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Association study of SNCA gene polymorphisms with schizophrenia in a Chinese North Han population

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Abstract. – OBJECTIVE: Previous studies suggested that the alpha-synapse protein *(SNCA)* gene and its coding product α-synuclein (α-Syn) may play a role in the pathogenesis of neurodegenerative diseases. The mutation of *SNCA* can influence the formation of nerve fibers and the function of dopaminergic neurons, and that may be related to addictive behavior, such as alcohol dependence. *SNCA* may overlap with the pathogenesis of schizophrenia and Parkinson's disease or alcohol dependence associated with the dopamine pathway. The aim was to determine the association between three *SNCA* SNPs (rs3822086C/T, rs11931074G/T, and rs356219A/G) and schizophrenia in a Chinese North Han population.

PATIENTS AND METHODS: A total of 878 subjects, with or without schizophrenia, were included in our study. DNA purification, Polymerase Chain Reaction (PCR) amplification, and subsequent restriction fragment length polymorphism (RFLP) analysis were manipulated to determine genotypes.

RESULTS: Between the schizophrenia group and healthy group, neither the genotype nor allele frequencies of rs3822086C/T, rs11931074G/T, or rs356219A/G differed significantly in either the total sample or the subgroups. In the haplotype analysis, the ATT and GTT haplotype frequencies differed significantly between the patients and controls in the total sample (χ^2=6.052, *p*=0.0139; χ^2=4.508, *p*=0.0337). In the female subgroup, the ATT haplotype frequency differed significantly between the patients and controls (χ^2=4.219, *p*=0.04).

CONCLUSIONS: There was no association between SNCA polymorphisms and schizophrenia in the North Han Chinese population, and the ATT haplotype may be a susceptibility factor for schizophrenia.

Key Words:
SNCA, Gene polymorphism, Schizophrenia, Chinese.

Introduction

α-Synuclein (α-Syn), coded by SNCA, is a member of the presynaptic protein family, which is mainly expressed in central nervous system (CNS) neurons. The *SNCA* gene and its product α-Syn have been found in the major pathological tissue of Lewy body dementia, Parkinson's disease (PD), and multiple system atrophy (MSA), so it is believed that the *SNCA* gene and α-Syn may play a role in the pathological mechanism of progressive age-related neurodegenerative diseases[1-4]. These diseases such as PD and Lewy body dementia can affect the loss of dopamine neurons of the substantia nigra and nucleus basalis. In the affected region of the brain, the accumulation of protein is known as a Lewy body (DLB)[5,6], with the filamentous α-Syn being the characteristic of these diseases, and α-Syn plays a role in dopamine homeostasis through its intervention in reticulin-mediated endocytosis[7,8].

In genetics, *SNCA* plays an important role in the survival of neurological diseases, and *SNCA* mutation, described as early as 1997, can increase the expression of *SNCA*[9,10]. Through the study of the corresponding diseases instead of mental diseases, it was found that *SNCA* mutation can affect the dynamics and morphological changes of nerve fibers and affect the function of dopamine neurons[11]. Animal models have shown synaptic defects and neurotransmitter disorder in *SNCA* overexpressing mice, reflecting changes in prebasal ganglion neurodegeneration and affecting the level of DA in the striatum. The upregulating of SNCA expression can also inpromote the occurrence and progression of PD as mediator in mouse model[12,13]. It may also be the cause of PD and other neurodegenerative diseases. Furthermore, there have been a lot of researches on the

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correlation between *SNCA* gene SNPs and PD, which is also caused by the abnormality of dopaminergic neurons. Emelyanov et al[14] showed that *SNCA* SNPs rs356165A/G and rs356219A/G are associated with PD intensity. Moreover, studies in North American, Korean, Italian, and Chinese populations showed that *SNCA* is a susceptibility gene for PD and showed that a gene–gene, gene–environment complex enhances PD pathogenicity[15-18].

