Common variants in *SLC6A2*, *SLC6A3*, *DRD2*, and major depressive disorder: an association study in the Chinese Han population

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Psychiatric Genetics 2017, **27**:103–104

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Received 5 December 2016 **Accepted** 5 January 2017

Major depressive disorder (MDD) is a chronic, debilitating neuropsychiatric illness with a lifetime prevalence of up to 17% (Kessler *et al*., 2003). It is expected to be the second leading cause of disability worldwide by the year 2020 (Simon, 2003). Noradrenergic and dopaminergic pathway genes, as the key candidates, have emerged in a number of studies, although the consequences are not consistent (Lopez-Leon *et al*., 2008; Bosker *et al*., 2011). In the present study we investigated the association of the variance of three dopaminergic and noradrenergic pathway genes (*SLC6A2*, *SLC6A3*, and *DRD2*) with MDD.

A total of 568 unrelated patients with MDD (260 men and 308 women, age: 45.94 ± 13.13 years, onset age: 26.20 ± 9.20 years) and 846 healthy controls (485 men and 361 women, age: 33.93 ± 10.25 years) of Chinese Han origin were recruited into this case–control study. Each patient was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) criteria, by two independent psychiatrists. All participants signed an informed consent form. The ethics committee from the Human Genetics Center of Shanghai approved this study.

Seven single nucleotide polymorphisms (SNPs) of *SLC6A2*, *SLC6A3*, and *DRD2* were genotyped by MassARRAY Analyzer 4 platform (Sequenom Inc., San Diego, California, USA). SHEsis (*http://analysis.bio-x.cn/myAnalysis.php*) was used for the Hardy–Weinberg equilibrium, the distributions of allele frequency and genotype frequency, as well as pairwise linkage disequilibrium (LD). Haplotype analysis was carried out using Haploview software (Daly Lab at the Broad Institute; Cambridge, Massachusetts, USA) initially and then confirmed on SHEsis. To further verify the results, R package 'genetics' was adapted to assess the association between these SNPs and MDD in co-dominant, dominant, recessive, overdominant, and log-additive models. The stratified analysis by sex was conducted on R using logistic regression. Besides, gene–gene interaction was performed using the open-source java software multifactor dimensionality reduction, v.3.0.2.

All of the seven SNPs were confirmed to be in Hardy–Weinberg equilibrium. The genotypes for these polymorphisms in patients and controls were distributed as follows: rs1362621 AA 281 : 431, AG 235 : 336, GG 38 : 78; rs2242446 CC 49 : 93, CT 237 : 361, TT 260 : 388; rs5564 CC 19 : 24, CT 148 : 236, TT 378 : 580; rs3863145 CC 506 : 752, CT 41 : 87, TT 1 : 2; rs2550956 CC 408 : 654, CT 137 : 183, TT 11 : 6; rs2234689 CC 1 : 2, CG 47 : 12, GG 501 : 767; rs7131056 AA 89 : 167, AC 274 : 395, CC 191 : 282. Rs2550956 showed marginally significant differences in allelic ($P = 0.033$) and genotypic frequencies ($P = 0.04$) between cases and controls, but no significant differences for the five genetic models. The pair SNPs rs1362621–rs2242446 emerged to be in strong linkage disequilibrium block ($D' = 0.97$). And haplotypes rs1362621–rs2242446–rs5564 (global $P = 0.036$) and rs3863145–rs2550956 (C–T) ($P = 0.029$) demonstrated significant association with MDD. Gene–gene interaction analyses displayed a three-loci interaction among rs2242446, rs5564, and rs7131056 for MDD ($P = 0.0153$). No heterogeneity was found in the stratified analysis by sex.

The results suggested that the SNP–SNP interaction and gene–gene interaction might have a stronger effect on the susceptibility of MDD than a single variation or gene. Furthermore, as *SLC6A2* and *DRD2* are involved in the dopaminergic pathway and noradrenergic pathway, this may imply that we should consider the combined effect of different classical hypotheses of MDD, such as dopamine hypothesis and norepinephrine hypothesis (Lambert *et al*., 2000). In conclusion, our study suggests that the three genes *SLC6A2*, *SLC6A3*, and *DRD2* may

DOI: 10.1097/YPG.0000000000000163

play a role in MDD in the Chinese Han population. Considering the limitation of incomplete SNP coverage and relatively small sample size, larger genetic studies containing more comprehensive polymorphisms are needed for a more solid conclusion.

Acknowledgements

The authors appreciate the contribution of the members participating in this study, as well as the psychiatrists who helped us with diagnosis.

This work was supported by the 973 Program (2010CB529600), the National Key Technology R&D Program (2012BAI01B09, 2009CB825606), the National Nature Science Foundation of China (81121001, 31171237), the Shanghai Municipal Commission of Science and Technology Program 09DJ1400601, the Shanghai Leading Academic Discipline Project (B205) and the Shanghai Key Laboratory of Psychotic Disorders (13dz2260500 14K-08), the National Key Technology R&D Program (2016YFC1201701).

Conflicts of interest

There are no conflicts of interest.

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