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Case Control Study

ABCB9 polymorphism (rs61955196) is associated with schizophrenia in Chinese Han population

Xin-Wei Li, Ming-Yuan Zhang, Zhi-Jun Li, Li-Zhe Ai, Meng-Di Jin, Ning-Ning Jia, Meng-Tong Xie, Yu-Qing Yang, Wei-Zhen Li, Lin Dong, Qiong Yu

Abstract

BACKGROUND

Schizophrenia (SCZ) is a complex disease which can be affected by both genetic and environmental factors. Prenatal famine exposure may cause changes in DNA methylation levels of genes. Meanwhile, maternal nutrition during pregnancy is a pivotal environmental factor in the development of schizophrenia. DNA methylation may be an intermediate factor mediating exposure to famine during pregnancy and SCZ, and DNA methylation quantitative trait locus (meQTLs) might serve as a promising tool for linking SCZ and prenatal famine.

AIM

To analyze the association between prenatal famine exposure and schizophrenia risk in Northeast Han Chinese through DNA methylation related loci.

METHODS

A total of 954 Han Chinese from Northeast China were recruited, including 443 patients with SCZ and 511 healthy controls. The participants were further divided into famine (born in 1960-1962) and non-famine (born in 1963-1965) groups to investigate the effect of prenatal famine exposure. Four single-nucleotide polymorphisms (SNPs) selected according to relevant literatures were genotyped, namely rs11917047 in *PTPRG*, rs2239681 in *IGF2*, rs3842756 in *INSIGF* and rs61955196 in *ABCB9*. DNA were extracted from peripheral blood samples, and the genotypes of each these SNP loci were detected using the improved Multiple Ligase Detection Reaction multiple SNP typing technique. The associations between the DNA methylation related SNPs and SCZ risk, prenatal famine, and their interactions were analyzed using logistic regression analysis and generalized multifactor dimensionality reduction (GMDR) software.

RESULTS

Based on the sequencing data, genotype distributions and allele frequencies of the four selected SNPs were determined. All genotype frequencies of the four SNPs in healthy control group were tested for deviation from Hardy-Weinberg equilibrium ($P > 0.05$). Logistic regression analysis showed that rs61955196 was significantly associated with SCZ risk in the log-additive model (OR, 1.22; 95%CI, 1.01-1.48; $P = 0.040$). We also found that the rs61955196 allele was related with an enhanced risk of SCZ (G>C, OR, 1.22; 95%CI, 1.01-1.47; $P = 0.042$). However, no associations were observed between rs11917047, rs2239681, rs3842756 and SCZ risk. Under the optimal genetic model, no significant association of famine with the four SNPs was seen. Though the gene–gene interactions between rs2239681 and rs61955196 were found in GMDR analysis, none of the gene-gene interactions and gene-famine interactions were associated with the risk of SCZ.

CONCLUSION

Our study suggested that rs61955196 in *ABCB9* was associated with SCZ susceptibility in Northeast Han Chinese, providing insight into genetic effects on SCZ.

Key Words: Schizophrenia; Prenatal famine; rs61955196; DNA methylation; *ABCB9* polymorphism

Li XW, Zhang MY, Li ZJ, Ai LZ, Jin MD, Jia NN, Xie MT, Yang YQ, Li WZ, Dong L, Yu Q. ABCB9 polymorphism (rs61955196) is associated with schizophrenia in Chinese Han population. *World J Psychiatry* 2022; In press

Core Tip: Prenatal famine exposure may cause changes in DNA methylation levels of genes, while maternal nutrition is a pivotal environmental factor for schizophrenia (SCZ). To analyze the association between prenatal famine exposure and SCZ risk, we recruited 443 SCZ patients and 511 healthy controls with four single-nucleotide polymorphisms genotyped, which were previously identified as DNA methylation

quantitative trait locus. Our study observed significant differences in rs61955196 genotype distribution and allele frequency between SCZ patients and healthy controls for the first time, suggesting that rs61955196 in *ABCB9* was associated with schizophrenia susceptibility among Northeast Han Chinese population.

INTRODUCTION

Schizophrenia (SCZ) is a complex disease affected by both genetic and environmental factors, which is often characterized by symtoms such as hallucinations, social withdrawals, delusions, and cognitive dysfunction[1, 2]. The global point prevalence of schizophrenia was estimated to be 0.28% (0.24%–0.31%) in 2016 which contributes 13.4 (95% UI: 9.9–16.7) million years of life lived with disability to burden of disease globally[3]. And China was assessed to show the highest prevalence of 0.42% among global countries, which raises necessity for us to conduct research enrolling local Chinese participants to reveal practical the status and underlying biological mechanisms of SCZ for its management and treatment.

