIA1,* and *GRM7*genes analyzed in this study.

SNP ID*	Gene	Chromosome†	Allele‡	Function
rs79526501	*GRIK4*	120575721	C/G	Upstream
rs4582985	*GRIK4*	120683332	C/G	Intron
rs11218016	*GRIK4*	120824045	A/C/T	Intron
rs6589847	*GRIK4*	120845175	A/G	Intron
rs56275759	*GRIK4*	120858207	C/T	Upstream
rs472792	*GRIA1*	153491624	G/T	Upstream
rs3828595	*GRIA1*	153492161	C/G/T	Upstream
rs478962	*GRIA1*	153527327	C/T	Intron
rs12658202	*GRIA1*	153599994	A/C	Intron
rs812389	*GRIA1*	153603565	A/G	Intron
rs9814881	*GRM7*	7156915	A/C/G	Intron
rs13353402	*GRM7*	7424591	A/G	Intron
rs9870680	*GRM7*	7487868	C/T	Intron
rs1531939	*GRM7*	7575338	C/G	Intron

* According to the dbSNP database.
† The SNP Chromosome positions are based on the NCBI human genome build GRCh38.
‡ The allele under the slash is the minor allele.

in a total volume of 5 μL, with 10 ng genomic DNA, using the cycling conditions recommended by the manufacturer. Detailed information about primers and PCR conditions is available on request. The determination of genotypes was performed by researchers who were blind to the clinical outcome of the antidepressant treatment. The clinical laboratory of the West China Hospital was participants in it.

2.4. Statistical analysis

Differences in demographic between responders and non-responders were calculated by the Student *t* test (age, age onset, body mass index, and HAMD score) or Pearson χ^2 test (gender, marital states, educated, and family history). The SPSS Statistics version 22 and R software (Lucent Technologies, NJ, version 3.2.2.) were used to carry out the above analyses.

The online software SHEsis (http://202.120.31.177/myanalysis.php) was used to analyze allelic and genotypic distributions and pairwise linkage disequilibria (LD).[26] χ^2 test was used to compare the discrepancies of allele and genotype frequencies between responders and non-responders. We used HaploView version 4.2 to estimated LD of all pairs of SNPs with D', which is the standard measurement.[27] Hardy–Weinberg equilibrium (HWE) was calculated on SHEsis. Odd ratios (ORs) and their 95% confidence intervals (CIs) were also figured out. Further analyses of genotype frequency between groups were compared using R in 5 genetic models. The logistic regression analysis was used to test the relationships between variables and treatment outcomes. The lowest Akaike information criterion (AIC) in the 5 model was considered as the best one.[28] The FDR was adjusted to control the procedure by R (version 3.2.2.). FDR is the expected proportion of false discoveries among the discoveries. It can discover more real differences compared with other methods.[29] For all analyses, *P* values were 2 tailed and $P < .05$ means statistical significances.

3. Results

3.1. Demographic

In our study, a total of 193 patients with MDD were recruited, 175 patients completed the 6-week venlafaxine treatment. Detailed information of demographic was listed in Table 2. 146 patients actually responded to venlafaxine treatment in the end of week 6 and the rate was 83.4%. The responders had an end-point value of HAMD of 16.24 ± 5.49. The significant difference cannot be found between responders and non-responders in age, BMI, number of episode, HAMD baseline, family history, educate background, or gender ($P > .05$) except the 6-week HAMD score. Therefore, it is reasonable to conclude that no systematic differences potentially affect clinical outcomes between responders and non-responders.

3.2. Genotype and allele frequencies

None of the SNPs were significantly deviate Hardy–Weinberg equilibrium ($P < .05$) (shown in Table 3). The allele type and genotype of rs6589847 and rs56275759 in *GRIK4* significantly associated with MDD patients after venlafaxine treatment at week 6 (rs6589847: $P = .017$, $P = .016$; rs56275759: $P = .010$, $P = .030$ respectively). Rs11218016 locus within *GRIK4* showed statistical significance in allele distribution ($P = .029$). The genotype of rs9870680 within *GRM7* gene associated with antidepressant treatment ($P = .025$). There were no significant associations in the other genetic variants between responders and non-responders. LD between the 14 markers was conducted between the response and non-response groups. No Strong LD was observed between the 2 groups (data not shown).

