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The Correlation Between Peripheral Blood Micro-Ribonucleic Acid Expression Level and Personality Disorder in Patients with Schizophrenia

ABSTRACT

Objective: Schizophrenia patients often have personality disorders; schizophrenia patients with personality disorders are more difficult to treat and have a worse prognosis. Early identification of this group of patients and early intervention can achieve better prognosis. Therefore, it is very important to explore effective biomarkers and early diagnosis for the prognosis of schizophrenia. The primary purpose of this paper is to explore the relationship between plasma miRNA expression level and personality disorder with schizophrenia.

Methods: Gene microarrays in miRNA files were employed, and the plasma of peripheral blood of 82 schizophrenic patients and 43 healthy control subjects were examined. Real-time reverse transcription polymerase chain reaction detection were performed to explore the results. Spearman correlation analysis was used to analyze the correlation between expression level of miRNAs and Personality Diagnosis Questionnaire-4 score.

Results: The results showed that miR-1273d, miR-1303, miR-3064-5p, miR-3131, miR-3687, miR-4428, miR-4725-3p, and miR-5096 were up-regulated in schizophrenic patients. Compared to healthy control subjects, the difference was statistically significant ($P < .05$). Schizophrenic patients with schizoid, paranoid, schizotypal, and obsessive compulsive traits had negative correlation with miR-1303, miR-3131, miR-4428, and miR-5096 expression level ($r = -0.40$ to -0.62, $P < .05$); there were no significant differences in the other miRNAs. Correlation with other personality traits was not significant ($P > .05$). The stepwise regression analysis indicated that miR-5096, miR-3131, and miR-1273d have a significant predictive effect on the schizoid trait ($P < .01$). MiR-4428 and miR-1303 had a significant predictive effect on the schizotypal trait ($P < .01$). MiR-5096, miR-4428, and miR-4725-3P had a significant predictive effect on the paranoid trait ($P < .05$). MiR-4428, miR-1303, and miR-5096 had a significant predictive effect on the obsessive compulsive trait ($P < .05$).

Conclusion: The expression levels of miR-1273d, miR-1303, miR-3064-5p, miR-3131, miR-3687, miR-4428, miR-4725-3p, and miR-5096 were up-regulated in the peripheral blood of patients with schizophrenia, and these miRNAs are expected to be diagnostic biomarkers for accurate diagnosis of schizophrenia. The expression levels of miR-1303, miR-3131, miR-1273d, miR-4428, miR-4725-3p, and miR-5096 have significant predictive effects on personality disorder in schizophrenia.

Keywords: miRNA, personality disorder, schizophrenia, correlation

Introduction

Schizophrenia (SZ) is a disease of brain dysfunction, and the complex interaction of environmental factors, biological, and genetic leads to the occurrence of schizophrenia.[1] Schizophrenia often occurs in young adults, with perceptual, thinking, emotional, and behavioral disorders.[2] Schizophrenia accounts for more than half of psychiatric inpatients, and half of patients end up with a mental disability. The course of the disease is often prolonged, bringing a serious burden to society and their families,[3,4] and patients with schizophrenia

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often have personality disorders. Schizophrenia patients with personality disorders are more difficult to treat and have a worse prognosis. Early identification of this group of patients and early intervention can improve the prognosis. Therefore, it is very important to explore effective biomarkers and early diagnosis for the prognosis of schizophrenia.

The studies showed that schizophrenia is a kind of neurodevelopmental disorder regulated by multiple genes.[5] Many researchers have suggested that genetic factors play an important part in the pathogenesis, prognosis, efficacy, and recurrence,[6-10] and the heritability of schizophrenia is 60-80%.[11] microRNAs (miRNAs) are a class of non-coding RNAs that are approximately 22 nucleotides in length.[12] Many studies have reported the importance of miRNA networks in neuronal development and regulation of brain function, and it is closely related to schizophrenia and other mental disorders.[13,14] These results suggest that miRNA can be used as a new biomarker for schizophrenia.[15,16]

To explore the potential role of miRNA as biomarkers, previous studies have shown a correlation between miRNA and schizophrenia. However, some miRNA expression levels were upregulated, while others were downregulated. There is no consistent conclusion from the current studies. We observe that miRNAs are usually collected from brain tissues,[17,18] and the difficulty of brain biopsy and the acquisition of brain tissues are often from postmortem patients,[19] which leads to certain limitations in obtaining miRNA with abnormal expression from brain tissue. As the expression profile of miRNA in peripheral blood changes with the physiological and pathological conditions of the body, it has important clinical application value. In our team's previous studies, the researchers explored the correlation between miRNA expression and schizophrenia,[20,21] and this study further validates the results of the previous study.

