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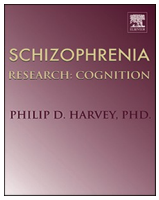

Association between the *HHEX* polymorphism and delayed memory in first-episode schizophrenic patients

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ABSTRACT

The hematopoietically-expressed homeobox gene (*HHEX*) played a critical role in regulating the immune system that the abnormality of which was involved in the psychopathology and cognitive deficits of psychiatric disorders. The aim of this study was to investigate the effect of *HHEX* rs1111875 polymorphism on the susceptibility and cognitive deficits of first-episode schizophrenic patients (FSP). We assessed cognitive function in 239 first-episode patients meeting DSM-IV for schizophrenia, and 368 healthy controls using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The *HHEX* rs1111875 polymorphism was genotyped. Our results showed that the allelic and genotypic frequencies of *HHEX* rs1111875 polymorphism didn't differ between FSP and healthy controls (both $p > 0.05$) after adjusting for sex and age. Cognitive test scores in FSP were significantly lower than those in healthy controls on all scales (all $p < 0.001$) except for the visuospatial/constructional score ($p > 0.05$) after adjusting for covariates. There was a significant genotype ($p < 0.05$) rather than genotype × diagnosis ($p > 0.05$) effect on the delayed memory score after adjusting for covariates. The *HHEX* rs1111875 polymorphism was significantly associated with the delayed memory score in FSP ($p < 0.05$), but not in healthy controls ($p > 0.05$) after adjusting for covariates. Our findings supported that the *HHEX* rs1111875 polymorphism did not contribute to the susceptibility to FSP. However, this polymorphism might influence the delayed memory in FSP. Moreover, FSP had poorer cognitive function than healthy controls except for the visuospatial/constructional domain.

1. Introduction

Cognitive deficits have been considered a core feature of psychiatric disorders, especially schizophrenia (Condray and Yao, 2011). Cognitive deficits of schizophrenia have been reported to mainly exist in the following domains, such as memory, language, attention, learning, cognitive processing speed, and executive functioning (Mclntosh et al., 2011; Han et al., 2012; Hui et al., 2013, 2016). These cognitive deficits occur prior to the onset of other psychotic symptoms and commonly persist throughout the duration of illness (Rund, 1998; Lieberman et al., 2001; Hughes et al., 2003; Dickerson et al., 2004). Cognitive deficits may further influence their treatments, rehabilitation, quality of life, and even employment for schizophrenia (Shean, 2007; Harvey, 2009). Moreover, genetic factors have been reported to contribute to about 79 % of the variability in abstract reasoning, 70 % of the variability in verbal reasoning skills, and 50 % of the variability in memory ability (Bouchard and McGue, 1981; McClearn et al., 1997; Benyamin et al., 2005; Johnson et al., 2007). Taken together, these studies support the notion that genetic factors may play a critical role in cognitive deficits of first-episode schizophrenic patients (FSP).

The hematopoietically-expressed homeobox protein (HHEX) is a member of the homeobox family of transcription factors that is encoded by the *HHEX* gene in humans (Bedford et al., 1993; Hromas et al., 1993). The mutations of *HHEX* gene on chromosome 10q23.33 are mainly involved in the developmental processes including immune and nervous systems (Keng et al., 2000; Martinez Barbera et al., 2000; Hallaq et al., 2004; Stuckey et al., 2011). The immune developmental hypothesis for schizophrenia has been supported by several lines of evidence including the increased serum levels of inflammatory markers (C-reactive protein/CRP, and interleukin-6/IL-6) (Fan et al., 2017; Miller et al., 2011, 2014;

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Wu et al., 2016), the imbalanced proinflammatory and anti-inflammatory mechanisms (Muller and Schwarz, 2006; Wu et al., 2016), and the association between inflammatory process and abnormal brain structure and function in individuals with schizophrenia (Frodl and Amico, 2014). Several genetic studies have further confirmed the role of immune system by detecting the susceptible genes and chromosomal regions as the risk loci of schizophrenia (Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009; Li et al., 2011; Ripke et al., 2011, 2014). Thus, it is possible that the variables of *HHEX* gene regulate the immune system that the abnormality of which is linked to the etiology of FSP (Keng et al., 2000).

