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Association between single nucleotide polymorphisms in MiR219-1 and MiR137 and susceptibility to schizophrenia in a Chinese population

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ABSTRACT

Schizophrenia is one of the most common mental disorders to severely affect human health worldwide. Single nucleotide polymorphisms (SNPs) within related genes are candidate susceptible factors for the disorder. Rs107822 within MiR219-1 and rs1625579 within MiR137 were genotyped in 589 cases and 622 controls to investigate the possible association between the loci and schizophrenia in a Chinese population. Our results showed significant association between rs107822 and the disorder in allele (C vs. T: adjusted OR = 0.773, 95%CI = 0.655–0.912), co-dominant (TC vs. TT: adjusted OR = 0.734, 95%CI = 0.571–0.943; CC vs. TT: adjusted OR = 0.655, 95%CI = 0.459–0.936), dominant (TC + CC vs. TT: adjusted OR = 0.707, 95%CI = 0.559–0.895), and recessive (CC vs. TC + TT: adjusted OR = 0.724, 95%CI = 0.524–0.999) models, respectively. Meanwhile, negative associations were also observed between rs107822 and the disorder in male and female subgroups, and genotype CC of the locus was significantly associated with a lower positive symptom score of PANSS compared to genotype TT carrier in the cases group. However, we didn't observe a significant association between rs1625579 and the disorder. These findings indicate that rs107822 within MiR219-1 might be involved in pathogenesis of schizophrenia and that genotypes TC, CC and allele C of the locus are protective factors for schizophrenia in a Chinese population.

1. Introduction

Schizophrenia is a one of the most common psychiatric disorders that ranks among the top ten leading causes of long-term disability [1], and approximately 1% of the general population suffer from this disorder worldwide [2]. Despite the rapid advance in research on schizophrenia, the etiology of the disorder remains poorly understood. It is known that interactions between environmental and personal genetic factors can lead to the disorder, especially personal genetic background that plays a dominant role in onset of schizophrenia [3–5]. Some studies showed that aberrant expressions of mRNAs and proteins were observed in brain tissue of schizophrenia patients [6–8], indicating that these encoding genes and their regulated factors including microRNA (miRNA) were involved in initiation and progression of the disorder.

MiRNA is an endogenous, abundant, small, non-coding and single-stranded RNA of 17–25 nucleotides that can bind to the 3′-untranslated region (UTR) of targeted mRNA to regulate the expression at posttranscriptional level [9–11]. It regulates about one third of related genes and plays an important role in physiological and pathophysiological processes, such as cell proliferation and differentiation [12–14], organ growth and development [15] and occurrence of neurological and psychiatric diseases [9,11]. Single nucleotide polymorphism (SNP) in miRNA can lead to aberrant expression or secondary structure change of the product and SNP within 3′-UTR binding site of its targeted gene may affect the affinity between them [16–18]. And accumulating evidence reveals that lots of miRNAs are expressed in bran tissue, and the most of them are involved in differentiation and apoptosis of nerve cell and brain development [12,13,15]. Moreover, aberrant expressions of miRNAs are observed in brain tissue of neuropsychiatric disorders patients including schizophrenia [9,19], suggesting that abnormal expression of specific miRNA might be an important element in development of schizophrenia.

MiR-137, a brain-enriched expression miRNA, is an important element in regulation of embryonic neural stem cells differentiation [20], neuron proliferation and development [21], and synapsis maturation [22]. Dysregulation of miR-137 can lead to abnormal expression of its targeted genes, eventually leading to neuropsychiatric disorders [23]. Rs1625579, which is an intron SNP in MiR-137, has been identified as a susceptible locus for

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schizophrenia in a genome wide association study recently [24]. However, emerging case-control studies showed an inconsistent result in Chinese population [25–28].

MiR-219-1 is an important regulator in n-methy1-D-aspartate glutamate receptors (NMDAR)-mediated glutamate signal pathway [29]. The pathway is involved in synaptic plasticity and fast neurotransmission in brain, and disruption of its signal pathway can lead to schizophrenia [30,31]. Calcium/calmodulin-dependent protein kinase II gamma subunit (*CAMKIIG*) is a component of the signal pathway, and it is a targeted gene of miR-219-1. Inhibition of miR-219-1 in the murine brain can significantly modulate behavioral responses by disrupting NMDAR signal transmission in vivo [29]. Rs107822 is an allele T/C alternated polymorphism which is located in flanking sequence-37 bp of pre-miR-219-1. Since emerging studies showed that SNP in miRNA or 3′-UTR of its targeted gene could affect the transcription process or interaction between hsa-miR-219-1 and mRNA 3′-UTR of its targeted gene. So we hypothesized that rs107822 within pri-miR-219-1 would affect its structure or expression, leading to neuropsychiatric disorders such as schizophrenia.