In addition, schizophrenia patients have a certain degree of personality disorder.[22] Schizotypal disorder is characterized by erratic behavior, eccentric beliefs, and fantastical thinking that has been shown to be significant predictors of schizophrenia. Therefore, personality disorders can be used as risk factors for schizophrenia.[23] Previous studies have shown that schizotypal disorder and schizophrenia share common psychophysiological features and similar brain morphological changes.[24] Based on the close correlation between schizophrenia and miRNA, we speculate that personality disorder is also correlated with miRNA expression. Is there any correlation between miRNA expression and personality disorder in schizophrenia patients? There are few studies on plasma miRNA expression and schizophrenia patients with personality disorder at present. This paper attempts to explore miRNA expression levels in peripheral blood plasma of schizophrenia and the correlation between miRNA expression levels and personality disorder in patients with schizophrenia.

MAIN POINTS

- *The expression levels of miR-1273d, miR-1303, miR-3064-5p, miR-3131, miR-3687, miR-4428, miR-4725-3p, and miR-5096 were upregulated in the peripheral blood of patients with schizophrenia. These miRNAs are expected to be diagnostic biomarkers for accurate diagnosis of schizophrenia.*
- *Schizophrenic patients with schizoid, paranoid, schizotypal, and obsessive compulsive traits had negative correlation with miR-1303, miR-3131, miR-4428, and miR-5096 expression level.*
- *The expression levels of miR-1303, miR-3131, miR-1273d, miR-4428, miR-4725-3p, and miR-5096 have a significant predictive effect on personality disorder in schizophrenia.*

Material and Methods

Recruitment and Procedures

The samples were collected from the patients of outpatient department and psychiatry department of No. 102 Hospital of Chinese People's Liberation Army. The study was agreed upon by the Medical Ethics Committee, and all subjects or their family members (guardians) signed informed consent. Ethical approval was obtained from the Ethics Committee of No. 102 Hospital of Chinese People's Liberation Army (Approval No: 2014-340-1).

Participants

Schizophrenia group: Inclusion criteria: patients who met the diagnostic criteria for schizophrenia in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*); schizophrenia patients with first episode or patients who had not taken antipsychotic drugs within 3 months before recruitment; age ranging from 15 to 60 years. Exclusion criteria: suffering from other mental disorders; suffering from physical diseases such as diabetes and hyperthyroidism; suffering from neurological diseases such as epilepsy and brain trauma; having a history of alcohol or drug abuse; blood transfusion history within 1 month before enrollment; and having received modified electroconvulsive treatment within 3 months before recruitment. A total of 82 patients were enrolled, including 39 males and 43 females, age 15-60 (28.55 ± 11.55) years.

Control group: the staff of our hospital and health examination personnel; the control group and the case group were matched one by one in age, gender, and ethnicity, eliminating the bias caused by gender, age, and ethnicity. Inclusion criteria: no family history of schizophrenia, no major traumatic events in the past 1 month, and no history of blood transfusion in the recent 1 month. Forty-three healthy people were recruited, 23 females and 20 males, aged from 16-60 (29.40 ± 12.48) years, with no statistical significance compared with the SZ group ($P = .903$).

Microarray Analysis

Whole blood (5 mL) was collected in an ethylenediaminetetraaceti c acid (EDTA) anticoagulant tube from each subject and processed within 1 hour. Peripheral blood mononuclear cells (PBMCs) were isolated through density gradient centrifugation and stored at −80°C until use. Total RNAs were extracted from the PBMCs with the mirVanaTMmiRNA Isolation Kit (Ambion, LOT:1406120 AM1561, Austin, TX, USA) according to the manufacturer's protocol. To ensure a robust analysis for the following procedures, samples with an RNA integrity number inferior to 8 were excluded. Samples of RNA from 3 SZ patients (male, 20 years; male, 21 years; female, 19 years) and 3 controls (male, 20 years; male, 21 years; female, 19 years) were used for miRNA microarray profiling. microiRNA expression was measured by Affymetrix miRNA 3.0 array (Affymetrix, Santa Clara, CA, USA). The sample labeling, microarray hybridization, and washing were performed based on the manufacturer's standard protocols. Briefly, total RNA was tailed with Poly A and then labeled with biotin. Afterwards,

the labeled RNAs were hybridized onto the microarray. After washing and stained the slides, the arrays were scanned by the Affymetrix Scanner 3000 (Affymetrix). The scanned images were analyzed using Expression Console software (version 1.3.1, Affymetrix).

