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Association analysis of CHRNA3 polymorphisms with schizophrenia in a Chinese Han population

A case-control study

Guixin Li, MD[a,b,c], Mei Bai, MD[a,b,c], Chenghao Guo, MD[d], Linhao Zhu, MD[a,b,c], Li Wang, MD, PhD[a,b,c], Dongya Yuan, MD, PhD[a,b,c], Tianbo Jin, MD, PhD[a,b,c,d,*], Yongjun He, MD, PhD[a,b,c,*]

Abstract

Schizophrenia (SCZ) is a highly heritable, chronic, severe psychiatric disorder associated with significant financial costs to families and societies. In this case-control study, we investigated the associations between seven SNPs in *CHRNA3* gene and the risk of SCZ.

A total of 1071 (384 cases and 687 controls) unrelated subjects were recruited for our association study. Seven candidate tagging SNPs in CHRNA3 gene (rs3743077, rs1317286, rs938682, rs12914385, rs2869546, rs3743075, rs8040868) selected in HapMap database were genotyped by Sequenom MassARRAY. Finally, association analysis was conducted under various models.

According to our results, in genetic model analysis, rs12914385 and rs8040868 are associated with decreased risk of SCZ in female subgroup; rs3743075 is associated with decreased risk of SCZ in subgroup with age <45; while rs3743077 and rs2869546 are associated with increased risk of SCZ. Haplotype analysis suggested that the 3 variants comprised 1 block, and that the haplotype $A_{rs938682}C_{rs12914385}C_{rs2869546}$ was significantly correlated with an increased risk of SCZ in the subgroup with age ≥45.

Our data indicate potential associations between CHRNA3polymorphisms and SCZ susceptibility, and the significant variants identified in our study may be used as genetic biomarkers for SCZ susceptibility in Chinese Han population.

Abbreviations: 95% CI = confidence interval, GWASs = genome-wide association studies, HWE = Hardy–Weinberg equilibrium, MAF = minor allele frequency, OR = odds ratio, PPI = prepulse inhibition, SCZ = Schizophrenia, SNP = single nucleotide polymorphism.

Keywords: Chinese Han population, CHRNA3, polymorphisms, schizophrenia

1. Introduction

Schizophrenia (SCZ), named by Dr Bleuler in 1908, is a highly heritable, chronic, severe psychiatric disorder with a lifetime risk of approximately 1% in the general population worldwide.[1] Due to the high heterogeneity, the symptoms of schizophrenia are divided into 4 groups: positive, negative, cognitive, and mood symptoms.[2] Schizophrenia is diagnosed based on criteria in either the APA fifth edition of the DSM 5 or the WHO' ICD-10. As an enigmatic illness, schizophrenia places a substantial burden on patients, their families, and society.[3] However, the exact pathogenesis of schizophrenia remains unknown and, despite large numbers of trials of potential therapies, the efficacy of pharmacological treatments is poor for many schizophrenia patients.[4]

Multiple genetic and environmental factors contribute to disturbances in brain function and development that result in schizophrenia.[5] Risk factors for SCZ include urbanicity, migration, sex, season of birth pregnancy, and birth complications.[6] The heritability of schizophrenia estimated of approximately 80% to 85% by monozygotic twin and adoption and family studies, indicating that genetic factors may play an important role in the pathophysiology of SCZ.[7] Recently, several genome-wide association studies (GWASs) of schizophrenia have identified around 30 schizophrenia-associated loci, but the replication results remain controversial and ambiguous.

The associations between CHRNA3 polymorphisms and schizophrenia risk have not been investigated in the northern Chinese Han population. We, therefore, conducted an extensive association analysis to evaluate the roles of CHRNA3 gene polymorphisms and haplotypes on susceptibility to esophageal cancer in a population of northwestern Chinese patients from a single case-control study. Seven SNPs were selected and examined in the present study and our results may shed new light on the association between CHRNA3 and SCZ in Chinese Han population.

