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ORIGINAL ARTICLE

Expression of BDNF-Associated lncRNAs in Parkinson's disease

Mohammadarian Akbari[1] · Mahdi Gholipour[2] · Bashdar Mahmud Hussen[3,4] · Mohammad Taheri[5] · Solat Eslami[6,7] · Arezou Sayad[8] · Soudeh Ghafouri-Fard[8]

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Abstract

Decreased level of neurotrophic factor brain-derived neurotrophic factor (BDNF) has been supposed to participate in the pathoetiology of Parkinson's disease (PD). However, the underlying mechanisms of its dysregulation and the functional network between this factor and other transcripts have not been elucidated. In the current study, we measured expressions of *BDNF*, and four related long non-coding RNAs, namely *BDNF-AS*, *MIR137HG*, *MIAT* and *PNKY* in blood of PD patients and normal controls to find their expression levels in these patients and propose a possible mechanism for dysregulation of BDNF in PD patients. Notably, we detected down-regulation of all transcripts in the circulation of PD patients compared with controls. There was no significant difference in expression of either gene between male and female PD patients or patients receiving L-Dopa versus those receiving other drugs. Expression of none of genes was correlated with age, disease duration, disease stage, MMSE or UPDRS. Dynamic principal component analysis showed that expression levels of these genes almost clearly separated samples collected from healthy controls and PD patients into their respective groups. This suggests that the observed lncRNAs differences are associated with the pathophysiology of PD, and these lncRNAs might constitute an important biomarker signature for PD.

Keywords BDNF · BDNF-AS · MIR137HG · MIAT · PNKY · Parkinson's disease

✉ Arezou Sayad
ar.sayad@sbmu.ac.ir

✉ Soudeh Ghafouri-Fard
s.ghafourifard@sbmu.ac.ir

1 Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

2 Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

3 Department of Pharmacognosy, College of Pharmacy, Hawler Medical University, Erbil, Kurdistan Region, Iraq

4 Center of Research and Strategic Studies, Lebanese French University, Erbil, Kurdistan Region, Iraq

5 Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

6 Dietary Supplements and Probiotic Research Center, Alborz University of Medical Sciences, Karaj, Iran

7 Department of Medical Biotechnology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran

8 Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Introduction

The neurotrophic factor brain-derived neurotrophic factor (BDNF) has been shown to have neuroprotective and neuroregenerative effects (Palasz et al. 2020). Different studies in animal models of Parkinson's disease (PD) have verified the impact of BDNF on enhancement of the viability of dopaminergic neurons, improvement of dopaminergic neurotransmission and amelioration of motor function (Tsukahara et al. 1995; Klein et al. 1999; Sun et al. 2005). Moreover, levels of this neurotrophic factor have been found to be decreased in both PD patients and animal models of PD (Howells et al. 2000; Wang et al. 2016; Huang et al. 2018). Based on these observations, BDNF has been suggested as a therapeutic agent in PD (Palasz et al. 2020). Yet, direct transfer of exogenous BDNF or efforts to promote BDNF expression through gene therapy methods have not been successful in treatment of PD (Palasz et al. 2020). Thus, understanding the mechanisms of BDNF down-regulation in PD is important.

The naturally occurring antisense RNA from *BDNF* locus (*BDNF-AS*) has been shown to influence expression of *BDNF*

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transcript and protein (Modarresi et al. 2012). A previous literature search has revealed functional association between BDNF and a number of long non-coding RNAs (lncRNAs) (Rezaei et al. 2021), namely *MIR137HG*, *MIAT* and *PNKY* (Badrlou et al. 2021). Moreover, correlation analyses have revealed significant correlations between their expressions in patients with schizophrenia as well as healthy controls (Badrlou et al. 2021). Based on these findings, we aimed to assess expression of *BDNF*, *BDNF-AS*, *MIR137HG*, *MIAT* and *PNKY* in PD patients to find their expression levels in the peripheral blood of these patients and propose a possible mechanism for dysregulation of BDNF in PD patients. The criteria for selection of these lncRNAs were their participation in the pathobiology of neuropsychiatric disorders and their functional correlation with the neurotrophic factor BDNF.

Materials and methods

Patients and controls

Patient and controls

Blood specimens were obtained from 50 PD cases (13 females and 37 males) and 50 healthy individuals (17 females and 33 males). PD cases were recruited during January 2020–April 2021 from University-affiliated hospitals. The criteria suggested by the International Parkinson and Movement Disorder Society (Postuma et al. 2015) were used for assessment of cases. Those with history of current or chronic infections, neoplastic disorders or other systemic disorders were excluded. The functional disability associated with PD was evaluated using H&Y staging system (Poewe 2012). Mini-Mental State Examination (MMSE) score was used to screen for PD dementia, with values below 26 regarded as possible dementia (Arevalo-Rodriguez et al. 2015). Unified Parkinson's Disease Rating Scale (UPDRS) score was used to appraise the severity and progression of PD (Ebersbach et al. 2006). Control subjects had no personal or family history of any neuropsychiatric disorders. The study protocol was confirmed by ethical committee of Shahid Beheshti University of Medical Sciences. All PD patients and controls signed the informed consent forms.