The role of α-Syn itself in mental illness and schizophrenia is unknown, but Casey et al[19] have shown that the *SNCA* gene may be associated with the development of human impulses, including addiction and aggressive behavior. There have been some researches on alcohol dependence and alcohol addiction, which showed that *SNCA* has a significant gene overlap with other genes in many major areas of mental disorders[20]. These findings were achieved thanks to advances in bioinformatics and molecular biology, that provide a method for identifying candidate genes related to addictive behaviors like alcohol dependence[21]. Yang et al[22] found that *SNCA* contributes to the genetic mechanism of alcohol dependence. In patients with alcohol dependence, they found variability in carrying of the *SNCA* gene. The expression of the *SNCA* gene is closely related to the degree of alcohol dependence, which may be associated with the effect of α-Syn encoded by the *SNCA* gene on the function of dopamine[22]. The pathogeneses of both alcohol addiction and PD reflect the role of SNCA in dopaminergic neurons, while the pathogenesis of schizophrenia is mainly related to dopamine-derived disorders such as cortex-marginal striatal circulation[23]. Early changes in DA derived from multirisk factors and genetic variations are central features of schizophrenia[24]. Based on previous studies on *SNCA* and its effects on neuronal morphology and function and dopamine pathway, we believe that the *SNCA* gene may be related to schizophrenia.

To date, no research has been conducted on the relationship between the *SNCA* gene and schizophrenia. Therefore, we decided to use the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method to identify the associations between three single nucleotide polymorphisms (SNPs) (rs3822086C/T, rs11931074G/T, rs356219A/G) of the *SNCA* gene and schizophrenia in the Chinese North Han population, in order to provide evidence supporting the further study of the genetic mechanism of schizophrenia.

Patients and Methods

Study Subjects

All schizophrenic participants–a total of 360 in this study–were supplemented from unrelated hospitalized patients in specialized hospitals in Liaoning Province, where they mainly received routine medication. They were diagnosed jointly by at least two psychiatrists in accordance with the diagnostic criteria for schizophrenia in the fourth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV). The subjects included 229 males (mean age: 46.1 ± 9.529 years; range: 18-64 years) and 131 females (mean age: 45.5 ± 9.343 years; range: 18-62 years); the mean age of initial onset was 27.49 ± 8.309 years; the exclusion criteria were organic brain disorders including PD and other neurodegenerative diseases, mental retardation, comorbid psychiatric disorders, and serious physical illnesses. The healthy control group consisted of subjects without psychiatric disorders or serious physical illnesses; there were 518 subjects in total, including 252 males (mean age: 30.94 ± 7.974 years; range: 19-58 years) and 266 females (mean age: 29.79 ± 7.948 years; range: 19-56 years), chosen from the same region as the schizophrenia group. All subjects signed an informed consent form, and we obtained the approval of the Ethics Committee of China Medical University.

Genotype Determination

DNA purification, PCR amplification, and subsequent RFLP analysis[25] were performed to determine genotypes. The primers (TaKaRa, Dalian, China) for rs3822086C/T, rs11931074G/T, and rs356219A/G, respectively, were as follows sense: 5'-AGAGCAGAGAGGGTGTTGGT-3', antisense: 5'-AATCACAACCACACAACAGCAAT-3'; sense: 5'-TCTATTCCGCCCATCCTGTG-3', antisense: 5'-AGAGCAACACAAAGATCACATAGT-3'; sense: 5'-TGTAATGTGAGGGCTCAAAAACG-3', antisense: 5'-ACACTAAACCCCAACATACGCT-3'. The restriction endonucleases (New England Biolabs, Bejing, China) for rs3822086C/T, rs11931074G/T, and rs356219A/G were TaqαI, BsrI, and HpyCH4IV, respectively, and the reaction temperatures were 65°C, 65°C, and 37°C, respectively. Genotypes were determined through electrophoresis.

Statistical Analysis

In this study, the χ^2-test (or Fisher's exact value test) was performed using SPSS software 22.0 version (SPSS, IBM, Armonk, NY, USA)[25]. Hap-

loview software version 4.2 (http://www.broad.mit.edu/mpg/haploview) was used to detect linkage disequilibrium and haplotype[26]. All data used the frequency, percentage (%), and mean±standard deviation ($M\pm SD$), and $p<0.05$ was considered a statistically significant difference.