Moreover, it is hypothesized that the abnormality of immune system may play a core role in cognitive deficits of schizophrenia (Fineberg and Ellman, 2013; Miller et al., 2014). This hypothesis is supported by several lines of evidence. For example, several clinical studies have shown that the interaction between the inflammation and nervous system may influence cognitive deficits (Dantzer et al., 2008), including the decrease in premorbid cognitive function (Brown et al., 2001; Ellman et al., 2009), and the deficits of executive ability following schizophrenic onset (Brown et al., 2001). Animal studies further support the significant associations among cognitive behavior, immune system, and nervous system (Meyer, 2014; Labouesse et al., 2015; Khandaker et al., 2015). Interesting, the variants of *HHEX* gene are also found to strongly contribute to regulating the immune system and nervous development (Keng et al., 2000; Martinez Barbera et al., 2000; Hallaq et al., 2004; Stuckey et al., 2011). In addition, several previous studies have found that there are significant associations among the *HHEX* rs1111875 polymorphism, impaired glucose tolerance and schizophrenia (Chen et al., 2016; Staiger et al., 2008; Pivovarova et al., 2009). However, no study has examined the *HHEX* polymorphism in relation to the etiology and cognitive deficits of schizophrenia. Therefore, the aim of this study is to investigate whether the *HHEX* rs1111875 polymorphism may play an important role in the susceptibility and cognitive deficits of FSP.

2. Methods

2.1. Subjects

This study was performed between August 2016 and July 2019. A total of 239 FSP (male/female = 134/105) were recruited from the inpatient unit in Suzhou Guangji Hospital, Suzhou Medical College of Soochow University. The inclusion criteria were: a) patients aged 18–48 years; b) an acute episode at study intake that met DSM-IV criteria for schizophrenia; c) no previous exposure to antipsychotic medications; and d) able to provide written informed consent and take part in psychopathology assessment. Diagnoses were confirmed by the structured clinical interview for DSM-IV (SCID). The psychopathology severity of FSP was assessed using the positive and negative syndrome scale (PANSS) (Kay et al., 1987).

Healthy controls (N = 368; male/female = 155/213) were Han Chinese recruited at the same period from the local community. Psychiatry disorders were ruled out in healthy controls by the SCID conducted by a psychiatrist. None of healthy controls presented a personal or family history of psychiatric disorders.

A complete medical history and physical examination were obtained from FSP and healthy controls. All subjects were physically healthy and any subjects with abnormalities including cardiovascular disease, cerebrovascular disease, infections, cancer, unstable diabetes, uncontrolled hypertension and pregnancy, were excluded. Neither FSP nor healthy controls suffered from drug or alcohol abuse/dependence that was determined by the laboratory urine test. This study received approval from the institutional review board of Suzhou Guangji hospital, Suzhou Medical College of Soochow University, and written informed consent was obtained from all subjects.

2.2. Cognitive tests

We assessed cognitive function using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Form A) (Randolph et al., 1998). The RBANS includes 12 subtests that were used to calculate a total score and 5 index scores. The test indices consist of immediate memory, delayed memory, attention, visuospatial/constructional, and language. The RBANS was previously translated into Chinese version and its clinical validity and test-retest reliability were established in healthy controls and individuals with schizophrenia (Zhang et al., 2009). The RBANS index scores were the standardized scores in this study.