Expression assays

Approximately 3–5 mL of peripheral blood was obtained from cases and healthy persons in EDTA-blood collection tubes. Total RNA was extracted from these specimens using GeneAll extraction kit (Seoul, South Korea). After assessment of the quality and quantity of RNA, cDNA was made from roughly 50–70 ng of RNA using BioFact™ kit (Seoul, South Korea). PCR was performed using Ampliqon real time PCR master mix (Denmark). Reactions were accomplished in StepOnePlus™ RealTime PCR System (Applied Biosystems, Foster city, CA, USA). PCR conditions and primers were similar to our recent study (Badrlou et al. 2021).

Statistical analysis

The Statistical Package for the Social Sciences v.18.0 (SPSS Inc., Chicago, IL) was used for statistical purposes.

Table 1 General demographic/clinical data of PD cases

Parameters	Values		
Sex (number)	Male		37
	Female		13
Age (Years, mean ± SD (range))	Male		69.64 ± 10.59 (47–89)
	Female		66.46 ± 12.6 (38–85)
Duration (Years, mean ± SD (range))	Male		3.18 ± 3.65 (1–12)
	Female		5.38 ± 9.76 (1–36)
MMSE (mean ± SD (range))	Male		22.84 ± 3.032 (17–29)
	Female		23.08 ± 2.499 (19–26)
UPDRS (mean ± SD (range))	Male		23.92 ± 7.418 (13–41)
	Female		26.31 ± 9.437 (16–42)
Hoehn & Yahr stage (Number)	I	Male	8
		Female	3
	II	Male	18
		Female	5
	III	Male	11
		Female	5
Drug administration (number)	L-DOPA		44
	L-DOPA+ Bromtriptin		2
	Other drugs		4

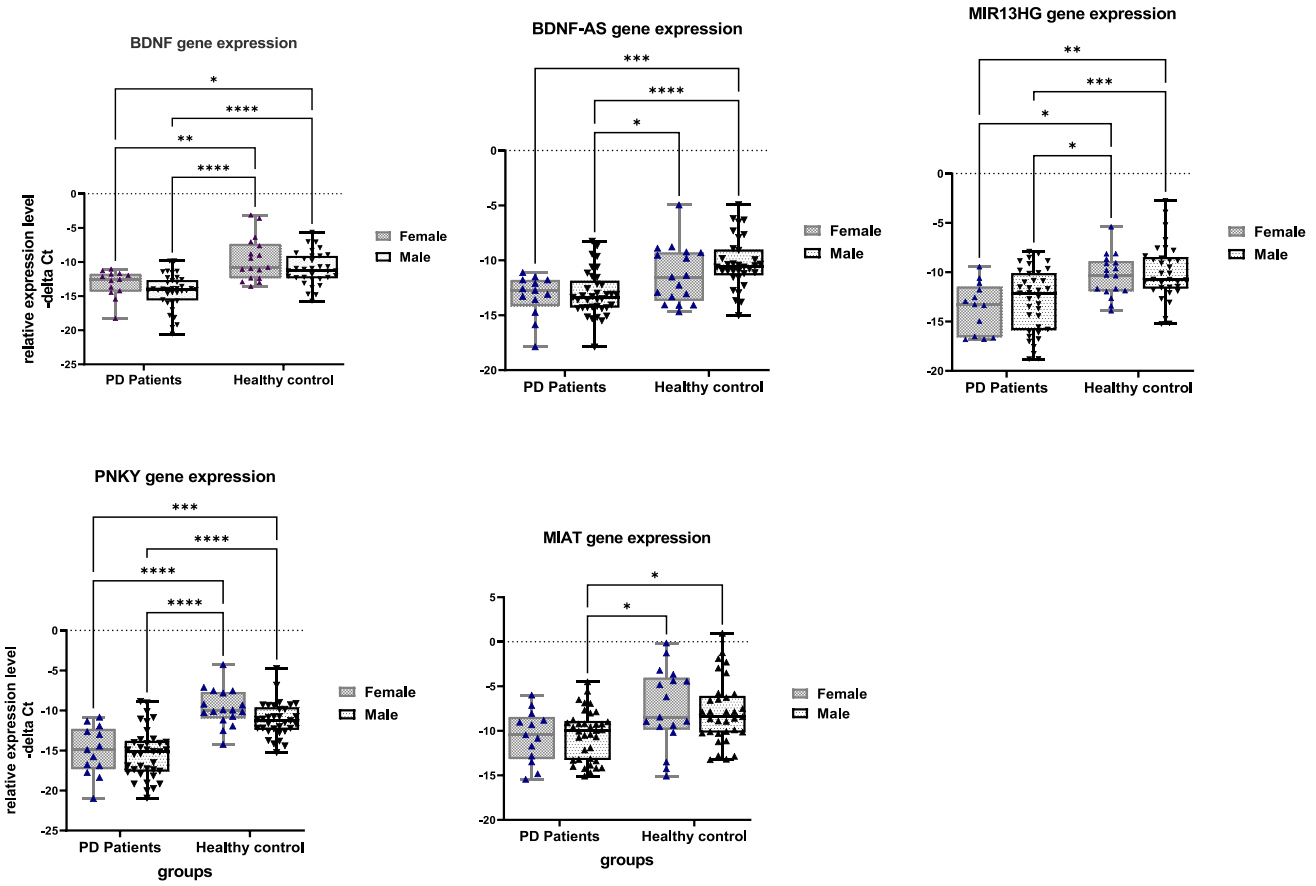

Fig. 1 Relative expression levels of *BDN*F and 4 lncRNAs in PD patient subgroups (male and female) versus control subgroups (male and female) (* *P* value <0.05, ** *P* value <0.001 and **** *P* value <0.0001)

