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Expression Levels of miR -124a, miR-545-3p and BDNF in the Peripheral Blood Mononuclear Cells Are Associated with the Severity of Autism

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Abstract

Background: People with autism frequently exhibit poor social skills, communication difficulties, and repetitive and stereotyped behaviors. MicroRNAs (miRNAs) are potential and promised targets in developing of new treatment strategies for autism. This study aimed to assess the relative expression of miR-124a, miR-34a-3p, miR-545-3p, miR-153, and BDNF in the blood samples of autistic children.

***Methods*:** The children autism rating scale (CARS) was used to determine the severity of autism and to confirm the diagnosis. Blood samples were obtained from 50 patients and 40 age-/sex-matched healthy controls. Expressions of miR-545-3p, miR-34a-3p, miR-124a, and BDNF were evaluated using qRT-PCR. Pearson's correlation coefficient and regression analysis were used to check correlations between relative expressions of the miRNAs and BDNF. Biomarker potencies were assessed by ROC curve analysis.

Results: qRT-PCR analysis showed that the relative expressions of miR-545-3p, miR-34a-3p, miR-124a, and BDNF were significantly higher in the patients' group than the healthy controls. However, the relative expression of miR-153 was significantly lower in the case group than the control group. The relative expression of miR-124a was positively correlated with those of miR-545-3p and BDNF among the patients group. Also, the relative expressions of miR-545-3p and BDNF were positively correlated with each other. The ROC curve data also indicated that miR-124a, miR-34a-3p, miR-545-3p, miR-153, and BDNF could be possible diagnostic biomarker for CARS diagnosis (AUC=0.8328, AUC=0.8354, AUC=0.6727, AUC=0.8518 and AUC=0.8214, respectively).

Conclusions: Deregulation of miR-124a, miR-454-3p and BDNF might be considered as potential biomarkers for severity of autism.

Keywords: Autistic children, Autism, Biomarker, Brain-derived neurotrophic factor, Gene expression, miRNA.

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Introduction

Children with childhood autism have behavioral, social, and communication difficulties (1, 2). Data from the World Health Organization show that 6.25 out of every 1,000 people worldwide are affected by autism spectrum disorder (ASD) (3). It affects roughly 1 in every 59 children and continues into adulthood (4). Autism's exact cause and etiology are still unknown but involvement of some genetic changes has been described (2, 5, 6).

MicroRNAs (miRNAs) are non-coding

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RNA molecules with 22–25 nucleotide sequences that have been found to regulate biological processes (7, 8). In the brain, miRNAs are widely distributed and have a variety of crucial roles in regulating neuronal regeneration, neural plasticity, and neuron function (9, 10). Few studies have investigated the role of miRNAs in ASD and due to the low efficacy of current treatments, miRNAs have been considered as prospective biomarkers to improve ASD diagnosis, prognosis, and therapy (11).

One of the miRNAs with the highest level of expression in human and mouse brains is microRNA124a (miR-124a). Three loci, miR-124a-1, miR-124a-2, and miR-124a-3, are responsible for encoding miR-124as in both the human and mouse genomes. In the mouse brain, pri-miR-124a-1 is the most abundantly expressed one, while pri-miR-124a-3 is hardly expressed (12). A recent study also revealed that miR-124a, which was initially thought to be a brain-specific miRNA in mammals, was expressed at higher levels during the development of the embryonic pancreas (13).

Recent research on multiple sclerosis found that miR-34a positively controls the expression of the glutamate transporter I (GLT1) in vitro, possibly increasing protection through the transfer of exosomes from neurons to astrocytes (14). The mature versions of miR-34a include miR-34a-5p and miR-34a-3p (15). miR-34a is over-expressed in the cerebellar cortex of Valproic acid-exposed ASD mouse model. It directly targets *Bcl2* and decreases the *Bcl2* mRNA level, leading to increased apoptosis (16), which is consistent with the low level of BCL2 in the parietal lobe of ASD patients (17).