2.3. Genotyping

Five-milliliter peripheral blood was used to extract genomic DNA with a salting-out method (Tian et al., 2006). QuantStudio™ Dx Real-Time PCR Instrument with a 384-well format (Thermo Fisher Scientific Inc., USA) was used for genotyping the *HHEX* rs1111875 polymorphism by TaqMan® single nucleotide polymorphism (SNP) genotyping method according to the protocol of this instrument. The TaqMan probe and primes ID of this polymorphism was C_11214581_10. Duplicate samples and negative controls (without DNA) were set of quality assurance of genotyping. A research assistant who was blinded to the clinical status performed genotyping, and concordance for duplicate samples was 100 % for all assays.

2.4. Statistical analysis

The deviations from Hardy–Weinberg equilibrium (HWE) were assessed using the HWSIM program (Cubells et al., 1997). The *HHEX* rs1111875 allelic and genotypic frequencies were compared between FSP and healthy controls using Chi Squared (χ^2) tests. Group differences were compared using Student *t*-tests or one-way analysis of variance (ANOVA) for continuous variables and χ^2 for categorical variables.

We applied analysis of covariance (ANCOVA) to construct an analytical model of 2 (FES versus healthy controls) × 3 (AA versus AG versus GG of *HHEX* rs111875). The genotypes of *HHEX* rs111875 were regarded as the independent variables, and the RBANS total score and 5-subindex scores were regarded as the dependent variables, with sex, age and education as covariates according to previous studies (Hui et al., 2013). Firstly, the comparisons of all RBANS scores were perfected between FES and healthy controls after adjusting for covariates. Second, the comparisons of all RBANS in all subjects were perfected among AA, AG and GG of *HHEX* rs111875 after adjusting for covariates. Finally, the main effect of genotype x diagnosis on all RBANS scores in all subject was tested after adjusting for covariates. When ANOVA identified significant differences in the RBANS cognitive scores according to the genotypic group in FSP or healthy controls, the effects of sex, age, and education were tested by adding these variables to the model of ANCOVA as covariates. SPSS version 17.0 was used to perform the statistical analysis. Data were presented as the mean and SD, and all *p* values were 2-tailed, with the significance level set at 0.05.

The power of sample was calculated with quanto software (Gauderman, 2002), with known risk allele frequencies, a schizophrenia population prevalence of 1 %, and examining log additive, recessive and dominant models. The significance level was set at a *p*-value of 0.05.

3. Results

The demographic characteristics were summarized in Table 1. FSP and healthy controls significantly differed in sex, age, and education (all $p < 0.05$). The distributions of *HHEX* rs1111875 genotypes were consistent with HWE in both FSP and healthy controls (both $p > 0.05$). There were no significant differences in the *HHEX* rs1111875 allelic and genotypic distributions between FSP and healthy controls, as shown in

Table 1
The demographic and clinical data between first-episode schizophrenic patients (FSP) and healthy controls.

Variable	Healthy controls (n = 368)	FSP (n = 239)	Statistic (*p* value)
Sex (male/female)	155/213	134/105	11.30 (0.001)**
Age (years)	44.50 ± 13.90	32.26 ± 13.04	117.93 (<0.001)***
Education (years)	9.83 ± 5.72	8.77 ± 3.29	6.70 (0.01)*
PANSS scores			
Positive symptoms		17.27 ± 5.88	
Negative symptoms		18.56 ± 7.01	
General psychopathology		30.66 ± 7.52	
Total score		66.49 ± 15.52	

Note: * indicates the significance difference, *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

Table 2
Comparisons of the allele and genotype frequencies of *HHEX* rs1111875 between FSP and healthy controls.

Variable	Healthy controls (n = 368)	FSP (n = 239)	χ^2	*p*
Allele frequencies (%)				
A	211 (28.7 %)	120 (25.1 %)	1.86	0.17
G	525 (71.3 %)	358 (74.9 %)		
Genotype frequencies (%)				
A/A	30 (8.2 %)	16 (6.7 %)	1.94	0.38
A/G	151 (41.0 %)	88 (36.8 %)		
G/G	187 (50.8 %)	135 (56.5 %)		

Note: *HHEX* = hematopoietically expressed homeobox. There were still not differences in the allele and genotype frequencies between FSP and healthy controls by adjusting for sex and age (both $p > 0.05$).