Table 2 The results of expression study of *BDNF* and 4 lncRNA in peripheral blood of patients with Parkinson diseases compared with healthy controls. The expression ratio of each gene (mean and 95% Confidence interval of mean) is shown as the ratio of expression of the first group compared to the second group in each column (*shows significance)

lncRNAs		Total patients vs. Controls	Male patients vs. Male Controls	Female patients vs. Female Controls	Female patients vs. Male patients
BDNF	Expression ratio (95% CI)	0.09 (0.03–0.240)	0.102 (0.03–0.3)	0.084 (0.015–0.45)	2.11 (0.48–9.18)
	Adjusted *P* Value	<0.0001*	<0.0001*	0.001	0.55
BDNF-AS	Expression ratio (95% CI)	0.177 (0.06–0.47)	0.14 (0.05–0.37)	0.25 (0.05–1.14)	0.87 (0.23–3.23)
	Adjusted *P* Value	<0.0001*	<0.0001*	0.089	0.99
MIR13HG	Expression ratio (95% CI)	0.13 (0.04–0.34)	0.136 (0.04–0.47)	0.10 (0.01–0.71)	0.59 (0.11–3.2)
	Adjusted *P* Value	<0.0001*	0.0006	0.014	0.85
PNKY	Expression ratio (95% CI)	0.039 (0.014–0.105)	0.05 (0.01–0.17)	0.023 (0.003–0.14)	1.26 (0.26–6.07)
	Adjusted *P* Value	<0.0001*	<0.0001*	<0.0001*	0.97
MIAT	Expression ratio (95% CI)	0.158 (0.059–0.42)	0.167 (0.03–0.72)	0.11 (0.01–1.06)	0.89 (0.12–6.4)
	Adjusted *P* Value	<0.0001*	0.01	0.059	0.99

Graphs were depicted using GraphPad Prism version 9.0 for Windows, (GraphPad Software, La Jolla California, USA). Expressions of *BDNF* and 4 lncRNAs were calculated in each sample using the following formula: Efficiency adjusted Ct of normalizer gene (*B2M*) - Efficiency adjusted Ct of target gene method (comparative –delta Ct method). A two-way ANOVA was used to analyze effects of disease and gender on expression level of lncRNA in peripheral blood of patients and controls. Tukey post hoc test was used for multiple comparisons between subgroups. In addition, − delta Ct values were plotted in Figures as box and whisker plots. Median [line], mean [cross], interquartile range [box], and minimum and maximum values were shown in these figures.

