Influence of genetic polymorphisms in homocysteine and lipid metabolism systems on antidepressant drug response

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Abstract

Background Chronic lesions of small blood vessels and capillaries may play a role in the pathogenesis of depression. As the genes associated with these vascular risk factors may be involved in depression, these genetic polymorphisms may affect the efficacy of antidepressants. This study was performed to investigate the roles of methylenetetrahydrofolate reductase (MTHFR), apolipoprotein E (ApoE), and apolipoprotein A4 (ApoA4) genetic polymorphisms in antidepressant response in depressive patients.

Methods A total of 281 Han Chinese patients received a single antidepressant drug for at least 6 weeks. The Hamilton Depression Rating Scale (HAMD-17) was used to evaluate the severity of depressive symptoms and the therapeutic effects of the drug administered. Eight single nucleotide polymorphisms (SNPs) of MTHFR, ApoE, and ApoA4 genes were detected using gene chips. Differences in clinical variables between the responders and non-responders, as well as between remission and non-remission groups, were examined using the independent samples t test and Pearson's χ 2 test. In addition, the associations of single loci and haplotypes with treatment response were analyzed.

Results Among the eight SNPs in four genes, two SNPs (ApoA4 rs5101 and rs675) were eliminated as they had a MAF < 5%.Haplotype(C-A) in MTHFR (rsl801133 and rs1801131) was significantly associated with better antidepressant response in the 8-week antidepressant group overall (P = 0.0007), and in the male subgroup (P = 0.003), and serotonin norepinephrine reuptake inhibitor (SNRI) subgroup (P = 0.001). The ApoE rs405509 C allele was significantly associated with poorer antidepressant response in the 6-week male subgroup (P = 0.004), while the 405509 AA genotype was associated with better antidepressant efficacy in the 6-week antidepressant group overall (P = 0.006) and male subgroup (P = 0.002).

Conclusions Genetic polymorphisms of MTHFR, ApoE, and ApoA4 may be associated with the efficacy of antidepressants, in which the haplotype (rs1801131-rs1801133) A–C type was associated with better antidepressant efficacy, especially in males and in patients using SNRIs. The efficacy of antidepressants may be better in ApoE rs405509 A allele and AA genotype carriers, but worse in ApoA4 rs5092 G allele and GG genotype carriers.

Background

Major depressive disorder (MDD) is a common mental disorder with high rates of morbidity, recurrence, and suicide [1, 2]. Although newer antidepressant drugs are generally well tolerated and relatively effective, only 30–40% of patients achieve full remission [3]. Partial remission results in greater suffering among patients, as well as higher costs [4]. The variability in antidepressant drug response can be attributed to several factors, including genetic and environmental influences [5]. Therefore, several authors have attempted to identify variables that could predict antidepressant response, and have suggested several predictors, including clinical, psychosocial, psychophysiological, neuropsychological, neuroimaging, and genetic markers. It has also been suggested that combinations of these variables may improve predictions of treatment response [6–8]. Genetic factors are thought to play a pivotal role in individual responses to antidepressant treatment [9]. Genetic research generally focuses on polymorphisms of target proteins, which are related to the mechanisms of action of antidepressant drugs.

Several studies have shown high folate deficiency prevalence rates in depression [10, 11], presumably because of its impact on neurotransmitter synthesis, which relies on the folate-dependent one-carbon pathway. Low folate level may dampen antidepressant response, increase the risk of depressive relapse, and delay improvement in individuals treated with antidepressants [12]. Folate supplementation appears to improve the response to selective serotonin