Micro-Ribonucleic Acid Selection

Combined with domestic and foreign literature, 10 miRNAs were selected for further polymerase chain reaction (PCR) validation. The 10 miRNAs targeted were selected by an extensive survey of the literature in the PubMed database, the Springer database, and the university of British Columbia Library database. From 2000 to May 2020, all published studies of mRNAs that may be associated with schizophrenia were searched and analyzed.

Scale Assessment

Personality Diagnosis Questionnaire 4 (PDQ-4) was used by 3 attending psychiatrists or psychologists to evaluate the subjects in the SZ group. Before the evaluation, all researchers were involved in unified training, unified methodology, and a standardized test process. Personality Diagnosis Questionnaire 4 includes 10 diagnostic factors for personality disorders. Yang et al's[25] study showed that PDQ-4 had good reliability and validity indexes, with retest reliability coefficients ranging from 0.50 to 0.80 ($P < .01$) and Cronbach's α coefficient of 0.56-0.78, which met the requirements of psychometrics and were suitable for the assessment of personality disorders in China.

Micro-Ribonucleic Acid Preparation

Five milliliters of whole blood from all subjects was collected using an EDTA anticoagulant tube. The plasma from the whole blood was transferred into a 2 mL disposable microcentrifuge tube with RNase/DNase-free after centrifugation and kept in the refrigerator at −80℃ for future use. Two milliliters of plasmawas used for miRNA preparation, following the manufacturer's instructions with the miRNeasy Serum/Plasma Kit (Qiagen). All miRNA samples were stored in the refrigerator at −80℃. As recommended by the manufacturer (Qiagen), miR-39 synthesized by *Caenorhabditis elegans* was used as a spike-in and normalization control.[26,27]

Quantitative Real-Time Reverse Transcription Polymerase Chain Reaction

The plasma miRNA was transformed into cDNA, this process by a reverse transcription reaction using the TaqMan microRNA Reverse Transcription Kit. TaqMan microRNA Assays provide miRNA-specific stem loop primers. The primer sequences of the tested miRNA are shown in Table 1. The real-time reactions were performed according to the manufacturer's specifications and operate on an Applied Biosystems 9700 PCR instrument (Foster City, CA, USA). The reverse transcription polymerase chain reaction (RT-PCR) was operated in a 5mL reaction solution containing 2.5 mL TaqMan Universal PCR Master Mix II, 0.25 mL miRNA-specific primer/probe mixture, and 2.25 mL diluted RT cDNA products. The PCR reaction was performed in a 7900HT rapid RT-PCR system. SDS (SDS V2.0.1) software was used to collect RT-PCR data. To analyze the relative levels of miRNA, we used the miR-39 synthesized by *Caenorhabditis elegans* as a normalized control. In previous studies, this synthetic miRNA was often used as a control to analyze target miRNA levels in peripheral blood. The relative expression level of the measured miRNA in peripheral blood was calculated using the $2^{-\Delta\Delta Ct}$ method.

Table 1. Gene Identification and Primer Sequences of the Micro-Ribonucleic Acids Tested in the Current Study

Micro-Ribonucleic Acid ID	Target Sequence for Primer
miR-1273d	GAACCCAUGAGGUUGAGGCUGCAGU
miR-1303	UUUAGAGACGGGGUCUUGCUCU
miR-21	UCUGGCUGUUGUGGUGUGCAA
miR-3064-5p	UCGAGGACUGGUGGAAGGGCCUU
miR-3131	CCCGGACAGGCGUUCGUGCGACGU
miR-3687	CAAGGAGACGGGAACAUGGAGC
miR-3916	UGGGGAAGGCGUCAGUGUCGGG
miR-4428	GUUUCACCAUGUUGGUCAGGC
miR-4725-3p	CAACACCAGUCGAUGGGCUGU
miR-5096	AAGAGGAAGAAAUGGCUGGUUCUCAG
cel-miR-39	UCACCGGGUGUAAAUCAGCUUG

Statistical Analysis

All the obtained data were analyzed using DataAssist 3.0 version and Statistical Package for the Social Sciences 17.0 version (SPSS Inc.; Chicago, IL, USA) statistical software. The statistical significance level was established as 0.05. The normality test (K-S test) was performed on the expression level of miRNA. The differences of miRNA expression levels between the SZ group and the control group were analyzed by Wilcoxon rank–sum test, as the data are not appropriate for the normal distribution. The correlation between miRNA expression level and scale scores (PDQ-4 score) were detected by Spearman correlation coefficient. Multiple linear stepwise regression analysis was used to select the statistically significant miRNA. The principles of entry and exclusion equations were the minimum acceptable limit of deleting a variable was 0.15, and the maximum acceptable limit of adding a variable was 0.1.

