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RESEARCH

Assessment of Expression of lncRNAs in Autistic Patients

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Abstract
Autism is a severe neurodevelopmental condition with unknown pathobiology. Nevertheless, multiple pieces of evidence suggest long non-coding RNA (lncRNA) dysregulation may be a contributing factor to this disorder. We investigated the association between the expression of five specific lncRNAs and autism. Peripheral blood was collected from 30 children with autism and 41 healthy children. The expression levels of *PCAT-29*, *lincRNA-ROR*, *LINC-PINT*, *lincRNA-p21*, and *PCAT-1* were calculated. Then, their significance as biomarkers was also evaluated. The expression of *LincRNA-ROR* (27 times), *LINC-PINT* (5.26 times), *LincRNA-p21* (4.54 times), *PCAT-29* (16.66 times), and *PCAT-1* (25 times) genes was significantly decreased in patients compared to the control group (p values < 0.05). According to the ROC curve analysis for each lncRNA, *LincRNA-ROR*, *LINC-PINT*, *LincRNA-p21*, *PCAT-29*, and *PCAT-1* lncRNAs with diagnostic power of 0.85, 0.67, 0.64, 0.74, and 0.84, respectively, could be used as diagnostic biomarkers for autism. Additionally, significant positive correlations were reported between expression levels of *PCAT-1* and *PCAT-29* genes. Moreover, a positive correlation was detected between expression levels of *lincRNA-ROR* and patients' age. The current study shows further pieces of evidence for deregulation of lncRNAs in autistic patients that show these lncRNAs may play an important part in the pathogenesis of ASD. However, the role of lncRNA in the neurobiology of autism needs to be investigated further.

Keywords Biomarkers · Autism · *PCAT-29* · *LincRNA-ROR* · *LINC-PINT* · *LincRNA-p21* · *PCAT-1*

Introduction

Autism is a neurodevelopmental disorder characterized by social communication defects, repetitive behaviors, and varying cognitive disabilities (Lord et al. 2020; Eyring and Geschwind 2021). It affects all societies, regardless of culture, race, ethnicity, or socioeconomic status (Lord et al. 2020). By 2020, the estimated prevalence of autism have risen to 1 in 36 children, with boys being 3.8 times more likely to be affected (Maenner et al. 2023). Autism is highly inheritable (74–93%), with many genetic loci and risk variants impacting early brain development (Lord et al. 2020).

The precise biological processes responsible for autism are still not fully understood (Ghafouri-Fard et al. 2023a). However, researchers suggested that the malfunction of various signaling pathways may play a role in its development (Jiang et al. 2022; Ghafouri-Fard et al. 2022). Long non-coding RNAs (lncRNAs) are crucial in modulating signaling pathways, serving as functional factors with multiple significant functions (Ghafouri-Fard et al. 2022). Furthermore, the involvement of various lncRNAs in the pathogenesis of autism has been extensively documented (Akbari et al. 2022; Pourtavakoli et al. 2024). These transcripts play crucial roles in gene expression regulation and epigenetic control and also function as scaffolds for protein complexes (Mattick et al. 2023). Extensive expression of lncRNAs in the human brain indicates their role in the brain development and potential involvement in the molecular pathogenesis of neurodevelopmental disorders (Srinivas et al. 2023). Many psychiatric disorders such as schizophrenia, autism, and anxiety are associated with the deregulation of lncRNA expression (Baruah et al. 2022; Dini et al. 2024). Here, we

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evaluated the expression levels of five lncRNAs, namely, LincRNA-ROR, LINC-PINT, LincRNA-p21, PCAT-29, and PCAT-1, in children with autism and healthy children. The lncRNAs chosen were based on their established involvement in the progression of neurological conditions and their impact on the pathways and cellular processes associated with the development of autism.

Long intergenic non-protein coding RNA, a regulator of reprogramming (LincRNA-ROR), regulates key pluripotency factors such as Oct4, Sox2, and Nanog (Wang et al. 2013). Research has shown that the absence of LincRNA-ROR results in the induction of apoptosis, indicating its crucial involvement in the p53 network (Grossi et al. 2016). The findings of another study showed that both LincRNA-ROR and p53 exhibited higher levels of expression in glioblastoma. Upregulation of p53 could potentially contribute to the elevation of LincRNA-ROR in glioblastoma (Toraih et al. 2019). The expression levels of LincRNA-ROR were found to be altered in individuals suffering from neurodegenerative and neurodevelopmental disorders (Ghafouri-Fard et al. 2023b). Furthermore, LincRNA-ROR was elevated in patients diagnosed with schizophrenia when compared to control groups. However, a significant difference in expression was observed exclusively among female subgroups when analyzing sex-based variations. Additionally, the expression of this lncRNA was linked to the age of patients with schizophrenia (Fallah et al. 2019).