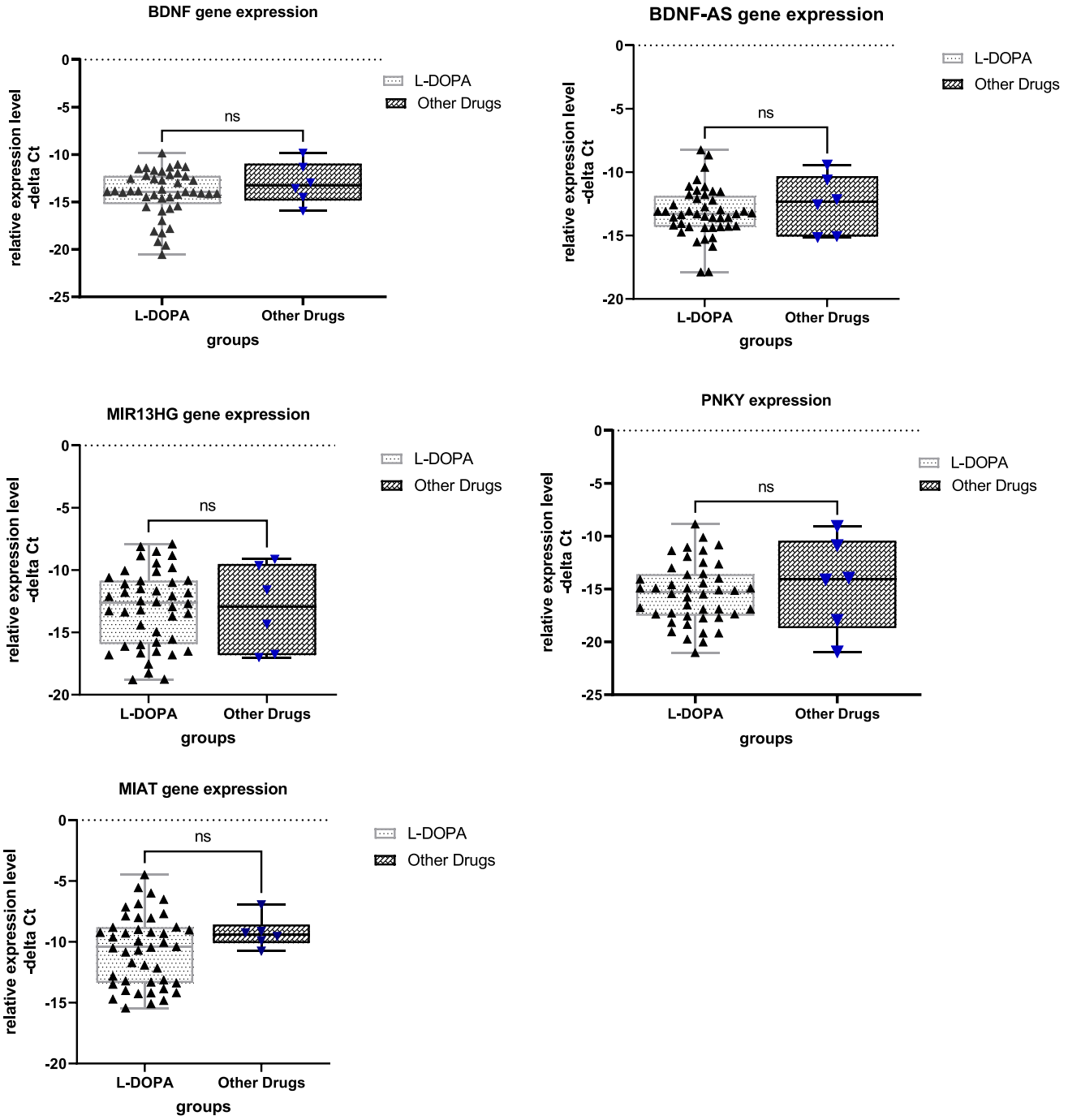

Fig. 2 Relative expression of *BDNF* and 4 lncRNAs in PD patients receiving different drugs, as described by –delta Ct values (Ct Housekeeping gene- Ct Target gene)

The delta delta Ct value was determined by subtracting the delta Ct of the control sample from the individual delta Ct of the test sample (Livak and Schmittgen 2001). The fold change of the test sample relative to the control sample was determined by $2^{-\text{delta delta Ct}}$ and was shown as mean and 95% CI of mean in the figures and table.

The correlations between transcript levels of studied genes were evaluated using regression model and Bonferroni correction for multiple comparisons. Partial correlation between expression levels of genes and age of study participants, disease stage (Hoehn & Yahr stage), disease duration, MMSS and UPDRES was described by R and *P* values.

The receiver operating characteristic (ROC) curves were depicted to appraise the diagnostic power of expression levels of *BDNF* and 4 lncRNAs. Youden's J parameter was measured to find the optimum threshold. *P* value <0.05 was considered as significant.

The significance of difference in mean values of *BDNF* and 4 lncRNAs expression (mean of –delta Ct method) between two subgroups of patients using L-DOPA and other drugs was computed using the t-test.

Dynamic principal component analysis of lncRNA expression profile was used to cluster samples via Gene Expression software (GenEx SW, Multid Analysis AB, Göteborg, Sweden). Normalized values were used for principal component analysis. Heatmaps were generated by using using GenEx software.

Result

General data of participants

Table 1 summarizes general data of PD cases.

Expression assays

Figure 1 depicts Relative expression levels of *BDN*F and 4 lncRNAs in PD patient subgroups.

Expression of *BDNF* was lower in total patients compared with total controls (Expression ratio (ER) (95% CI) = 0.09 (0.03–0.240), adjusted *P* value < 0.0001), in male patients compared with male controls (ER (95% CI) = 0.102 (0.03–0.3), adjusted *P* value < 0.0001), and in female patients compared with female controls (ER (95% CI) = 0.084 (0.015–0.45), adjusted *P* value = 0.001).

Expression of *BDNF-AS* was lower in total patients compared with total controls (ER (95% CI) = 0.177 (0.06–0.47), adjusted *P* value < 0.0001) and in male patients compared with male controls (ER (95% CI) = 0.14 (0.05–0.37), adjusted *P* value < 0.0001).

Similarly, expression of *MIR13HG* was lower in total patients compared with total controls (ER (95% CI) = 0.13 (0.04–0.34), adjusted *P* value < 0.0001), in male patients compared with male controls (ER (95% CI) = 0.136 (0.04–0.47),

Table 3 The results of partial correlation between expression of *BDNF* and 4 lncRNAs and age, disease duration, disease stage, MMSE and UPDRS (Controlled for sex)

Parameters	Age		BDNF		BDNF-AS		MIR13HG		PNKY		MIAT		Disease stage (Hoehn & Yahr stage)		Disease duration		MMSE		UPDRS	
	R	*P* value	R	*P* value	R	*P* value	R	*P* value	R	*P* value	R	*P* value	R	*P* value	R	*P* value	R	*P* value	R	*P* value
Age	1	0	0.13	0.37	0.135	0.35	0.18	0.21	0.19	0.17	0.24	0.08	0.19	0.18	−0.09	0.51	−0.6	<0.0001	0.11	0.43
Disease duration	−0.09	0.51	−0.11	0.43	0.023	0.87	0.089	0.54	0.12	0.39	0.04	0.78	0.55	<0.0001	1	0	−0.38	0.006	0.5	0.0002
Disease stage (Hoehn & Yahr stage)	0.19	0.18	−0.09	0.53	0.16	0.24	−0.015	0.92	0.16	0.26	−0.05	0.69	1	0	0.55	<0.0001	−0.58	<0.0001	0.66	<0.0001
MMSE	−0.6	<0.0001	−0.13	0.37	−0.047	0.75	−0.2	0.16	−0.14	0.32	−0.19	0.18	−0.58	<0.0001	−0.38	0.006	1	0	−0.33	0.02
UPDRS	0.11	0.43	0.002	0.98	0.11	0.43	−0.13	0.36	0.17	0.23	−0.007	0.96	0.66	<0.0001	0.5	0.0002	−0.33	0.02	1	0