Results

The Hardy-Weinberg equilibrium (HWE) coincidence test indicated that the genotype distribution of the three SNPs (rs3822086C/T, rs11931074G/T, and rs356219A/G) did not deviate from the Hardy-Weinberg genetic balance in either the schizophrenia group (χ^2 = 0.020, 0.147, 0.254; p = 0.993, 0.938, 0.884, respectively) or the control group (χ^2 = 0.562, 0.814, 1.804; p = 0.776, 0.674, 0.406, respectively), indicating that all the subjects in the study were from a natural population and had population representativeness.

Statistical analysis of the associations between the SNPs of the *SNCA* gene and schizophrenia showed that there was no significant difference in either allele frequency or genotype frequency among the three SNPs (rs3822086C/T, rs11931074G/T, rs356219A/G) between the schizophrenia (case) group and the control group. No significant differences were found between the dominant model and the recessive model in the two groups. Furthermore, gender specificity analysis showed no significant difference in allele frequency or genotype frequency between the two subgroups (Table I). In the three SNPs (rs3822086C/T, rs11931074G/T, rs356219A/G) of the case group, there was no significant difference in the age of the first onset of schizophrenia among the three genotypes (TT/CC/CT, TT/GG/GT, AA/GG/AG) (χ^2 = 0.303, 1.051, 0.131; p = 0.860, 0.591, 0.931, respectively).

The results of linkage disequilibrium (LD) testing using Haploview version 4.2 for the three SNPs in the case group and the control group showed strong LD among rs3822086C/T, rs11931074G/T, and rs356219A/G both in the general population and in the male and female subgroups. In the general population, the findings were as follows: for rs3822086C/T and rs356219A/G, D' = 0.968, r^2 = 0.876; for rs11931074C/T and rs356219A/G, D' = 0.977, r^2 = 0.858; for rs11931074C/T and rs3822086C/T, D' = 0.986, r^2 = 0.935 (Figure 1). In the male subgroup, the findings were as follows: for rs3822086C/T and rs356219A/G, D' = 0.961, r^2 = 0.877; for rs11931074C/T and rs356219A/G, D' = 0.968, r^2 = 0.84; for rs11931074C/T and rs3822086C/T, D' = 0.991, r^2 = 0.926 (Figure 2). In the female subgroup, the findings were as follows: for rs3822086C/T and rs356219A/G, D' = 0.978, r^2 = 0.874; for rs11931074C/T and rs356219A/G, D' = 0.989, r^2 = 0.88; for rs11931074C/T and rs3822086C/T, D' = 0.979, r^2 = 0.945 (Figure 3).

In further haplotype analysis, we found that the frequencies of haplotype ATT and haplotype GTT differed significantly between the case group and the control group in the general population (χ^2 = 6.052, p = 0.0139; χ^2 = 4.508, p = 0.0337; Table II). Further gender analysis indicated that the frequency of haplotype ATT differed significantly between the case group and the control group in the female subgroup (χ^2 = 4.219, p = 0.04; Table II). In the male subgroup, there was no significant difference in the frequency of haplotypes ATT and GTT between the case group and the control group, and there was also no significant difference in the frequency of other haplotypes between the two groups in either the general population or the subgroups (Table II).

Discussion

Schizophrenia is a complex and strongly inherited disorder in which both genes and environmental factors play a role in the pathogenesis of the disease, but Husted et al[27] have shown that the effect of early environmental exposure on the expression of schizophrenia is also predicated on the presence of strong genes, which indicates the importance of genetic factors in schizophrenia. Studies on the etiology and mechanism of schizophrenia and other mental diseases have been devoted to improving our understanding on the etiological mechanism of schizophrenia by continually discovering new genes or new locus variations related to schizophrenia. Although it has been 20 years since *SNCA* was identified as the first gene responsible for familial PD, the *SNCA*-encoded α-Syn is still a mysterious protein[28]. There is also no direct evidence of its association with schizophrenia, while the study of the *SNCA* gene is more focused on animal studies, which showed that α-Syn is related to the dysfunction of dopamine metabolism[29]. However, biochemical studies on the distribution of α-Syn enzyme in the Brodmann region of 80 elderly human subjects (41 schizophrenia, 12 senile depression and bipolar disorder, and 27 control subjects) by autopsy showed that α-Syn does exist in the brains of patients with chronic schizophrenia and bipolar disorder, and it can be

Table I. Distribution of alleles and genotypes of three SNPs between two groups in general and sub-group population.