Long intergenic non-protein coding, P53-induced transcript (LINC-PINT) has a direct interaction with the polycomb repressive complex 2 (PRC2) to modulate the expression of its target genes (Xu et al. 2019). This lncRNA is expressed in neurons and is up-regulated in several regions of the brain in individuals affected by neurodegenerative diseases (Simchovitz et al. 2020).

Long intergenic non-coding RNA p21 (LincRNA-p21) regulates a varied range of biological processes, such as apoptosis and cell cycle transition via affecting Notch signaling, JAK/STAT3, and AKT/mTOR pathways (Winkler et al. 2022; Amirinejad et al. 2020). Cross-talk with different miRNAs is one of the mechanisms by which lincRNA-p21 can alter these processes (Amirinejad et al. 2020). The activation of microglia cells and the increase in the expression levels of inflammatory mediators, as well as the induction of apoptosis in dopaminergic neurons, are observed upon the expression of lincRNA-p21 (Ye et al. 2018). Furthermore, lincRNA-p21 has been found to be upregulated in the early stages of Parkinson's disease and continues to increase during disease progression, particularly in cases of brain stem type Parkinson's disease (Kraus et al. 2017).

Moreover, the reduction in the blood levels of lincRNA-p21, lincRNA-ROR, and LINC-PINT could be potentially associated with a higher susceptibility to bipolar disorder (Maloum et al. 2022).

Prostate cancer-associated transcript 29 (PCAT-29) is considered to be a tumor suppressor inhibiting cell proliferation, migration, tumor growth, and metastasis (Al Aameri et al. 2017). An increase in PCAT-29 lncRNA expression has been documented in individuals diagnosed with major depressive disorder (Seki et al. 2019). PCAT-1 regulates cell response to genotoxic stress. It may also act as a sponge for miRNAs that regulate cell growth (Xiong et al. 2019).

These lncRNAs were demonstrated to have crucial involvement in the modulation of neurological responses and the differentiation of neuronal cells. Thus, in the current study, we compared the expression levels of these lncRNAs in the peripheral blood of children with autism and healthy individuals. We aimed to investigate any association between changes in their expression levels and autism and assess their potential as valuable biomarkers for diagnostic and prognostic purposes. The objective was to gain insights into the role of these lncRNAs in the development of autism and explore their potential as biomarkers for the disorder.

Methods and Material

Subjects

We performed this study on peripheral blood samples from 30 patients and 41 healthy controls. Samples were collected from the hospitals of Shahid Beheshti and Hamadan Universities of Medical Sciences. The research excluded children with neuropsychiatric conditions other than autism, metabolic disorders, or immune-related issues, as well as those with comorbid attention deficit hyperactivity disorder. Healthy children included in the study had no prior history of neuropsychiatric or developmental disorders. Table 1 presents the subjects' demographic data, and detailed information of all samples are presented in Supplementary file 1. The patients were diagnosed using the DSM-5 criteria. Informed consent was obtained from all participants' parents. The Ethical Committee of Shahid Beheshti University of Medical Sciences permitted this study, and it was conducted under the institution's ethical standards (IR.SBMU.MSP.REC.1399.290).

Table 1 Participants' demographic data

	Patients ($n=30$)		Control ($n=41$)	
	Male	Female	Male	Female
Numbers	19	11	30	11
Average age ± SD	6 ± 1.4		6 ± 1.74	

Experiments

A total of 5 ml of peripheral blood samples were collected from both the patient and control groups in the EDTA tubes. Total RNA was then extracted using the RNXplus (Cinagen, Tehran, Iran) RNA extraction kit, following the guidelines provided by the manufacturer. The quality and quantity of the extracted RNA were evaluated using gel electrophoresis and nanodrop spectrophotometer, respectively. Any DNA contamination was removed using DNase I.