reuptake inhibitors (SSRIs) [13, 14]. One particular focus with respect to the connection between folate and depression has been the enzyme methylenetetrahydrofolate reductase (MTHFR) [15], which synthesizes 5-methyltetrahydrofolate, a carbon donor involved in the methylation of homocysteine (Hcy) to methionine. This enzyme is encoded by the MTHFR gene on chromosome 1 locus q36.3 in humans. A1298C missense mutation (cytosine-to-thymine) in the MTHFR gene results in an alanine-to valine substitution that renders MTHFR thermolabile, and may lead to elevated plasma Hcy, a vascular risk factor [16]. Many recent studies on vascular depression have suggested that chronic lesions in small blood vessels and capillaries could play a role in the pathogenesis of depression [17]. Furthermore, various lines of research have suggested a higher prevalence of homozygous or heterozygous thermolabile MTHFR genotypes in depressed individuals [18, 19]. Therefore, the first purpose of this study was to investigate how MTHFR genetic polymorphisms affect antidepressant efficacy.

Apolipoproteins (Apo) are lipid-binding proteins involved in the transport of lipids in plasma. Several studies suggested that changes in serum lipid composition may be related to MDD [20]. Apolipoprotein E (ApoE) is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. Accumulating evidence indicates that apoE polymorphism affects multiple physiopathological pathways in coronary heart disease and Alzheimer's disease (AD) [21, 22]. ApoE, including epsilon 2 (ε2), ε3, and ε4 alleles, is encoded by a polymorphic gene located on chromosome 19 [21]. Although protective effects of ApoE ε2 have been reported in MDD, and ApoE ε4 may be associated with late-onset depression [23], the conclusions of previous studies were not in complete agreement. The present study focused on the ApoE gene promoter region and coding region to investigate the relationships between polymorphic loci and antidepressant efficacy. Apolipoprotein A4 (ApoA4) is another protein involved in lipid metabolic regulation, and has been shown to activate lecithin-cholesterol acyltransferase and cholesterylester transfer protein [24]. Data-driven analysis showed that ApoA4 has very high accuracy for discriminating individuals with remitted late-life depression (LLD) compared to never-depressed control participants [25].

A single genetic variant cannot explain the consistent variability observed in patient response to psychiatric treatment [26]. Major genetic variations in the Hcy and lipid metabolism pathways could explain more of the variance than a single genetic polymorphism. Therefore, we analyzed polymorphisms in a group of genes involved in the Hcy and lipid metabolism pathways, to determine whether inheritance of specific polymorphisms was associated with responses to a variety of commonly prescribed antidepressants and gain a better understanding of the roles of both genetic and clinical factors in the response to antidepressant treatment.

Methods

Subjects

The subjects were Han Chinese inpatients referred to five psychiatric hospitals (Beijing, Changsha, Huaian, Nanjing, and Yangzhou). All patients were 18–60 years old and fulfilled the criteria for a diagnosis of MDD according to the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) [27]. All subjects had a new diagnosis, or had recently relapsed, and all were drug-free for over 2 weeks and had a baseline score ≥ 18 on the 17-item HAMA(HDRS-17) [28], having presented with depressive symptoms for at least 2 weeks before entry into the study. The diagnoses were made by two independent senior psychiatrists and were confirmed by a third psychiatrist blinded to the previous evaluations. Exclusion criteria included documented history of a diagnosis on Axis 1 (including substance misuse, schizophrenia, schizoaffective disorder, bipolar disorder, generalized anxiety disorder, panic disorder or obsessive–compulsive disorder) of DSM-IV, personality disorder, mental retardation, pregnancy, lactation, primary organic disease or other illness impairing psychiatric evaluation, or a history of electroconvulsive therapy within the previous 6 months. Newly diagnosed patients were also excluded if they had a manic episode in

the 12 months following entry. All subjects provided written informed consent for participation in the study, which was approved by the ethics committee of each participating hospital, in accordance with the Declaration of Helsinki. A flow chart of subject recruitment is shown in Chart 1.