SNPs	Total case-group, n (%)	Total control-group, n (%)	χ^2	*p*	OR (95% CI)	Male case-group, n (%)	Male control-group, n (%)	χ^2	*p*	OR (95% CI)	Female case-group, n (%)	Female control-group, n (%)	χ^2	*p*	OR (95% CI)
rs3822086C/T															
Genotypes															
TT	92 (25.6)	157 (30.3)				60 (26.2)	75 (29.8)				32 (24.4)	82 (30.8)			
CC	78 (21.7)	103 (19.9)				52 (22.7)	45 (17.9)				26 (19.8)	58 (21.8)			
CT	190 (52.8)	258 (49.8)	2.394	0.304		117 (51.1)	132 (52.4)	1.975	0.372		73 (55.7)	126 (47.4)	2.588	0.280	
Alleles															
T	374 (51.9)	572 (55.2)			1.140	237 (51.7)	282 (56.0)			1.185	137 (52.3)	290 (54.5)			1.093
C	346 (48.1)	464 (44.8)	1.825[a]	0.189	(0.942-1.380)	221 (48.3)	222 (44.0)	1.708[a]	0.196	(0.919-1.527)	125 (47.7)	242 (45.5)	0.348[a]	0.596	(0.813-1.471)
Recessive															
model	282 (78.3)	415 (80.1)			1.114	177 (77.3)	207 (82.1)			1.351	105 (80.2)	208 (78.2)			0.888
CC/TT+TC	78 (21.7)	103 (19.9)	0.412[a]	0.553	(0.801-1.551)	52 (22.7)	45 (17.9)	1.753[a]	0.211	(0.865-2.112)	26 (19.8)	58 (21.8)	0.202[a]	0.697	(0.529-1.492)
Dominant															
model	268 (74.4)	361 (69.7)			0.789	169 (73.8)	177 (70.2)			0.838	99 (75.6)	184 (69.2)			0.725
CC+TC/TT	92 (25.6)	157 (30.3)	2.362[a]	0.129	(0.584-1.068)	60 (26.2)	75 (29.8)	0.754[a]	0.417	(0.562-1.249)	32 (24.4)	82 (30.8)	1.756[a]	0.196	(0.451-1.167)
rs11931074G/T															
Genotypes															
TT	98 (27.2)	157 (30.3)				66 (28.8)	76 (30.2)				32 (24.4)	81 (30.5)			
GG	71 (19.7)	99 (19.1)				47 (20.5)	43 (17.1)				24 (18.3)	56 (21.1)			
GT	191 (53.1)	262 (50.6)	0.991	0.612		116 (50.7)	133 (52.8)	0.949	0.626		75 (57.3)	129 (48.5)	2.694	0.254	
Alleles															
T	387 (53.8)	576 (55.6)			1.077	248 (54.1)	285 (56.5)			1.102	139 (53.1)	291 (54.7)			1.068
G	333 (46.2)	460 (44.4)	0.586[a]	0.465	(0.890-1.304)	210 (45.9)	219 (43.5)	0.559[a]	0.475	(0.854-1.421)	123 (46.9)	241 (45.3)	0.192[a]	0.705	(0.794-1.437)
Recessive															
model	289 (80.3)	419 (80.9)			1.040	182 (79.5)	209 (82.9)			1.255	107 (81.7)	210 (78.9)			0.841
GG /TG+TT	71 (19.7)	99 (19.1)	0.051[a]	0.862	(0.740-1.460)	47 (20.5)	43 (17.1)	0.945[a]	0.351	(0.793-1.986)	24 (18.3)	56 (21.1)	0.407[a]	0.595	(0.494-1.432)
Dominant															
model	262 (72.8)	361 (69.7)			0.860	163 (71.2)	176 (69.8)			0.938	99 (75.6)	185 (69.5)			0.738
TG+GG/TT	98 (27.2)	157 (30.3)	0.982[a]	0.327	(0.638-1.159)	66 (28.8)	76 (30.2)	0.103[a]	0.765	(0.633-1.389)	32 (24.4)	81 (30.5)	1.564[a]	0.238	(0.458-1.189)
rs356219A/G															
Genotypes															
AA	81 (22.5)	107 (20.7)				51 (22.3)	48 (19.0)				30 (22.9)	59 (22.2)			
GG	81 (22.5)	145 (28.0)				55 (24.0)	70 (27.8)				26 (19.8)	75 (28.2)			
AG	198 (55.0)	266 (51.4)	3.375	0.187		123 (53.7)	134 (53.2)	1.266	0.544		75 (57.3)	132 (49.6)	3.419	0.185	
Alleles															
A	360 (50.0)	480 (46.3)			0.863	225 (49.1)	230(45.6)			0.869	135 (51.5)	250 (47.0)			0.834
G	360 (50.0)	556 (53.7)	2.290[a]	0.132	(0.714-1044)	233 (50.9)	274(54.4)	1.174[a]	0.301	(0.675-1.120)	127 (48.5)	282 (53.0)	1.445[a]	0.257	(0.620-1.121)
Dominant															
model	279 (77.5)	373 (72.0)			0.747	174 (76.0)	182 (72.2)			0.822	105 (80.2)	191 (71.8)			0.631
AA+AG/GG	81 (22.5)	145 (28.0)	3.352[a]	0.071	(0.546-1.021)	55 (24.0)	70 (28.8)	0.882[a]	0.351	(0.546-1.238)	26 (19.8)	75 (18.2)	3.225[a]	0.086	(0.380-1.046)
Recessive															
model	279 (77.5)	411 (79.3)			1.115	178 (77.7)	204 (81.0)			1.218	101 (77.1)	207 (77.8)			1.042
AA/GG+AG	81 (22.5)	107 (20.7)	0.429[a]	0.558	(0.805-1.545)	51 (22.3)	48 (19.0)	0.762a	0.430	(0.782-1.895)	30 (22.9)	59 (22.2)	0.026[a]	0.898	(0.632 -1.718)