DNA methylation is a heritable epigenetic modification which alters gene expression[4]. Studies have demonstrated that overall DNA hypomethylation is evident in SCZ patients, while treatment with haloperidol might increase methylation[5, 6]. In other words, DNA methylation, which can regulate gene expression, is closely associated with the risk of SCZ [7-10].

Although the peak incidence rate of SCZ appears in adolescence and early adulthood, many believe that its etiological origin exists much earlier in one's life, which includes exposure to environmental and genetic factors. The exposure occurred in the early stages of life development along with a cumulative effect during the later stages may eventually lead to the appearance of symptoms[11]. Among the environmental factors, maternal nutrition during pregnancy acts an early and vital role in the occurrence and development of SCZ [12, 13]. Studies have shown that prenatal famine exposure may cause changes in DNA methylation levels of genes. Malnutrition during pregnancy, especially the lack of maternal protein and folic acid, seriously affects fetal development

which will result in changes in DNA methylation[14]. Empirical studies of the Great Famine of China in 1959-1961 and the Dutch famine in 1944-1945 both showed that prenatal famine exposure led to an obviously increased risk of SCZ [15-17]. It was found that those who were born during the famine are twice as likely to have SCZ in their later years as normal people[16]. Therefore, we propose that prenatal nutritional deficiencies may increase the risk of SCZ by altering DNA methylation status.

In recent years, genome-wide association studies (GWAS) have been effectively used for studying genetic variation associated with SCZ [18, 19]. As DNA methylation tends to be sensitive to environmental factors, DNA methylation quantitative trait locus (meQTLs) seems more promising. They can be derived by GWAS mapping levels of DNA methylation in genotyped individuals and defined loci at which DNA methylation is influenced by genetic variation[20], with a superiority of higher consistency throughout one's life than DNA methylation itself. There have already been reports revealing the role of meQTLs in SCZ risk, which promote the feasibility of them serving as a useful tool for SCZ-related research[21, 22]. However, the results from GWAS studies are often not repeatable due to the enormous number for detection and heterogeneity of genetic information regarding people from different races and regions[23]. Given the high SCZ prevalence in China and current lack of available genetic data covering native patients, we find it necessary to conduct reseach collecting genetic data among Chinese individuals.

Here we intend to analyze the associations between single-nucleotide polymorphisms(SNPs) identified as meQTLs with the risk of SCZ and prenatal famine exposure among the Han population in Northeast China. We recruited SCZ patients and healthy controls with comparable age including individuals born between 1959 and 1961 with prenatal famine exposure, and collected their peripheral blood samples for genotyping. We selected four SNPs which were previously reported as meQTLs, and determined their associations between SCZ and prenatal famine along with their interactions. We hope our work may provide more practical reference in management of SCZ.

MATERIALS AND METHODS

Study subjects

A desired sample size of 417 was calculated by the software Quanto with a proper power before the recruitment of participants, with a unmatched case-control rate of 1.2, an estimated population risk of 1% for SCZ, a log-additive model gene with allele frequency of 0.1 and genetic effect of 1.5 and a type I error rate of 0.05 by 2-sided test. According to the desired sample size and the inclusion and exclusion criteria, a total of 954 Han Chinese from Northeast China were finally recruited between 2010 and 2012, including 443 SCZ patients and 511 healthy people. The patients were recruited from the Siping Psychiatric Hospital and Sixth Hospital of Changchun City (Jilin, China). Each patients was diagnosed according to the Tenth Revision of International Classification of Diseases (ICD-10) for SCZ and confirmed by at least two experienced psychiatrists. Those with neurological disorders, severe organic lesions, and drug dependence were excluded. Subjects in the healthy control group matching the patients by gender and age were recruited from the Changchun Municipal Centre for Disease Control and Prevention, in order to get a comparable propotion of famine-exposed individuals between two groups and a similar ratio of gender. The healthy subjects were required to have no history of mental illness and were in good health without any known disease at the time of recruitment. Furthermore, subjects who were in uterus between 1959 and 1961 were regarded to be exposed to famine. And then they were divided into two groups, namely famine group (born in 1960-1962) and the non-famine group (born in 1963-1965), according to whether they were exposed to famine before birth All methods were performed in accordance with the relevant guidelines and regulations. The study adhered to the tenets of the Declaration of Helsinki, and was approved by the Ethics Committee of the School of Public Health of Jilin University (Approval No: 2014-03-11). All participants signed the informed consent.