Two mature miRNA products, miR-545-3p and miR-545-5p, are produced from pre-miR-545. Various human cell types express both of these miRNAs (18). A study found that the level of the miR-545-3p could significantly distinguish Alzheimer's patients from Parkinson's patients and normal individuals (19). A comprehensive miRNA expression profiling using saliva samples has revealed miR-545-3p as a top downregulated miRNA in ASD patients (20). miR-153 is a highly conserved miRNA in human and mouse that promotes neurogenesis and its expression level is changed in neurological diseases (21). It was shown that the miRNA-153 could induce expression of the brain-derived neurotrophic factor (BDNF) and promotes proliferation of the hippocampal neurons and thereby alleviates autism symptoms via inhibition of Janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling (22). During development and in the mature brain, BDNF affects specific neuronal populations' survival, morphology, differentiation, and synaptic strength (23-25). Neuronal activity brought on by sensory input can influence BDNF expression to some extent (26). BDNF also regulates local protein synthesis at dendrites, which promotes synaptic plasticity, learning, and memory (25). It was reported that the plasma level of BDNF is increased in ASD patients compared to the non- ASD controls (27).

Here we compared the expression levels of miR-124a (NR_029668), miR-34a-3p (NR_029610), miR-545-3p (NR_030258), miR-153 (NR_029688), and BDNF (NM_001709) in blood samples from autistic children and healthy controls. Additionally, the relationship between the expression levels of miR-124a, miR-34a-3p, miR-545-3p, miR-153, and BDNF and patient clinical parameters such as age, gender, and HS-CRP (high-sensitivity C-reactive protein) was investigated.

Materials and Methods

Patient Selection and Diagnostic Test

The study included 50 patients referred to Children's Department of Ali Akbar Mashhad Hospital. The severity of autism was evaluated and the diagnosis of autism confirmed using the Childhood Autism Rating Scale (CARS). The cut-off point for autism diagnosis was 29.5. Mild-to-moderate autism scores range from 30 to 36.5, whereas severe autism scores range from 37 to 60. Additionally, autism was

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confirmed and distinguished in children with CARS > 30 from different developmental conditions such as Rett's disorder, Asperger's disorder, and Childhood disintegrative disorder using the Diagnostic Statistical and Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (1).

The healthy control group also included 40 people according to the age and sex of the patients and without symptoms of autism spectrum disorder. Written consent was obtained from all participants in the study. The patients were excluded from the study if they had other nervous system and autoimmune diseases. Also, patients older than 15 and those taking medication other than routine for nervous system disease were excluded from the study. A history was also taken from the control group. If any anti-inflammatory drugs, steroids, cytotoxic or immunosuppressive drugs were used, participants were excluded from the study.

A 5 mL blood sample was collected in the EDTA-treated vials from autistic children and healthy volunteers and was delivered to the genetics laboratory.

Reverse transcription polymerase chain reaction (RT-PCR) analysis

Peripheral Blood Mononuclear Cells (PBMC) were collected by centrifugation and total cellular RNA from the blood cells was extracted using TriZol reagent (Invitrogen, Thermo Fisher Scientific, USA) according to the manufacturer's instructions. A NanoDrop spectrophotometer (Thermo Fisher Scientific, USA) was used to measure the concentration of total RNA, and 2 µg of RNA was treated with DNAse I (Invitrogen) and used for the reverse transcription using the high-capacity cDNA reverse transcription kit. Primers of miR-124, miR-153, miR-545-3p, miR-34a, and BDNF genes were designed using the NCBI site, and the U6 gene was used as the internal control.

A total of 1 µg of extracted RNA was reverse-transcribed into cDNA using the miRNA reverse primer and assessed by qRT-PCR using Power SYBR Green Master Mix (Applied Biosystems, USA). qRT-PCR reactions were duplicated. The data were exported to Microsoft Excel for further analysis. The delta-delta Ct method was used to calculate the relative expression of the gene of interest. The following thermocycling conditions were used for RT-PCR: 10 minutes at 95 °C, 45 cycles of 30 seconds at 95 °C, 30 seconds at 60 °C, 30 seconds at 72 °C, followed by 5 minutes at 72 °C (Corbett Rotor-Gene 6000, Qiagen GmbH).

Statistical analysis

Normality of the data was checked using the Shapiro-Wilk test. For the non-normal and normal data the Mann-Whitney test and Student's t- test was used respectively. The chi-square test was used to investigate the relationship between qualitative variables. Pearson's correlation coefficient and regression were used to check the relationship between variables. The statistical analysis was carried out using SPSS v.26 and GraphPad Prism 9, and the significance level of the tests was set at less than 5%.