Table 2 ($\chi^2 = 1.86$, $p = 0.17$; $\chi^2 = 1.94$, $p = 0.38$, respectively). We still did not find their differences between the two groups after adjusting for sex and age (both $p > 0.05$). Further analysis found that the *HHEX* rs1111875 polymorphism was not significantly associated with PANSS total score, PANSS negative symptom, PANSS positive symptom, and PANSS general psychopathology in FSP (all $p > 0.05$).

The RBANS data were available for 180 FSP and 367 healthy controls. The RBANS total and index scores grouped by the *HHEX* rs1111875 polymorphism were summarized in Table 3. The RBANS total score ($F = 76.15$, $p < 0.001$), immediate memory score ($F = 41.90$, $p < 0.001$), attention score ($F = 46.50$, $p < 0.001$), language score ($F = 103.42$, $p < 0.001$), and delayed memory score ($F = 51.39$, $p < 0.001$) in FSP were significantly lower than those that in healthy controls except for the visuospatial/constructional index ($F = 2.95$, $p = 0.09$) after adjusting for sex, age, and education. There was a significant genotype effect of this polymorphism on delayed memory score after adjusting for covariates ($F = 4.04$, $p = 0.02$). However, this polymorphism did not influence immediate memory score ($F = 1.85$, $p = 0.16$), attention score ($F = 1.19$, $p = 0.30$), language score ($F = 2.29$, $p = 0.10$), visuospatial constructional score ($F = 0.05$, $p = 0.95$), and RBANS total score ($F = 2.35$, $p = 0.10$). Moreover, there was no significant genotype × diagnosis effect on the RBANS total score ($F = 0.55$, $p = 0.58$), immediate memory score ($F = 0.54$, $p = 0.58$), attention score ($F = 0.47$, $p = 0.63$), language score ($F = 0.16$, $p = 0.85$), visuospatial constructional score ($F = 0.40$, $p = 0.67$), and delayed memory score ($F = 1.80$, $p = 0.17$) after adjusting for covariates.

Further analysis showed that the delayed memory score significantly differed according to the genotypic group (A/A group versus A/G groups versus G/G group) in FSP after adjusting for covariates ($F = 3.74$, $p = 0.03$), but not in healthy controls ($F = 2.00$, $p = 0.14$) (Fig. 1).

This total sample had 0.76–0.99 statistical power to detect this polymorphism associated with FSP through dominant, recessive or log additive inheritance, with a genetic effect of 2 (alpha = 0.05, two tailed test).

4. Discussion

To our knowledge, this is the first report to investigate the correlation of *HHEX* rs1111875 polymorphism with the susceptibility and cognitive deficits of FSP. We had three main findings: 1) this polymorphism was not associated with the susceptibility to FSP; 2) the RBANS total and index scores in FSP were significantly lower than those in healthy controls except for the visuospatial/constructional domain; and 3) This polymorphism influenced the delayed memory score in FSP.

This study identified that the *HHEX* rs1111875 polymorphism did not contribute to the susceptibility to FSP, which was consistent with our previous study reporting no significant association between this polymorphism and individuals with chronic schizophrenia (Zhao et al., 2016). However, previous studies have shown that this polymorphism was a functional locus that played an important role in the susceptibility to several disorders (Staiger et al., 2008; Pivovarova et al., 2009). Moreover, the variants of *HHEX* gene have been reported to influence developmental processes, especially nervous and immune systems (Keng et al., 2000; Martinez Barbera et al., 2000; Hallaq et al., 2004; Stuckey

Table 3
Comparisons of total and index scores on the RBANS by diagnostic and genotype groupings.