Since many variable genetic factors may affect the response to treatment, we further analyzed those positive SNPs. R was used to exam the SNPs in 5 genetic models between response and non-response groups. The results are shown in Table 4. Similar association was found among the polymorphisms. Within

Table 2

Demographic characteristic of all patients.

	Responders n = 146		non-responders n = 29			
Features	**mean**	**SD**	**mean**	**SD**	***t*/χ^2**	***P* value**
Age, yr	35.93	12.81	37.16	12.48	−0.473	.639
Height	165.24	6.95	165.92	8.00	−0.471	.640
Weight	60.97	9.79	61.55	13.09	−2.752	.784
BMI, kg/m^2	22.23	3.15	22.23	4.68	0.011	.991
Age of onset, yr	29.07	14.39	33.88	13.00	−1.669	.104
HAMD baseline	25.31	5.34	24.33	5.08	0.911	.367
HAMD 6 week	16.24	5.49	6.04	3.57	9.614	**.000**
Gender	N	%	N	%	0.000	1.000
Male	70	0.48	14	0.48		
Female	76	0.52	15	0.52		
Family history, %	N	%	N	%	2.828	.093
Yes	23	0.16	9	0.31		
No	123	0.84	20	0.69		
Educated	4.07	1.22	4.16	1.10	2.685	.847
Educated Year	12.55	4.37	12.95	3.85	−0.459	.649
Marital status, %	N	%	N	%	3.569	.468
Never married	49	0.34	13	0.45		
Married	88	0.60	13	0.45		
Divorced or remarried	9	0.06	3	0.10		

Significant *P* ($P < .05$) values are in bold.
SD = standard deviation.

Table 3

Genotype and allele distributions of *GRIA1, GRIK4,* and *GRM7* polymorphisms in responders and non-responders.