To produce cDNA from 3 µg of purified total RNA, the RT-PCR Pre-Mix Kit (BIOFACT™, South Korea) was used. Quantitative real-time PCR was performed using 7.5 µl of BIOFACT™ PCR Master Mix (High Rox including SYBR Green I), 10 ng cDNA, and 200 nM of each primer. Primer sequences provided in Table 2 were designed using GeneRunner v3.5 and Oligo7 (Rychlik 2007). The relative gene expression levels were determined by the housekeeping gene B2M, serving as an internal control. The average ΔCT for both the case and control groups was calculated, and then by using the Livak method (ratio = $2^{-\Delta\Delta Ct}$), fold changes of each gene expression were computed (Livak and Schmittgen 2001). Quality control checks were implemented in several steps, including assessment of abnormal amplification, evaluation of melting curves, assessment of variations between PCR replicates, inclusion of positive and negative control samples in each run, and evaluation of expression stability of the selected reference gene (B2M) among samples.

Statistical Analyses

Statistical analyses were performed using GraphPad Prism version 8.0.2 (GraphPad Software, Inc., San Diego, CA, USA), and a P value < 0.05 was deemed significant. The Kolmogorov–Smirnov test was employed to assess the normal distribution of the dataset. Because the samples had a normal distribution, the t-test was utilized to compare the expression levels of lncRNAs and identify any significant differences between patients and controls. The Pearson correlation coefficient was employed to assess the correlations between gene expression and participants' clinical features, such as age. The ROC curve was used to determine the specificity and sensitivity of genes mentioned as possible biomarkers.

Results

Gene Expression Levels

We observed a significant decrease in the expression levels of lncRNAs in patients with autism compared to healthy children. In detail, lincRNA-ROR was 27 times lower (p value < 0.0001) (Fig. 1 A and F), LINC-PINT was 5.26 times lower (p value = 0.013) (Fig. 1 B and F), lincRNA-p21 was 4.54 times lower (p value = 0.029) (Fig. 1 C and F), PCAT-29 was 16.66 times lower (p value = 0.0004) (Fig. 1 D and F), and PCAT-1 was 25 times lower (p value < 0.0001) (Fig. 1 E and F) in the patient group (Table 3). In the gender-specific comparison, we evaluated differences in the expression levels of lncRNAs in female and male patients compared to their respective healthy counterparts. Specifically, both female and male patients showed significantly decreased expression levels for lincRNA-ROR (p value = 0.0041 and p value < 0.0001, respectively), PCAT-29 (p value = 0.029 and p value = 0.004, respectively), and PCAT-1 (p value = 0.0014 and p value < 0.0001, respectively) (Fig. 2 A, D, and E, respectively). LINC-PINT demonstrated a significant decrease in female patients (p value = 0.0387), but this trend was not statistically significant in male patients (p value = 0.0989) (Fig. 2 B). Lastly, while lincRNA-p21 showed decreased expression levels in both genders, the difference was insignificant (female p value = 0.3909, male p value = 0.0535) (Fig. 2 C). We detected no significant decline when comparing expression levels between the female and male populations (Table 3).

Table 2 Primers used in real-time PCR

Gene	Forward primer (5′ to 3′)	Reverse primer (5′ to 3′)	Product size (bp)
LincRNA-ROR	TATAATGAGATACCACCTTA	AGGAACTGTCATACCGTTTC	170
LINC-PINT	AGGAGGGAACGAGGCAGGGA	AGCTCAGATCAGCAAGGCAG	129
LincRNA-p21	GGGGATAAGCACCACTAATG	TATAGGCAATCACAGAGCAC	171
PCAT-29	CAGCACCATCACATGCCTCCA	CCAAATCAAGTCACATGCCGAT	145
PCAT-1	CGCAAAGGAACCTAACTGGAC	GTCTCCGCTGCTTTATAACCC	187
B2M	CCACTGAAAAAGATGAGTATGCCT	CCAATCCAAATGCGGCATCTTCA	126