Results

Microarray Analysis

Microarray analysis results showed that a total of 33 miRNA were identified to be significantly different from the control group. Thirty-two upregulated and 1 downregulated miRNAs were found (Table 2).

Comparison of Micro-Ribonucleic Acid Expression Levels Between Control Group and Schizophrenia Group

According to the method mentioned above, 10 miRNAs (miR-1273d, miR-1303, miR-3687, miR-3064-5p, miR-3131, miR-4428, miR-4725-3p, miR-5096, miR-3916, and miR-21) were further analyzed. The Wilcoxon rank–sum test showed that the ΔCT values of 8 miRNAs (miR-1273d, miR-1303, miR-3064-5p, miR-3131, miR-3687, miR-4428, miR-4725-3p, and miR-5096) in the SZ group were significantly higher than those in the control group ($P < .05$), there were no significant differences in miR-3916 and miR-21 between the SZ group and the control group ($P = .75$, $P = .57$), Table 3.

Spearman Correlation Coefficient of Micro-Ribonucleic Acid Expression Levels and Personality Disorder in Schizophrenia Patients

A total of 75 valid questionnaires (effective rate 91.46%) were obtained by excluding 7 invalid questionnaires from 82 patients with schizophrenia. Spearman correlation coefficient was made between the score of personality disorder and miRNA expression level in the SZ group. As shown in Table 4, schizoid, paranoid, obsessive-compulsive,

Table 2. Chip Screening for Schizophrenia

Probe Set ID	FC (abs)	Regulation	*P*
miR-1228	2.298578	Up	.022
miR-1246	4.513534	Up	.003
miR-1273d	11.57571	Up	.002
miR-1303	4.630197	Up	.039
miR-1908	2.563516	Up	.024
miR-1910	3.567002	Up	.021
miR-21	4.740135	Up	.004
miR-3064-5p	7.426971	Up	.012
miR-3131	5.398245	Up	.003
miR-3156-5p	2.949549	Up	.023
miR-3188	2.517869	Up	.012
miR-3617	2.598172	Up	.045
miR-3687	6.095347	Up	.049
miR-3916	3.60074	Up	.002
miR-3937	3.387137	Up	.018
miR-4271	3.49536	Up	.008
miR-4428	4.275544	Up	.031
miR-4436b-5p	3.036439	Up	.018
miR-4467	3.554171	Up	.008
miR-4486	2.262619	Up	.011
miR-4488	2.259933	Up	.037
miR-4492	4.855994	Up	.039
miR-4506	2.894774	Up	.007
miR-4508	4.061554	Up	.028
miR-4646-5p	2.126904	Up	.047
miR-4708-5p	2.599784	Up	.042
miR-4725-3p	4.710764	Up	.012
miR-4753-5p	2.093268	Up	.002
miR-5096	4.022421	Up	.022
miR-885-3p	3.059504	Up	.029
miR-885-5p	3.372775	Up	.036
miR-92b	2.615707	Up	.033
miR-4701-3p	2.950271	Down	.040

FC (abs): absolute fold change.

and schizotypal personality traits were significantly negatively correlated with the expression level in miR-1303, miR-3131, miR-4428, and miR-5096 ($P < .05$ or .01). There was no significant correlation with other personality trait ($P > .05$).

Table 3. The Difference of Micro-Ribonucleic Acid Expression Level Between Control Group and Schizophrenia Group (ΔCT)

miRNA	SZ Group (Median)	Control Group (Median)	*P*
miR-1273d	11.25	12.75	.004
miR-1303	7.64	10.22	.017
miR-21	2.28	2.25	.572
miR-3064-5p	12.70	13.66	.046
miR-3131	15.86	19.78	<.001
miR-3687	1.34	2.28	<.001
miR-3916	10.59	10.10	.757
miR-4428	15.86	19.78	.001
miR-4725-3p	15.58	19.76	.001
miR-5096	0.84	1.77	.001

**$P < .01$.

Multiple Linear Analysis of Influencing Factors of Personality Disorder in Schizophrenia