Chart 1. Flow chart of recruited subjects. Abbreviations: SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Antidepressant treatment and clinical evaluation

A total of 281 Han Chinese patients received a single antidepressant drug prescribed according to local clinical practice guidelines for at least 6 weeks, and 275 cases were followed up for 8 weeks. We interviewed each patient biweekly and recorded treatment duration, dosage, outcome, and compliance, using the HDRS-17 to assess the severity of symptoms and therapeutic efficacy while blinded to patient genotypes. A meeting was held for investigators from the different sites before commencement of the study for assessment, training, and standardization of techniques. The assessing psychiatrists at different clinical centers showed high interrater agreement regarding outcomes and side effects. Dose increases of the antidepressant drugs prescribed at baseline were allowed if the patient had not achieved Clinical Global Impression (CGI) change scores indicating “much improved” or “very much improved.” Concomitant psychotropic medications were not permitted, except for low-dose benzodiazepine anxiolytic (alprazolam, 0.4–0.8 mg/day; estazolam, 1–2 mg/day) for alleviation of insomnia. Drug side effects were assessed with the Treatment Emergent Symptom Scale (TESS) (Guy, 1976) every 2 weeks, and drug compliance was also monitored routinely via interviews with nursing staff. “Response” was defined as a reduction of at least 50% in the HDRS-17 total score after 6 weeks of treatment, while “remission” was defined as a total HDRS-17 score $\leq$ 7 points after 8 weeks of treatment, according to the Guidelines for Biological Treatment of Unipolar Depressive Disorders of the World Federation of Societies of Biological Psychiatry [29]. Patients requiring a change in antidepressant drug or demonstrating non-adherence were excluded from the study.

Gene selection and genotyping methods

Three candidate genes were selected based on evidence for the involvement of vascular risk factors and lipid metabolism in the mechanism of depression, including MTHFR, ApoE, and ApoA4 genes (see Introduction). Eight single nucleotide polymorphisms (SNPs) were detected with minor allele frequency (MAF) values of > 5% in the Asian population, according to the dbSNP and HapMap databases and using gene chips.

Blood was collected in 5-ml EDTA vacutainers and stored at −80°C until genotyping. Genomic DNA was extracted using an NPK-100 Magextractor-genome kit (Toyobo, Osaka, Japan). After quality assessment, DNA samples (250 ng each) were genotyped by Berkeley Biotech Inc. (Menlo Park, CA) using GoldenGate assays (Illumina Inc., San Diego, CA). All of the SNPs selected for the custom oligo pooled assays had Illumina design scores > 0.6. All of our samples had Illumina 10% GenCall scores > 0.4 and call rates > 90%. Genotype data on SNPs were generated using Beadstudio 3.0 (Illumina) and were exported in Excel format for further analysis.

Statistical analysis

Differences in clinical variables between responder and non-responder groups, as well as remission and non-remission groups, were evaluated by Student's *t* test or Pearson's χ^2 test using SPSS software (version 13.0; SPSS Inc., Chicago, IL). Haploview 4.0 was used to analyze Hardy–Weinberg equilibrium (HWE), MAF, percentage of successful genotyping for each marker (%gene), and linkage disequilibrium (LD; both D' and r^2). In addition, the associations of single loci and haplotypes with treatment response were analyzed using Unphased 3.0.13 (http://www.mrc-bsu.cam.ac.uk/personal/frank/software/unphased/). Corrected *P*-values for multiple testing in the allelic, genotypic, and haplotype association analyses are reported for 1,000 permutations of randomly distributed phenotypes over all selected genotypes within a single gene.

Results

A total of 281 patients completed a 6-week antidepressant treatment course. Among these patients, 205 achieved a response, defined as a 50% improvement in the HDRS score. The demographic and clinical characteristics of patients in the responder and non-responder groups are shown in Table 1. There were no significant differences between the 6-week responder and non-responder groups in sex, age, drugs used, years of education, or family history of mood disorders. However, the baseline HDRS-17 score was significantly different between these two groups ($t = 2.891$, $P=0.004$).