Results

Analyzing the clinicopathological features of the subjects

Fifty patients with autism spectrum disorder were included in the study. 68% of the patients were girls and 32% were boys. Of the 50 patients studied, 25 had mild autism and 25 had severe autism. The mean age of the patients was 7.5 ± 1.95 years. The study also included 40 healthy controls and the mean age of the controls was 7.8 ± 1.8 years. There was no statistically significant difference between the control and case groups regarding age (P-Value=0.147) (Fig. 1A). Also, there was no significant difference between the two groups regarding gender variable (P-Value=0.134) (Fig. 1B). However, the two groups were matched regarding the age and gender parameters. But the HS-CRP (high-sensitivity C-reactive protein) difference was statistically significant between the two groups (P-Value=0.0001) (Fig. 1C).

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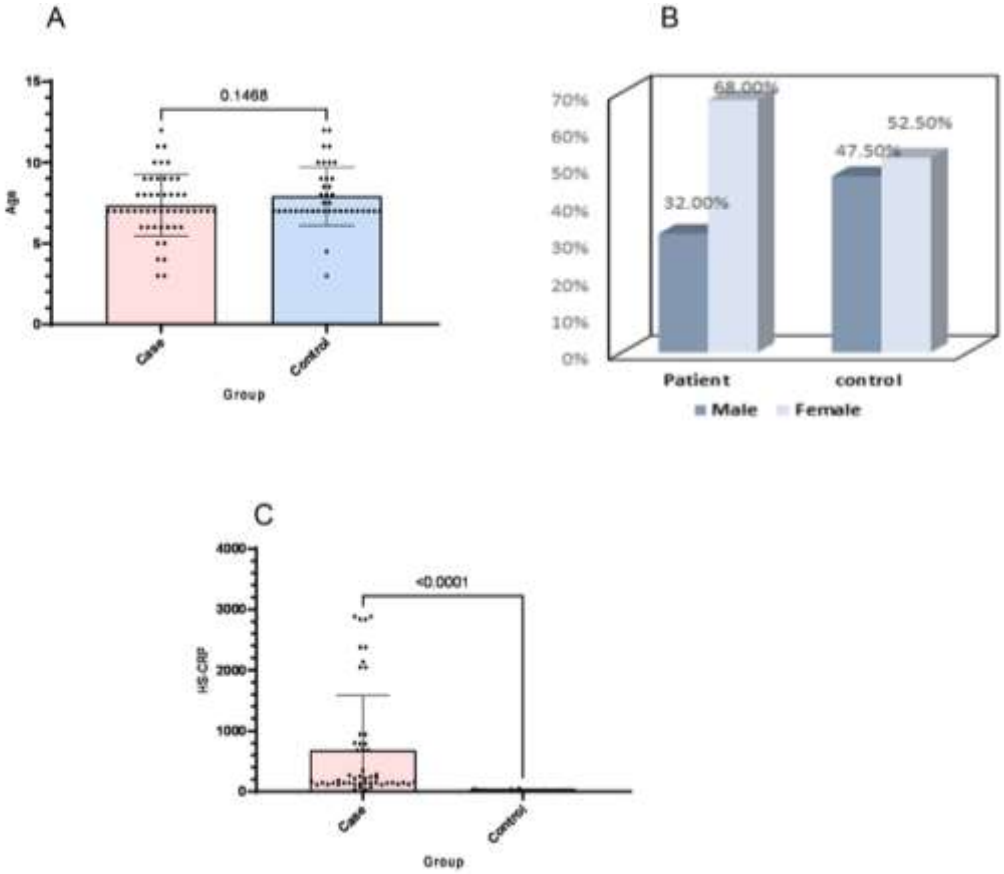

Fig. 1. Clinicopathologic characteristics of case and control groups. The variables of (A) Age, (B) Gender, and (C) HS-CRP have been compared between case and control groups.