*$p<0.05$.

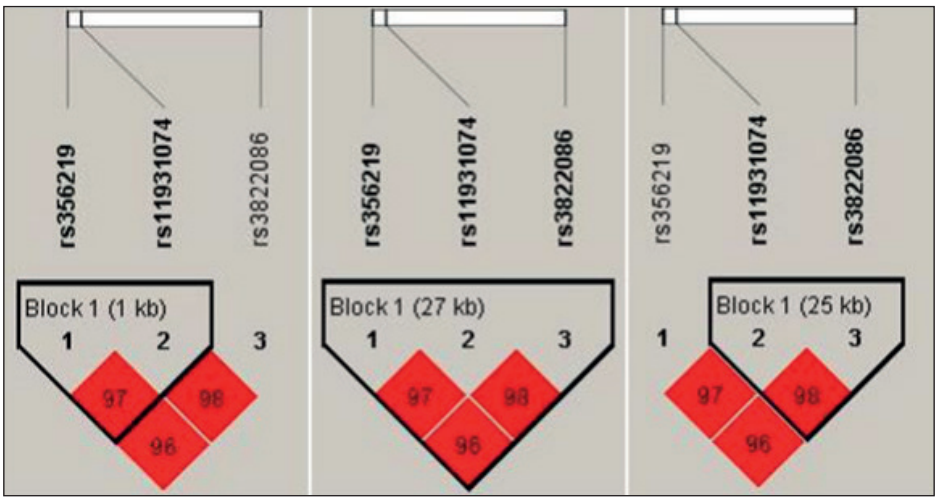

Figure 1. Linkage disequilibrium of three SNPs between the schizophrenia group and the control group in general population.

concluded that α-Syn is related to the pathological mechanism of mental disorders[30]. Studies have also shown that serum α-Syn levels are associated with schizophrenia, but Demirel et al[31] found that serum α-Syn levels in schizophrenic patients were lower than those in healthy people, but the specific effects of α-Syn on schizophrenia are unclear. However, the proliferation of α-Syn causes the disease to develop into mild Parkinson's disease 10 years after the onset of the disease in patients with schizophrenia whose main clinical symptoms are delusions and auditory hallucinations[32], and it is unclear whether α-Syn is associated with the brain structure and function differences found in the study by comparing the multi-modal magnetic resonance imaging of first-episode schizophrenia patients and chronic schizophrenia patients[33]. α-Syn encoded by the *SNCA* gene may play a role in the development and outcome of schizophrenia. However, there has been no study on the association between *SNCA* gene and schizophrenia.