A total of 275 patients completed 8-week antidepressant treatment. Among these patients, 144 achieved remission, defined as an HDRS-17 score ≤ 7 points. There were no significant differences in age, number of years of education, family history, baseline HDRS-17 score, or antidepressant agents used between remission and non-remission groups (all $P>0.05$), while the proportion of male patients and number of episodes were significantly higher in the non-remission group than the remission group ($t = 2.381$, $P=0.018$ and $t = -1.983$, $P=0.049$, respectively), as shown in Table 1 and 2.

Among the eight SNPs of the three genes investigated, two (ApoA4 rs5101 and rs675) were eliminated as they had MAF < 5%, while the remaining six SNPs were subjected to further statistical analyses. LD analysis showed that two SNPs (rs1801133, rs1801131) of the MTHFR gene were in near 100% LD (D' = 1.0, $r^2 = 0.177$), while two other SNPs (rs405509, rs439401) of the ApoE gene were in strong LD (D' = 0.961, $r^2 = 0.505$). The other SNPs showed no LD.

Analysis of single-locus effects revealed that two of the six remaining SNPs (rs405509, rs5092) had statistically significant associations with antidepressant response (Table 3; only significant allele and genotype association results are shown). The ApoE rs405509 A allele was significantly associated with better antidepressant response in the 6-week male subgroup ($\chi^2 = 8.445$, $P = 0.004$). Moreover, the ApoE rs405509 AA genotype was associated with better antidepressant efficacy than the AC genotype in the 6-week male subgroup ($\chi^2 = 9.768$, $P = 0.002$), which withstood permutation testing. The ApoA4 rs5092 G allele was associated with poorer antidepressant response in the 6-week male subgroup ($\chi^2 = 4.334$, $P = 0.037$), SNRI subgroup ($\chi^2 = 7.241$, $P = 0.007$) and 8-week female subgroup ($\chi^2 = 4.014$, $P = 0.045$), which withstood permutation testing. Furthermore, the ApoA4 rs5092 GG genotype was significantly associated with antidepressant efficacy in the 6-week male subgroup ($\chi^2 = 4.059$, $P = 0.034$) and SNRI subgroup ($\chi^2 = 6.964$, $P = 0.008$). Compared to the AA and AG haplotypes, the GG haplotype was associated with reduced likelihood of a good response (male subgroup, odds ratio [OR]: 0.26, 95% confidence interval [CI] = 0.08–0.87; SNRI subgroup, OR: 0.13, 95% CI = 0.02–0.65). However, the significance in the male subgroup did not withstand permutation correction.

We examined the associations of haplotypes derived from the SNPs in MTHFR and ApoE with antidepressant response, limiting our analysis to haplotypes with a frequency of 5%. Table 4 shows that the haplotype (C-A) in MTHFR (rs1801133 and rs1801131) was significantly associated with antidepressant response in the 8-week antidepressant group overall (χ^2 = 11.39, *P* = 0.0007), male subgroup (χ^2 = 8.767, *P* = 0.003), and SNRI subgroup (χ^2 = 10.51, *P* = 0.001). In comparison to the T-A haplotype and C-C haplotype, the C-A haplotype was associated with increased likelihood of good remission in the group overall (OR = 1.718, 95% CI = 1.178–2.505), and in the male subgroup (OR = 1.971, 95% CI = 1.088–3.572) and SNRI subgroup (OR = 2.251, 95% CI = 1.24–4.085). As shown in Table 5, haplotype (G-A) in ApoE (rs7412 and rs405509) was significantly associated with antidepressant response in the 6-week male subgroup (χ^2 = 8.687, *P* = 0.003) In comparison to the A-A haplotype, the G-A haplotype was associated with increased likelihood of a good response (OR = 1.24, 95% CI = 0.12–12.9). Haplotype (G-C) in ApoE (rs7412 and rs405509) was significantly associated with antidepressant response in the 6-week SNRI subgroup (χ^2 = 8.24, *P*=0.0041). In comparison with the A-A haplotype, the G-C haplotype was associated with increased likelihood of a good response (OR = 1.04, 95% CI = 0.19–5.64). All of the results outlined above withstood permutation testing.