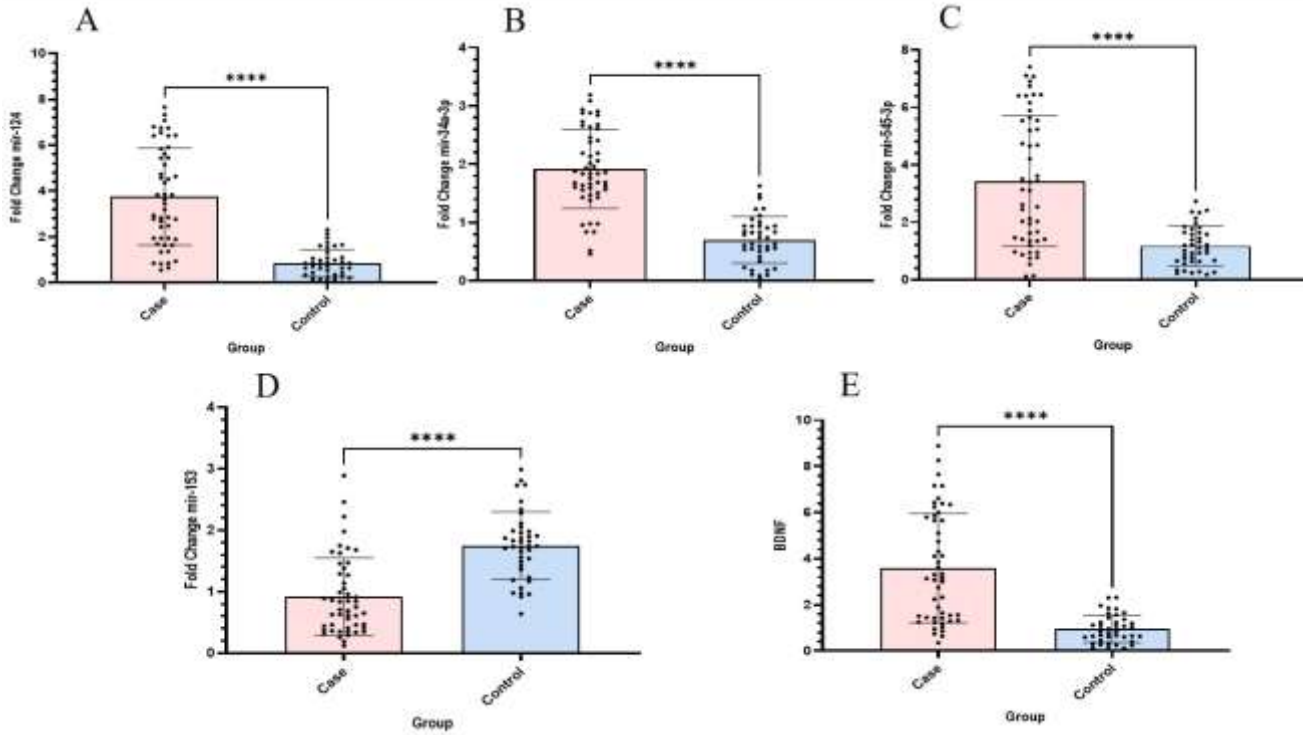

Fig. 2. Relative expression levels of studied genes. Relative expression levels of: A) miR-124a, B) miR-34a-3p, C) mir-545-3p, D) miR-153, and E) BDNF were compared between the case and control groups. **** represents p<0.0001

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Relative expression of the studied genes

Relative expression of the miR-124a, miR-34a-3p, miR-545-3p, miR-153 and BDNF gene were assessed by qRT-PCR. Relative expressions of miR-124a, miR-34a-3p, miR-545-3p and BDNF were significantly increased in cases in comparison with the control samples ($p < 0.0001$ for all), but miR-153 showed a significant decrease in cases ($p < 0.0001$) (Fig. 2).

Biomarker potential of studied mi-RNAs and BDNF

The receiver operating characteristic curve (ROC) curve analysis was utilized to evaluate the biomarker potency of miR-124a, miR-34a-3p, miR-545-3p, miR-153, and BDNF expression levels for peripheral blood mononuclear cells (Fig. 3). The results indicated that miR-124a (AUC=0.8328, sensitivity=63.64%, specificity=89.66%, p<0.0001), miR-34a-3p (AUC=0.8354, sensitivity=72.50%, specificity=85.71%, p<0.0001), miR-545-3p (AUC=0.6727, sensitivity=71.43%, specificity=54.55%, p=0.0144), miR-153 (AUC=0.8518, sensitivity=76.00%, specificity=77.50%, p<0.0001) and BDNF (AUC=0.8214, sensitivity=77.14%, specificity=75.00%, p<0.0001) expressions represented a good potential for distinguishing between patients and controls samples of severity of autism.