In order to investigate the association between rs 107822 within MiR-219-1 and rs1625579 of MiR-137 and susceptibility to schizophrenia, a hospital-based case-control study including 589 clinical confirmed schizophrenia and 622 healthy checking-up individuals was carried out in present study.

2. Materials and methods

A total of 589 clinical confirmed and unrelated schizophrenia patients (275 males: mean age = 39.51 ± 14.15; 314 females: mean age = 43.33 ± 14.82 years) and 622 healthy checking-up individuals (291 males: mean age = 39.70 ± 13.3 years; 331 females: 41.08 ± 14.3 years) with free of clinical symptom and without any other disease from January of 2014 to March of 2015 in the Nantong Fourth People's Hospital were recruited in present study. The psychiatric evaluation of each patients were performed by three psychiatrists according to the DSM-IV criteria for schizophrenia and psychotic symptoms were evaluated according to structured interviews for the Positive and Negative Symptom Scale (PANSS). The controls were healthy checking-up individuals without personal or family history of neuropsychiatric disorder or any abuse of addictive drug. All included individuals are of Chinese Han nationality, which consists of more than 95% of the general population. 1 ml heparin-anticoagulated peripheral blood sample of each participant was collected and stored at −80 °C till extraction. The baseline characteristics such as sex, age, smoking and drinking were retrieved from medical record. This study was approved by the Ethical Committee of Nantong Fourth People's Hospital and all written informed consents were obtained from all participants.

Human genomic DNA was extracted from 200 μl heparin-anticoagulated peripheral blood using Tiangen human blood genome isolation Kit (Tiangen, Beijing, China) according to the manufacturer's protocol. DNA concentration and purity were detected by Ultraviolet spectrophotometer (Eppendorf, Hambrug, German), DNA concentration of all eligible sample should be higher than 200 ng/μl and A260/A280 ratio should be in the interval of 1.8–2.1.

Genotypes of rs1625579 and rs107822 were detected by TaqMan genotyping discrimination assay using ABI7500 PCR system (Applied Biosystems, Foster City, USA). The detection was performed in a total volume of 5 μl which contained 10 ng genomic DNA temple, 2.5 μl 2 * TaqMan PCR MasterMix, 2.5 μl 20 * SNP Assay (including primer and FAM/VIC probe). After initial denaturation at 95 °C for 10 min, samples were amplified through 40 cycles (92 °C for 15 s, 60 °C for 1 min). Primer and probe sequences of the two lociwere used according to the description by Guella et al. [32] and Cheong et al. [33], respectively. In order to validate the result, 5% PCR products were randomly selected to DNA sequencing.

Genotype frequencies of the two loci in case and control groups were obtained by counting. Hardy–Weinberg equilibrium (HWE) software was used to evaluate the genotypes of the loci in controls whether or not was fit for HWE. Two-sided student *T* test was selected to compare the difference in quantitative data and personal chi-square test was used to examine distribution difference of allele or genotype in two groups. Odds ratios (ORs) and 95% confidence intervals (95%CIs) were selected to estimate the strength between the two loci and risk of schizophrenia. All statistics were performed using SPSS software 17.0 (SPSS Inc., Chicago, IL, USA) and $p < 0.05$ was considered as statistical significance.

3. Results

DNA concentration of all samples was higher than 200 ng/μl, and purity was in the interval of 1.8–2.1, thus all samples were included in our study. The baseline characteristics of two groups were described in Table 1. Clinical global impression rating scales (CGI) in cases was 5.31 ± 0.60, and there was no significant difference in age, sex, status of smoking and drinking, BMI, Glu, TG, CHO, LDL and HDL in two groups.