Discussion

We investigated the association of genetic variation in folate and lipid metabolism-related genes with antidepressant response in patients with major depression, and found significant effects of single polymorphisms in MTHFR, apoE, and apoA4.

In the MTHFR gene, the haplotypes C-A of rs1801133 and rs1801131 were associated with better antidepressant effects in the group overall, and in the male and SNRI subgroups. This may have been because there are mutations in both T-A and C-C haplotypes that result in decreased MTHFR enzyme activity, increased blood Hcy levels, and decreased folate levels [30]. Bottilieri et al. reported that folic acid supplementation can protect brain function by reducing Hcy [31, 32], and also that increased levels of Hcy and/or decreased levels of folate resulted in decreased levels of S-adenosyl methionine (SAM) in cerebrospinal fluid; meanwhile, SAM as a methyl donor for serotonin (5-HT) and catecholamine pathways exerted significant antidepressant effects and was shown to have better efficacy than imipramine [33]. The above findings support the conclusion that low levels of Hcy and high levels of folic acid have an effect on the efficacy of antidepressants, and that their antidepressant effects may be related to changes in DNA methylation. However, it has been suggested [34] that folic acid and vitamin B12 do not clearly enhance the efficacy of antidepressants, and that the use of folic acid and vitamin B12 can only prevent further increases in Hcy but cannot reduce its level; this may be related to differences among studies in the folic acid and vitamin B12 doses used .

This study further showed that only C-A haplotype carriers in the male subgroup experienced higher antidepressant efficacy; this was not seen in the female subgroup. This may have been due to the higher folate concentrations and lower Hcy levels in women [35], which compensates for reduced MTHFR enzyme activity, thus making it difficult to detect the relationship between this gene polymorphism and antidepressant efficacy. In addition, women have higher estrogen levels, and estrogen can also weaken the correlation between MTHFR gene polymorphism and antidepressant efficacy to some extent by lowering Hcy levels [36].

In addition, the efficacy of antidepressants was greater in C-A haplotype carriers in the SNRI subgroup. It has been reported that 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 4-hydroxy-3-methoxyphenylethylene in the cerebrospinal fluid of patients with depression, along with high levels of Hcy and lower levels of 4-hydroxy-3-

methoxyphenylglycol (MHPG), represent impaired metabolism of 5-HT, dopamine (DA), and norepinephrine (NE) [37], but the main mechanism remains unclear. In contrast to SSRIs, SNRIs have a 5-HT reuptake inhibitory effect, as well as NE and mild DA reuptake inhibition; therefore, SNRIs have greater effects against the neurotoxicity associated with a high Hcy level. SSRIs have a single drug target, so there was little difference in efficacy between haplotypes in the SSRI subgroup.

The ApoE gene plays an important role in regulating lipid metabolism and maintaining cholesterol balance. The SNP, rs7412 (C526T), is a functional site in the ApoE gene; it is mutated, resulting in replacement of arginine with cysteine. This study indicated that this polymorphism is closely related to lipid metabolism. Although rs405509 (219A/C), which is located in the promoter region upstream of the gene, has not been confirmed to be a functional site, this study showed that its polymorphism is associated with antidepressant efficacy. Therefore, further studies regarding this site are required.