Gene	SNP ID	Allele frequency		OR[95%CI]	χ^2	*p*-value	Genotype frequency			χ^2	*P* value	HWE
GRIK4	rs79526501	C	G				C/G	G/G	C/C			
	responder	230 (0.787)	62 (0.212)	1.684[0.759~3.739]	1.673	0.195	52 (0.356)	5 (0.034)	89 (0.609)	1.953	.376	0.736
	non-responder	50 (0.862)	8 (0.137)				8 (0.275)	0 (0)	21 (0.724)			0.689
	rs4582985	C	G				C/G	G/G	C/C			
	responder	127 (0.434)	165 (0.565)	1.016 [0.575~1.794]	0.002	0.956	71 (0.486)	47 (0.321)	28 (0.191)	2.915	.232	0.991
	non-responder	25 (0.431)	33 (0.568)				19 (0.655)	7 (0.241)	3 (0.103)			0.195
	rs11218016	C	T				C/C	C/T	T/T			
	responder	204 (0.698)	88 (0.301)	0.53 [0.298~0.943]	4.754	**0.029**	71 (0.486)	62 (0.424)	13 (0.089)	4.884	.086	0.994
	non-responder	32 (0.551)	26 (0.448)				8 (0.275)	16 (0.551)	5 (0.172)			0.824
	rs6589847	G	A				G/G	G/A	A/A			
	responder	245 (0.839)	47 (0.16)	0.462 [0.242~0.882]	5.654	**0.017**	104 (0.712)	37 (0.253)	5 (0.034)	8.19	**.016**	0.757
	non-responder	41 (0.706)	17 (0.293)				13 (0.448)	15 (0.517)	1 (0.034)			0.409
	rs56275759	C	T				C/C	C/T	T/T			
	responder	149 (0.51)	143 (0.489)	2.138 [1.18~3.875]	6.47	**0.010**	35 (0.239)	79 (0.541)	32 (0.219)	7.006	**.030**	0.607
	non-responder	19 (0.327)	39 (0.672)				2 (0.068)	15 (0.517)	12 (0.413)			0.644
GRIA1	rs472792	T	G				T/T	G/T	G/G			
	responder	258 (0.883)	34 (0.116)	0.823 [0.36~1.884]	0.211	0.645	114 (0.78)	30 (0.205)	2 (0.013)	1.049	.591	0.999
	non-responder	50 (0.862)	8 (0.137)				21 (0.724)	8 (0.275)	0 (0)			0.689
	rs3828595	G	T				G/G	G/T	T/T			
	responder	253 (0.866)	39 (0.133)	2.081 [0.713~6.067]	1.873	0.171	108 (0.739)	37 (0.253)	1 (0.006)	2.052	.358	0.517
	non-responder	54 (0.931)	4 (0.068)				25 (0.862)	4 (0.137)	0 (0)			0.923
	rs478962	C	T				C/C	C/T	T/T			
	responder	249 (0.852)	43 (0.147)	1.496 [0.605~3.699]	0.771	0.379	107 (0.732)	35 (0.239)	4 (0.027)	1.023	.599	0.859
	non-responder	52 (0.896)	6 (0.103)				23 (0.793)	6 (0.206)	0 (0)			0.824
	rs12658202	C	A				C/C	C/A	A/A			
	responder	223 (0.763)	69 (0.236)	1.186 [0.594~2.365]	0.235	0.627	89 (0.609)	45 (0.308)	12 (0.082)	0.849	.653	0.210
	non-responder	46 (0.793)	12 (0.206)				18 (0.62)	10 (0.344)	1 (0.034)			0.963
	rs812389	G	A				G/A	A/A	G/G			
	responder	53 (0.181)	239 (0.818)	1.615 [0.694~3.758]	1.26	0.261	47 (0.321)	96 (0.657)	3 (0.02)	2.679	.261	0.601
	non-responder	7 (0.12)	51 (0.879)				5 (0.172)	23 (0.793)	1 (0.034)			0.600
GRM7	rs9814881	A	G				A/A	G/G	G/A			
	responder	261 (0.893)	31 (0.106)	1.603 [0.543~4.729]	0.743	0.388	118 (0.808)	3 (0.02)	25 (0.171)	0.843	.655	0.497
	non-responder	54 (0.931)	4 (0.068)				25 (0.862)	0 (0)	4 (0.137)			0.923
	rs13353402	G	A				G/G		G/A			
	responder	281 (0.962)	11 (0.037)	NA [NA~NA]	2.255	0.133	135 (0.924)	11 (0.075)	2.331	0.126	.897	
	non-responder	58 (1)	0 (0)				29 (1)		0 (0)			1.000
	rs9870680	C	T				C/T	T/T	C/C			
	responder	69 (0.236)	223 (0.763)	0.635 [0.344~1.17]	2.142	0.143	47 (0.321)	88 (0.602)	11 (0.075)	7.344	**.025**	0.426
	non-responder	19 (0.327)	39 (0.672)				17 (0.586)	11 (0.379)	1 (0.034)			0.204
	rs1531939	C	G				C/G	G/G	C/C			
	responder	66 (0.226)	226 (0.773)	1.119 [0.56~2.236]	0.102	0.749	48 (0.328)	89 (0.609)	9 (0.061)	0.336	.845	0.766
	non-responder	12 (0.206)	46 (0.793)				10 (0.344)	18 (0.62)	1 (0.034)			0.963

Pearson *P* value, significant *P* ($P<.05$) values are in bold.
HWE = Hardy–Weinberg equilibrium, OR = odds ratio.

GRIK4 gene, according to the lowest AIC, rs11218016 in log-Additive genetic model was the best ($P=.031$). Rs6589847 exhibited a stronger significant difference in genotype between responders and non-responders ($P=.006$) in over-dominant genetic model. Rs56275759 polymorphism between them revealed differences genotype distribution ($P=.023$) in codominant model. For the rs9870680 marker in *GMR7*, the analysis between 2 groups showed different genotypes distribution in recessive genetic model ($P=.008$). The genotype of rs6589847, rs56275759, and rs9870680 was still associated with venlafaxine treatment after FDR correction ($P=.018$, $P=.042$, $P=.040$, respectively).

4. Discussion

Our studies investigated the association between genetic variation in glutamatergic receptor genes and response to venlafaxine treatment in MDD patients and found significant associations for SNPs in *GRIK4* and *GMR7*. According to HAMD criteria, as many as 83.4% of patients were positive to treatment response in our study, which was consistent with previous studies.[8,30] The gene and polymorphism were selected based on the research of MDD association studies or other antidepressant treatments.[14,19,22,31] We intended to examine the previous genetic analyses of the MDD treatment cohort.