adjusted *P* value = 0.0006), and in female patients compared with female controls (ER (95% CI) = 0.10 (0.01–0.71), adjusted *P* value = 0.014). Expression of *PNKY* was similarly decreased in three comparisons (ER (95% CI) = 0.039 (0.014–0.105), 0.05 (0.01–0.17) and 0.023 (0.003–0.14), respectively; *P* values < 0.0001 for all comparisons).

Finally, *MIAT1* was down-regulated in in total patients compared with total controls (ER (95% CI) = 0.158 (0.059–0.42), adjusted *P* value < 0.0001) and in male patients compared with male controls (ER (95% CI) = 0.167 (0.03–0.72), adjusted *P* value = 0.01).

Expression of none of genes was different between female and male patients (Table 2).

There was no significant difference in expression of either gene between PD patients receiving L-Dopa versus those receiving other drugs (Fig. 2).

Expression of none of genes was correlated with age, disease duration, disease stage, MMSE or UPDRS (Table 3).

Disease duration was classified into 3 groups (1–5, 6–10 and more than 10 years).

Expression of *BDNF* was correlated with expression of other genes in both study groups except of *MIR13HG* among patients. Expression of *BDNF-AS* was correlated with expressions of *MIR13HG* and *MIAT* among controls and with expression of *PNKY* among both study groups. Expression of *MIR13HG* was correlated with expression of *MIAT* and *PNKY* only among controls. Finally, *MIAT* and *PNKY* levels were correlated among controls (Table 4).

Then, we depicted ROC curves for assessment of diagnostic power of BDNF and 4 lncRNAs (Fig. 3).

PNKY had the best parameters among assessed genes. This lncRNA differentiate total PD cases from total controls with AUC value of 0.88. In sex-based comparisons, *PNKY* had AUC values of 0.94 and 0.85 among females and males, respectively. *BDNF* could differentiate total cases from total controls with AUC value of 0.84 (Table 5).

Principal component analysis (PCA) of *BDNF* and 4 lncRNAs expression profiles showed that expression data of the studied genes could partially cluster samples collected from healthy controls (blue squares) and PD patients (green squares) into their respective groups (Fig. 4).

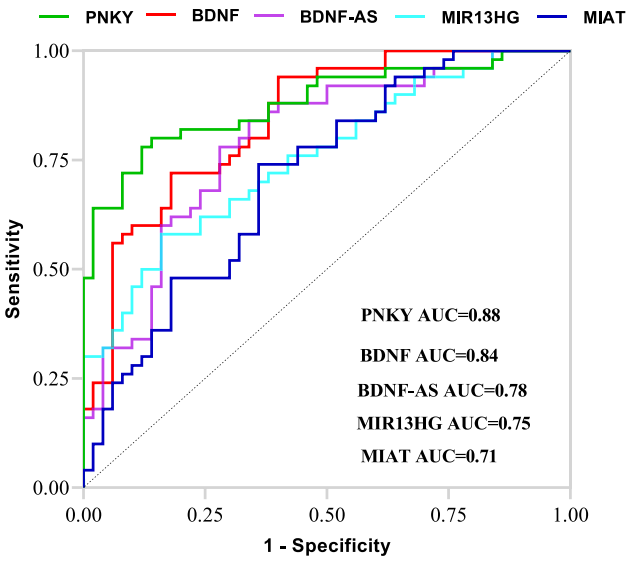

Fig. 3 ROC curves of *BDNF* and 4 lncRNAs transcript levels in PD.

Then, we performed dynamic principal component analysis (DPCA) of expression profiles of *BDNF* and four lncRNAs to determine how these differentially expressed genes were distributed among the samples from PD patients and healthy controls (Fig. 6). DPCA excluded lncRNA *BDNF-AS* with low standard deviation. So, expression data of *BDNF* and 3 lncRNAs was used to cluster samples collected from healthy controls (blue squares) and PD patients (green squares) into their respective groups. As shown in Fig. 5, expression levels of these genes almost clearly separated the samples collected from healthy controls and PD patients into their respective groups.

Finally, we depicted Log2 Fold Change Heat Map (Fig. 6).