2. Methods

2.1. Ethics and consent

The study was approved by the Ethics Committee of the Xizang Minzu University and Northwest University, and complied with

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[a] Key Laboratory of Molecular Mechanism and Intervention Research for Plateau Diseases of Tibet Autonomous Region, [b] Key Laboratory of High Altitude Environment and Genes Related to Diseases of Tibet Autonomous Region, [c] Key Laboratory for Basic Life Science Research of Tibet Autonomous Region, School of Medicine, Xizang Minzu University, Xianyang, Shaanxi, [d] Key Laboratory of Resource Biology and Biotechnology in Western China, Northwest University, Ministry of Education, Xi'an, Shaanxi, China.

[*] Correspondence: Tianbo Jin and Yongjun He, #6 East Wenhui Road, 712082 Shaanxi, China (e-mails: jintianbo@gmail.com; 545139647@qq.com).

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the Declaration of Helsinki. Written informed consents were obtained from all participants prior to participation in the study.

2.2. Study participants and sample collection

A total of 1071 (384 cases and 687 controls) unrelated subjects were recruited for our association study. Cases were all clinically diagnosed with SCZ by trained psychiatrist post hoc according to Diagnostic Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria.[8] Patients with complicating diagnoses of mental retardation, organic brain damage, neurological disorders, autoimmune disorders, and low comprehension skills were excluded from the study. Healthy controls with no evidence of SCZ or other diseases were randomly selected from healthy people who did medical examination in hospital during the same period. Additionally, the participants are northern Chinese people who live in Xi'an city or nearby. After signing the informed consents, 5 mL venous blood samples were collected from each subject into tubes containing EDTA, then centrifuged and stored at −80°C.

2.3. SNP selection and genotyping

Seven candidate tagging SNPs in *CHRNA3* gene (rs3743077, rs1317286, rs938682, rs12914385, rs2869546, rs3743075, rs8040868) were selected in HapMap database with a minor allele frequency (MAF)>5%. Genomic DNA was extracted from whole-blood sample by using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Ltd, Xi'an. China) in accordance with manufacturer's protocol.[9] Then, the concentration of DNA was measured by NanoDrop 2000, and qualified samples were stored at −80°C for the next genotyping. MassARRAY Assay Design 3.0 software (Sequenom, San Diego, CA) was used to design multiplexed MassEXTEND assay.[10,11] Genotyping was performed using Sequenom MassARRAY RS1000 (Sequenom, Inc) in accordance with the manufacturer's protocol.[12,13] Finally, SequenomTyper 4.0 Software (Sequenom Inc) was used to manage and analyze the data.[14]

2.4. Statistical analysis

Statistical analyses in this study was conducted by Microsoft Excel and the SPSS 19.0 statistical package (SPSS, Chicago, IL) as previously described.[15] Hardy–Weinberg equilibrium (HWE) was assessed for the frequency of each SNP using a goodness-of-fit $\chi 2$ test on the control subjects. The distribution differences of demographic characteristics (gender and age) and genotype were analyzed by χ^2 tests.[16] ORs and 95% CI were calculated by using unconditional logistic regression analysis with adjustment for age and gender. The genetic models (codominant, dominant, recessive, log-additive) analyses were conducted by a web-based software SNPStats.[17] Finally, we used Haploview software package (version 4.2) and the SHEsi software platform (http://www.nhgg.org/analysis/) to perform linkage disequilibrium analysis and haplotype-based associations adjusted by gender and age. In addition, all *P* values presented in this study are 2-sided, and $P \leq .05$ was considered statistically significant.[18,19]

3. Results

3.1. Study population

The demographic information of this study was shown in Table 1. A total of 1071 (384 cases and 687 controls) participants were recruited in this case-control study. There were 201 men (52.3%) and 183 women (47.7%) in the case group, and 387 men (56.3%) and 300 women (43.7%) in the control group. The mean age of the cases was 36.58 ± 13.73 years and that of the controls was 48.56 ± 9.56 years. In addition, age occurred significant difference between cases and controls ($P < .0001$) while gender did not ($P = .208$).

