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Genetic association between CELF4 rs1557341 polymorphism and neuroticism in Chinese Han population

Neuroticism is a dimension of personality which often presents negative emotions such as stressful, anxiety, anger and a low degree of emotional stability. Previous studies have indicated personality traits have prominent correlation with mental disorders, especially for neuroticism. High neuroticism is demonstrated associated with major depressive disorder (MDD) (Kendler and Myers, 2010), schizophrenia (Van Os and Jones, 2001) and other psychiatric disorders, making neuroticism an essential phenotype for psychiatric genetic researches. Differences in neuroticism are stable among individuals throughout their life. Meta-analysis of twin studies suggest that about 40% of individual differences in personality are caused by genetic factors (Vukasovic and Bratko, 2015). However, the underlying genetic mechanisms are still elusive. Genome-wide association studies have probed several remarkable single nucleotide polymorphisms (SNPs) associated with neuroticism based on western cohorts (Okbay et al., 2016). The purpose of this study was therefore to investigate whether the results can be generalized to the Chinese Han population.

In this study, we recruited 727 unrelated Chinese Han participants (280 males and 447 females, age: 20.22 ± 1.79). The informed consents have been obtained from all participants and they filled out the questionnaire measuring neuroticism. The Ethics Committee of the Bio-X Institutes, Shanghai Jiao Tong University has approved this research. Genomic DNA was collected from peripheral blood for each participant using the standard phenol-chloroform method. We selected five SNPs from a previous genome-wide association study (Okbay et al., 2016), which were reported to be associated with neuroticism. Their minor allele frequencies are higher than 0.05 in East Asians. All SNPs were genotyped by the matrix-assisted laser desorption/ionization time of flight(MALDI-TOF) mass spectrometer on MassARRAY® Analyzer 4 platform (Sequenom, San Diego, CA). Assay Design Suite v2.0 from the Mysequenom online software was used for probes and primers design. For neuroticism, our measure was the participant's score on an 8 items version of the neuroticism scale from the Big Five Inventory. SHEsisPlus (http://shesisplus.bio-x.cn/SHEsis.html) was applied for Hardy-Weinberg equilibrium, allelic and genotypic distributions. The association between candidate SNPs with neuroticism was analyzed through R package 'SNPassoc' (http://www.r-project.org/).

Among all five SNPs (rs1557341, rs12903563, rs12938775, rs2150426, rs2572431) tested, rs2150426 was deviated from the Hardy–Weinberg equilibrium (deleted for further analysis). The genotype distributions for the remaining four SNPs were as follows: rs1557341 GG 355(48.8%), GT 306(42.1%), TT 66(9.1%); rs12938775 TT 262(36.0%), CT 352(48.4%), CC 113(15.5%); rs12938775 AA 366(50.3%), GA 312(42.9%), GG 49(6.7%); rs2572431 AA 228(31.4%), AG 365(50.2%), GG 134(18.4%). In terms of genetic association study for neuroticism, rs1557341 showed significant individual differences ($P = 0.018$, ß (95%CI) = −1.820 (−3.329 to −0.310)). The five genetic models were run to further explore this result. We found that the T/T genotype was correlated with lower score of neuroticism. In other words, individuals with T/T genotype are at lower risk to be neuroticism. rs1557341 is located at Chr18:37,547,464, intron region of CELF4. Genome-wide association studies have found CELF4 as a candidate gene for neuroticism. CELF4 is expressed mainly in glutamatergic neurons of the cerebral cortex and hippocampus. Glutamate is the major excitatory neurotransmitter in the brain and serves as the metabolic precursor to gamma-aminobutyric acid (GABA) through glutamic acid decarboxylase (GAD). Enhanced activity of the glutamatergic cerebral systems and the decreased GABAergic cerebral systems activity are involved in mental disorders. Subjects with mood disorders have been discovered with GABA neurotransmission system deviance and low GABA levels (Brambilla et al., 2003). In addition, GAD genes have been suggested to be responsible for individual differences in neuroticism. Prior studies have emphasized the important role of CELF4 in synaptic plasticity and excitatory neurotransmission regulation. CELF4 insufficiency causes neurobiological abnormalities due to general neurotransmission impairment. Thus, we suspected that the variation in CELF4 gene may contribute to the balance of glutamate-GABA cycle and lead to individual differences in neuroticism through regulating glutamate and GABA levels. To our knowledge, little studies have focused on the role of CELF4 locus in neuroticism. Our study firstly revealed rs1557341 is associated with neuroticism in Chinese Han population. As neuroticism is a polygenic trait influenced by many genetic variants with small effect, the current study may provide new possibilities for uncovering the neurobiological mechanism of neuroticism. Besides, studies have suggested that genetic factors for neuroticism and psychiatric disorders are largely shared. The CELF4 locus identified in this study therefore offers a distinct direction for future work on genetics of psychiatric disorders as well. Several potential limitations should be taken into consideration. Neuroticism was obtained at one time point, confounding the effects of individual-specific environment, which may influence the genetic effects. Besides, all participants are Chinese Han origin and sample size is relative small, these results may not generalize to other groups.

In conclusion, our study suggests that the CELF4 gene may play a role in neuroticism in Chinese Han population. Taking the limitation of relative small sample size into consideration, further studies should be conducted with a larger sample size for more conclusive conclusions. Besides, further association of CELF4 and other psychiatric disorders which are phenotypically linked to neuroticism should be investigated. Overall, the novel genetic variant identification provides new insights into the neurobiology of neuroticism and related mental disorders.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.136.

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