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Association of lncRNA expression and coping style, personality trait in GAD patients

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Abstract:
Background*: Generalized anxiety disorder (GAD) is chronic anxiety disorders with a genetic inheritance, lncRNA, as a regulator of epigenetic mechanism of mental disorder, may exert a crucial role in pathological process of GAD. This study aims to explore abberant expression and the association of lncRNA expression level and coping style, personality trait in GAD patients.*
Materials and Methods: *In this case controlled study, 130 GAD patients and 40 health controls were recruited. 10 differential expressed lncRNAs verified by gene chip and RT – PCR in 131 GAD patients. Then correlation analysis of lncRNA expression and coping styles, personality trait was carried out.*
Results: *the lncRNAs expression levels of NONHSAT029028(PR5), NONHSAT101077(PR6), NONHSAG049179(PR7), NONHSAT031726(PR8), NONHSAT131696(PR10) in GAD patients were significantly downregulated and controls($p<0.05$ or 0.01). The expression level of PR5 and PR7 were positively correlated with negative coping style($p<0.05$); the ΔCt value of PR5, PR6, PR7, PR8, PR10 were negatively correlated with paranoid personality, obsessive personality, narcissistic personality, avoidant personality($p<0.05$).*
Conclusion: *The lncRNAs expression levels were downregulated and correlated with coping style, personality trait in GAD patients.*
Key Word*: GAD; lncRNA; Coping style; Personality trait*

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I. Introduction

Generalized anxiety disorder (GAD) is chronic anxiety disorders characterized with sustainable, excessive and uncontrolled concerns, always come up with some mental or physical symptoms. The female usually has higher GAD prevalence than the male which caused negative impact on patients' physical and mental health, education, social and vocational functioning and overall quality of life[1, 2]. However, the current diagnosis of GAD is mainly based on symptomatology which is prone to produce subjective bias. The etiology and pathogenesis of GAD, which are still not very clear, could furtherly impair treatment response and prognosis of GAD.

According to previous studies, it is indicated that heredity is one of pathological mechanism which may be a break in the early diagnosis and treatment of GAD[3, 4]. The non-coding RNA (ncRNA) can be divided into two types according to the length of the transcript: small ncRNA (small ncRNA, <200nt) and long chain non-coding RNA (lncRNA, >200nt). lncRNA, discovered in 2002 by Okazaki with a length more than 200 nt, was initially considered as a transcription product of RNA polymerase Ⅱ and have no biological function[5]. With the further research of lncRNA, only a small number of lncRNAs were found to be well characterized by which have conservative form of secondary structure, shear and subcellular localization. By comparing the expression patterns to reconstruct evolutionary of the homologous lncRNA and protein coding in quadrupeds family, The conservative and specificity suggest that lncRNAs may perform the biological function of synaptic transmission process, placenta through tiny RNA[6-8].

Recent studies have verified that lncRNAs are related to mental illness. Studies on schizophrenia and depression about lncRNAs have confirmed that expression levels of lncRNA in Peripheral blood mononuclear cells (PBMCs) in schizophrenic and depression patients were altered compared with healthy people, which can be used as a potential biomarker for clinical diagnosis evaluation of the treatment[10-11]. DISC1was reported to be associated with the development of schizophrenia, major depression, bipolar disorder and such mental disease, while the lncRNA DISC2 can regulate the expression of DISC1 which may be a potential marker for the treatment of mental illness[12, 13]. A miRNA study on GAD also verified that 5 specified miRNAs in PBMCs of anxiety patients were closely related to their pathogenesis and miR-663 expression level in monocytes of GAD

patients were highly correlated with the symptoms of psychological anxiety[14].

By microarray, altered expressed lncRNAs of GAD patients were screened in this study, of which, 10 lncRNAs were selected for RT-PCR study in a validation samples. The relationships of lncRNAs with coping styles, social support and personality characteristics were analyzed so as to explore the connections between them.

II. Materials And Methods

This case controlled study was carried out on GAD patients of Center of Mental Disorder Prevention & Treatment, No.904 Hospital, Changzhou, Jiangsu, China from May 2018 to February 2021. A total of 130 patients and health controls respectively participated in this study.

Study Design: Case controlled study.

Study Location: In Center of Mental Disorder Prevention & Treatment, No.904 Hospital, Changzhou, Jiangsu, China.

Study Duration: May 2018 to February 2021.

Sample size: Respectively 130 patients and health controls.

