**GRIK4 and GRM7 gene may be potential indicator of venlafaxine treatment responses 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 based 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, SSRIls = 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...
advantages such as better tolerance and higher remission rate in MDD compared with selective serotonin reuptake inhibitor (SSRIs) and other antidepressants. 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). 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.

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. 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. 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. 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. GRIA3 and GRIK2 are associated with treatment-emergent suicidal ideation. Otherwise, within up to 6 weeks of treatment with several types of antidepressants, GRIK4 is not significantly associated with Caucasian MDD patients. 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 and we carried out the association study between GRIK4, GARI, and GRM7 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). 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.

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 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 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 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.
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 χ² 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/myanalyzer.php) was used to analyze allelic and genotypic distributions and pairwise linkage disequilibria (LD). Hardy–Weinberg equilibrium (HWE) was calculated on SHEsis. Odd ratios (ORs) and their 95% confidence intervals (CIs) were also figured out. Further analysis of genotype frequency between groups were compared using R in 5 genetic models. The logistic regression analysis was used to test the relations and pairwise linkage disequilibria (LD).

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 = .023). There were no significant associations in the other genetic variants between responders and non-responders.

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

| Features               | Responders n=146 | non-responders n=29 | t/χ² | 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 | .007    |
| BMI, kg/m²             | 22.23 ± 3.15     | 22.23 ± 4.68        | 0.011 | .991    |
| Age of onset, yr       | 29.07 ± 14.39    | 23.33 ± 10.00       | -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                 | Male             | 70 ± 0.48           | 14    | 0.000   |
|                        | Female           | 76 ± 0.52           | 15    | 0.52    |
| Family history, %      | 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  | .007    |
| Educated Year          | 12.55 ± 4.37     | 12.95 ± 3.85        | -0.459 | .640    |
| Marital status, %      | 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.
GRK4 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 GRM7, 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 GRK4 and GRM7. 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.[8,10] 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 influence 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 GRK4 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, GRK4 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 GRK4 gene were associated antidepressant response in Chinese Han MDD patients.[16] 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 GRK4

### Table 3

Genotype and allele distributions of GRIA1, GRK4, and GRM7 polymorphisms in responders and non-responders.

| Gene   | SNP ID        | Allele frequency | OR[95%CI] | Genotype frequency | HWE | P value |
|--------|---------------|------------------|-----------|--------------------|-----|---------|
| GRIA1  | rs7525501     | T∥G              | 1.000     |                    |     |         |
|        | responder     | T∥G              | 1.000     |                    |     |         |
|        | non-responder | T∥G              | 1.000     |                    |     |         |
| GRK4   | rs6589847     | T∥G              | 1.000     |                    |     |         |
|        | responder     | T∥G              | 1.000     |                    |     |         |
|        | non-responder | T∥G              | 1.000     |                    |     |         |
|        | rs56275759    | T∥G              | 1.000     |                    |     |         |
|        | responder     | T∥G              | 1.000     |                    |     |         |
|        | non-responder | T∥G              | 1.000     |                    |     |         |
|        | rs9870680     | T∥G              | 1.000     |                    |     |         |
|        | responder     | T∥G              | 1.000     |                    |     |         |
|        | non-responder | T∥G              | 1.000     |                    |     |         |

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

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Table 4
Logistic regression analysis of associations between the genotypes in rs11218016, rs6589847 rs56275759, and rs9870680 and venlafaxine efficacy in MDD patients.

| SNP        | Co-dominant | Dominant | Recessive | Over-dominant | log-Additive |
|------------|-------------|----------|-----------|---------------|--------------|
| rs11218016 |             |          |           |               |              |
| C/C        | 71 (48.6)   | 71 (48.6)| 133 (91.1)| 84 (57.5)     | 146 (83.4)   |
| T/C        | 62 (42.5)   | 75 (51.4)| 13 (8.9)  | 62 (42.5)     | 146 (83.4)   |
| T/T        | 13 (8.9)    | 8 (27.6) | 5 (17.2)  | 5 (17.2)      |              |
| OR [95% CI]| 1           | 0.44     | 1         | 0.47          | 0.52         |
| AIC        | 158.2       | 0.085    | 0.034     | 0.065         | 0.031        |
| P value    | .085        | 0.142    | 0.085     | 0.21          | 0.085        |
| FDR adjusted |            |          |           |               |              |

rs6589847

| Co-dominant | Dominant | Recessive | Over-dominant | log-Additive |
|-------------|----------|-----------|---------------|--------------|
| G/G         | 104 (71.2)| 104 (71.2)| 109 (74.7)    | 146 (83.4)   |
| G/A         | 37 (25.3) | 42 (28.8) | 37 (25.3)     | 146 (83.4)   |
| A/A         | 5 (3.4)   | 5 (3.4)   | 5 (3.4)       | 146 (83.4)   |
| OR [95% CI]| 1         | 0.31      | 1             | 1             |
| AIC        | 155.5     | 0.022     | 0.007         | 0.023         |
| P value    | .022      | 0.029     | 0.018         | 0.033         |
| FDR adjusted |          |           |               |               |

rs56275759

| Co-dominant | Dominant | Recessive | Over-dominant | log-Additive |
|-------------|----------|-----------|---------------|--------------|
| T/T         | 32 (21.9)| 32 (21.9)| 67 (45.9)     | 146 (83.4)   |
| C/T         | 79 (54.1)| 79 (54.1)| 79 (54.1)     | 146 (83.4)   |
| C/C         | 35 (24)  | 35 (24)  | 35 (24)       | 146 (83.4)   |
| OR [95% CI]| 1        | 1.97     | 1.97          | 1.97          |
| AIC        | 156.3    | 0.023    | 0.008         | 0.023         |
| P value    | .027     | 0.048    | 0.029         | 0.033         |
| FDR adjusted |          |          |               |               |

rs9870680

| Co-dominant | Dominant | Recessive | Over-dominant | log-Additive |
|-------------|----------|-----------|---------------|--------------|
| T/T         | 88 (60.3)| 88 (60.3)| 32 (21.9)     | 146 (83.4)   |
| C/T         | 47 (23.2)| 47 (23.2)| 79 (54.1)     | 146 (83.4)   |
| C/C         | 11 (7.5) | 11 (7.5) | 35 (24)       | 146 (83.4)   |
| OR [95% CI]| 1        | 0.35     | 1             | 2.31          |
| AIC        | 156.3    | 0.027    | 0.029         | 0.023         |
| P value    | .037     | 0.048    | 0.027         | 0.023         |
| FDR adjusted |          |          |               |               |

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.\[30\] 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.\[17\] 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 GMR7 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 GMR7 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 ethnicities. 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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