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Association study between *ABCB1*, *ABCB6* and *ABCG1* polymorphisms and major depressive disorder in the Chinese Han population

To the editors,

Major depressive disorder (MDD), one of the most common mental illnesses worldwide, remains a leading cause of morbidity and mortality. In light of the strong evidence of heritability, association studies through rare or common variants have been carried out to find genetic clues to MDD etiology (Levinson et al., 2014).

ATP-binding cassette (ABC) transporters are a large protein superfamily in human beings. In the brain, ABC transporters locate in various cells and predominantly gather at the blood-brain barrier (BBB). Thus, they basically isolate the brain from harmful and toxic compounds (Hartz and Bauer, 2011). Mutations in the members of ABC transporters have been found to be linked to several human diseases including psychiatric illness such as Alzheimer's disease (AD). Previous studies showed *ABCB1* polymorphisms influence the therapeutic response of antidepressants and associate with MDD (Fujii et al., 2012; Jelen et al., 2015). To

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further verify the role of *ABCB1* and to evaluate the possible role of *ABCB6* and *ABCG1* polymorphisms in Chinese MDD patients, an independent case-control study was performed including 568 unrelated Han Chinese patients (308 females and 260 males, age: 36.0±12.9) and 1034 (446 women and 588 men, age: 34.06 ± 10.00) healthy individuals who were recruited from the West China Hospital during April 2005 to September 2006. All of the patients were assessed by two skillful psychiatrists based on *DSM-IV-TR* Axis I criteria for MDD and got at least 18 points on 17-item Hamilton Depression Rating Scale (HAMD). Patients were excluded if they had other mental disorders except MDD or other significant medical conditions or sequelae of serious illness. This study was approved by human ethics committee of Sichuan University (Sichuan, China). All patients offered written informed consent before enrollment.

We chose nine SNPs in *ABCB6* (rs1109866, rs1109867, rs3731885 and rs3755047), *ABCB1* (rs6946119, rs28401781, rs4148739 and rs3747802) and *ABCG1* (rs182694) which were from NCBI dbSNP database (www.ncbi.nlm.nih.gov/SNP). Genotyping was carried out by a matrix-assisted laser desorption/ionization

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time-of-flight (MALDI-TOF) mass spectrometer using the MassARRAY® Analyzer 4 platform (Sequenom, CA, USA). All statistics analysis was performed by SHEsis (http://analysis.bio-x.cn/myAnalysis.php). The differences of allele and genotype frequency between MDD patients and healthy individuals were compared with χ^2 test. Linkage disequilibrium of all pairs of SNPs was estimated using *D'* according to the standard measurement. Odds ratios (ORs) and their 95% confidence intervals (CIs) were obtained. We used R (version 3.2.2) to assess genetic models and each genetic model was adjusted by gender and province. For all analyses, *P*-values were two tailed and $P < 0.05$ was considered to be statistically significant.

Nine SNPs we tested were all in Handy–Weinberg equilibrium. Significant differences were detected in the allelic distributions of rs1109866, rs1109867 and rs3731885 between MDD patients and controls (rs1109866: $P = 0.029$, $Chi^2 = 4.79$; rs1109867: $P = 0.021$, $Chi^2 = 5.29$; rs3731885: $P = 0.045$, $Chi^2 = 4.01$, respectively). Rs1109867 and rs3731885 showed modestly significant associations with MDD in genotype frequencies (rs1109867: $P = 0.042$, $Chi^2 = 6.32$; rs3731885: $P = 0.039$, $Chi^2 = 6.49$, respectively). We found carriers of rs1109866 C/C (OR = 0.45, CI =

((0.22~0.92)), rs1109867 G/G (OR = 0.44, CI = (0.21~0.93)) and rs3731885 A/A (OR = 0.25, CI = (0.07~0.85)) were at a decreased MDD risk. Rs1109866-rs1109867-rs3731885-rs3755047 in *ABCB6* were in strong linkage disequilibrium (*D'* = 0.99). Results in the log-additive genetic model displayed that rs1109867 variants were in the association with MDD (OR = 0.80, *P* = 0.034, after adjusting for age and sex).

To date, researchers mostly focus on the SNPs rs1045642, rs2032582, and rs2032583 of *ABCB1* influencing the therapeutic response of antidepressants and the susceptibility of MDD (Fujii et al., 2012; Jelen et al., 2015). Murphy et al. tested whether *ABCG1* genetic variations linked to suicidal behavior but there was no positive evidence (Murphy et al., 2011). Both *ABCB6* and *ABCB1* are the members of the ABCB subfamily with similar gene structure. Functionally, it's proved that *ABCB1* plays an important role in drug resistance and *ABCB6* links to several human diseases. Besides, there is no published data on the effect of *ABCB6* and *ABCG1* gene polymorphism on the risk of MDD. Additionally, we firstly investigated the susceptibility of 4 SNPs (rs6946119, rs28401781, rs4148739 and rs3747802) which

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located in *ABCB1* for MDD. Regretfully, with respect to the 4 SNPs of *ABCB1*and 1 SNP of *ABCG1*, there was no significant difference in genotype or allele distribution. Since the SNPs we selected did not cover the whole gene region, we cannot exclude the probability that *ABCG1* might be predictors of MDD susceptibility. Moreover, we had tried to gain more information for the association between *ABCB1* polymorphism and the risk of MDD in Chinese Han population. In our study, *ABCB6* may contribute to the risk of MDD on basic allelic and genotypic analysis. This finding further strengthens that ABC transporters link with MDD and there is functional connection among the members of ABC transporters. Meanwhile, the result provides an idea for genetic studies on MDD. However, no SNPs on ***ABCB1, ABCB6* and *ABCG1*** were found to be associated with MDD after multiple test correction. There are some potential reasons like our sample is not huge enough.

In summary, our studies firstly indicate that *ABCB6* might contribute to the risk of MDD in Chinese Han population.

Conflict Declaration

None.

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