Discussion

BDNF has effective impact on survival and organization of dopaminergic neurons and therefore defect in its production can lead to neuron death in PD (Howells et al. 2000). In fact,

Table 4 Correlations between expressions of *BDNF* and 4 lncRNAs in study groups. (R values are presented; after correction for multiple comparisons (Bonferroni correction), P value less than 0.0025 was accepted as significant, ns: not significant)

BDNF-AS	Controls	0.66*	<0.0001						
	Patients	0.47*	0.0005						
MIR13HG	Controls	0.51*	0.0001	0.45*	0.001				
	Patients	−0.006	ns	0.17	ns				
PNKY	Controls	0.65*	<0.0001	0.45*	0.0009	0.52*	0.0001		
	Patients	0.55*	<0.0001	0.56*	<0.0001	0.11	ns		
MIAT	Controls	0.44*	0.0014	0.36	0.008	0.38	0.005	0.46*	0.0007
	Patients	0.31	0.024	0.22	ns	0.092	ns	0.12	ns
		r	*P* value	r	*P* value	r	*P* value	r	*P* value
		BDNF		*BDNF-AS*		*MIR13HG*		*PNKY*	

Table 5 Detailed parameters of ROC curve analyses

Genes→	*BDNF*				*BDNF-AS*				*MIR13HG*				*PNKY*				*MIAT*			
Parameters	AUC ± SD	Sensitivity	Specificity	P Value	AUC ± SD	Sensitivity	Specificity	P Value	AUC ± SD	Sensitivity	Specificity	P Value	AUC ± SD	Sensitivity	Specificity	P Value	AUC ± SD	Sensitivity	Specificity	P Value
Total patients vs. total controls	0.84 ± 0.038	0.72	0.82	<0.0001	0.78 ± 0.045	0.78	0.72	<0.0001	0.75 ± 0.047	0.58	0.84	<0.0001	0.88 ± 0.034	0.78	0.88	<0.0001	0.71 ± 0.051	0.74	0.64	<0.0001
Female patients vs. Female controls	0.82 ± 0.075	0.92	0.70	0.0024	0.67 ± 0.098	1	0.41	0.098	0.82 ± 0.075	0.69	0.82	0.0028	0.94 ± 0.09	1	0.76	<0.0001	0.71 ± 0.09	1	0.41	0.051
Male patients vs. Male controls	0.84 ± 0.047	0.78	0.81	<0.0001	0.82 ± 0.05	0.67	0.90	<0.0001	0.73 ± 0.05	0.54	0.84	0.0006	0.85 ± 0.046	0.75	0.90	<0.0001	0.70 ± 0.06	0.75	0.63	0.0026

extreme down-regulation of BDNF in neurons might predispose them to PD-associated neuron damage and induce their degeneration (Howells et al. 2000). Previous studies have demonstrated down-regulation of BDNF in both PD patients and animal models of PD (Howells et al. 2000; Wang et al. 2016; Huang et al. 2018). In the current study, we verified down-regulation of this neurotrophic factor in the circulation of PD patients compared with healthy controls. Moreover, we showed down-regulation of four BDNF-associated lncRNAs in these patients, among them being the antisense transcript from *BDNF* locus. Down-regulation of *BDNF-AS* has been shown to protect dorsal root ganglion neurons from neurotoxic effects of bupivacaine, possibly via induction of neurotrophin TrkB cascade (Zhang et al. 2016). On the other hand, BDNF/TrkB expression has been reported to be decreased in the substantia nigra of PD patients (Jin 2020). Thus, the observed down-regulation of *BDNF-AS* in the circulation of PD patients might be a compensatory mechanism to induce TrkB cascade and reduce the PD-associated neuron injury.

MIR137HG is the host gene for miR-137, a miRNA that is associated with a number of psychiatric disorders such as autism, intellectual disability and schizophrenia. In fact, miR-137 has a role in the regulation of synaptic plasticity and a number of signaling pathways in neurons (Thomas et al. 2018). Down-regulation of *MIR137HG* in the circulation of patients with PD might represent a possible mechanism for altered synaptic plasticity in these patients. Recent studies have demonstrated the impact of dopamine deficiency in the striatum on induction of synaptic changes in the basal ganglia nuclei (Chu 2020). These changes trigger the abnormal pattern of activity

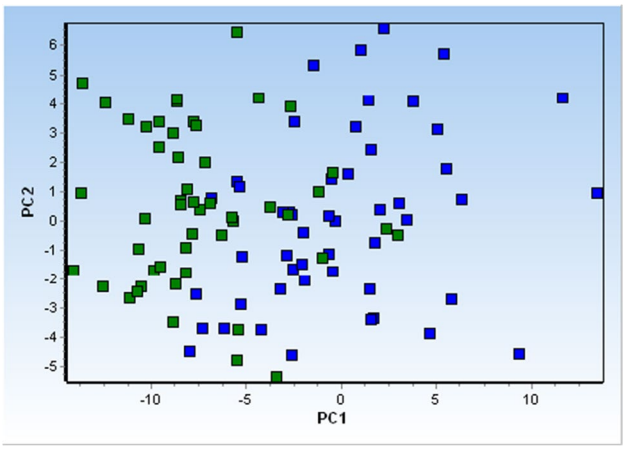

Fig. 4 Principal component analysis (PCA) of expression profiles of *BDNF* and 4 lncRNAs in patients with Parkinson diseases compared with healthy controls. Expression data of the studied genes could partially cluster samples collected from healthy controls (blue squares) and patients with Parkinson (green squares) into their respective groups. Normalized values were used for PCA