Subjects & selection method: The study population was drawn from GAD patients who presented to Center of Mental Disorder Prevention & Treatment, No.904 Hospital and Health controls were recruited from the nearby community without any family history of major psychiatric disorders (e.g., Schizophrenia, major depressive disorder and bipolar disorder) within the last 3 generations were recruited by convient sampling. Patients and healthy controls were matched in age, ethnicity, and gender.

Inclusion criteria:

1. Meet the diagnostic criteria of DSM-Ⅴ.
2. All patients were of Han ethnicity.
3. First visit or without any clinical treatment before enrollment.

Exclusion criteria:

1. Patients with any anxiolytic for at least 3 months before enrollment.
2. Patients with severe medical disease, structural brain disorders, mental retardation, mood incongruent psychotic symptoms, and substance abuse.
3. Patients who had brain injury causing traumatic amnesia longer than 24h and who achieved blood transfusion within 1 month or electroconvulsive therapy within 6 months.

2.2 Procedure methodology

After written informed consent was obtained, a well-designed questionnaire was used to collect the data of the recruited patients. The questionnaire included Simplied Coping Style Questionnaire (SCSQ), Personality Diagnostic Questionnaire (PDQ)[16, 17].

The next step is slood collection and RNA extraction. Whole blood (5ml) was collected from each subject using EDTA anticoagulant tube and processed within 2 hours. Peripheral Blood Mononuclear Cells (PBMCs) were isolated from the blood by centrifuged, then transferred into fresh RNase/DNase-free 2ml microcentrifuge tube, and stored at –80 °C for use. Total RNAs were extracted from PBMCs with RNasy Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol, and were quantified using NanoDrop ND-1000 (Thermo Scientific, Delaware, ME, USA).

According to microarray results, 10 candidate lncRNAs (ENST00000505825(PR1), NONHSAT103134(PR2), NONHSAG017299(PR3), NONHSAT078768(PR4), NONHSAT029028 (PR5), NONHSAT101077(PR6), NONHSAG049179(PR7), NONHSAT031726(PR8), TCONS_l2_00010607(PR9), NONHSAT131696(PR10)) were chosen for further validation with qRT-PCR. Blood samples from 130 GAD patients and 40 healthy controls were used to validated the findings from lncRNA profiling. Total RNAs were isolated from the PBMCs using Trizol reagent (Invitrogen, USA) for quantitative detection of lncRNA. Complementary DNA was synthesized using the Reverse Transcription TaqMan LncRNA Reverse Transcription Kit (TaqMan RNA reverse transcription kit, American ABI company) according to the manufacturer's instructions. Real-time fluorescence quantitative PCR was carried out according to the instruction manual of TaqMan kit (TaqMan general hybrid kit II, USA ABI).

Statistical analysis

All data were statistically analyzed using GraphPad Prism 6.0 and SPSS21.0 software. T test was used to compare the expression levels of miRNA between all patient and control groups. Spearman correlation analysis was used to analyze the expression level of lncRNA and coping style, and personality traits. All

statistical test were two-tailed, and $p < 0.05$ was considered as statistically significant.

III. Result

3.1 Comparison of lncRNA expression in GAD patients and controls

As shown in table 1, the lncRNAs expression levels of PR5, PR6, PR7, PR8, PR10 in GAD patients were significantly downregulated and controls(p<0.05 or 0.01).

Table no1: Comparison of lncRNA expression in GAD patients and normal controls(NC) ($\bar{x}$ + s)

TargetID	GAD (n=130)	NC (n=130)	*t* value	*p* value
PR1	7.19±2.44	8.39±2.65	-2.249	0.126
PR2	7.07±3.51	8.17±2.57	-2.137	0.054
PR3	7.11±2.87	8.30±2.98	-2.328	0.091
PR4	7.14±2.85	8.51±2.61	-2.654	0.139
PR5	6.49±3.05	7.81±2.50	-3.50	0.013
PR6	7.81±3.11	9.14±2.55	-3.56	0.011
PR7	6.63±3.09	7.58±2.46	-3.14	0.035
PR8	8.92±3.13	10.54±2.86	-4.21	0.002
PR9	8.36±2.84	8.97±2.73	-1.86	0.201
PR10	7.02±2.91	8.19±2.44	-3.34	0.021

3.2 Correlation analysis of lncRNA expression and coping style in GAD patients

Table no2 shows the expression level of PR5 and PR7 were positively correlated with negative coping style(p<0.05).