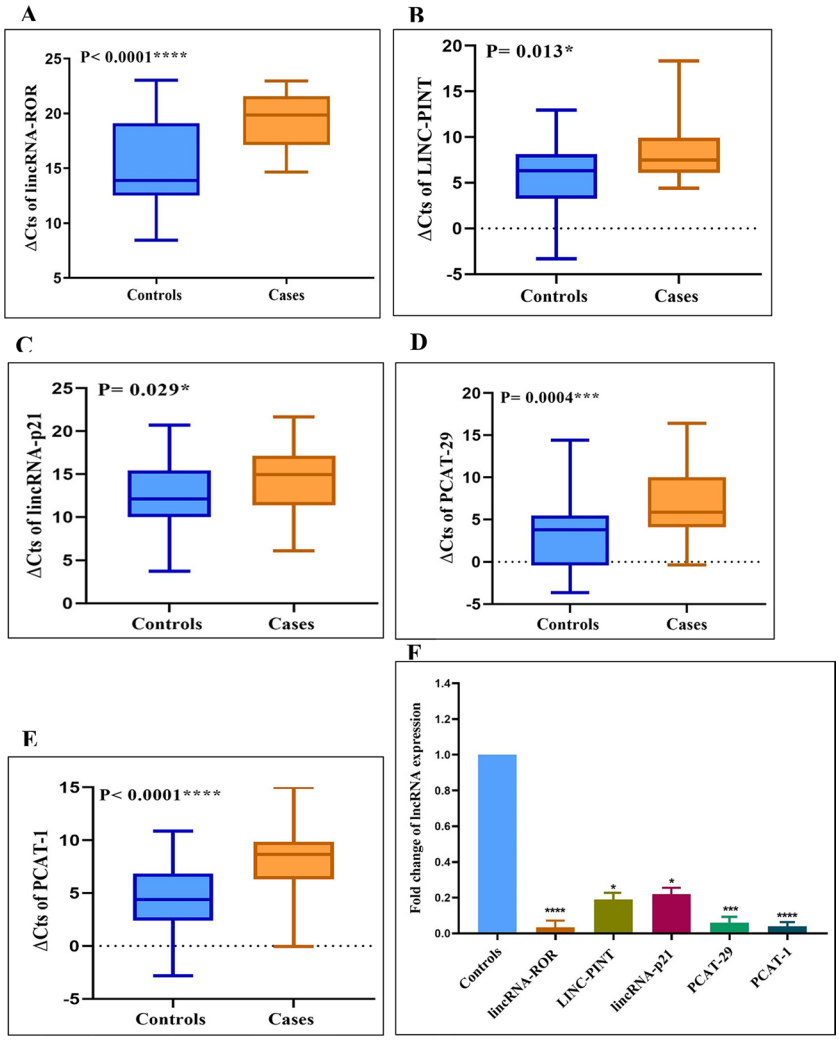

Fig. 1 The expression of lncRNAs in blood samples of autistic patients and controls. Expression analyses were normalized ($\Delta Ct = Ct_{\text{target gene}} - Ct_{\text{reference gene}}$) by comparing them to B2M internal control. ΔCts of lincRNA-ROR (**A**), LINC-PINT (**B**), lincRNA-p21 (**C**), PCAT-29 (**D**), and PCAT-1 (**E**). **F** The relative expression (fold change $= 2.^{-\Delta\Delta Ct}$) of lncRNAs shows downregulation of these genes in autistic patients compared with controls. $^{*}P < 0.05$, $^{***}P < 0.001$, $^{****}P < 0.0001$

Table 3 Relative expression of lncRNAs in children with autism disorder and healthy controls

lncRNAs	Parameters	Total patients ($n = 30$)/ total controls ($n = 40$)	Male patients ($n = 19$)/ male controls ($n = 30$)	Female patients ($n = 11$)/ female controls ($n = 11$)
lincRNA-ROR	Mean ΔCts	20.41/14.86	19.81/14.679	21.44/15.261
	Fold change	0.035	0.028	0.013
	P value	< 0.0001****	**< 0.0001****	**0.0041****
LINC-PINT	Mean ΔCts	8.28/5.92	8.43/6.088	8.002/5.474
	Fold change	0.19	0.19	0.17
	P value	0.013*	**< 0.0001****	**0.038***
lincRNA-p21	Mean ΔCts	14.46/12.32	13.91/11.55	15.48/14.052
	Fold change	0.22	0.196	0.38
	P value	0.029*	0.053	**0.39**
PCAT-29	Mean ΔCts	7.02/3.03	7.25/3.11	6.56/2.803
	Fold change	0.06	0.45	0.06
	P value	0.0004***	0.004**	0.029*
PCAT-1	Mean ΔCts	8.68/4.16	8.82/4.061	8.31/4.44
	Fold change	0.04	0.036	0.06
	P value	< 0.0001****	< 0.0001****	0.0014**