Although many previous studies on *SNCA* and PD in China and other regions have confirmed that *SNCA* is associated with PD, *SNCA* is a susceptibility gene for PD. Notably, on the basis of the strong association between *SNCA* rs356219 and PD in gene studies from the United States to Europe, the results in a large sample of the Chinese Han population showed that rs356219 was susceptible to sporadic PD, similar to previous studies in Asian populations[34]. In another study in China by

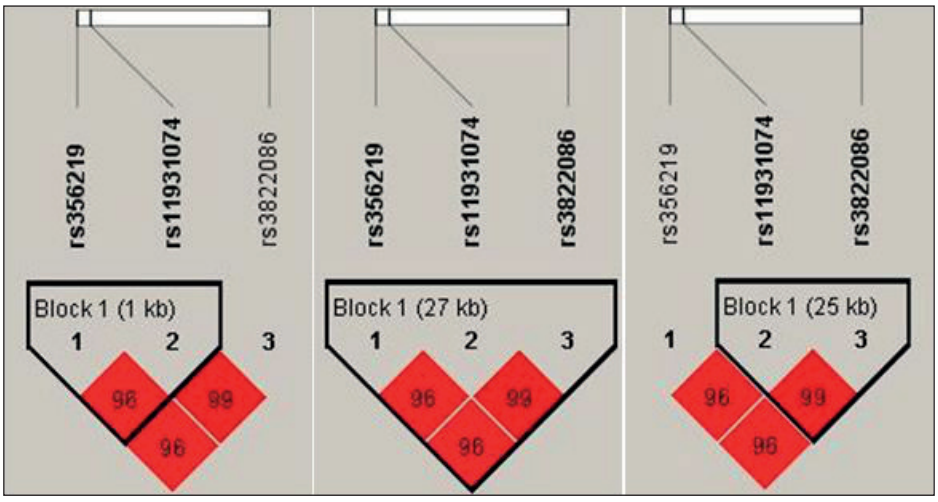

Figure 2. Linkage disequilibrium of three SNPs between the schizophrenia group and the control group in male subgroups.

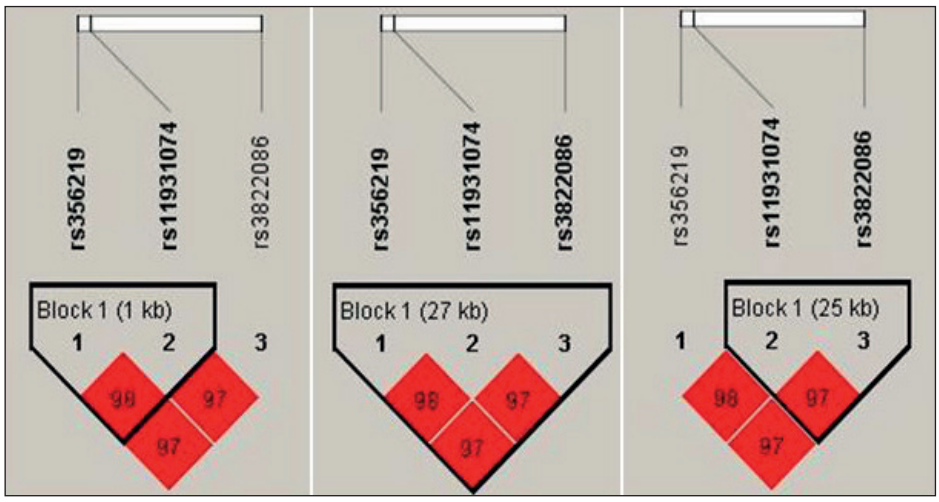

Figure 3. Linkage disequilibrium of three SNPs between the schizophrenia group and the control group in female subgroups.