Genomic DNA Extraction and Genotyping

In the first step, we collected peripheral blood samples from the participants and further extracted genomic DNA. Then, DNA content and purity were determined based on the ratio of OD_{260}/OD280. Combining the feasibility of the detection method and the previous publications, we selected four SNPs (rs11917047 in *PTPRG*、rs2239681 in *IGF2*、rs3842756 in *INSIGF* and rs61955196 in *ABCB9*) which have been confirmed as meQTLs, and the SNPs themselves or the genes they belong to were assessed to be associated with SCZ[21, 24-26].

Then, the genotypes of these SNP locus were detected using the iMLDR (improved Multiple Ligase Detection Reaction) multiple SNP typing technique (Shanghai Tian Hao Biological Technology Co. Ltd.). Using the Assay Design software 3.1, we successfully designed primers for the four meQTL SNPs. And the primer sequences for each SNP were as follows:

rs11917047-F AGATGAAAGATTGGGGTGTGGGTA, and
rs11917047-R GCTGGTACCCAACCAGGAACAC;
rs2239681-F ATGGGCAAATCAGCCTGAAGAG, and
rs2239681-R GTGTGCAAGAGGGGTGAAAGGT;
rs3842756-F TCCACAGGGACTCCATCAGAAA, and
rs3842756-R CCTGTGGCTCAGGGTCCAGTAT;
rs61955196-F GCTGCAAGGTCGGAGCTGAG, and
rs61955196-R TGGGAGGAGTTTGCCACAGG.

Statistical analysis

Deviation of the genotypes from Hardy-Weinberg equilibrium (HWE) between the SCZ patients and healthy individuals was assessed using a c^2 goodness-of-fit test. Logistic regression analysis was used to examine the relationship between SNPs and the risk of SCZ as well as the association of famine with SNPs with age and sex adjusted as covariates. The online genetic analysis software, SNPStats, was used to select the optimal genetic model according to the Akaike information criterion (AIC) and Bayesian information criterion (BIC). Generalized multifactor dimensionality reduction

(GMDR) analysis was conducted to analyze the gene-gene interactions which is a rather critical component in investigating genetic information for multifactorial diseases, and the gene-environment interactions were analyzed by crossover analysis based on logistic regression analysis. Except for the above specified, all statistical analyses were performed by SPSS 24.0 software. *P* value < 0.05 was considered to be statistically significant.

RESULTS

Based on the SNP sequencing data, genotype distributions and allele frequencies of the four selected SNPs in SCZ patients (*n* = 443) and healthy controls (*n* = 511) were determined and the detailed data are shown in Table 1. All genotype frequencies of the four SNPs in health control group were in accordance with Hardy-Weinberg equilibrium (*P* > 0.05). Logistic regression analysis showed that, compared with those carrying wild homozygote (CC) of rs61955196, subjects carrying the mutant homozygote (GG) had a higher risk of SCZ (OR = 1.54; 95%CI: 1.03-2.30; *P* = 0.037). We also found that the rs61955196 allele was related with an enhancing risk of SCZ (OR = 1.22; 95%CI: 1.01-1.47; *P* = 0.042). The frequency of the rs61955196-G allele was 40.5% in case group, which was significantly higher than that of 36.6% in control group (*P* < 0.05). No associations were observed between SCZ patients and HC regarding different genotypes or alleles of the rest three SNPs.

Based on the findings, we dug into the association between genotypes of rs61955196 and SCZ risk using multiple genetic models. As shown in Table 2, a significant association between rs61955196 and SCZ in the log-additive model was revealed (*OR* = 1.22; 95%CI: 1.01-1.48; *P*=0.040). In the codominant model, we also found the association of rs61955196 with SCZ in the GG *vs* CC genotype comparison. No obvious effect of rs61955196 on the risk of SCZ was found in other models (*P* > 0.05).

To investigate the relationship of meQTLs and prenatal famine exposure, we analyzed the associations between the four SNPs with famine. Totally, 492 subjects were exposed to prenatal famine including 220 SCZ patients and 272 healthy controls. As

shown in Table 3, based on the AIC, the inheritance model for rs11917047 and rs2239681 was recessive, codominant for rs3842756, and overdominant for rs61955196. SCZ patients and healthy controls were further divided into famine group and non-famine group. Logistic regression analysis indicated that under the optimal genetic model, there was no significant association of famine with the four SNPs in either the SCZ group or HC ($P > 0.05$).