Table 1

The demographic information of this study.

Variable	Cases n = 384	Controls n = 687	*P* values
Gender			
Male	201 (52.3%)	387 (56.3%)	208
Female	183 (47.7%)	300 (43.7%)	
Age, year (mean ± SD)	36.58 ± 13.733	48.56 ± 9.559	<.0001

3.2. Association between CHRNA3 polymorphisms and SCZ risk

Table S1, http://links.lww.com/MD/C280 summarizes the basic information of polymorphisms we selected, including alleles (A/B), MAF of case and control, and the association between alleles and SCZ risk. All of the 7 SNPs were in HWE among the control subjects ($P > .05$). However, no associations were observed between the alleles and SCZ risk in an allele model. We then assessed an association between each SNP and SCZ risk in an unconditional logistic regression analysis, which was performed using four models: codominant, dominant, recessive, and log-additive model. But unfortunately, we still didn't find any associations (Table S2, http://links.lww.com/MD/C280).

3.3. Stratified analysis of CHRNA3 polymorphisms and the risk of SCZ adjusted by gender or age

We further conducted association analysis stratified by gender and age. The information of SNPs after stratification was listed in Table 2. SNPs in all 4 subgroups are in Hardy–Weinberg equilibrium in the control subjects ($P > .05$). In the subgroup with age ≥45, 2 SNPs were found to be significantly associated with an increased risk of SCZ (rs3743077T/C, OR = 1.62, 95% CI: 1.17–2.24, $P = .004$; rs2869546, OR = 1.54, 95% CI: 1.11–2.15, $P = .01$). We also compared the genotype frequencies between cases and controls. For rs3743077 and rs2869546, results indicated that the genotype frequency distributions differed between the cases and controls in the subgroup with age ≥45 (rs3743077, $P = .007$; rs2869546, $P = .025$), whereas there was no significant difference in other 3 subgroups (Table 3).

Next, genetic models were used to further identify the associations between the SNPs and the risk of SCZ. As shown in Table 4, there was no association between rs12914385 or rs8040868 and the risk of SCZ among males, whereas the associations between those SNPs and the risk of SCZ among females under models were stronger than those in the non-stratified analysis. In female subgroup, rs12914385 was found to be associated with decreased risk of SCZ in recessive model (OR = 0.82, 95% CI: 0.54–1.26, $P = .026$); and rs8040868 is associated with decreased risk of SCZ in codominant model (OR = 0.94, 95% CI: 0.6–1.46, $P = .018$ for the C/T genotype), recessive model (OR = 0.33, 95% CI: 0.15–0.75, $P = .005$) and

Table 2

Association analysis between SNPs in CHRNA3 with SCZ stratified by gender and age.