This study showed that serum cholesterol levels in patients with depression were significantly lower than those in healthy people, and serum cholesterol levels have also been shown to be associated with the efficacy of antidepressants. Sonawalla et al. [38] reported that patients with depression treated with a standard dose of fluoxetine (20 mg/d) had high serum cholesterol levels (≥ 200 mg/dl); with lower cholesterol levels, the curative effect is diminished, the tendency toward chronic disease is greater, and the possibility of recurrence is higher; related research on refractory depression reached a similar conclusion. The above studies suggested that the effects of the ApoE gene polymorphism on the efficacy of antidepressants may be related to the concentration of cholesterol in the body. Excessive cholesterol concentration may affect 5-HT transporters and/or various 5-HT receptors. The function of the 5HT neurons cytomembrane structure has an adverse effect. As another possible explanation, patients with hypercholesterolemia are more likely to have vascular and anxiety disorders, which would affect the efficacy of antidepressants. However, studies have yielded inconsistent results, suggesting that the incidence of depression is lower in the higher blood lipid state, and that high blood lipids may have certain antidepressant effects. For example, Mase et al. [39] reported that low serum high-density lipoprotein (HDL-C) is a marker of suicidal behavior in depression, and may induce immune or inflammatory reactions in depression. Mischoulon et al. [40] also reported that foods rich in docosahexaenoic acid (DHA) are associated with a lower incidence of depression, while DHA deficiency (e.g., alcoholism and postpartum) is associated with a higher incidence of depression. The discrepancies between the above studies may be related to differences in the subjects and indicators of blood lipid levels.

In addition, studies on the association between the ApoE gene and depression and antidepressant efficacy have focused on the common alleles of this gene, ε2, ε3, and ε4, and some studies confirmed that the ApoE gene ε4 allele was associated with greater efficacy of antidepressants [41–43]. Bizzarro et al. [44] reported a significant association between AD and rs405509 CC genotypes when exploring the association between AD and an ApoE gene promoter, suggesting that rs405509 may play a role in the pathogenesis of AD. Lescai et al. [45] also reported that haplotype A-ε4, consisting of rs4905509 and ε4, can increase the risk of late-onset AD by reducing ApoE expression levels. Therefore, we hypothesized that the rs405509 polymorphism may have strong LD with other functional SNPs, such as the ε4 allele, and thus alter the biological function of the ApoE gene to influence the efficacy of antidepressants.

The function of rs5092 (29A/G) located in the promoter region of the ApoA4 gene, is still unclear and there have been few studies related to this site. However, in an exploration of gene function, the polymorphism of the ApoA1/C3/A4 gene cluster on chromosome 11q23-24 was shown to be related to blood lipids. These three genes show a high degree of identity and evolved from the same ancestral gene. The ApoA1 and ApoA4 genes have the same transcriptional direction, while ApoC3 is transcribed in the opposite direction [45]; moreover, its polymorphic variation

can lead to hypertriglyceridemia [46]. This site may affect the synthesis of ApoA4, and the blood lipid level, by altering transcription of the ApoA4 gene.

Analyses of the ApoE and ApoA4 genes indicated correlations between each polymorphic site and the efficacy of antidepressants in the male subgroup, but not in the female subgroup; the latter also required a longer treatment cycle (8 weeks). This may have been related to differences in lipid levels between male and female patients, and to differences in the pharmacokinetics of antidepressants.

Further studies are required regarding other polymorphic sites of these genes, and the analyses should be extended to other metabolic enzymes to capture the variation in Hcy and lipid metabolic pathways more comprehensively. In addition, as the placebo effect also plays a role in antidepressant treatment, a placebo control group should be included to exclude such effects and other, non-pharmaceutical factors. Regarding the sites shown to be associated with the efficacy of antidepressants in the present study, studies with larger sample sizes are needed to verify their accuracy and lay a foundation for personalized medicine.

Conclusions

This study demonstrates that genetic polymorphisms of MTHFR, ApoE, and ApoA4 may be associated with the efficacy of antidepressants, in which the haplotype (rs1801131-rs1801133) A–C type was associated with better antidepressant efficacy, especially in males and in patients using SNRIs. The efficacy of antidepressants may be better in ApoE rs405509 A allele and AA genotype carriers, but worse in ApoA4 rs5092 G allele and GG genotype carriers. Confirmation of these preliminary results across independent populations and further pharmacogenomics exploration might lead to novel strategies for individualized, rational and successful antidepressant drug treatment.