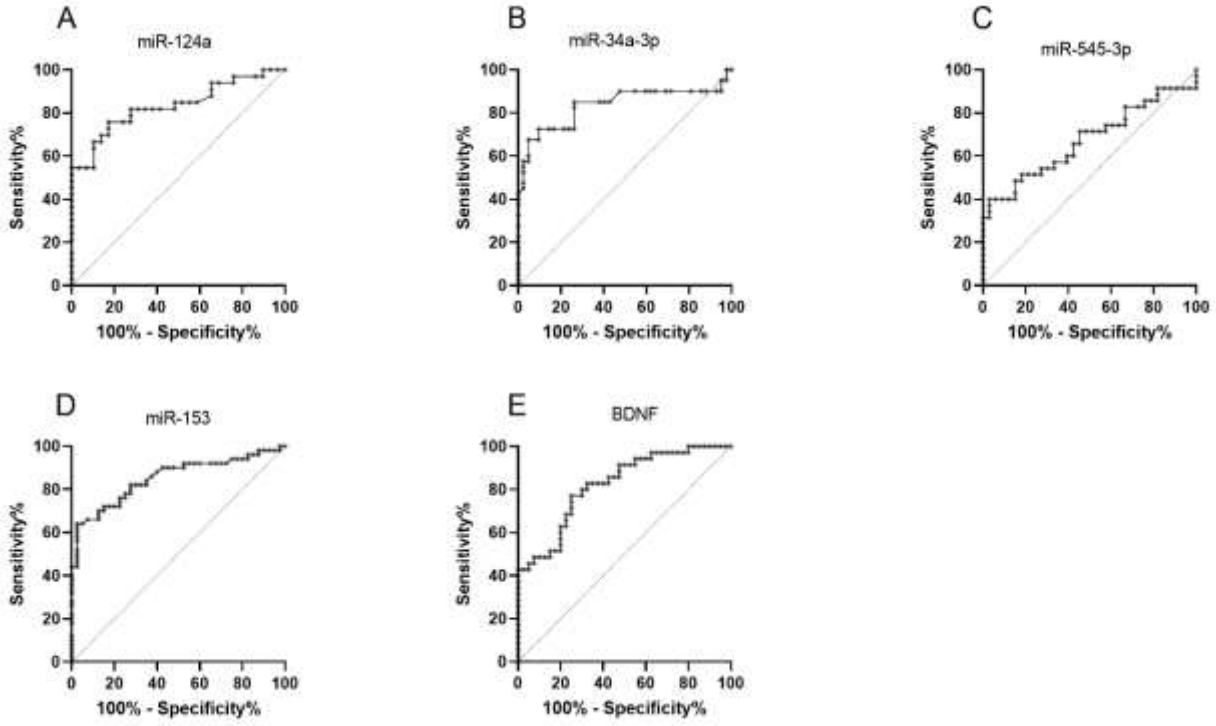

Fig. 3. ROC curves represent (A) miR-124a, (B) miR-34a-3p, (C) miR-545-3p, (D) miR-153, and (E) BDNF biomarker potency.

Association between the severity of autism and expression of studied miRNAs

The patients' group was divided into the mild and severe autism subgroups based on the CARS scores of the patients. Of the 50 patients examined, 25 had mild and 25 had severe autism. To analyze the association between the CARS scores and expression of the studied miRNAs, firstly, the normality of the data was checked using the Shapiro-Wilk test. The normality hypothesis was rejected for all data ($P< 0.05$), so the Mann-Whitney U-test was used for further analysis. As outlined in Table 1, the relative expression levels of the BDNF, miR-545-3p and miR-124 were significantly associated with severe autism ($P<0.05$**).

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Table 1. Association between autism severity and miRNA relative expression. 0 and 1 stand for the mild and severe autism, respectively.