SNP ID	A/B	MAF		HWE *P*	ORs	95% CI		*P*
		Case	Control					
Male								
rs3743077	T/C	0.234	0.226	.470	1.045	0.785	1.390	.765
rs1317286	G/A	0.087	0.093	.124	0.930	0.609	1.420	.736
rs938682	G/A	0.445	0.434	.256	1.047	0.821	1.335	.710
rs12914385	T/C	0.261	0.279	.527	0.913	0.696	1.199	.514
rs2869546	C/T	0.226	0.224	.560	1.014	0.760	1.353	.925
rs3743075	T/C	0.468	0.471	.838	0.985	0.773	1.254	.900
rs8040868	C/T	0.331	0.338	.306	0.968	0.750	1.250	.803
Female								
rs3743077	T/C	0.273	0.238	.751	1.201	0.893	1.617	.225
rs1317286	G/A	0.060	0.087	1.000	0.674	0.402	1.130	.132
rs938682	G/A	0.456	0.438	.289	1.077	0.829	1.399	.578
rs12914385	T/C	0.227	0.262	.457	0.828	0.610	1.123	.223
rs2869546	C/T	0.273	0.237	1.000	1.208	0.897	1.627	.213
rs3743075	T/C	0.475	0.473	.010	1.008	0.776	1.309	.952
rs8040868	C/T	0.257	0.312	.285	0.763	0.570	1.021	.069
<45								
rs3743077	T/C	0.229	0.244	.488	0.921	0.690	1.229	.577
rs1317286	G/A	0.081	0.094	1.000	0.847	0.548	1.309	.455
rs938682	G/A	0.467	0.414	.791	1.239	0.967	1.588	.090
rs12914385	T/C	0.253	0.290	.213	0.830	0.630	1.093	.185
rs2869546	C/T	0.229	0.245	.597	0.916	0.686	1.224	.554
rs3743075	T/C	0.448	0.492	.300	0.840	0.656	1.075	.165
rs8040868	C/T	0.304	0.337	.151	0.860	0.661	1.119	.262
≥45								
rs3743077	T/C	0.319	0.225	.892	1.618	1.168	2.243	.004
rs1317286	G/A	0.056	0.088	.139	0.607	0.324	1.135	.115
rs938682	G/A	0.407	0.447	.774	0.850	0.628	1.149	.291
rs12914385	T/C	0.222	0.262	.327	0.806	0.566	1.148	.231
rs2869546	C/T	0.306	0.222	1.000	1.543	1.110	2.147	.010
rs3743075	T/C	0.532	0.462	.293	1.328	0.986	1.789	.062
rs8040868	C/T	0.273	0.321	.232	0.795	0.571	1.106	.173

Table 3

Comparison of genotype frequencies between cases and controls.

SNP ID	Genotype	Male		*P*	Female		*P*	<45		*P*	≥45		*P*
		Case	Control		Case	Control		Case	Control		Case	Control	
rs3743077	TT	10	17	.940	14	18	.483	16	12	.531	8	23	.007
	TC	74	141		72	107		93	93		53	155	
	CC	117	229		97	175		164	135		47	269	
rs1317286	GG	2	6	.858	0	2	.319	2	2	.774	0	6	.341
	GA	31	60		22	48		40	41		12	67	
	AA	168	321		161	250		231	197		96	374	
rs938682	GG	44	67	.237	36	62	.420	63	42	.234	17	87	.561
	GA	91	201		95	137		129	114		54	224	
	AA	66	118		52	99		81	83		37	134	
rs12914385	TT	19	27	.110	8	23	.333	24	24	.375	3	26	.370
	TC	67	162		67	111		90	91		42	182	
	CC	115	198		108	166		159	125		63	239	
rs2869546	CC	9	17	.995	15	17	.442	16	12	.528	8	22	.025
	CT	73	138		70	107		93	92		50	153	
	TT	119	229		98	173		164	133		50	269	
rs3743075	TT	45	84	.895	42	78	.400	54	62	.278	33	100	.174
	TC	97	194		88	126		134	111		49	209	
	CC	58	106		51	94		82	66		26	134	
rs8040868	CC	26	39	.224	10	33	.102	31	32	.558	5	40	.280
	CT	81	183		74	121		104	97		49	207	
	TT	94	164		99	146		138	110		54	200	

Table 4

Associations between SNPs and the risk of SCZ under genetic models (stratified by gender).