The gentoype and allele distributions of rs107822 and rs1625579 in cases and controls were described in Table 2. *p*-Value of HWE in two SNPs were larger than 0.05 ($\chi^2 = 0.002$, *p*-value = 0.988 for rs107822; $\chi^2 = 0.004$, *p*-value = 0.952 for rs1625579), suggesting that genotype distributions of the loci were conformed to HWE. Genotype TT, TC, CC and allele T, C frequencies of rs107822 within MiR-219-1 in case and control groups were 43.1% and 35.2%, 44.3% and 48.2%, 12.6% and 16.6%, 65.3% and 59.3%, 34.7% and 40.7%, respectively. Comparing to genotype TT of the locus, frequencies of genotype TC ($p = 0.022$, adjusted OR = 0.734, 95%CI = 0.571–0.943) and CC ($p = 0.007$, adjusted OR = 0.655, 95%CI = 0.459–0.936) were significantly decreased in cases, and a negative association was examined between allele C of the locus and risk of schizophrenia ($p = 0.003$, adjusted OR = 0.773, 95%CI = 0.655–0.912). The significant association was also observed in dominant ($p = 0.005$, adjusted OR = 0.707, 95% CI = 0.559–0.895), recessive ($p = 0.049$, adjusted OR = 0.724, 95% CI = 0.524–0.999) models. However, we did not observe any significant difference of genotype and allele frequencies of MiR-137 rs1625579 between two groups in co-dominant, dominant, recessive, over-dominant and allele models.

When stratifying cases into male and female subgroups, genotype CC (13.4% vs. 20.6%, $p = 0.022$, adjusted OR = 0.571, 95% CI = 0.352–0.928), and allele C (35.1% vs. 41.4%, $p = 0.028$, adjusted OR = 0.765, 95%CI = 0.600–0.975) of rs107822 were significantly associated with a decreased risk of schizophrenia in male subgroup. Meanwhile, negative associations were also observed between rs107822 and the disorder in co-dominant (45.2% vs. 54.1%, $p = 0.010$, adjusted OR = 0.640, 95%CI = 0.460–0.897 for TC vs. TT), dominant (57.0% vs. 67.1%, $p = 0.009$, adjusted OR = 0.650, 95%CI = 0.440–0.901), over-dominant (45.2% vs. 54.1%, $p = 0.027$, adjusted OR = 0.700, 95%CI = 0.516–0.960) and allele (34.4% vs. 40.0%, $p = 0.038$, adjusted OR = 0.780, 95%CI = 0.623–0.989) genetic models in female subgroups (Table 3).

Results of association between rs107822, rs1625579 and PANSS scores were showed in Table 4. As shown in Table 4, rs1625579 was not associated with total, positive symptom, negative symptom and general symptom scores in case group. Whereas, only positive symptom score in patient harbored genotype CC of rs107822 was significantly lower than those carrying genotype TT.

Table 1
Clinical features of case and control groups in present study.

Variables	Cases (589)	Percentage (%)	Controls (622)	Percentage (%)	*p*-Value
Age (years, M + SD)	41.56 ± 15.97		40.63 ± 8.52		0.577*
Male/female	275/314	47.4%/52.6%	291/331	48.4%/51.6%	0.721#
Smoking (Yes/No)	277/312	47.0%/53.0%	295/327	47.4%/52.6%	0.889#
Drinking (Yes/No)	230/359	39.0%/61.0%	220/402	35.4%/64.6%	0.185#
BMI (kg/m^2)	22.87 ± 0.67	–	23.02 ± 0.81	–	0.672*
Glu (mm/L)	5.68 ± 1.95	–	5.44 ± 0.75	–	0.721*
TG (mml/L)	1.27 ± 0.78	–	1.37 ± 0.90	–	0.823*
CHO (mml/L)	4.33 ± 0.95	–	5.30 ± 1.03	–	0.522*
LDL (mm/L)	2.24 ± 0.69	–	2.43 ± 0.68	–	0.786*
HDL (mm/L)	1.33 ± 0.33	–	1.35 ± 0.29	–	0.894*
CGI score	5.31 ± 0.60	–	–	–	–

* *p*-Value was calculated by two-sided student *T* test.
\# *p*-Value was calculated by chi-square test; CGI: clinical global impression rating scales.

Table 2
Genotype and allele distributions of rs107822 within miR-219-1 and rs1625579 of miR-137 in cases and controls.