	Group	Normality	Min	Max	Mode	Mean	SD	P-value
miR-153	**0**	0.007	0.190	2.460	0.750	0.954	0.637	U=-0.427 P=0.669
	1	0.006	0.120	2.890	0.710	0.884	0.636	
miR-545-3p	**0**	0.248	0.540	4.210	1.950	2.032	1.009	U=-3.88 P=0.0001**
	1	0.001	0.120	7.420	5.550	4.848	2.321	
miR-34a-3p	**0**	0.443	0.460	3.190	1.840	1.813	0.734	U=-0.602 P=0.547
	1	0.015	0.980	3.090	1.860	2.024	0.616	
miR-124	**0**	0.001	0.550	7.660	1.940	2.306	1.624	U=-4.93 P=0.0001**
	1	0.085	2.770	7.330	5.450	5.214	1.452	
BDNF	0	0.001	0.354	6.616	1.425	1.760	1.265	U=-5.56 P=0.0001**
	1	0.306	3.010	8.890	5.660	5.429	1.683	

Correlation between different variables among the patient and control

A simple linear regression analysis was conducted to find out any correlation between the studied variables. In the patient group, this analysis revealed that the relative expressions of miR-545-3p (r=0.54, p=0.0001) and miR-124 (r=0.786, p=0.0001) were positively correlated with the relative expression of BDNF (Table 2).

Also, there was a positive correlation between the relative expressions of miR-545-3p and miR-124 (r=0.369, p=0.008) (Fig. 4). The correlation analysis between these variables among the control group did not reveal any significant correlation (Table 3).

Table 2. The Correlation of different indicators in the patients' group.

		HS-CRP	miR-153	miR-545-3p	miR-34a-3p	miR-124a	BDNF
HS-CRP	**Pearson Correlation**	1	0.185	0.085	0.066	0.140	0.010
	Sig. (2-tailed)		0.197	0.559	0.648	0.330	0.947
mir-153	**Pearson Correlation**	0.185	1	-0.059	0.183	-0.180	-0.016
	Sig. (2-tailed)	0.197		0.684	0.204	0.211	0.912
miR-545-3p	**Pearson Correlation**	0.085	-0.059	1	0.012	0.369	0.54
	Sig. (2-tailed)	0.559	0.684		0.936	0.008**	0.000**
miR-34a-3p	**Pearson Correlation**	0.066	0.183	0.012	1	0.018	0.194
	Sig. (2-tailed)	0.648	0.204	0.936		0.903	0.176
miR-124a	**Pearson Correlation**	0.140	-0.180	0.369	0.018	1	0.786
	Sig. (2-tailed)	0.330	0.211	0.008**	0.903		0.000**
BDNF	**Pearson Correlation**	0.010	-0.016	0.54	0.194	0.786	1
	Sig. (2-tailed)	0.947	0.912	0.000**	0.176	0.000**	

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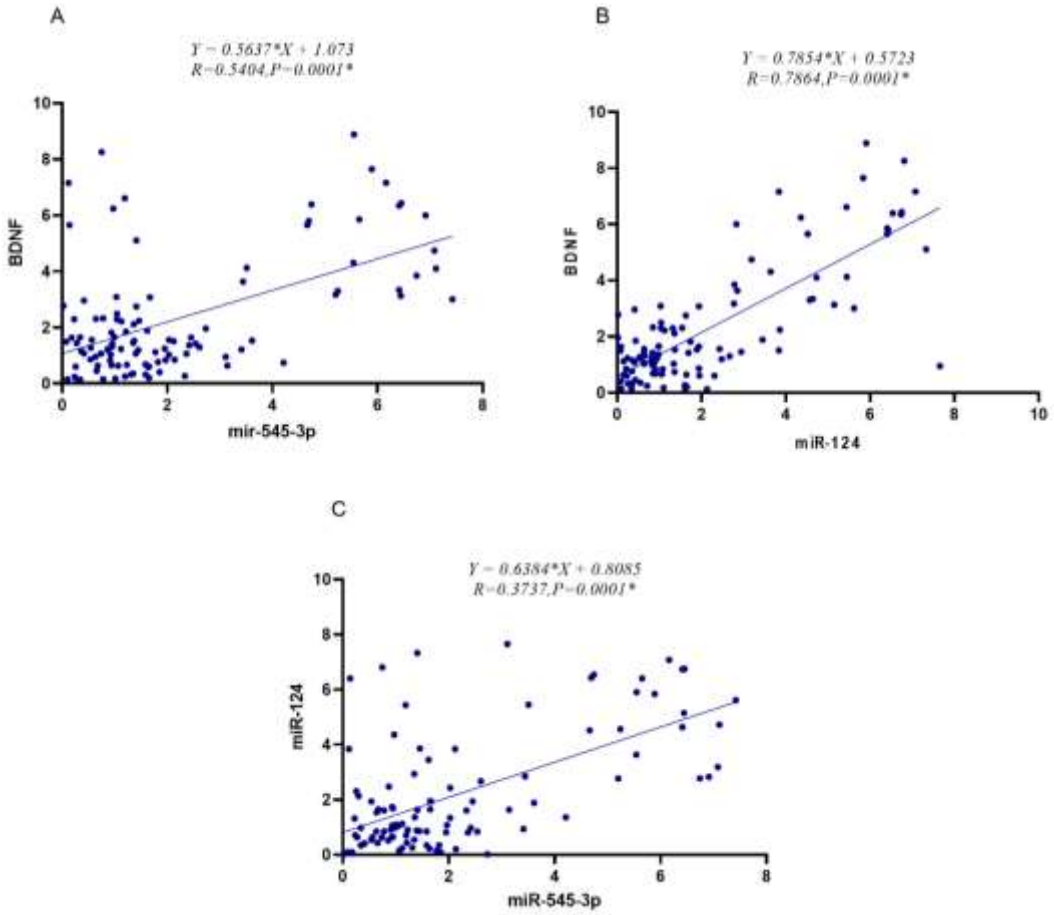