				Male				Female			
Model	**Genotype**	**Control**	**Case**	**OR (95% CI)**	***P* value**	**AIC**	**BIC**	**OR (95% CI)**	***P* value**	**AIC**	**BIC**
rs12914385											
Codominant	C/C	198 (51.2%)	115 (57.2%)	1	.46	628.5	646	1		522.6	539.3
	T/C	162 (41.9%)	67 (33.3%)	0.77 (0.51–1.17)				0.95 (0.61–1.49)	.081		
	T/T	27 (7%)	19 (9.4%)	0.96 (0.47–1.98)				0.36 (0.14–0.92)			
Dominant	C/C	198 (51.2%)	115 (57.2%)	1	.27	626.9	640	1		524.8	537.3
	T/C-T/T	189 (48.8%)	86 (42.8%)	0.80 (0.55–1.18)				0.82 (0.54–1.26)	.37		
Recessive	C/C-T/C	360 (93%)	182 (90.5%)	1	.86	628	641.2	1		520.6	533.1
	T/T	27 (7%)	19 (9.4%)	1.07 (0.53–2.16)				0.37 (0.15–0.93)	.026		
Log-additive	—	—	—	0.89 (0.66–1.20)	.44	627.5	640.6	0.76 (0.54–1.07)	.11	523	535.5
rs8040868											
Codominant	T/T	164 (42.5%)	94 (46.8%)	1	.65	628.5	646	1		519.6	536.3
	C/T	183 (47.4%)	81 (40.3%)	0.87 (0.58–1.31)				0.94 (0.60–1.46)	.018		
	C/C	39 (10.1%)	26 (12.9%)	1.14 (0.60–2.14)				0.32 (0.14–0.75)			
Dominant	T/T	164 (42.5%)	94 (46.8%)	1	.68	627.2	640.4	1		524.2	536.7
	C/T-C/C	222 (57.5%)	107 (53.2%)	0.92 (0.63–1.36)				0.77 (0.51–1.18)	.24		
Recessive	T/T-C/T	347 (89.9%)	175 (87.1%)	1	.52	627	640.1	1		517.7	530.2
	C/C	39 (10.1%)	26 (12.9%)	1.22 (0.67–2.22)				0.33 (0.15–0.75)	.005		
Log-additive	—	—	—	1.00 (0.75–1.33)	1	627.4	640.5	0.70 (0.51–0.98)	.033	521.1	533.6

additive model (OR = 0.70, 95% CI: 0.51–0.98, $P = .033$). As shown in Table 5, the results indicated that rs3743075 was associated with decreased risk of SCZ in recessive model in the subgroup with age <45 (OR = 0.57, 95% CI: 0.34–0.94, $P = .027$). In subgroup with age ≥45, rs3743077 and rs2869546 were found to be associated with increased risk of SCZ in codominant model (OR = 1.94, 95% CI: 1.25–3.01, $P = .0096$; OR = 1.75, 95% CI: 1.12–2.71, $P = .033$), dominant model (OR = 1.93, 95% CI: 1.26–2.96, $P = .0023$; OR = 1.76, 95% CI: 1.15–2.69, $P = .0091$) and additive model (OR = 1.61, 95% CI: 1.15–2.26, $P = .0056$; OR = 1.53, 95% CI: 1.09–2.14, $P = .014$).

Table 5

Associations between SNPs and the risk of SCZ under genetic models (stratified by age).