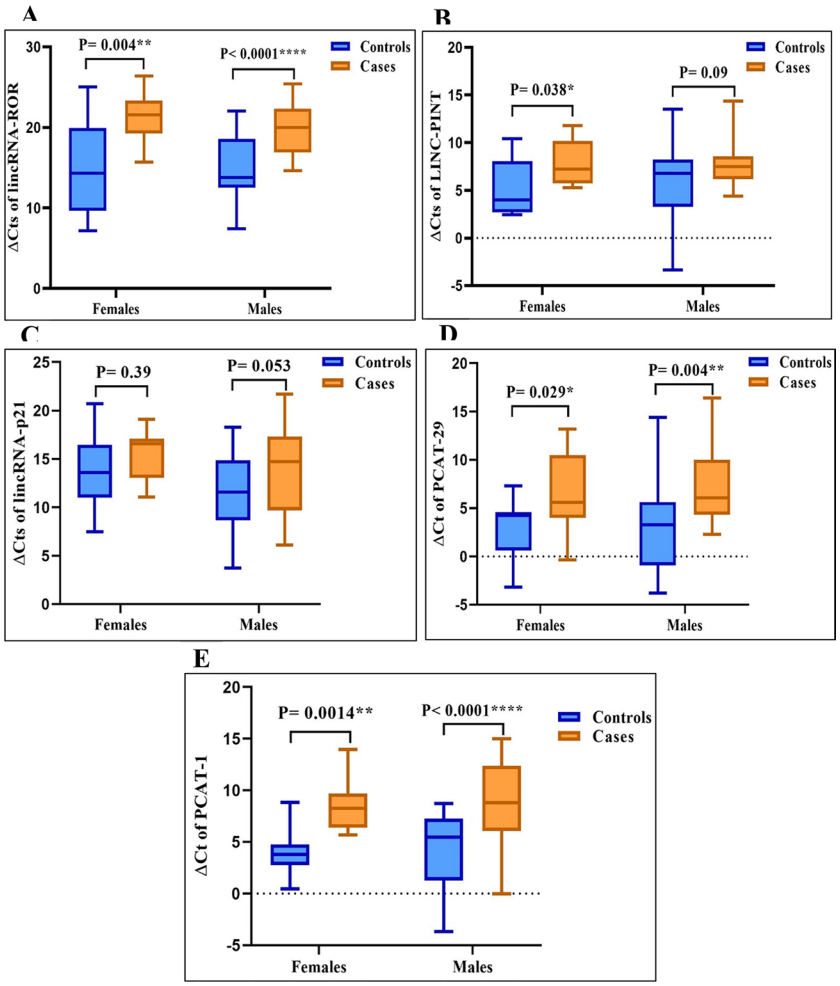

Fig. 2 Expression analysis of lncRNAs in the blood samples of autistic patients in comparison with controls based on gender. Expression analyses were normalized by comparing them to B2M internal control. ΔCts of lincRNA-ROR (**A**), LINC-PINT (**B**), lincRNA-p21 (**C**), PCAT-29 (**D**), and PCAT-1 (**E**). Expression analyses were normalized (ΔCt = Ct target gene –Ct reference gene) by comparing them to B2M internal control. *$P < 0.05$, ** $P < 0.01$, ****$P < 0.0001$

Correlation Analysis

Figure 3A shows the pairwise correlations between expression levels of lncRNAs in this study. A significant positive correlation was identified between PCAT-29 and PCAT-1 ($r = 0.36$, p value = 0.0004) and between LINC-PINT and PCAT-1 ($r = 0.46$ and p value = 0.011). No other two genes showed such a correlation. Correlations between clinical features and expression levels were also analyzed. Figure 3B illustrates a significant positive correlation between the expression of *lincRNA-ROR* and patient age ($r = 0.46$, p value = 0.0092), indicating an increase in its expression as the patient's age increases. However, the correlations of age with the other four lncRNAs were not significant, as their p values were greater than 0.05 (Fig. 3C–F).

ROC Curve Analysis

To evaluate the diagnostic power of these lncRNAs for autism, ROC curve analysis was performed. LincRNA-ROR demonstrated the highest area under the ROC curve (AUC) of 0.85 (p value < 0.0001) with a sensitivity of 86.67% and a specificity of 65.85%, indicating its superiority in differentiation between groups. Closely following was PCAT-1 with an AUC of 0.84 (p value < 0.0001), a sensitivity of 80%, and a specificity of 70.73%. The AUC of PCAT-29, LINC-PINT, and lincRNA-p21 were 0.74 (p value = 0.0005), 0.67 (p value = 0.0138), and 0.64 (p value = 0.0394), respectively. These findings suggest that all tested lncRNAs could be used as potential biomarkers for autism to differentiate between patient and healthy conditions (Fig. 4).