Locus	Model	Genotype and allele	Cases	Controls	*p*-Value*	OR and 95%CI#	
			(589)	(622)		[1]	[2]
Rs107822	Co-dominant	TT	254(43.1%)	219(35.2%)			
		TC	261(44.3%)	300(48.2%)	0.022	0.750(0.587–0.959)	0.734(0.571–0.943)
		CC	74(12.6%)	103(16.6%)	0.007	0.619(0.437–0.878)	0.655(0.459–0.936)
	Dominant	TT	254(43.1%)	219(35.2%)			
		TC/CC	335(56.9%)	403(64.8%)	0.005	0.717(0.569–0.904)	0.707(0.559–0.895)
	Recessive	TT/TC	515(87.4%)	519(83.4%)			
		CC	74(12.6%)	103(16.6%)	0.049	0.724(0.524–1.000)	0.724(0.524–0.999)
	Over-dominant	TT/CC	328(55.7%)	322(51.8%)			
		TC	261(44.3%)	300(48.2%)	0.172	0.854(0.681–1.071)	0.847(0.673–1.067)
	Allele	T	769(65.3%)	738(59.3%)			
		C	409(34.7%)	506(40.7%)	0.003	0.776(0.658–0.915)	0.773(0.655–0.912)
Rs1625579	Co-dominant	TT	512(86.9%)	540(86.8%)			
		GT	72(12.2%)	79(12.7%)	0.820	0.961(0.683–1.352)	0.963(0.684–1.355)
		GG	5(0.9%)	3(0.5%)	0.496	1.758(0.418–7.393)	1.714(0.409–7.275)
	Dominant	TT	512(86.9%)	540(86.8%)			
		GT/GG	77(13.1%)	82(13.2%)	0.955	0.990(0.709–1.383)	0.991(0.710–1.385)
	Recessive	TT/GT	584(99.1%)	619(99.5%)			
		GG	5(0.9%)	3(0.5%)	0.496	0.566(0.135–2.379)	0.570(0.135–2.401)
	Over-dominant	TT/GG	517(87.8%)	543(87.3%)			
		GT	72(12.2%)	79(12.7%)	0.802	1.045(0.743–1.470)	1.043(0.741–1.468)
	Allele	T	1096(93.0%)	1159(93.2%)			
		G	82(7.0%)	85(6.8%)	0.901	1.020(0.745–1.397)	1.021(0.745–1.398)

* *p*-Value was calculated by chi-square test.
\# OR: odds ratio, 95%CI: 95% confidence interval, [1]: crude OR and 95%CI, [2]: OR and 95%CI was adjusted by age, sex and status of smoking and drinking.

4. Discussion

Data from emerging evidence supports the general consensus that schizophrenia is a heterogeneous and complex disorder with genetic, environmental, psychological and social components [34]. The disorder is leaded by dysfunction of related protein encoding and non-coding genes that are involved in initiation and progression of the disease. MiR-137 and MiR-219-1 are involved in regulation of neuron development and maturation [20–22] as well as NMDAR-signal pathway in synaptic plasticity and brain fast neurotransmission [30,31], respectively. Genetic variations of the two miRNAs may affect transcription process or binding ability between the miRNA and its targeted gene and contribute to aberrant expression of them, eventually triggering onset of neuropsychiatric disorders including schizophrenia.

In our study, we conducted a case-control study including 589 clinical confirmed schizophrenia patients and 622 healthy checking-up controls to investigate the association between rs107822 within MiR-219-1 and rs1625579 within MiR-137 and risk of the disorder. Our results showed that rs107822 were significantly associated with a decreased risk of schizophrenia in co-dominant, dominant, recessive and allele models, there was a negative association between the locus and the disorder in male and female subgroups, and genotype CC of the locus were significantly associated with a lower positive symptom score of PANSS comparing to genotype TT in cases group, indicating that rs107822 within MiR-219-1 was involved in pathogenesis of schizophrenia, it might be a susceptible locus and genotype TC and CC and allele C of the locus might be protective factors for this disorder. Rs107822 has been reported to affect the biological process from pri-miRNA-219-1 to pre-miR-219-1 [35]. The SNP can influence the secondary structure of pri-miR-219-1, and structure of pri-miR-219-1 carrying allele T may be more stable than it harbored allele C [36]. MiR-219-1 was located at schizophrenia susceptible region of 6p21, and it was significantly up-regulated in the brain dorsolateral prefrontal area and serum of schizophrenia patients [31,37]. Additionally, miR-219-1 can bind with *CAMKIIG* 3′-UTR to regulate transcription and translation of the targeted gene [38]. Since *CAMKIIG* is an important downstream signal molecular in NMDAR signal pathway [39] and aberrant expression of CAMKIIG contributed to dysfunction of NMDAR signal pathway [40], leading to occurrence of schizophrenia.