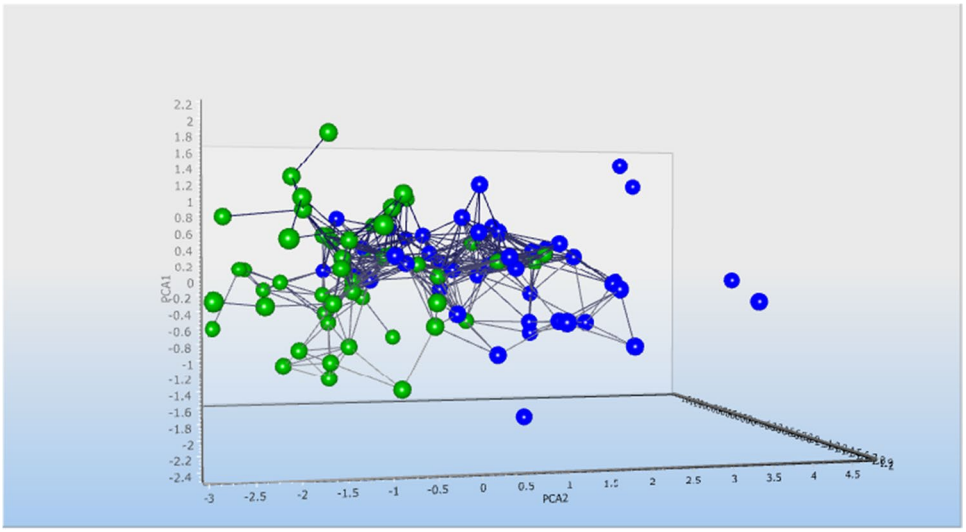

Fig. 5 Dynamic principal component analysis (DPCA) of expression profiles of *BDNF* and four lncRNAs. DPCA was used to filter out and exclude lncRNAs with low standard deviation. *BDNF-AS* was excluded from analyses. Expression data of *BDNF* and 3 lncRNAs was used to cluster samples collected from healthy controls (blue squares) and patients with Parkinson (green squares) into their respective groups. Normalized values were used for principal component analysis

through the network between corticobasal, ganglial and thalamocortical regions, thus contributing to motor dysfunction in PD (Chu 2020).

A set of experiment in rat model of hypoxia/ischemia has shown that *MIAT* has a role in reduction of neuron apoptosis via miR-211/GDNF (Li et al. 2019). Thus, down-regulation of this lncRNA might predispose neurons to apoptotic death.

PNKY has a role in neurodevelopment. Lack of *Pnky* expression in the cortex has been shown to result in the production of the projection neuron from neural stem cells in a cell-autonomous manner and changes in the cortical stratification after birth (Andersen et al. 2019). Further studies are needed to find the importance of this mechanism in the pathoetiology of PD.

Correlation analysis showed disturbances in the normal pattern of correlation between mentioned genes among patients with PD, implying absence of normal functional connections between them in this context.

ROC curve analyses indicated the appropriateness of *PNKY* and *BDNF* as peripheral markers for PD. Moreover, DPCA of expression profiles of *BDNF* and lncRNAs showed that expression data of *BDNF* and 3 lncRNAs could cluster samples collected from healthy controls and PD patients into their respective groups. This suggests that the observed lncRNAs differences are associated with the pathophysiology of PD, and these lncRNAs might constitute an important biomarker signature for PD.

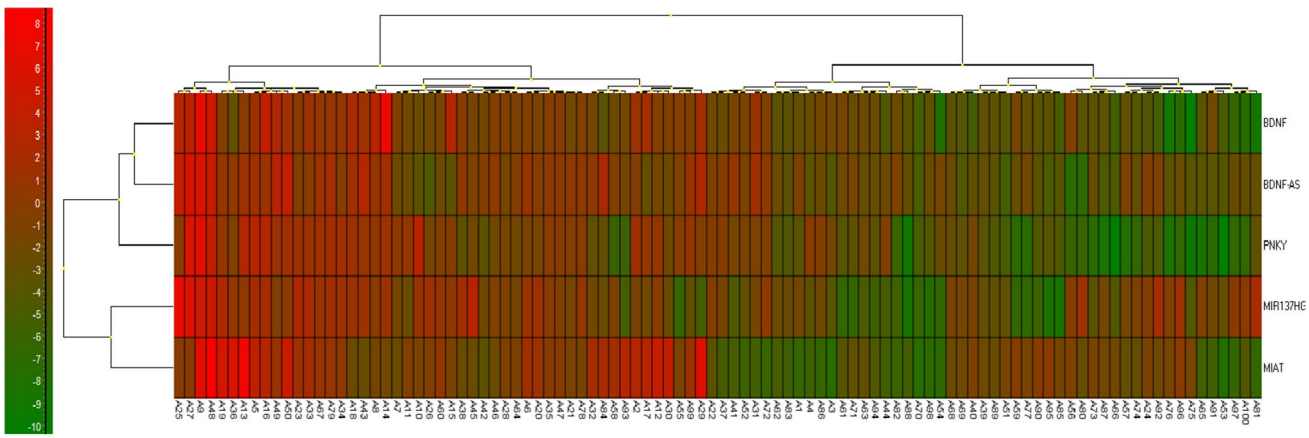

Fig. 6 Log2 Fold Change Heat Map. A heat map for the subjects with Parkinson diseases and healthy control. Log2 fold change was calculated based on delta Ct value compared to the control samples. Red color implies decreased expression while green implies increased expression. LncRNAs on the right are clustered using a hierarchical clustering method (Ward's method, Euclidean distances) and 4 clusters were found. Cluster 1 = *BDNF* and *BDNF-AS*; Cluster 2 = *PNKY*; Cluster 3 = *MIR13HG*; Cluster 4 = *MIAT*. Most of patient samples (A1-A50) were located on the left side with decreased expression of studied gene in this work

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Authors' contributions SGF wrote the manuscript and revised it. AS supervised and designed the study. SJ, BMH and HHJ performed the experiment. SE analyzed the data. MD was the clinical consultant and assessed patients for inclusion in the study. All authors read and approved the submitted version.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participant All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1400.568). All methods were performed in accordance with the relevant guidelines and regulations.