RBANS	Healthy controls			FSP			Diagnose	Genotype	Diagnose × Genotype
	A/A (n = 30)	A/G (n = 151)	G/G (n = 186)	A/A (n = 14)	A/G (n = 65)	G/G (n = 101)	F[a], (*p* value)	F[b], (*p* value)	F, (*p* value)
Immediate memory	82.9 ± 17.7	75.9 ± 18.3	74.9 ± 16.6	65.9 ± 14.3	62.5 ± 15.9	63.4 ± 17.2	41.90 (<0.001)***	1.85 (0.16)	0.54 (0.58)
Attention	91.0 ± 20.7	88.4 ± 21.1	87.4 ± 18.8	77.6 ± 17.6	72.1 ± 16.3	72.0 ± 19.2	46.50 (<0.001)***	1.19 (0.30)	0.47 (0.63)
Language	96.9 ± 14.7	93.6 ± 13.8	94.7 ± 12.6	77.6 ± 17.9	71.2 ± 16.5	71.4 ± 18.2	103.42 (<0.001)***	2.29 (0.10)	0.16 (0.85)
Visuospatial/ constructional	82.1 ± 13.7	79.6 ± 16.6	79.6 ± 15.0	74.1 ± 15.0	76.2 ± 16.9	75.7 ± 15.3	2.95 (0.09)	0.05 (0.95)	0.40 (0.67)
Delayed memory	91.9 ± 10.4	86.3 ± 16.0	86.2 ± 14.9	75.0 ± 16.9	66.0 ± 18.8	71.0 ± 19.8	51.39 (<0.001)***	4.04 (0.02)*	1.80 (0.17)
Total score	85.4 ± 13.8	80.3 ± 16.4	80.1 ± 14.9	67.6 ± 14.5	63.3 ± 13.1	64.7 ± 14.9	76.15 (<0.001)***	2.35 (0.10)	0.55 (0.58)

[a] There were significant differences in cognitive scores between FSP and healthy controls except for the visuospatial/constructional score after adjusting for sex, age and education (all ***$p < 0.001$).

[b] There were significant genotype effect on the delayed memory score after adjusting for sex, age and education ($F = 4.04$, *$p = 0.02$).