However, we did not observe the significant association between rs1625579 within MiR-137 and susceptibility to schizophrenia in our study. The results showed that rs1625579

Table 3
Stratifying analysis between rs107822 within miR-219-1 and schizophrenia based on gender.

Stratification	Model	Genotype and allele	Cases	Controls	*p*-Value*	Adjusted OR and 95%CI#
Male	Co-dominant	TT	119(43.3%)	110(37.8%)		
		TC	119(43.3%)	121(41.6%)	0.606	0.910(0.632–1.309)
		CC	37(13.4%)	60(20.6%)	0.022	0.571(0.352–0.928)
	Dominant	TT	119(43.3%)	110(37.8%)		
		TC/CC	156(56.7%)	181(62.2%)	0.185	0.795(0.570–1.118)
	Recessive	TT/TC	238(86.6%)	251(79.4%)		
		CC	37(13.4%)	60(20.6%)	0.058	0.652(0.412–1.019)
	Over-dominant	TT/CC	156(56.7%)	170(58.4%)		
		TC	119(43.3%)	121(41.6%)	0.686	1.071(0.766–1.450)
	Allele	T	357(64.9%)	341(58.6%)		
		C	193(35.1%)	241(41.4%)	0.028	0.765(0.600–0.975)
Female	Co-dominant	TT	135(43.0%)	109(32.9%)		
		TC	142(45.2%)	179(54.1%)	0.010	0.640(0.460–0.897)
		CC	37(11.8%)	43((13.0%)	0.160	0.696(0.420–1.155)
	Dominant	TT	135(43.0%)	109(32.9%)		
		TC/CC	179(57.0%)	222(67.1%)	0.009	0.650(0.440–0.901)
	Recessive	TT/TC	277(88.2%)	288(87.0%)		
		CC	37(11.8%)	43((13.0%)	0.640	0.898(0.600–1.432)
	Over-dominant	TT/CC	172(54.8%)	152(45.9%)		
		TC	142(45.2%)	179(54.1%)	0.027	0.700(0.516–0.960)
	Allele	T	412(65.6%)	397(60.0%)		
		C	216(34.4%)	265(40.0%)	0.038	0.780(0.623–0.989)

* *p*-Value was calculated by chi-square test.
\# OR: odds ratio, 95%CI: 95% confidence interval, OR and 95%CI was adjusted by age, sex and status of smoking and drinking.

Table 4
Association between rs107822 within miR-219-1 and PANSS scores in case group.

Characteristics	Rs107822 Genotype			Rs1625579 Genotype		
PANSS scores	CC	CT	TT	GG	GT	TT
Total	86.90 ± 12.35	86.13 ± 13.11	88.33 ± 11.89	85.56 ± 13.28	85.98 ± 12.67	85.26 ± 13.08
Positive symptom	23.56 ± 3.32*	25.49 ± 4.96	26.88 ± 4.45	25.34 ± 3.43	24.98 ± 4.01	25.23 ± 3.98
Negative symptom	20.56 ± 7.43	18.32 ± 8.32	19.78 ± 7.98	20.11 ± 6.98	19.96 ± 7.03	20.01 ± 7.00
General symptom	42.78 ± 8.70	42.32 ± 7.90	41.67 ± 8.21	40.11 ± 7.90	41.04 ± 7.89	40.02 ± 7.78

* Positive symptom score of rs107822 CC genotype individuals is significantly lower than TT genotype carrier.

was unlikely to have a major relevance to this disorder and genotype and allele of the locus couldn't be susceptible factors for the disease. Yuan et al reported that either allele or genotype of the locus was not associated with the disease in a case-control and meta-analysis in Chinese population [27]. Meanwhile, results of Wang et al also reported no significant association between them [28]. However, an positive association between the locus and schizophrenia was reported in Chinese population and European Caucasian ancestry [24–26], respectively. The following causes may account for this conflict result. Populations from different geographical area may exist heterogeneity of personal genetic background. Although individuals are all Chinese population in different regions [25,26,28], frequency of allele C within rs1625579 is inconsistent with each other. Additionally, small sample size in case and control groups may attenuate statistical power in our study [41].

In conclusion, our findings indicated that rs1625579 within MiR-137 was not associated with schizophrenia, however MiR-219-1 rs107822 was involved in pathogenesis of schizophrenia, and genotype TT, TC, and allele C of the locus were protective factors for the disorder. With limitation of our study, further multiple central and well-designed epidemiological study with large sample size are warrant to conduct to validate our findings.

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