Consent of publication Not applicable.

Competing interests The authors declare they have no conflict of interest.

References

Andersen RE, Hong SJ, Lim JJ, Cui M, Harpur BA, Hwang E, Delgado RN, Ramos AD, Liu SJ, Blencowe BJ, Lim DA (2019) The long noncoding RNA Pnky is a trans-acting regulator of cortical development in vivo. Dev Cell 49:632–642 e7

Arevalo-Rodriguez I, Smailagic N, Roqué I, Figuls M, Ciapponi A, Sanchez-Perez E, Giannakou A, Pedraza OL, Bonfill Cosp X, Cullum S (2015) Mini-mental state examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). The Cochrane database of systematic reviews 2015:CD010783–CD010783

Badrlou E, Ghafouri-Fard S, Omrani MD, Neishabouri SM, Arsang-Jang S, Taheri M, Pouresmaeili F (2021) Expression of BDNF-associated lncRNAs in treatment-resistant schizophrenia patients. J Mol Neurosci 1–11

Chu H-Y (2020) Synaptic and cellular plasticity in Parkinson's disease. Acta Pharmacol Sin 41:447–452

Ebersbach G, Baas H, Csoti I, Müngersdorf M, Deuschl G (2006) Scales in Parkinson's disease. J Neurol 253:iv32–iv35

Howells D, Porritt MJ, Wong J, Batchelor P, Kalnins R, Hughes A, Donnan G (2000) Reduced BDNF mRNA expression in the Parkinson's disease substantia nigra. Exp Neurol 166:127–135

Huang Y, Yun W, Zhang M, Luo W, Zhou X (2018) Serum concentration and clinical significance of brain-derived neurotrophic factor in patients with Parkinson's disease or essential tremor. J Int Med Res 46:1477–1485

Jin W (2020) Regulation of BDNF-TrkB signaling and potential therapeutic strategies for Parkinson's disease. J Clin Med 9:257

Klein RL, Lewis MH, Muzyczka N, Meyer EM (1999) Prevention of 6-hydroxydopamine-induced rotational behavior by BDNF somatic gene transfer. Brain Res 847:314–320

Li E-Y, Zhao P-J, Jian J, Yin B-Q, Sun Z-Y, Xu C-X, Tang Y-C, Wu H (2019) LncRNA MIAT overexpression reduced neuron apoptosis in a neonatal rat model of hypoxic-ischemic injury through miR-211/GDNF. Cell Cycle (Georgetown, Tex) 18:156–166

Livak KJ, Schmittgen TD (2001) Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) method. Methods 25:402–408

Modarresi F, Faghihi MA, Lopez-Toledano MA, Fatemi RP, Magistri M, Brothers SP, van der Brug MP, Wahlestedt C (2012) Inhibition of natural antisense transcripts in vivo results in gene-specific transcriptional upregulation. Nat Biotechnol 30:453–459

Palasz E, Wysocka A, Gasiorowska A, Chalimoniuk M, Niewiadomski W, Niewiadomska G (2020) BDNF as a promising therapeutic agent in Parkinson's disease. Int J Mol Sci 21:1170

Poewe W (2012) Global scales to stage disability in PD: the Hoehn and Yahr scale. Rating Scales Parkinsons Dis 115–122

Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G (2015) MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 30:1591–1601

Rezaei O, Nateghinia S, Estiar MA, Taheri M, Ghafouri-Fard S (2021) Assessment of the role of non-coding RNAs in the pathophysiology of Parkinson's disease. Eur J Pharmacol 896:173914

Sun M, Kong L, Wang X, Lu X-G, Gao Q, Geller AI (2005) Comparison of the capability of GDNF, BDNF, or both, to protect nigrostriatal neurons in a rat model of Parkinson's disease. Brain Res 1052:119–129

Thomas KT, Gross C, Bassell GJ (2018) microRNAs sculpt neuronal communication in a tight balance that is lost in neurological disease. Front Mol Neurosci 11:455–455

Tsukahara T, Takeda M, Shimohama S, Ohara O, Hashimoto N (1995) Effects of brain-derived neurotrophic factor on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism in monkeys. Neurosurgery 37: 733–739; discussion 739–41

Wang Y, Liu H, Zhang B-S, Soares JC, Zhang XY (2016) Low BDNF is associated with cognitive impairments in patients with Parkinson's disease. Parkinsonism Relat Disord 29:66–71

Zhang Y, Yan L, Cao Y, Kong G, Lin C (2016) Long noncoding RNA BDNF-AS protects local anesthetic induced neurotoxicity in dorsal root ganglion neurons. Biomed Pharmacother 80:207–212