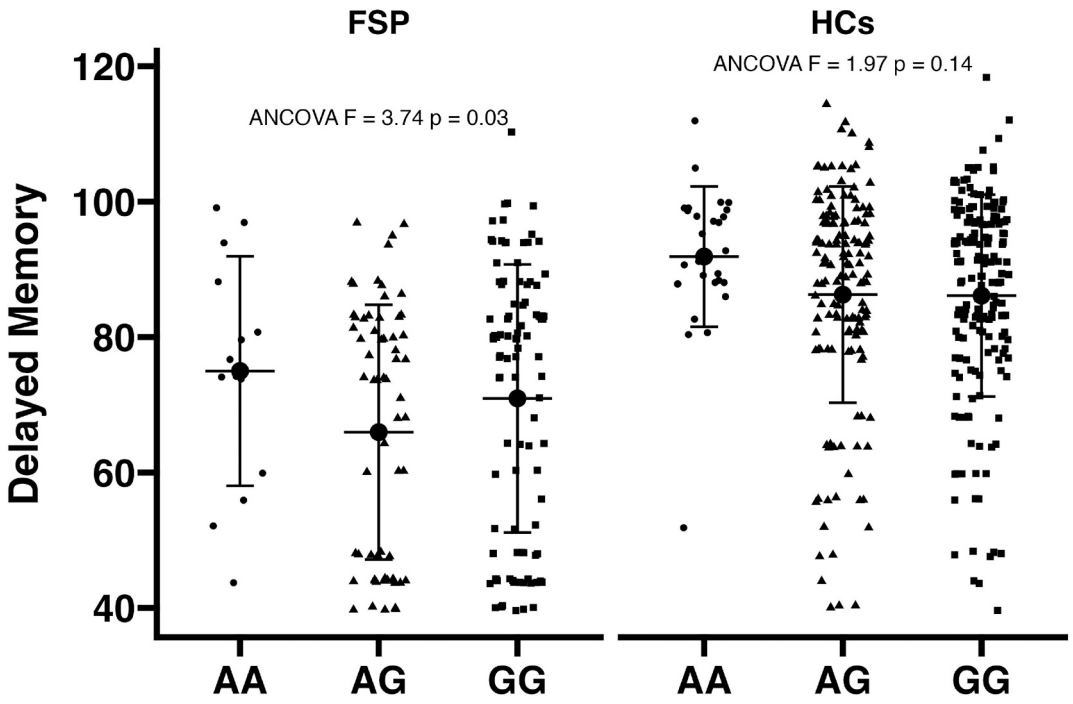

Fig. 1. After adjusting for sex, age and education, there was significant difference in delayed memory score among AA (75.0 ± 16.9) versus AG (66.0 ± 18.8) versus GG (71.0 ± 19.8) of *HHEX* rs1111875 in FSP (F = 3.74, $p = 0.03$), but not showed difference in delayed memory score among AA (91.9 ± 10.4) versus AG (80.3 ± 16.4) versus GG (80.1 ± 14.9) of this polymorphism in healthy controls (HCs) (F = 1.97, $p = 0.14$).

et al., 2011). Several serum studies also indicated that the abnormality of immune system might be involved in the etiology of schizophrenia (Muller and Schwarz, 2006; Fan et al., 2017; Miller et al., 2011, 2014; Wu et al., 2016), which was significantly associated with the abnormality of brain structure and function in individuals with schizophrenia (Frodl and Amico, 2014). Previous genome-wide association studies (GWAS) further confirmed that the immune system-associated genetic loci could contribute to the susceptibility to schizophrenia (Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009; Li et al., 2011; Ripke et al., 2011, 2014). Collectively, these findings all supported that the variables of *HHEX* gene may be associated with the susceptibility to schizophrenia by regulating immune system (Keng et al., 2000). The above divergent findings may be due to the following reasons. First, the *HHEX* rs1111875 polymorphism might not influence the immune system in individuals with schizophrenia. Second, other functional polymorphisms of this gene could contribute to the developmental process of immune system in individuals with schizophrenia. Finally, other factors could play a role in the developmental process of immune system in individuals with schizophrenia, such as *HHEX* and other gene interaction, *HHEX* and environment interaction, and *HHEX* haplotype analysis. Thus, further studies should be still required.

This study found that FSP had more significant cognitive deficits than healthy controls in almost all cognitive domains except for the visuospatial/constructional domain. This finding was consistent with our previous studies in FSP (Hui et al., 2013; Zhang et al., 2013) and individuals with chronic schizophrenia (Hui et al., 2015, 2016). Several foreign studies also further supported our finding in FSP by the case-control study design (Riley et al., 2000; Laurel et al., 2002; Addington et al., 2003). However, the inconsistent findings also were found in individuals with schizophrenia. For example, several previous studies found a significant difference in the visuospatial/constructional score between individuals with schizophrenia and healthy controls (Dickerson et al., 2004; Laurent et al., 2007; Gogos et al., 2010), but not in the attention score between the two groups (Christopher et al., 2002). The different findings of cognitive deficits in individuals with schizophrenia may be due to the multiple and complex factors, including race, sex, age, education, smoking, duration of illness and antipsychotic medications. Therefore, longitudinal cohort studies in FSP should be performed to confirm our findings.