Then, we conducted ROC curve analyses in males and females, separately (Table 4). While p values remained significant in both groups for LincRNA-ROR and PCAT-1, p values for LINC-PINT and PCAT-29 were significant only among females and males, respectively.

Discussion

Identification and characterization of lncRNAs that are involved in the neurodevelopmental processes and mental diseases are necessary for revealing the complex transcriptional processes in brain development. Many of the genes

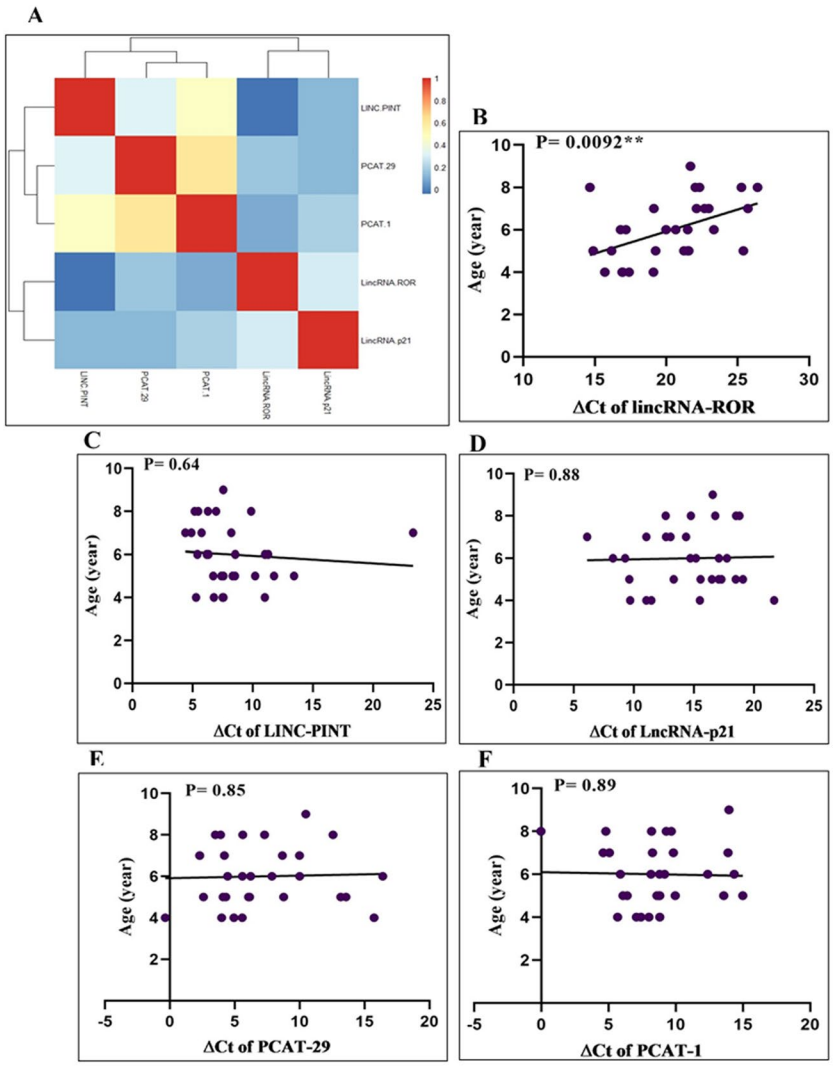

Fig. 3 Correlation analysis. **A** A heat map illustrating the Pearson correlation among gene expression levels across various samples. The red color indicates a high degree of correlation between samples, while blue signifies a low correlation. **B–F** scatter plot of correlation analysis between age and expression levels of lncRNAs in patients with autism disorder. $^{**}P < 0.01$

that are controlled by our investigated lncRNAs in this study are involved in brain development or are associated with neurodevelopmental and mental disorders. Therefore, we suggest their involvement in autism pathogenesis based on previous studies showing their function and association in similar conditions.

Previous studies have proven that PCAT-29 is significantly associated with glioma, the most common malignant brain tumor (Al Aameri et al. 2017). Besides, its expression is increased in major depressive disorder (Seki et al. 2019). Moreover, PCAT-29 downregulates miR-494, which regulates PTEN (Lu et al. 2021). Since mutations in PTEN are one of the key factors in microcephaly, cognitive impairment, seizure, and autism (Dhaliwal et al. 2021), the observed decline of PCAT-29 expression in our study suggests that this gene is involved in autism pathogenesis. In other words, a decrease in PCAT-29 might lead to a decline in PTEN, affecting neural cell growth and synaptic functions in the central nervous system, and causing many autism symptoms.

