

microRNAs involved in Parkinson's disease: A systematic review

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Abstract. The aim of the present study was to determine the expression of blood microRNAs (miRNAs) involved in PD in humans. For this purpose the following electronic databases were selected: MEDLINE by Pubmed, Scopus and Web of Science. The search strategy included the proposed descriptors in the Medical Subject Headings. There were no restrictions with respect to the language of the publication. In the study selection two independent reviewers initially evaluated studies that were identified by the search strategy according to titles and abstracts. The reviewers evaluated (also unassisted) the complete articles and selected studies according to the eligibility criteria specified above. Studies that were not in accordance with the adopted criteria were excluded according to the boundaries imposed by the search strategy. The following data were extracted from the selected studies: Publication identification, location where the study was conducted, study design, the sample size, the participants' characteristics, the miRNAs involved in PD, the miRNA detection and analysis method, and the type of miRNA dysregulation in PD. Through this systematic review of the literature published over the last 10 years, the expression of 91 different miRNAs were analyzed in the context of PD, with the expression of 39 of these miRNAs differing significantly between individuals with PD and healthy controls and/or between treated and untreated patients with PD. The miRNAs were extracted from mononuclear cells, leukocytes, plasma, serum and peripheral blood, and the majority of the studies used reverse transcription-quantitative polymerase chain reaction (RT-qPCR), which is considered to be the gold standard for miRNA analysis.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, and it is estimated to affect ~1% of individuals >60 years of age and 4.1-4.6 million people worldwide (1). PD is a highly heterogeneous, progressive neurodegenerative disease, clinically characterized by tremors, bradykinesia, stiffness, and eventually postural instability (2). These symptoms may have variable progression (3) and are attributed to a loss of dopaminergic neurons in the substantia nigra (1). The pathology may involve other regions of the brain, including the amygdala, the cingulate gyrus and the superior cortical regions, resulting in the development of dementia and psychosis (1).

Previously, a number of reviews focusing on microRNAs (miRNAs) have demonstrated notable underlying molecular mechanisms corresponding to the pathogenesis of PD (1-7). It should be noted that the discovery of miRNAs broadened the potential of diagnostic markers and therapeutic targets for human diseases, influencing the majority of mechanisms responsible for neurodegenerative diseases (1), including PD (7).

miRNAs are small, endogenous, non-coding RNA molecules (length, 19-24 nt) that are cleaved from a partially duplexed 70-80-nt precursor, known as pre-miRNA (7). miRNAs regulate gene expression of the target mRNA at the post-transcriptional level via imperfect pairing with the 3'-untranslated region (3'-UTR). This affects numerous biological processes, including the cell cycle, differentiation, proliferation, apoptosis and the cellular stress response. Thus, as previous studies have suggested the importance of miRNAs in PD pathogenesis, and in the disturbance of processes associated with the regulation of genes implicated in its development (1-7), the aim of the present study was to determine the expression of blood miRNAs involved in PD in humans via a systematic review of the literature published over the last 10 years.

Materials and methods

Eligibility criteria. The present systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO; no. CRD42015019973) and follows the

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recommendations proposed by the Preferred Reporting Items for Systematic Reviews and Meta-analyses: The PRISMA Statement (8).

Randomized and non-randomized studies of miRNAs in PD in humans where the miRNAs were obtained from blood samples were included. The previous studies were indexed on the previously selected databases, had abstracts available, were fully accessible online and were published within the past 10 years. There were no language restrictions.

Search strategy. The electronic databases MEDLINE via Pubmed (www.ncbi.nlm.nih.gov/pubmed), Scopus (Elsevier; www.scopus.com) and Web of Science (webofknowledge.com) were selected. The search strategy included the keywords proposed in medical subject headings (Table I). All the searches were conducted in September 2015. EndNote 3.4 (Thomson Reuters Corporation, Ontario, Canada) was used to manage reference material during searches.

Study selection and data extraction. The titles and abstracts of all of the articles identified by the search strategy were independently evaluated by two authors of the present study. These authors also evaluated the full articles and made their selections according to the pre-specified eligibility criteria. Disagreements between the reviewers were resolved by consensus.