In this study, GMDR was used to import and analyze the interactions between rs11917047, rs2239681, rs3842756, and rs61955196. The impact of gene–gene interaction on the risk of SCZ was summarized in Table 4. The multifactor model 2 (rs2239681×rs61955196) presented the best cross-validation consistency, which had a testing-balanced accuracy of 55.8%. Figure 1 showed the interaction model of this gene–gene interaction between rs2239681 and rs61955196. However, no significant association of gene-gene interaction with the risk of SCZ was found in this model.

Crossover analysis based on a multiplicative model of logistic regression were conducted to determine the interactions between the SNPs and famine in SCZ patients (Table 5). None of the interactions between the genotypes of the four loci of SNPs rs11917047/rs2239681/rs3842756/rs61955196 with the risk of famine were statistically significant ($P > 0.05$).

DISCUSSION

Based on existing reports, we selected 4 susceptibility loci of SNPs related to SCZ as the starting point for analysis, which are rs11917047 in *PTPRG*, rs2239681 in *IGF2*, rs3842756 in *INSIGF* and rs61955196 in *ABCB9* respectively. This study used meQTL SNPs to analyze data from representative samples of northeastern Chinese, and found the differences of rs61955196 genotype distribution with allele frequency between SCZ patients and healthy control subjects for the first time. Rs61955196 is located in the 5'UTR of the *ABCB9* gene, encoding the *ABCB9* protein which belongs to the ATP-binding cassette (*ABC*) transporter family. The *ABC* gene can be divided into seven different subfamilies (*MRP, ABC1, OABP, ALD, GCN20, MDR/TAP, White*)[27], and the

ABCB9 protein is a member of the *MDR/TAP* subfamily. *ABC* family and *ABCB9* are reported to be involved in progression of multiple maglinant tumors and chemoresistance[28-31], but little research has been done on the relationship between ABCB9 gene and SCZ. Previous studies have done little research on the relationship between *ABCB9* gene and SCZ, but current evidence suggests that *ABCB9* is positively associated with the risk of SCZ[32], which is in accordance to our findings to some extent.

Increasing studies have shown that epigenetic modifications are associated with the pathogenesis of SCZ, and DNA methylation is a crucial one regulating gene expression, which may be a key factor in the pathogenesis of SCZ[33, 34]. Our results showed that the methylation locus rs61955196 increased the risk of SCZ in the log-additive model. However, we did not observe the association between the methylation loci located in the other three genes and SCZ, which is inconsistent with existing studies. For example, Arnaud *et al*[35] discovered that the *PTPRG* gene containing the rs11917047 Locus was associated with SCZ. The receptor protein tyrosine phosphatase *PTPRG* is a ligand for members of the contact protein family, which are linked to autism spectrum disorders. The interpretation for these disagreements may be due to the disparity in the target population as we studied is the Han population in Northeast China, which is different from other studies in race, sample size and geographic location.

It is a pity that we did not find the association of prenatal exposure to famine with DNA methylation loci. A recent study also reported that maternal risk alleles for neurodevelopmental disorders, primarily attention-deficit/hyperactivity disorder were associated with prenatal exposures, but nor for SCZ or autism spectrum disorder[36]. Nevertheless, there have been many supportive evidence regarding the positive relationship between SCZ and prenatal famine exposure. Robert[37] discovered that maternal nutritional deficiency may result in permanent abnormal DNA methylation with the potential to affect gene expression. In addition, since human is unable to synthesize folic acid which is necessary for normal DNA methylation, the lack of folic acid which hinders the production of methyl donors might affect gene expression

related to neurodevelopmental processes. Prenatal famine leads to undernutrition during fetal development is believed to further promote the risk of SCZ in offspring[38]. Cuntong *et al*[39] also used data from a nationally representative sample to analyze the association of prenatal famine exposure with the risk of SCZ. The results showed that famine population had a higher risk of SCZ compared to the non-famine cohorts. This pattern was found throughout different subsample, such as the urban/rural population[40]. Therefore, we still believe that it is vital to continue exploring the association of prenatal famine exposure with DNA methylation and SCZ in the future.