Fig. 4. Regression plots indicating correlations between the relative expressions of the a) miR-454-3p and BDNF, b) miR-124 and BDNF, and c) miR-545-3p and miR-124.

Table 3. The Correlation of different indicators in the control group

		HS-CRP	miR-153	miR-545-3p	miR-34a-3p	miR-124	BDNF
HS-CRP	Pearson Correlation	1	-0.234	0.178	-0.026	-0.224	-0.238
	Sig. (2-tailed)		0.147	0.271	0.872	0.165	0.140
miR-153	Pearson Correlation	-0.234	1	0.107	-0.038	-0.181	-0.095
	Sig. (2-tailed)	0.147		0.511	0.817	0.263	0.560
miR-545-3p	Pearson Correlation	0.178	0.107	1	-0.226	-0.289	-0.101
	Sig. (2-tailed)	0.271	0.511		0.161	0.070	0.535
miR-34a-3p	Pearson Correlation	-0.026	-0.038	-0.226	1	0.022	0.013
	Sig. (2-tailed)	0.872	0.817	0.161		0.892	0.934
miR-124	Pearson Correlation	-0.224	-0.181	-0.289	0.022	1	-0.101
	Sig. (2-tailed)	0.165	0.263	0.070	0.892		0.537
BDNF	Pearson Correlation	-0.238	-0.095	-0.101	0.013	-0.101	1
	Sig. (2-tailed)	0.140	0.560	0.535	0.934	0.537	

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Discussion

Results of the present study showed that the relative expressions of miR-124a, miR-34a-3p, miR-545-3p, and BDNF were significantly higher in the autistic people (Fig. 2). But, that of miR153 was significantly lower in the autistic people compared to the healthy controls.

We further assessed if there is any association between the relative expression of studied genes and severity of autism. Based on the CARS scores the patients were divided into mild and sever autism subgroups. The results showed that relative expressions of miR-124a, miR-545-3p and BDNF were positively associated with the sever autism. Interestingly, we also found out that relative expression of miR-454-3p was positively correlated with the relative expressions of BDNF and miR-124a in the patient group but not in the control group. Besides, the relative expression of miR-124a was positively correlated with the relative expression of BDNF.

Genetic factors account for roughly 80% of the risk of ASD, and siblings of autistic children have a higher risk than non-siblings (28). Autism is a highly heritable condition, yet less is known about the potential genes thought to be involved, despite epidemiological research linking the genetic component to autism (29). Several post-transcriptional processes, which involve microRNAs, regulate gene expression while maintaining the genetic code in the growing brain. In cases of autism, these systems are dysregulated, and patients with autism have altered miRNA expressions in their brains, blood, saliva, and olfactory precursor cells (30).

