Association study of KIBRA rs17070145 polymorphism with the risk of schizophrenia in the Han Chinese population

To the Editors:

Schizophrenia (SCZ) is a chronic and devastating psychiatric disorder with high heritability, which may affect approximately 1% of the world’s population. To date, however, the precise pathogenesis of SCZ is still unclear. A recent genome-wide association study demonstrated that a common single nucleotide polymorphism (SNP), rs17070145, within the KIBRA gene, also known as WWC1 (WW and C2 domain containing 1), might contribute to human memory processes (Papassotiropoulos et al., 2006). KIBRA belongs to the WWC family, which may influence synaptic plasticity, memory performance, and cognition through the interaction with a substrate of protein kinase C (PKCζ) (Vogt-Eisele et al., 2014). It is well known that neurocognitive impairments may be a core feature of SCZ. Vassos et al. (2010) attempted to replicate the association between KIBRA rs17070145 polymorphism and memory performance in the patients with psychosis (SCZ or bipolar disorder) and unaffected relatives as well as normal individuals. Importantly, they observed that rs17070145 polymorphism T allele carriers showed a better performance in principle component derived from immediate and delayed logical and visual memory tests compared with CC homozygotes in the combined samples, which is consistent with the original study (Papassotiropoulos et al., 2006). Therefore, the aim of this study was to investigate whether the KIBRA SNP rs17070145 influence susceptibility to SCZ in the Han Chinese population.

We recruited 1418 SCZ patients (530 women and 888 men, aged 46.0 ± 11.6 years at recruitment) including paranoid type (73.5%) and other types (26.5%) and 1124 unrelated healthy controls (503 women and 621 men, aged 45.0 ± 10.2 years at recruitment). The diagnosis of SCZ was confirmed by interviews with two or more experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID-I) and in accordance with criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV). Exclusion criteria included the presence of other mood or neurodevelopmental disorders, epilepsy, or mental retardation. The healthy controls were selected by professional psychiatrists through the Structured Clinical Interview for DSM-IV, Non-patients edition (SCID-NP), and those with mental illness were excluded. The study was approved by the Ethics Committee of the Wuxi Health Mental Center. Before being enrolled in the study, all patients and healthy subjects signed a consent form.

Genomic DNA of each sample was extracted from 150 μl of peripheral blood using a Blood Genotyping DNA Extraction Kit (Tiangen Biotech, Beijing, China). The SNP rs17070145 was genotyped by the Shanghai Biowing Applied Biotechnology Co., Ltd (www.biowing.com.cn) using the ligase detection reaction-polymerase chain reaction (LDR-PCR) method. The PCR primers for SNP rs17070145 are 5′-CCAAGGTTAAAATGGTGGC-3′ (forward) and 5′-AGGCTTGGAATCTCTTGAC-3′ (reverse). This PCR product and the LDR probes (AAAGGAGCTCGAGAACAGTGTG for ‘C’ allele detection; AAAGGAAAGTCAGGAACAGTTA for ‘T’ allele detection) were then subjected to a multiplex LDR reaction, with a DNA sequencer used to detect the products. The calling rate is approximately 97%. All statistics were performed through online SHEsis program (http://analysis.bio-x.cn/myAnalysis.php).

The results indicated the P value of HWE for KIBRA SNP rs17070145 is 0.950 in healthy controls. Additionally, the power of the present study for an allele is approximately 80% using PS software (assumption condition: α=0.05, P=0.2, n=1418, m=0.8, Ψ=1.3). No significant differences in allelic or genotype frequency distribution of KIBRA SNP rs17070145 were observed between SCZ and healthy control groups (OR=1.056, 95% CI=0.923–1.20, P=0.4255). Furthermore, a further stratified analysis by sex also failed to find the association of KIBRA SNP rs17070145 with susceptibility to SCZ (OR=1.096, 95% CI=0.918–1.308, P=0.3102 for male; OR=0.999, 95% CI=0.809–1.233, P=0.9920 for female).

To our knowledge, the evidence lines in response to the association of KIBRA SNP rs17070145 polymorphism with susceptibility to SCZ are still absent to date. Although, we hypothesized that KIBRA SNP rs17070145 may also influence the susceptibility to SCZ, the hypothesis was not supported in the present case-control study. Notably, KIBRA has become an important and attractive target for exploring human cognitive performance, while neurocognitive impairments may be a core feature of SCZ. Particularly, the association of KIBRA rs17070145 polymorphism with episodic memory impairments was found in early onset schizophrenia (EOS) (Vyas et al., 2014). Unfortunately, some of subjects are SCZ patients with repeated episodes in the present study. Thus, we could not accurately confirm the age of onset through inquiring the medical history. To avoid the confusing factor, we did not perform a stratified analysis based on the age of onset, which is a limitation in the study. Furthermore, predictive function from rSNPBase database (http://rsnp.psych.ac.cn/) indicates that the different genotype of rs7070145 may affect the mRNA levels of A disintegrin and metalloproteinase (ADAM9) by cis-regulatory mechanism. Interestingly, the polymorphisms within the ADAM9 gene were genetically associated with the risk of Alzheimer’s disease (AD) characterized by memory decline and cognitive dysfunction (Cong and Jia, 2011). Convergent lines of evidence as well as genetic linkage relationships suggest the potential interaction between KIBRA and ADAM9, for example SNP-SNP interaction network analyses, should be noticeable. Taken together, the present negative finding could not completely exclude the effects of KIBRA genetic variants on susceptibility to SCZ. We only investigate a single locus due to the constraint of fund, while the other genetic variants screened by linkage disequilibrium or sequencing should be further investigated.

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Conflict of interest

The authors report no conflicts of interest.

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References


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