Decreased LincRNA-ROR expression in glioma affects cell proliferation and stem cell renewal by inhibiting KLF4 (Toraih et al. 2019). In addition, LincRNA-ROR can act as a molecular sponge and disrupt the usual function of miR-145 (as it does in triple-negative breast cancer) (Eades et al. 2015), which also plays a vital role in regulating neurogenesis and neural stem cell differentiation (Morgado et al. 2016). A rise in the expression of LincRNA-ROR in schizophrenia has been reported, which is one of the co-occurring disorders with autism and has similar symptoms (Jovčevska and Videtič Paska 2021). These suggest that decreased LincRNA-ROR expression in autism patients, observed in this study, could increase neuron apoptosis and impair stress responses, a key process in the development of this disorder (Kim et al. 2017).

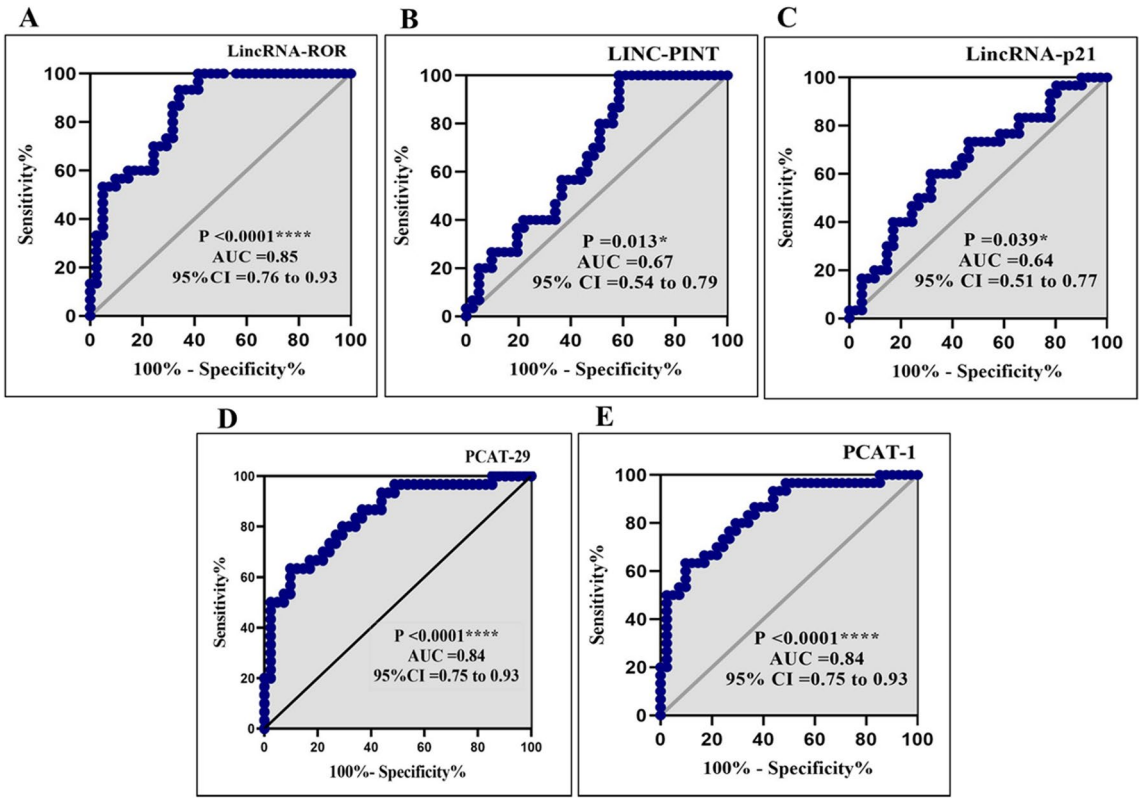

Fig. 4 ROC curve analysis. LincRNA-ROR (**A**), LINC-PINT (**B**), lincRNA-p21 (**C**), PCAT-29 (**D**), and PCAT-1 (**E**) can serve as potential biomarkers for the diagnosis of autism. *P* = *p* value, AUC = area under curve

Table 4 Detailed statistics of ROC curve analyses in females and males, separately