Abbreviations

5-HIAA: 5-hydroxyindoleacetic acid

5-HT: 5-hydroxytryptamine, serotonin

AD: Alzheimer’s disease

ApoA4: Apolipoprotein A4

ApoE:Apolipoprotein E

CGI: Clinical Global Impression

DA : Dopamine

DHA: Docosahexaenoic acid

DSM-IV: Diagnostic and Statistical Manual of the American Psychiatric Association

Hcy: Homocysteine

HDL-C:High-density lipoprotein

HDRS: Hamilton Depression Rating Scale

HVA: Homovanillic acid

HWE: Hardy–Weinberg equilibrium

LLD: Late-life depression

MAF: Minor allele frequency

MDD: Major depressive disorder

MHPG: 4-hydroxy-3-methoxyphenylglycol

MTHFR: Methylenetetrahydrofolate reductas

NE: Norepinephrine

SAM: S-adenosyl methionine

SNPs: Single nucleotide polymorphisms

SNRI: Serotonin norepinephrine reuptake inhibitor

SSRIs: Serotonin reuptake inhibitors

TESS: Treatment Emergent Symptom Scale

Declarations

Ethics approval and consent to participate

The authors state that the study was established according to the ethical guidelines of the Helsinki Declaration and was approved by the ethics committee of all participating hospitals, including Beijing Anding Hospital, the Second Xiangya Hospital of Central South University, Huaian No. 3 People's Hospital, Wutaishan Hospital of Yangzhou, Affiliated ZhongDa Hospital of Southeast University. Written informed consent was obtained from all subjects or guardian participants.

Consent for publication

Not applicable.

Availability of data and materials

The raw/processed data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study. The de-identified dataset used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that Yonggui Yuan as a member of Editorial Board.

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Authors' contributions

Zhijun Zhang and Yuan Yonggui designed the research protocal, Sun xiaoyan, Xu zhi and Pu mengjia .analyzed data; Yuan baoyu and Zhang zhijun wrote the paper. All authors read and approved the final manuscript.

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Tables

Table 1. Demographic characteristics of MDD patients and baseline HDRS-17 scores: comparison between responder and non-responder groups

Demographic characteristics	Responder (*n*=205)	Non-responder (*n*=76)	t / χ^2	*P*
Gender (male/female)	81/124	35/41	0.987	0.324
Age (years)	38.99±12.93	36.18±13.36	1.599	0.111
Education (years)	11.27±3.84	12.20±3.82	−1.800	0.073
Family history of mood disorder (yes/no)	29 (14.15%)	15 (19.74%)	−1.031	0.305
Baseline HDRS-17 score	28.18±5.68	26.01±5.32	2.891	**0.004**
Number of episodes	2.01±1.57	2.33±2.03	−1.394	0.164
Antidepressant (SSRI/SNRI)	114/91	50/26	1.569	0.119

Abbreviations: HDRS-17, 17-item Hamilton Depression Rating Scale; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 2. Demographic characteristics of MDD patients and HDRS-17 scores: comparison between remission and non-remission groups

Demographic characteristics	remission (*n*=144)	non-remission (*n*=131)	t / χ^2	*P*
Gender (male/female)	49/95	63/68	2.381	**0.018**
Age (years)	38.38±11.99	38.14±14.11	0.150	0.881
Education (years)	11.28±3.65	11.73±4.07	−0.957	0.340
Family history of mood disorders (yes/no)	20(13.89%)	22(16.79%)	−0.645	0.519
Baseline HDRS-17 score	27.03±5.71	28.00±5.36	−1.452	0.148
Number of episodes	1.88±1.30	2.30±2.06	−1.983	**0.049**
Antidepressant (SSRI/SNRI)	76/68	83/48	1.781	0.076

Abbreviations: HDRS-17, 17-item Hamilton Depression Rating Scale; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 3. Genetic association analysis of SNP genotype/allele versus response or remission status subgroups