The following data were extracted: Publication identification (first author and year of publication), location where the study was conducted (country), study design, the sample size, the participants' characteristics (gender, mean age, disease stage, mean disease duration), the miRNAs involved in PD, the miRNA detection and analysis method, and the type of miRNA dysregulation in PD.

Results

Literature search evaluated a total of 289 articles. The search enabled the identification of 289 articles, 76 of which were excluded as duplicates; 155 studies did not meet the eligibility criteria based on the titles and abstracts. A detailed evaluation indicated that nine studies were potentially relevant, and these were included in the review. Fig. 1 indicates the flowchart of this process.

Patient characteristics, analysis methods and miRNAs investigated were considered. The major characteristics of the studies included are described in Table II. Two studies were conducted in Spain (9,10), and two were conducted in Italy (11,12). The majority of the previous studies were cross-sectional (10-16). The sample size ranged from 7 (17) to 125 (10) individuals with PD. One study involved only male patients (17). The mean age of the participants ranged from 45 (13) to 72 (15) years. The PD stage (according to Hoehn and Yahr) ranged from I to V, and the mean duration of the disease ranged from 3 (13) to 9.6 (10) years.

Table III indicates the miRNAs involved in PD, the detection and analysis methods, and the identified microRNA dysregulation in PD. The expression of 91 different miRNAs was observed. miRNAs were extracted from mononuclear cells (14), leukocytes (17), plasma (9,15), serum (10,11), and

peripheral blood (12,13,16). The majority of the analyses used reverse transcription-quantitative polymerase chain reaction (RT-qPCR), which is considered to be the gold standard analysis method.

miR-30b, miR-30c and miR-26a were downregulated in the previous study by Martins *et al* (14). Khoo *et al* (15) demonstrated that miR-1826, miR-626, and miR-505 were upregulated, and miR-450b-3p was downregulated. Upon comparison of patients with PD and healthy controls, Cardo *et al* (9) observed that miR-331-5p was elevated. Botta-Orfila *et al* (10), when comparing patients with idiopathic PD and controls, observed a downregulation of miR-29c, miR-29-a and miR-19b. Valletunga *et al* (11) observed a downregulation of miR-30c and miR-148b in patients with PD compared with patients with multiple system atrophy (MSA).

miR-1, miR-22* and miR-29a were downregulated and differed between patients with PD and healthy controls, and miR-16-2a*, miR-26a2* and miR-30a were upregulated with a significant difference between patients with treated and untreated PD (13). Serafin *et al* (12) demonstrated the patients treated with L-dopa exhibited decreased miR-103a-3p, miR-30b-5p and miR-29a-3p levels. Alieva *et al* (16) observed an upregulation of miR-7, miR-9-3p, miR-9-5p, miR-129 and miR-132 in patients with treated PD compared with untreated patients.

Comparing gene expression in patients with PD and healthy controls prior to and following electrical stimulation (deep brain stimulation-DBS) and 1 h after stimulus cessation, Soreq *et al* (17) observed that miR-1249, miR-20a, miR-18b, miR-378c and miR-4293 decreased following electrical stimulation, and 1 h after stimulus cessation, miR-423, miR-365, miR-486, miR-1260 and miR-218 were increased and miR-652, miR-15a*, miR-29c, miR-29a, miR-376c and were miR-143 decreased.

Discussion

The main aim of the present study was to determine the expression of miRNAs that are involved in human PD and present in the blood. The analysis consisted of a systematic review of the literature of the past 10 years, and in the nine studies considered, 91 different miRNAs were identified. Among these miRNAs, 39 were significantly differentially expressed between groups as follows; i) Individuals with PD and healthy controls (9,10,14,15); ii) patients with PD and patients with systemic muscular atrophy (11); iii) patients with PD treated with levodopa and untreated PD (12,13,16); and iv) patients who received electrical stimulation and those who did not (17).

Martins *et al* (14) demonstrated miR-30b, miR-30c and miR-26a were downregulated. According to these authors, these three miRNAs are involved in the regulation of α -synuclein. The authors also discussed three common genes that are putative targets of these miRNAs, namely, ubiquitin specific peptidase (USP)6, E3 ubiquitin-protein ligase NEDD4 and USP3, and the roles of these proteins in glycosphingolipid biosynthesis and protein ubiquitination. Glycosphingolipids are related to ceramide metabolism, which has been associated with PD with regard to the glucocerebrosidase gene (18). Another important characteristic of PD is the presence of Lewy bodies and the ubiquitination of α -synuclein, which is

Table I. Descriptors used in the search strategy.