				<45				≥45			
Model	**Genotype**	**Control**	**Case**	**OR (95% CI)**	***P* value**	**AIC**	**BIC**	**OR (95% CI)**	***P* value**	**AIC**	**BIC**
rs3743077											
Codominant	C/C	135 (56.2%)	164 (60.1%)	1		535.3	556.5	1		545	566.5
	C/T	93 (38.8%)	93 (34.1%)	0.81 (0.52–1.27)	.64			1.94 (1.25–3.01)	.0096		
	T/T	12 (5%)	16 (5.9%)	1.03 (0.39–2.68)				1.90 (0.80–4.52)			
Dominant	C/C	135 (56.2%)	164 (60.1%)	1		533.5	550.5	1		543	560.2
	C/T-T/T	105 (43.8%)	109 (39.9%)	0.84 (0.55–1.28)	.41			1.93 (1.26–2.96)	.0023		
Recessive	C/C-C/T	228 (95%)	257 (94.1%)	1		534.1	551.1	1		551.6	568.9
	T/T	12 (5%)	16 (5.9%)	1.12 (0.43–2.86)	.82			1.41 (0.61–3.26)	.43		
Log-additive	—	—	—	0.90 (0.63–1.28)	.55	533.8	550.8	1.61 (1.15–2.26)	.0056	544.6	561.8
rs3743075											
Codominant	C/C	66 (27.6%)	82 (30.4%)	1		524.5	545.7	1		549.2	570.8
	C/T	111 (46.4%)	134 (49.6%)	0.99 (0.60–1.62)	.087			1.22 (0.72–2.05)	.19		
	T/T	62 (25.9%)	54 (20%)	0.56 (0.31–1.02)				1.69 (0.95–3.01)			
Dominant	C/C	66 (27.6%)	82 (30.4%)	1		526.7	543.6	1		548.8	566.1
	C/T-T/T	173 (72.4%)	188 (69.6%)	0.82 (0.51–1.30)	.4			1.37 (0.84–2.23)	.2		
Recessive	C/C-C/T	177 (74.1%)	216 (80%)	1		522.5	539.5	1		547.8	565
	T/T	62 (25.9%)	54 (20%)	0.57 (0.34–0.94)	.027			1.49 (0.94–2.38)	.098		
Log-additive	—	—	—	0.76 (0.57–1.02)	.069	524.1	541	1.30 (0.97–1.74)	.074	547.3	564.6
rs2869546											
Codominant	T/T	133 (56.1%)	164 (60.1%)	1		529.9	551.1	1		546.1	567.6
	C/T	92 (38.8%)	93 (34.1%)	0.79 (0.50–1.23)	.56			1.75 (1.12–2.71)	.033		
	C/C	12 (5.1%)	16 (5.9%)	0.99 (0.38–2.60)				1.85 (0.78–4.41)			
Dominant	T/T	133 (56.1%)	164 (60.1%)	1		528.1	545.1	1		544.1	561.3
	C/T-C/C	104 (43.9%)	109 (39.9%)	0.81 (0.53–1.24)	.33			1.76 (1.15–2.69)	.0091		
Recessive	T/T-C/T	225 (94.9%)	257 (94.1%)	1		529.1	546	1		550.2	567.4
	C/C	12 (5.1%)	16 (5.9%)	1.09 (0.42–2.81)	.86			1.45 (0.62–3.37)	.4		
Log-additive	—	—	—	0.87 (0.61–1.25)	.46	528.5	545.5	1.53 (1.09–2.14)	.014	544.9	562.2

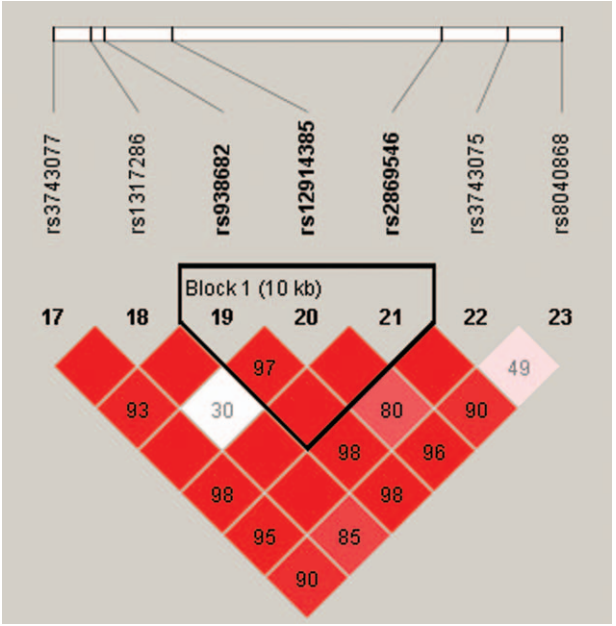

Figure 1. Haplotype block map for subgroup with age ≥45.

3.4. Association of CHRNA3 haplotypes with the risk of SCZ

In the subgroup with age ≥45, linkage disequilibrium analysis revealed a block in CHRNA3 (Fig. 1), including rs938682, rs12914385, and rs2869546. Further analyses of associations between CHRNA3 haplotypes and SCZ risk showed that haplotype "ACC" in the block was associated with a significantly increased risk of SCZ (Table 6). Additionally, we did not find any other meaningful associations between the haplotypes and SCZ risk.