Subgroups	SNPs (Gene/rs#)	Allele/Genotype	Response (%)	Non-response (%)	Remission (%)	Non-remission (%)	OR (95% CI)	χ^2	*P*	*P**
Male subgroup	ApoE/rs405509	A	129 (80)	43 (61)			1	8.445	**0.004**	<0.05
		C	33 (20)	27 (39)			0.41 (0.22–0.75)	8.445	**0.004**	
		AA	51 (63)	11(31)			1	9.768	**0.002**	0.009
		AC	27 (33)	21(60)			0.28(0.12–0.66)	7.165	**0.007**	
Male subgroup	ApoA4/rs5092	A G	98 (60) 64 (40)	32 (46) 38 (54)			1 0.55 (0.31–0.97)	4.334 4.334	**0.037** **0.037**	0.03
SNRI subgroup	ApoA4/rs5092	A G	98 (54) 84 (46)	17 (33) 35 (67)			1 0.42 (0.22–0.80)	7.241 7.241	0.007 **0.007**	0.005
		AA	23 (25)	2 (8)			1	3.721	0.054	
		AG	62 (54)	32 (64)			0.63 (0.27–1.43)	1.313	0.252	
		GG	16 (18)	11 (42)			0.13 (0.02–0.65)	6.964	**0.008**	0.019
Female subgroup	ApoA4/rs5092	A G			101 (53) 89 (47)	57 (42) 49 (58)	1 0.64 (0.41–0.99)	4.014 4.014	**0.045** **0.045**	0.03

Abbreviations: SNPs, single nucleotide polymorphisms; SNRI, serotonin norepinephrine reuptake inhibitor; OR, odds ratio; CI, confidence interval

*Adjusted *P*-value from 1,000 permutation tests

Table 4. Estimated haplotype frequency of the two MTHFR SNPs (rs1801133 and rs1801131) and results of haplotype analysis in remission and non-remission groups

Haplotype	Overall group					SNRI subgroup					Male subgroup				
	RM (%)	NR (%)	OR (95% CI)	*P*	*P**	RM (%)	NR (%)	OR (95%CI)	*P*	*P**	RM (%)	NR (%)	OR (95% CI)	*P*	*P**
T-A	117(41)	125(48)	1	0.095		58(43)	51(53)	1	0.115		40(41)	60(48)	1	0.310	
C-A	127(44)	79(30)	1.72 (1.18–2.51)	**0.0007**	0.002	64(47)	25(26)	2.25 (1.24–4.09)	**0.001**	**0.002**	46(47)	35(28)	1.97 (1.09–3.57)	**0.003**	**0.012**
C-C	44(15)	58(22)	0.81 (0.51–1.29)	0.039	>0.05	14(10)	20(21)	0.62 (0.28–1.34)	**0.025**	**>0.05**	12(12)	31(25)	0.58 (0.27–1.26)	**0.020**	**>0.05**

Abbreviations: RM, remission; NR, non-remission; SNRI, serotonin noradrenaline reuptake inhibitor; OR, odds ratio; CI, confidence interval.

*Adjusted *P*-value from 1,000 permutation tests

Table 5. Estimated haplotype frequencies of the two ApoE SNPs (rs7412 and rs405509) and the results of haplotype analysis in responders and non-responders

Haplotype	Male subgroup					SNRI subgroup				
	RM (%)	NR (%)	OR (95% CI)	*P*	*P**	RM (%)	NR (%)	OR (95% CI)	*P*	*P**
T-A						12 (7)	3 (5)	3.12 (0.23–42.27)	0.890	
G-A	125 (77)	41 (59)	1.24 (0.12–12.9)	**0.003**	**<0.05**	139 (77)	29 (55)	3.38 (0.57–19.42)	**0.006**	>0.05
G-C	27 (17)	17 (24)	0.66 (0.07–6.59)	0.162		26 (14)	17 (33)	1.04 (0.19–5.64)	**0.0041**	0.049

Abbreviations: RM, remission; NR, non-remission; SNRI, serotonin noradrenaline reuptake inhibitor; OR, odds ratio; CI, confidence interval