Glutamate is synthesized in presynaptic neurons and acts via metabotropic and ionotropic receptors. Glutamate level and glutamatergic neurotransmission are abnormal in patients with MDD. [32]Pharmacological compounds that influent the production of glutamate and the expression of its cognate receptors have been proposed as an alternative candidate treatment. The relationship between the glutamate-related genes and treatment response was highlighted by several studies.[33–35]

In *GRIK4* gene, 2 SNPs (rs6589847 and rs56275759) significantly associated with venlafaxine response after correction. The associations between response and non-response groups were confirmed by implementing R to make the results more convincing. To our knowledge, *GRIK4* is one of controversial MDD candidate genes in antidepressant response.[18,35] Previously study proved rs1954787 and rs11218030 were directly associated to both response and remission after treatment resistance in Caucasian sample.[10,18] Pu et al found rs1954787 of *GRIK4* gene were associated antidepressant response in Chinese Han MDD patients.[36] Discovery of polymorphisms in candidate gene seems a milestone, but the repetitions in subsequent studies are difficult to achieve. In Caucasian MDD patients, the analysis of *GRIK4*

Table 4

Logistic regression analysis of associations between the genotypes in rs11218016, rs6589847 rs56275759, and rs9870680 and venlafaxine efficacy in MDD patients.

SNP		responders	non-responders	OR [95% CI]	AIC	*P* value	FDR adjusted
rs11218016	Co-dominant						
	C/C	71 (48.6)	8 (27.6)	1	158.2	.085	0.142
	T/C	62 (42.5)	16 (55.2)	0.44[0.17–1.09]			
	T/T	13 (8.9)	5 (17.2)	0.29[0.08–1.04]			
	Dominant						
	C/C	71 (48.6)	8 (27.6)	1	156.7	.034	0.085
	T/C-T/T	75 (51.4)	21 (72.4)	0.4[0.17–0.97]			
	Recessive						
	C/C-T/C	133 (91.1)	24 (82.8)	1	159.6	.205	0.21
	T/T	13 (8.9)	5 (17.2)	0.47[0.15–1.44]			
	Over-dominant						
	C/C-T/T	84 (57.5)	13 (44.8)	1	159.6	.21	0.21
	T/C	62 (42.5)	16 (55.2)	0.6[0.27–1.34]			
	log-Additive						
	0,1,2	146 (83.4)	29 (16.6)	0.52[0.29–0.94]	156.5	**.031**	0.085
rs6589847	Co-dominant						
	G/G	104 (71.2)	13 (44.8)	1	155.5	.022	0.029
	G/A	37 (25.3)	15 (51.7)	0.31[0.13–0.71]			
	A/A	5 (3.4)	1 (3.4)	0.63[0.07–5.77]			
	Dominant						
	G/G	104 (71.2)	13 (44.8)	1	154	.007	0.018
	G/A-A/A	42 (28.8)	16 (55.2)	0.33[0.15–0.74]			
	Recessive						
	G/G-G/A	141 (96.6)	28 (96.6)	1	161.2	.995	0.995
	A/A	5 (3.4)	1 (3.4)	0.99[0.11–8.83]			
	Over-dominant						
	G/G-A/A	109 (74.7)	14 (48.3)	1	153.7	**.006**	**0.018**
	G/A	37 (25.3)	15 (51.7)	0.32[0.14–0.72]			
	log-Additive						
	0,1,2	146 (83.4)	29 (16.6)	0.46[0.24–0.89]	156	.023	0.029
rs56275759	Co-dominant						
	T/T	32 (21.9)	12 (41.4)	1	155.6	.023	0.038
	C/T	79 (54.1)	15 (51.7)	1.97[0.83–4.68]			
	C/C	35 (24)	2 (6.9)	6.56[1.36–31.6]			
	Dominant						
	T/T	32 (21.9)	12 (41.4)	1	156.7	.034	0.042
	C/T-C/C	144 (78.1)	17 (58.6)	2.51[1.09–5.8]			
	Recessive						
	T/T-C/T	111 (76)	27 (93.1)	1	156	.023	0.042
	C/C	35 (24)	2 (6.9)	4.26[0.96–18.81]			
	Over-dominant						
	T/T-C/C	67 (45.9)	14 (48.3)	1	161.1	.814	0.042
	C/T	79 (54.1)	15 (51.7)	1.1[0.5–2.44]			
	log-Additive						
	0,1,2	146 (83.4)	29 (16.6)	2.31[1.23–4.37]	153.9	**.007**	**0.042**
rs9870680	Co-dominant						
	T/T	88 (60.3)	11 (37.9)	1	156	.029	0.048
	C/T	47 (32.2)	17 (58.6)	0.35[0.15–0.8]			
	C/C	11 (7.5)	1 (3.4)	1.37[0.16–11.69]			
	Dominant						
	T/T	88 (60.3)	11 (37.9)	1	156.3	.027	0.048
	C/T-C/C	58 (39.7)	18 (62.1)	0.4[0.18–0.91]			
	Recessive						
	T/T-C/T	135 (92.5)	28 (96.6)	1	160.4	.39	0.390
	C/C	11 (7.5)	1 (3.4)	2.28[0.28–18.38]			
	Over-dominant						
	T/T-C/C	99 (67.8)	12 (41.4)	1	154.1	**.008**	**0.040**
	C/T	47 (32.2)	17 (58.6)	0.34[0.15–0.76]			
	log-Additive						
	0,1,2	146 (83.4)	29 (16.6)	0.64[0.35–1.18]	159.2	.158	0.198