Taking the miRNA expression levels of miR-1273d, miR-1303, miR-3064-5p, miR-3131, miR-3687, miR-4428, miR-4725-3p, and miR-5096 as the dependent variables, and personality disorder as the independent variable, multiple linear stepwise regression analysis was used to verify the relationship between miRNA expression levels and personality disorder. As shown in Table 5, miR-5096, miR-3131, and miR-1273d were entered into the schizoid personality trait regression function as independent variables, accounting for 31% of the schizoid personality trait ($P < .01$); miR-4428 and miR-1303 were entered into the schizotypal personality disorder regression equation as independent variables, accounting for 28% of the schizotypal personality trait ($P < .01$); miR-5096, miR-4428 and miR-4725-3p were entered into the paranoid personality trait regression equation as independent variables, accounting for 41% of the paranoid personality trait ($P < .01$); miR-5096, miR-4428, and miR-1303 were entered into the compulsive personality trait regression function, accounting for 19% of the compulsive personality trait ($P < .01$).

Discussion

Schizophrenia is a polygenic neuropsychiatric disease, with a lifetime prevalence of about 1% worldwide.[28] Its clinical symptoms mainly include hallucinations, delusions, and neurocognitive dysfunction. Schizophrenia occurs in young adults, has a long latent period, and the early symptoms are not obvious. It is often manifested as some

Table 4. Spearman Correlation Coefficient of Personality Diagnosis Questionnaire-4 score and Micro-Ribonucleic Acid in Schizophrenia Group (*r*)

	Schizoid	*P*	Schizotypal	*P*	Paranoid	*P*	Compulsive	*P*
miR-1273d	0.12	.758	0.09	.936	−0.15	.868	0.11	.816
miR-1303	−0.42	.023*	−0.57	.006**	−0.61	.003**	−0.52	.003**
miR-21	0.14	.614	−0.22	.685	−0.11	.912	0.04	.967
miR-3064-5p	0.19	.569	0.06	.953	0.17	.801	0.21	.761
miR-3131	−0.54	.002**	−0.61	.003**	−0.50	.026*	−0.45	.022*
miR-3687	−0.04	.915	0.11	.831	−0.24	.658	0.06	.875
miR-3916	0.08	.873	0.15	.793	−0.24	.614	−0.23	.654
miR-4428	−0.56	.001**	−0.52	.004**	−0.49	.035*	−0.60	.001**
miR-4725-3p	0.19	.532	0.30	.572	0.25	.576	0.11	.835
miR-5096	−0.40	.039*	−0.53	.004**	−0.49	.036*	−0.57	.002**

*$P < .05$; **$P < .01$.

Table 5. Multiple Linear Stepwise Regression Analysis of the Influencing Factors of Personality Disorder in Schizophrenia

Dependent Variable	Independent Variable	*B*	SE	*β*	*t*	*P*	R^2	Adjusted R^2	*P**
Schizoid	miR-1273d	−1.96	−0.887	−0.37	−6.25	<.001	0.31	0.23	<.001
	miR-3131	−1.13	−0.599	−0.51	−4.95	.009			
	miR-5096	−1.05	−0.611	−0.48	−5.28	.003			
Schizotypal	miR-1303	−1.21	−0.829	−0.46	−7.61	<.001	0.28	0.19	<.001
	miR-4428	−1.56	−0.695	−0.39	−6.24	<.001			
Paranoid	miR-4725-3p	−1.14	−0.741	−0.31	−5.31	.002	0.41	0.34	<.001
	miR-4428	−1.28	−0.652	−0.43	−4.93	.011			
	miR-5096	−1.51	−0.956	−0.36	−5.21	.005			
compulsive	miR-1303	−1.62	−0.825	−0.29	−4.28	.015	0.19	0.09	<.001
	miR-4428	−1.22	−0.496	−0.32	−6.24	<.001			
	miR-5096	−1.31	−0.551	−0.42	−8.45	<.001			

B, unstandardized regression coefficients; *β*, standardized regression coefficient; SE, standard error; *t*, *t*-test result of beta.
**P*-value of the multiple linear regression model.

personality and behavioral problems,[29,30] which are not easy to distinguish from other mental disorders. It delayed diagnosis and misdiagnosis, which are not good for early recognition, early intervention, prognosis, and rehabilitation treatment of schizophrenia. Therefore, exploring biomarkers of schizophrenia has great clinical value.