Gene	Female		Male	
	AUC	**P-value**	**AUC**	***P* value**
LincRNA-ROR	**0.85**	**0.0053****	**0.84**	**<0.0001****
LINC-PINT	**0.76**	**0.038***	0.64	0.095
LincRNA-p21	0.6	0.41	0.64	0.084
PCAT-29	0.71	0.094	**0.75**	**0.0031****
PCAT-1	**0.88**	**0.0023****	**0.82**	**0.0001*****

Raised LINC-PINT expression has been detected in Parkinson's disease (Bhattacharyya et al. 2021), and its accumulation has been observed in some regions of the brain in Alzheimer's and Huntington's diseases. This suggests a strong correlation between the up-regulation of LINC-PINT and the onset of neurodegeneration (Simchovitz et al. 2020; Reddy et al. 2021). Additionally, the reduction of LINC-PINT disrupts PRC2 function (Marín-Béjar et al. 2017). Based on the observed high expression of LINC-PINT in neural and microglial brain cells (Reddy et al. 2021), and significant role of PRC2 in the regulation of neurogenesis in the developing neocortex, responsible for higher-order functions such as sensory perception, cognition, and language (Elsen et al. 2018), we suggest the reduction of LINC-PINT expression in autism patients could account for some of the main autism symptoms.

Decreases in lincRNA-p21 expression in glioma stem cells (GSCs) have been linked to brain malignancies. These cells are directly associated with malignancy and angiogenesis in brain cells (Gimple et al. 2019). In addition, downregulation of miR-146b-5p in GSC cells (Wang et al. 2020) increases the Hu-antigen receptor (HuR) expression, leading to a decrease in lincRNA-p21 and an increase in β-catenin levels (Yang et al. 2016). Dysregulation of β-catenin disrupts the β-catenin/TGF pathway, which regulates expression of various genes, including NLGN3. Previous studies showed that NLGN3 overexpression leads to an increase in the number of synapses, altering the excitatory/inhibitory (E/I) ratio, which results in difficulties in higher cognitive function and social skills, which are important symptoms of autism (Guang et al. 2018). As the Wnt/β-catenin pathway is crucial for the formation of neurons, glial cells, and hippocampus, gain and loss of function mutations in this gene cause neurodevelopmental diseases such as Alzheimer's, Parkinson's, Huntington's, and autism (Caracci et al. 2021). Therefore, we

suggest that this decrease in lincRNA-p21 expression level in patients plays a significant role in autism pathogenesis.

Interestingly, both PCAT-1 and PCAT-29 expression levels rise in MDD patients (Seki et al. 2019). We also found that these two genes have a positive pairwise correlation. Additionally, previous research has reported increased expression of PCAT-1 upon treatment with a histone deacetylase (HDAC) inhibitor (Prensner et al. 2011). Alterations in the histone acetylation in various genes have been identified as a cause of autism due to their role in synaptic activities, neuronal excitability, and immune responses (Tseng et al. 2022). Moreover, studies have shown that parental or before-birth suppression of HDAC can delay brain neuron maturation and lead to changes in the synaptic molecules, ultimately contributing to autism symptoms (Kawanai et al. 2016). These findings underscore the interplay between gene expression, epigenetics, and neurodevelopmental disorders. In the context of autism, we propose that the observed reduction in PCAT-1 expression is associated with autism symptoms. However, the exact interactions or relationships that cause the effect of PCAT-1 on HDAC are not yet clear and need further research.

Conclusion

The study revealed that the expression levels of five lncRNAs examined—PCAT-29, lincRNA-ROR, LINC-PINT, lincRNA-p21, and PCAT-1—were significantly lower in individuals with autism compared to the healthy control group. ROC analysis indicated that these lncRNAs may serve as potential biomarkers for autism. Notably, the significant decrease in expression was observed in both genders for PCAT-29, lincRNA-ROR, and PCAT-1, while a significant reduction in LINC-PINT levels was specifically noted among girls with autism. Additionally, a positive correlation was identified between PCAT-29 and PCAT-1, as well as between the expression level of lincRNA-ROR and the age of the patients. To further substantiate these findings and to explore the underlying mechanisms of the observed associations, additional research with a larger sample size is warranted.

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Author Contribution SS and VE wrote the manuscript, analyzed the data, and performed the experiment. ZSF and SGF designed the study and revised the manuscript. All the authors read and approved the final manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval and Consent to Participate All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration. Informed consent forms were obtained from all parents. This study was approved by the ethical committee of Shahid Beheshti University of Medical Science (IR.SBMU.MSP.REC.1399.290).

Consent of Publication Not applicable.

Competing Interests The authors declare no competing interests.

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