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Letter to the Editor

Association study of NOS1 gene polymorphisms with the risk of schizophrenia in Chinese Han origin

Highlights

1. We investigated the association between the *NOS1* polymorphisms and schizophrenia.
2. The SNP rs1123425 demonstrated significant difference between schizophrenic patients and control subjects in genotype frequency.
3. The *NOS1* might be associated with schizophrenia in Chinese Han population.

To the editor

It is known that the schizophrenia (SZ) is resulted from genetic predisposition and environment factors, and the heritability is estimated at about 80% with the evidence in family and twin studies (Cardno and Gottesman, 2000). A lot of genetic association studies about SZ with candidate genes have been performed. Recently, Neuronal nitric oxide synthase (*NOS1*) was considered as a genetic risk factor for SZ due to the significant polymorphisms associated with SZ. Furthermore, the linkage analysis revealed that schizophrenia was significantly linked to 12q22-24 (Reif et al., 2006), on which is *NOS1* gene.

In this study, we investigated whether *NOS1* is associated with SZ in the Chinese Han population by examining seven new SNPs between schizophrenic patients and healthy controls. A total of 2068 persons participated in this study, including 1034 unrelated Han Chinese patients with schizophrenia (625 males and 409 females, age: 45.06 ± 12.88, onset age: 25.98 ± 9.65) and 1034 controls (588 males and 446 females, age: 34.06 ± 10.00). Each patient was diagnosed by two professional psychiatrists through DSM-IV criteria. Subjects in controls would be excluded if they have psychiatry disorder or drug abuse history in the first or second degree relatives. All of these participants have signed a formal informed consent. This research was supported by the Ethics Committee of the Human Genetics Center in Shanghai. DNA was extracted from peripheral blood based on phenol-chloroform method.

Given to the minor allele frequency(MAF) should be more than 0.05, we selected seven SNPs in *NOS1* (rs1105026, rs9658501, rs3741475, rs1047735, rs11068428, rs1123425, rs2293054). Herein, we use MassARRAY® Analyzer 4 platform (Sequenom, CA, USA) to genotype all SNPs. Statistical analysis was performed on SHSsis (http://analysis.bio-x.cn/myAnalysis.php) (Yong and Lin, 2005). For all above analyses, *P* values were two tailed and the significance level was set to 0.05. Then we used the R(version 3.2.2) to assess genetic models and each genetic model was adjusted by gender and province.

All of the SNPs were in Hardy-Weinberg equilibrium except rs2293054, so it would be excluded in further analysis. Only rs1123425 had a significant association with SZ in genotype frequency (rs1123425: P=0.017). Rs9658501-rs3741475 and rs1047735-rs11068428 were revealed as two blocks with strong LD ($D' > 0.9$). However, there is no significant association between these two blocks and SZ. For rs1123425, logistic regression tests showed that rs1123425 can adopt codominant and recessive models after adjusted by gender and province (codominant model: P=0.0295, GA vs GG: OR=0.95, CI=0.77–1.18, AA vs GG: OR=1.35, CI=1.02–1.78; recessive model: P=0.0088, GG/GA vs AA: OR=1.39, CI=1.09–1.77).

Rs1123425, which is located in the intron region of *NOS1* gene, was first found to have a slight association with SZ. Levels of *NOS1* protein differ in the distribution between SZ and healthy controls (AKYOL et al., 2004). So we would speculate that rs1123425 might affect the mRNA level of NOS1 and alter the amount of proteins. Although there is no further evidence to prove our result, many studies have shown that polymorphisms in *NOS1* are associated with the cognitive disorder in SZ. For example, in an association study between SZ patients and healthy controls, the risk G allele of rs6490121 was revealed to have an effect on verbal IQ and working memory (Donohoe et al., 2009). There are some limitations in this study, owing to the slight significant association result, we did not give a False Discovery Rate (FDR) or Bonferroni correction. Samples need to be enlarged for better analysis. And we also need further functional studies to confirm this result.

In conclusion, our result support the hypothesis that *NOS1* as a candidate gene for SZ in Chinese Han population.

Conflict of interest

All authors have no conflicts of interest in this work.

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