It was reported that miR-124a involves in the neurogenesis and can be used as a potent reprogramming factor to induce a neuronal state (16). It exists abundantly in the human brain and regulates neuronal fate determination (31). Consistent with our findings, Zhang et al. reported that miR124a plasma level was significantly higher in autistic boys than in the healthy sex- and age-matched controls (32). Besides, they showed that elevated levels of this miRNA can cause significant sociability deficits and myelin abnormality in mice. The miR-124a has been found to be crucial for neurogenesis, maturation, and progenitor proliferation in vertebrates, which is consistent with its pattern of expression in the developing CNS. Human induced pluripotent stem cells lacking miR-124a can develop into neurons when the transcription factors Neurog1 and Neurog2 are overexpressed and a small molecule-based culture environment is used. On the other hand, according to other investigations, miR-124a stimulates both adult and embryonic neurogenesis (12).

It was shown that miR-34a acts as a repressor of Shank3 in mouse hippocampal neurons (33). Consistent with our finding, miR-34-a up-regulates in the cerebellar cortex of ASD mice model. The activation of miR-34a directly caused loss of BCL2 levels in the parietal lobe of ASD patients (16, 34). It also is differentially expressed in the prefrontal cortex of patients with schizophrenia (35). The level of miR-34a-3p were significantly dysregulated in Amyotrophic lateral sclerosis (ALS) compared to controls, according to research by Rizzuti et al. who examined the expression profile of some miRNAs in the cerebrospinal fluid of familial and sporadic ALS patients. This study also found that patients with familial ALS had significantly higher levels of miR-34a-3p an in their cerebrospinal fluid, supporting the idea that these miRNAs play a role in disease development (36). In a study, Wegner et al. examined the correlation between the extent of the MRI lesion and the expression of miR-34a-3p and miR-34a-5p in ischemic brain tissue. They discovered that infarct size was positively correlated with the expression of miR-34a-5p and miR-34a-3p in ischemic brain tissue (15).

Although Kalemaj et al. reported that miR-545-3p was downregulated in the saliva samples of ASD patients (20), we observed that this miRNA is significantly up-regulated in the blood samples of the autistic subjects.

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This inconsistency might be due to the different source of body samples or more probably due to the very low number of ASD patients used for saliva sampling in the study by Kalemaj and colleagues. Among other miRNAs, miR-153 has been found to post-transcriptionally control the brain's levels of Alpha-Synuclein expression. Alpha-Synuclein, a crucial protein found in lewy bodies and linked to Parkinson's disease, is expressed at lower levels in neurons when miR-153 is overexpressed. Recent studies showed that miR-153 levels in PD patients are lower than in controls (37). Additionally, a different study revealed that miR-153 and Alzheimer's disease are related (38). Interestingly, our study found that autistic patients have lower levels of miR-153 than controls. Consistent with our finding, Yu-Hui et al. showed that autistic mice have down-regulated miR-153 in relation to the progression of autism. This research also showed that miR-153 targets the LEPR gene in autism. By suppressing the JAK-STAT signaling pathway and the LEPR gene, overexpression of miR-153 dramatically lowers apoptosis while enhancing BDNF production and hippocampal neuron proliferation. As a result, miR-153 might be a potential therapeutic target for autism (22). Furthermore, Barbosa et al. discovered that children with autism spectrum disorder had median BDNF levels that were moderately higher than those of typically developing children. They also discovered that BDNF can be used as a diagnostic biomarker for autism spectrum disorder (39). Similarly, the results of our study revealed that BDNF gene expression levels were higher in autistic children than in normal children.

In conclusion, this study revealed that expression level of miR-545-3p, miR-34a-3p, miR-124a, and BDNF were all considerably higher in the patient group compared to the control group, but miR-153 expression was significantly lower in the patients group. Furthermore, not only the higher expression of mir-124a, miR-545-3p and BDNF were related to the severity of autism, but their expression levels were positively correlated with each other. Also, ROC curve results suggest that miR-124a, miR-34a-3p, miR-545-3p, miR-153, and BDNF can be possible diagnostic biomarker in CARS diagnosis.

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Conflict of Interests

There is no conflict of interests to declare.

Ethical issues

Written informed consent was obtained from the parents of all participants. The study was approved by the ethical committee of the University of Tabriz.

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