Significant *P* value ($P<.05$) values are in bold.

AIC = Akaike information criterion, CI = confidence interval, OR = odds ratio.

SNPs was in accord with response or remission within up to 5 or 6 weeks of treatment.[35] Daniel et al investigated the association of *GRIK4* with antidepressant response by meta-analysis. They analyzed 2169 depressed patients and concluded *GRIK4* polymorphism rs1954787 was more likely to respond to antidepressant medications.[37] Two positive SNPs (rs6589847 and rs56275759) found in our study, had not been reported previously, and rs56275759 in *GRIK4* gene was related to MDD in association study.[22] The polymorphisms or *GRIK4* gene can be a candidate of a genetic factor aimed to predict antidepressant response.

Additionally, *GMR7* rs9870680 was significantly associated with antidepressant efficacy in MDD patients receiving drugs. *GRM7*, one of the Group III glutamate metabotropic receptors, is essential in modulating early antidepressant efficacy and antipsychotic response according to previous evidences.[38] The expression of *GRM7* has prominent role in neuronal signaling and maintaining cellular structure in MDD.[31,39] Genome-Wide Association Studies (GWAS) meta-analysis revealed that *GRM7* gene is one of the strong genes for association with MDD. Recent studies highlight the potential role of *GRM7* in risk for depressive symptoms and it also works as a profound therapeutic target.[40,41] A study in Caucasian and African–American MDD patients found that rs1083801 in *GRM7* associated with early response to citalopram. The result was tested in Caucasian, non-Hispanic samples, but the association between rs1083801 and citalopram response was only positive in female after stratification by gender.[42] Though meta-analysis of the GWAS of STAR*D for the MDD phenotype (1221 cases and 1636 controls) did not reveal genome-wide significant findings, the biological evidence suggests that *GRM7* merits further investigation.[31]

Our results cannot provide evidence for association of variations in *GRIA1* antidepressant treatment response. The polymeric markers rs707176 and rs6875572 within *GRIA1* cannot be associated with MDD and antidepressants in Korean in-patients.[19] In addition, evidence showed *GRIA1* associated with orgasm difficulty in Caucasian subjects, who were treated with SSRIs.[43] Since 5 SNPs did not cover all the region of *GRIA1* and the limited sample size, we predicted *GRIA1* gene may not affect venlafaxine response in our study.

Although we found 3 polymorphisms of *GRIK4* and *GRM7* gene associated with venlafaxine treatment in our participants, the result needed to be prudently interpreted. There are some limitations in our study. First, we did not use placebo as normal control as MDD patients are at the risk of suicide. A placebo control would offer a convincing estimation of the response rate and validate the association between the SNPs and venlafaxine treatment. Second, the influence of glutamate receptor gene on regulated response would be clearer if more SNPs detected and larger sample size used in our study. Indeed the demonstration regarding *GRIK4* and *GRM7* gene in antidepressant treatment response may provide a new clue to the mechanism of action of venlafaxine.

5. Conclusion

In summary, our results indicate that rs6589847 and rs56275759 in *GRIK4* and rs9870680 in *GRM7* might associate with venlafaxine treatment responses in the Chinese MDD individuals. No significant associations were observed for the *GRIA1* gene. It is necessary to replicate and verify this possibility with more samples and more ethnics. Despite those limitations, this study may provide a reference for future glutamate-related genes studies, particular in predicting SNRIs responses in population suffering MDD.

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