4. Discussion

In the present case-control study, we investigated the association between 7 SNPs and the risk of SCZ in Chinese Han population. In the overall analysis, we did not find any significant associations between SNPs and the risk of SCZ. Interestingly, however, some associations were found in analysis stratified by age or gender. In female subgroup, rs12914385 and rs8040868 are associated with decreased risk of SCZ. In analysis stratified by age, rs3743075 is associated with decreased risk of SCZ in subgroup with age <45; while rs3743077 and rs2869546 are associated with increased risk of SCZ. Additionally, in the subgroup with age ≥45, haplotype $A_{rs938682}C_{rs12914385}C_{rs2869546}$ was found to be associated with increased risk of SCZ.

Schizophrenia is a complex psychiatric disorder associated with significant financial costs to families and societies. According to a prevalence study of SCZ in China between 1990 and 2010, the prevalence of schizophrenia in China has more than doubled over the past 20 years.[20] Schizophrenia spectrum disorder has been reported to present sensorimotor-gating deficits (commonly measured by prepulse inhibition, PPI).[21] And PPI can be enhanced by nicotine, therefore it has been proposed that schizophrenia patients smoke to ameliorate their early attentional deficits.[22] This evidence is consistent with the idea that schizophrenia patients have a strongly increased likelihood of smoking.[23] CHRNA3 (cholinergic receptor nicotinic alpha 3 subunit) is an alpha-type subunit encoded by a locus located on chromosome 15q. In 2010, Petrovsky et al reported that sensorimotor gating is influenced by variations of the CHRNA3 gene, which might also have an impact on the course and severity of schizophrenia.[23] They found that rs1317286 was associated with PPI in schizophrenia in Caucasian population. It might be due to the ethnic differences, however, no associations were observed between rs1317286 and SCZ in the present study.

Despite this study showing some SNPs associated with SCZ susceptibility in stratified analysis, some limitations should be considered. First, our sample size was relatively small. Therefore, our findings must be confirmed in studies with larger sample sizes as well as in a meta-analysis. Second, the association between genetic polymorphisms and SCZ was not evaluated. Further studies with larger sample size are required to characterize the function of CHRNA3 and elucidate the mechanisms underlying the association between the CHRNA3 and SCZ susceptibility.

To our knowledge, it is first time to report for rs12914385 and rs8040868, a number of studies have reported associations between these 2 variants and lung cancer risk, and we found that these 2 variants are associated with decreased risk of SCZ in female subgroup.[24,25] Rs3743075 and rs2869546 are also previously reported to be associated with lung cancer in Americans and Chinese populations, respectively.[26,27] In addition, rs3743077 are reported to be associated with dizziness at first inhalation of cigarette.[28] In this study, we found that the 5 variants above are associated with SCZ in stratified analysis. However, due to the small sample size in our work, further study is needed to pin down the exact relationship among CHRNA3, smoking, and SCZ.

Author contributions

Conceptualization: Li Wang, Yongjun He, Tianbo Jin.
Data curation: Chenghao Guo.

Table 6

Associations between CHRNA3 haplotypes and SCZ risk in the subgroup with age ≥45.

					Crude analysis		Adjusted by age	
	rs938682	rs12914385	rs2869546	Freq	OR (95% CI)	*P* value	OR (95% CI)	*P* value
1	G	C	T	0.4374	1	—	1	—
2	A	T	T	0.2521	0.91 (0.61–1.36)	.64	0.92 (0.62–1.38)	.69
3	A	C	C	0.2397	1.54 (1.07–2.22)	.022	1.52 (1.05–2.19)	.026
4	A	C	T	0.0688	1.13 (0.61–2.11)	.69	1.15 (0.62–2.15)	.66
Rare	*	*	*	0.002	5.12 (0.31–84.63)	.25	4.87 (0.29–81.84)	.27

Formal analysis: Tianbo Jin.
Investigation: Guixin Li, Mei Bai, Linhao Zhu, Yongjun He.
Methodology: Li Wang.
Software: Linhao Zhu.
Validation: Dongya Yuan.
Visualization: Dongya Yuan.
Writing – original draft: Chenghao Guo.
Writing – review & editing: Chenghao Guo.

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