Table no2: Correlations of lncRNA Δ Ct values and coping styles in GAD patients(r)

Factors	PR5	PR6	PR7	PR8	PR10
Coping scores	0.098	0.066	0.064	0.023	0.081
Negative coping	0.204*	0.174	0.199*	0.135	0.155
Positive coping	-0.069	-0.079	-0.107	-0.088	-0.060
Note: * means p<0.05					

2.2 Correlation analysis of lncRNA expression with personality trait in GAD patients

As shown in Table no3, the ΔCt value of PR5, PR6, PR8, PR10 were negatively correlated with paranoid personality; the ΔCt value of PR6 PR8, PR10 were negatively correlated with obsessive personality; the ΔCt value of PR6, PR8 were negatively correlated with narcissistic personality; the ΔCt value of PR5, PR7, PR8 were negatively correlated with avoidant personality(p<0.05).

Table no3: Correlation of lncRNA expression with personality trait in GAD patients (r)

Dimensions	PR5	PR6	PR7	PR8	PR10
Paranoid personality	-0.239*	-0.246*	-0.180	-0.219*	-0.201*
Histrionic personality	-0.111	-0.134	-0.069	-0.131	-0.092
Obsessive personality	-0.188	-0.227*	-0.162	-0.209*	-0.209*
Schizoid personality	0.018	-0.018	0.077	-0.028	-0.008
Narcissistic personality	-0.164	-0.195*	-0.167	-0.223*	-0.171
Avoidant personality	-0.206*	-0.183	-0.198*	-0.207*	-0.185
Overpefect personality	-0.080	-0.091	-0.055	-0.080	-0.084
Schizotypal personality	0.040	0.010	0.088	0.021	0.041
Borderline personality	-0.013	-0.045	-0.006	-0.058	-0.045
Dependent personality	-0.045	-0.086	-0.052	-0.089	-0.057
Antisocial personality	-0.002	-0.047	0.022	-0.047	0.008
Note: * means p<0.05					

IV. Discussion

In this study, differently expressed lncRNAs in then PBMCs of GAD patients were screened by microarray. Then the top 10 lncRNAs were chosen for qRT-PCR validation and all of them were showed that the expression of PR5, PR6, PR7, PR8, PR10 were significantly downregulated in GAD patients. Studies have seen that lncRNAs can participate in development of brain and change the epigenetic modification of nerve cells dynamically[18, 19]. Therefore, we hypothesize that these 5 candidate lncRNAs could play a role in the pathogenesis of GAD.

This study found that expression level of PR5 and PR7 were positively correlated with negative coping style, which indicated the higher of the expression levels, the more of negative coping style would be. According to relevant study[20-22], coping style, played a remarkable intermediary effect between stressor and

anxiety response, was an important psychological factor which can arouse anxiety and furtherly cause immature defense mechanism.

It suggested that the ΔCt value of PR5, PR6, PR7, PR8, PR10 negatively correlated with paranoid personality, obsessive personality, narcissistic personality, avoidant personality. Some relevant studies have revealed that GAD patients along with neurasthenia symptoms tend to have negative emotion, and GAD patients with obsessive personality, avoidant personality were pone to have higher anxiety level and worse treatment effect[23, 24]. Based on this mental mechanism, expression levels of lncRNAs in GAD patients were down-regulated correspondingly.

In two previous studies about Alzheimer's disease (AD), the BC200(a kind of lncRNA associated with synaptic plasticity) was obviously changed in the brain tissue in AD patients and also found an apparent rise of BC200 in frontal cortex, which was associated with disease severity[25]. However, another study showed that 70% of BC200 in AD patients were found to be lower than that of in controls[26]. Due to the tissue specificity and time specificity of lncRNA expression, and the tissue specificity could be even more obvious than that of in protein[27], some scholars thought that an opposite results of lncRNAs expression levels in the same disease may be explained by the different tissues and diseasestages[28]. From this point of view, the study of lncRNA on anxiety still need to be further explored.

In recent years it has been considered as a great concern about relationship between lncRNA and mental illness, but how lncRNAs exactly involved in pathological mechanism of GAD remains unclear. Results of this study may provide an indication that coping style and personality trait may be mediators in process of lncRNA regulation.

V. Conclusion

In all, lncRNA expression were down-regulated in GAD patients and might be related to coping styles, personality trait.

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