The results of this study indicated that the expression levels of miR-1273d, miR-1303, miR-3064-5p, miR-3131, miR-3687, miR-4428, miR-4725-3p, and miR-5096 were significantly upregulated, except miR-3916 and miR-21. Elevated plasma miRNA expression levels have been reported in schizophrenia patients in previous studies,[31,32] which suggests that the results are similar to our study are similar and miRNA is closely associated with schizophrenia. However, the 8 miRNAs significantly upregulated in this study have not been reported in previous studies. This may be because most of the miRNAs selected in our previous studies are those that have been reported to be associated with schizophrenia. The miRNAs selected in this paper are those that may be associated with schizophrenia through a literature search. It may provide some help for researchers to discover new biomarkers of schizophrenia has great clinical value. MiR-1273d was found to be involved in hypoxia, immune, and inflammatory pathways.[33] MiR-1303 and miR-3064-5p regulate the permeability of the blood–brain barrier,[34,35] increasing the risk of viral infection or damage to the brain by toxic substances, ultimately leading to pathological changes in the central nervous system. MiR-4428 is involved in the PI3K-PKB signaling pathway that promotes cell survival.[36] MiR-3687, miR-4725-3P, and miRNA-5096 are involved in pathways that regulate glial cell tumorigenesis in the nervous system.[37-39] The above studies can partly explain why the miRNA in this study has abnormal expression in schizophrenia, because the above processes may lead to the occurrence and development of schizophrenia. Previous studies have also shown that miRNAs associated with schizophrenia have something in common and are related to the exposure and response of stressor,[40] and the correlation between the activation level of stress response and schizophrenia has also been reported, which seems to explain the differential expression of some mRNAs in schizophrenia. As candidate miRNAs were screened based on the basis of existing literature, the function of a single miRNA in the pathological process of schizophrenic patients could not be fully reflected. Therefore, the combined detection of the above miRNAs may improve sensitivity for the diagnosis of schizophrenia.

In addition, correlation and multiple linear analyses found that miR-1303, miR-3131, miR-1273d, miR-4428, miR-4725-3p, and miR-5096 had significant predictive effects on their personality disorders in schizophrenic patients. From a clinical point of view, paranoid, schizoid, and schizotypal personality disorders are usually considered as schizophrenia spectrum disorders, and the symptoms of these personality traits are usually characterized by subthreshold or attenuated forms of schizophrenia-related psychiatric symptoms. They include social withdrawal, apathy, and interest drops similar to the negative schizophrenic symptoms. At the same time, prodromal symptoms of schizophrenia have certain obstacles in interpersonal relationships, emotional expression, social behavior, social cognition, and other aspects.[41,42] It suggests that personality disorder may be a prodrome of schizophrenia. This may partly explain that miRNAs are not only associated with schizophrenia but also associated with personality disorders. From a genetic perspective, miRNAs were involved in cell proliferation, differentiation, and apoptosis and affect the development and maturation of the brain and extensively regulate neuroendocrine processes.[43,44] At the same time, personality disorder and schizophrenia are closely related to brain development and neuroendocrine.[45,46] The results indicated that miRNA may be involved in the pathophysiological process of both personality disorder and schizophrenia. This study could infer that miR-1303, miR-3131, miR-1273d, miR-4428, miR-4725-3p, and miR-5096 may be involved in the pathological path regulation of the occurrence and development of paranoid, schizotypal, and schizoid personality traits and schizophrenia.

In conclusion, the study found that the expression levels of miR-1273d, miR-1303, miR-3064-5p, miR-3131, miR-3687, miR-4428, miR-4725-3p, and miR-5096 were upregulated in the peripheral blood of patients with schizophrenia. These miRNAs are expected to be diagnostic biomarkers for accurate diagnosis of schizophrenia. The expression levels of miR-1303, miR-3131, miR-4428, miR-5096, miR-4725-3p, and miR-1273d have significant predictive effect on personality disorder in schizophrenia.

Limitations

One limitation of this study is the small sample size. Therefore, to verify these results larger cohorts are needed. In addition, the 10 miRNAs analyzed in this paper were obtained by reference to previous literature and microarray analysis, but not all miRNAs were analyzed. Therefore, a large whole-genome-wide sample analysis is needed in the future.

Availability of Data and Materials: *The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.*

Ethics Committee Approval: *The study was approved by the Ethics Committee of No. 102 Hospital of Chinese People's Liberation Army (Approval No: 2014-340-1, Date: November 9, 2014).*

Informed Consent: *Informed consent was obtained from the subjects and their guardians who agreed to take part in the study.*

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