Chen et al[35], the results of a study based on *SNCA* (rs3775444, rs3822086 and rs11931074) SNPs and PD in Caucasian populations also showed that *SNCA* was associated with PD. Furthermore, the association of the three SNPs (rs3822086C/T, rs-11931074G/T, rs356219A/G) in our study with PD has been confirmed. However, for schizophrenia and even other mental disorders, there is no definite related study. Based on previous researches on the *SNCA* gene, we used the case control method to investigate the association between *SNCA* gene SNPs and schizophrenia for the first time. In this study, the allelic frequencies, genotype frequencies, and dominant and recessive model frequencies of the three SNPs of *SNCA* gene were compared between schizophrenic patients and healthy controls. Unfortunately, the results showed no significant differences in these areas between the two groups, and we found no evidence directly supporting the association between *SNCA* gene polymorphism and schizophrenia. We also did not find the genotypes of the three SNPs to have an effect on the age of first onset of schizophrenia.

However, the results of our haplotype analysis between the two groups showed that the frequency of haplotype ATT was significantly higher (χ^2 = 6.052, p = 0.0139), while the frequency of haplotype GTT was lower in the schizophrenia group (χ^2 = 4.508, p = 0.0337). Further analysis of gender specificity showed that the frequency of ATT in the female subgroup was higher than that in the control group (χ^2 = 4.219, p = 0. 04), indicating that haplotype ATT may be a predisposing factor for schizophrenia and may be more likely to occur in the female population. Hence, although we found no evidence that single-allele polymorphism is associated with schizophrenia, combinations of alleles may be associated with schizophrenia, and there are some gender differences. Further research is needed to clarify these associations.

Besides, while our study was based on the relationship between schizophrenia and *SNCA* gene SNPs, our findings were similar to those of previous studies on the relationship between the *SNCA* gene and other mental disorders, such as alcohol dependence and alcohol addiction. While the study by Foroud et al[36] on alcohol dependence and related genotypes of 30 SNPs in a sample of European American descent found no evidence of a clear association between *SNCA* gene SNPs and alcohol dependence, further haplotype analysis support the link between *SNCA* gene SNPs and alcohol craving. We speculate that the overlap in the findings on different mental disorders may be related to the common pathogenesis of mental disorders.

In addition, it has been reported that α-Syn is associated with cognitive decline in the clinical manifestations of PD[37]. A study[38] of *SNCA* in 296 Chinese PD patients showed that the *SNCA* gene (rs11931074 and rs894278) was associated with the severity of motor cognitive symptoms in PD. However, it is not clear whether the *SNCA* gene also affects the development of cognitive dysfunction in schizophrenia, and further research is needed to determine this. Whether the mutation of *SNCA* can affect the cognitive or other symptoms of schizophrenic patients has not been explored. However, in the future, the relationship between the two can be clarified by adjusting

Table II. Haplotype distribution of three SNPs in general population and sub-groups.

Haplotype	Total frequence	Total case-control ratio	χ^2	*p*	Male frequence	Male case-control ratio	χ^2	*p*	Female frequence	Female case-control ratio	χ^2	*p*
GTT	0.514	0.483:0.535	4.508	0.0337	0.516	0.489:0.541	2.65	0.1036	0.510	0.473:0.528	2.119	0.145
AGC	0.444	0.448:0.441	0.098	0.7548	0.437	0.445:0.430	0.215	0.6425	0.451	0.454:0.449	0.017	0.8972
ATT	0.022	0.032:0.015	6.052	0.0139	0.021	0.029:0.014	2.42	0.1198	0.023	0.038:0.015	4.219	0.04
ATC	0.010	0.015:0.007	3.061	0.0802	0.013	0.017:0.010	1.024	0.3116	<0.01			

*$p<0.05$.

research methodologies, such as quantifying the clinical manifestations of schizophrenic patients according to cognitive and emotional changes or optimizing the design of experimental conditions.

Conclusions

In summary, the correlation between *SNCA* gene SNPs and schizophrenia was tested for the first time. It was determined that there is no association between *SNCA* gene SNPs and schizophrenia in a Chinese North Han population. However, there are some limitations in our research. Only three SNPs were selected for polymorphism analysis and research, which may have biased our conclusions. Therefore, our results only provide partial support for the conclusion that the *SNCA* gene is not associated with schizophrenia in the Chinese North Han population. In the future, we need to carry out studies covering larger samples and more SNPs, as well as further research in different ethnic populations, to better understand the effects of the *SNCA* gene on mental illness.

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Conflict of Interests

The authors declare that they have no conflicts of interests.

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