Meanwhile, this study had several limitations. First, we only adjusted for gender as we mainly focused on the genetic variants, and we were not able to explore some underlying confounders such as medication as we have directly excluded those who had any medical treatment in the past three months before enrollment. Second, as we did not collect sufficient information from the patients regarding illness-related parameters such as the severity or duration of disease, we could not rull out the possibility that the SNPs could be associated with SCZ under some specific conditions although we got negative results. Third, this study is a case-control study and the patients were recruited from hospitals, resulting in inevitable selection bias. Finally, limited by the feasibility and applicability of the detection method, we only selected four SNPs in this study, and the constrained selection may leave out other crucial SNPs related to DNA methylation.

CONCLUSION

Based on existing reports, we selected 4 susceptibility loci of SNPs related to SCZ as the starting point for analysis, which are rs11917047 in *PTPRG*, rs2239681 in *IGF2*, rs3842756 in *INSIGF* and rs61955196 in *ABCB9* respectively. This study used meQTL SNPs to analyze data from representative samples of northeastern Chinese, and found the differences of rs61955196 genotype distribution with allele frequency between SCZ patients and healthy control subjects for the first time. Rs61955196 is located in the 5'UTR of the ATP binding cassette subfamily B member 9 *(ABCB9)* gene, encoding the

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synthesize folic acid which is necessary for normal DNA methylation, the lack of folic acid which hinders the production of methyl donors might affect gene expression related to neurodevelopmental processes. Prenatal famine leads to undernutrition during fetal development is believed to further promote the risk of SCZ in offspring[38]. Cuntong *et al*[39] also used data from a nationally representative sample to analyze the association of prenatal famine exposure with the risk of SCZ. The results showed that famine population had a higher risk of SCZ compared to the non-famine cohorts. This pattern was found throughout different subsample, such as the urban/rural population[40]. Therefore, we still believe that it is vital to continue exploring the association of prenatal famine exposure with DNA methylation and SCZ in the future.

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ARTICLE HIGHLIGHTS

Research background

Schizophrenia (SCZ) is a severe mental disorder bringing heavy burden, which is closely related with genetic and environmental factors. Effect of prenatal exposure of famine on SCZ risk has been reported with intense interest. DNA methylation may be

an intermediate factor mediating prenatal famine and SCZ, and DNA methylation quantitative trait locus (meQTLs) can serve as a promising tool.

Research motivation

The lifetime prevalence of SCZ is approximately 1% around the world, and study has reported a highest age-standardized prevalence of SCZ for China. Meanwhile, the Chinese famine of 1959-1961 is a proper source of study subjects to investigate the effect of prenatal famine on SCZ with little available genetic data. As a result, we intend to conduct analyses for SCZ and prenatal famine using native subjects with collected genetic information, which may provide insights specifically for Chinese researchers and patients.

Research objectives

To investigate the associations of four single-nucleotide polymorphisms (SNPs) identified as meQTLs with the risk of SCZ and prenatal famine exposure along with their interactions among Northeast Han Chinese.

Research methods

We recruited 954 Han Chinese from Northeast China including 443 patients with SCZ and 511 healthy controls, and their peripheral blood samples were collected. 492 of them born in 1960-1962 were further allocated to famine group. Four SNPs were selected and genotyped, namely rs11917047 in *PTPRG*, rs2239681 in *IGF2*, rs3842756 in *INSIGF* and rs61955196 in *ABCB9*. The associations between the meQTLs and SCZ risk, prenatal famine, and their interactions were analyzed using logistic regression analysis and generalized multifactor dimensionality reduction (GMDR) software.

Research results

The genotype distributions along with allele frequencies of the four SNPs were determined among the Chinese participants. We found that rs61955196 was

significantly associated with SCZ risk in the log-additive model (OR, 1.22; 95%CI, 1.01-1.48; P = 0.040), and rs61955196 allele was related with an enhanced risk of SCZ (G>C, OR, 1.22; 95%CI, 1.01-1.47; P = 0.042). However, the other three SNPs were not associated with SCZ risk. No association was observed between the SNPs and prenatal famine. Gene-gene interactions were seen between rs2239681 and rs61955196, while no gene-gene or gene-famine interactions were associated with the risk of SCZ.

Research conclusions

Our results suggested that rs61955196 in *ABCB9* might be involved in SCZ susceptibility among Northeast Han Chinese.

Research perspectives

Our study provides a potential functional variant rs61955196 for SCZ susceptibility, and we recommend further research to extend the findings to different populations and verify its function. Though no evidence between SCZ and prenatal famine was found, we believe gathering comprehensive information for analyses regarding subgroups may help to reveal the association in the future.

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