Interesting, this study was the first to report that the *HHEX* rs1111875 polymorphism was significantly associated with the delayed memory in FSP, but not in healthy controls. The variants of *HHEX* gene have been reported to play a critical role in the developmental processes of nervous and immune systems (Keng et al., 2000; Martinez Barbera et al., 2000; Hallaq et al., 2004; Stuckey et al., 2011). The inflammation and nervous system interaction was further found to influence cognitive function in individuals with a clinical high risk of psychosis (Brown et al., 2001; Ellman et al., 2009), and executive function in FSP (Brown et al., 2001). Preclinical studies also have confirmed the effects of nervous and immune systems on cognitive behavior (Meyer, 2014; Labouesse et al., 2015; Khandaker et al., 2015). Moreover, several recent studies have indicated that the abnormality of immune system was involved in cognitive deficits of psychiatric disorders, especially schizophrenia (Fineberg and Ellman, 2013; Miller et al., 2014). Therefore, the underlying mechanisms which are responsible for the *HHEX* rs1111875 polymorphism influence on the delayed memory in FSP could reflect the mutations of *HHEX* gene resulting in the abnormalities of nervous and immune systems. However, our current study did not show that the *HHEX* rs1111875 polymorphism influenced cognitive performance in healthy controls, suggesting that the variants of this polymorphism were specific for the delayed memory deficits in FSP.

Several limitations should be noted in this study. First, the unmatched sex or hidden population stratification of our sample could be confounders. However, the Han Chinese in Suzhou area were ethnically relatively homogeneous. Moreover, no gender differences in the allelic and genotypic frequencies of *HHEX* rs1111875 polymorphism were observed in either FSP or healthy controls. A replication study with genomic controls or a family-based population study would help to address this limitation. Second, only one polymorphism was investigated because of limited resources enabled to us to only tag one of all the SNPs in the *HHEX* gene. In future, other variations that influence the *HHEX* expression and activation should also be genotyped to obtain

more comprehensive information. Third, a misclassification of genotype was possible in spite of our quality controls, but such misclassification would typically bias the results towards no effect. Fourth, the *HHEX* rs1111875 polymorphism had strong ethnic differences in its genetic frequencies which could lead to inconsistent results in different populations. For example, the A allele frequency of this polymorphism in healthy controls has been reported to be 32.5 % in the Iranian population (Mansoori et al., 2015). Thus, whether it was involved in the susceptibility and delayed memory deficits of FSP still should be investigated in the different ethnicities. Fifth, Although the RBANS was a well-established neurocognitive assessment tool, it was a fairly brief assessment that did not capture all aspects of cognitive function, such as executive function, sustained attention, and working memory. We assessed the cognitive function using the RBANS among many tools to test cognition of FSP due to the following reasons: 1) The RBANS was a widely used screening instrument in neuropsychological assessment that was designed to initially identify and characterize cognitive function in older adults (Randolph et al., 1998). The RBANS was also shown to be sensitive to detecting cognitive function, which was further applied to assess cognitive function in psychiatric disorders including schizophrenia and depressive patients (Dickerson et al., 2014). 2) In China, the RBANS was previously translated into Chinese version, and its clinical validity and test-retest reliability were established in healthy controls and patients with schizophrenia (Zhang et al., 2009). 3) Pervious studies on schizophrenia, type 2 diabetes, cigarette smoking, and alcohol use from Han Chinese population adopting the RBANS for cognitive measurement have just emerged (Hui et al., 2013; Zhen et al., 2013; Zhang et al., 2016). Finally, the relatively small sample size may influence the accuracy of current findings. Thus, a replication study should be conducted in a large sample.

In summary, the *HHEX* rs1111875 polymorphism did not influence the susceptibility to FSP. However, this polymorphism could play an important role in the delayed memory deficits in FSP. Moreover, FSP have poorer cognitive function than healthy controls except for the visuospatial/constructional domain. Our findings remain preliminary because of the limitations of this study and require replication in a larger sample with case-control matching in the different ethnicities.

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CRediT authorship contribution statement

Zhen Hua Zhu: Writing – original draft, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation. **Xu Yuan Yin:** Methodology, Investigation, Data curation. **Yuan Cai:** Writing – original draft, Data curation. **Ning Ning Jia:** Investigation, Data curation. **Pei Jie Wang:** Data curation. **Qi Qi:** Data curation. **Wen Long Hou:** Data curation. **Li Juan Man:** Data curation. **Li Hui:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors have no conflicts to disclose.

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