Topic	Descriptors
MicroRNAs	'MicroRNAs' (MeSH), 'MicroRNAs', 'MicroRNA', 'miRNAs', 'Micro RNA', 'RNA, Micro', 'miRNA', 'Primary MicroRNA', 'MicroRNA, Primary', 'Primary miRNA', 'miRNA, Primary', 'pri-miRNA', 'pri miRNA', 'RNA, Small Temporal', 'Temporal RNA, Small', 'stRNA', 'Small Temporal RNA', 'pre-miRNA', 'pre miRNA
Parkinson disease	'Parkinson Disease' (MeSH), 'Parkinson Disease', 'Idiopathic Parkinson's Disease', 'Lewy Body Parkinson Disease', 'Lewy Body Parkinson's Disease', 'Primary Parkinsonism', 'Parkinsonism, Primary', 'Parkinson Disease, Idiopathic', 'Parkinson's Disease', 'Parkinson's Disease, Idiopathic', 'Parkinson's Disease, Lewy Body', 'Idiopathic Parkinson Disease', 'Paralysis Agitans'

MeSH, medical subject headings.

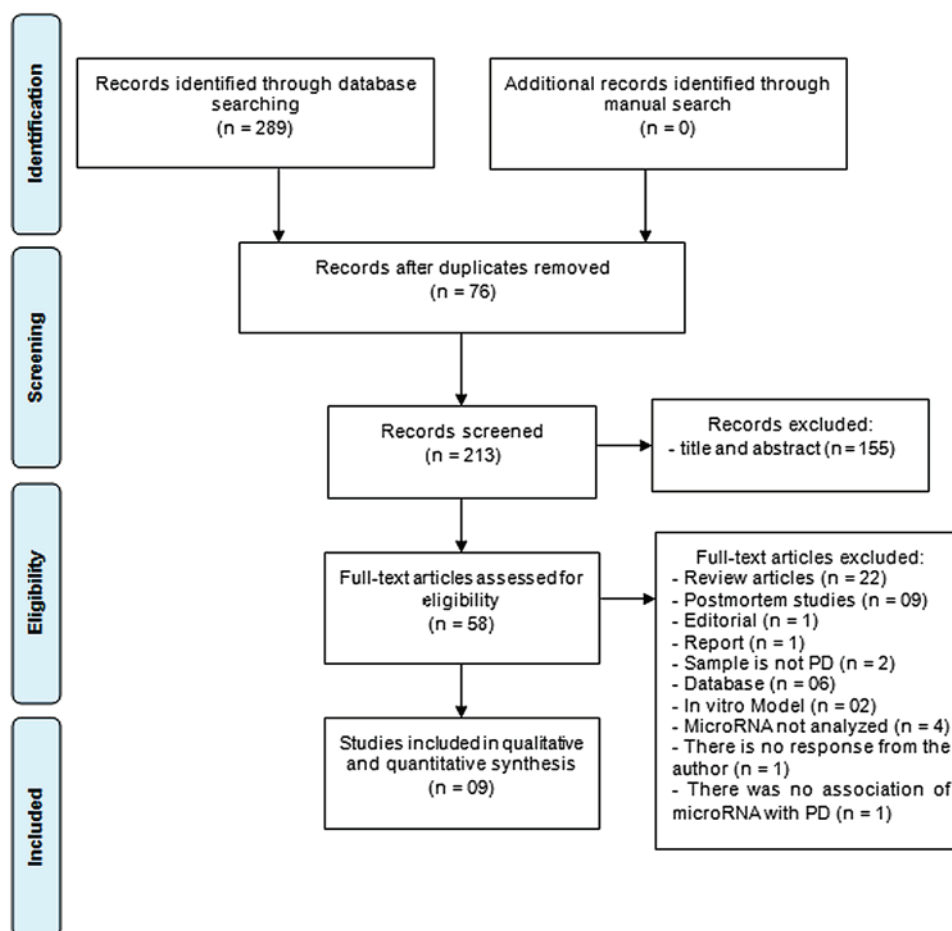


Figure 1. Flow diagram to summarize the search strategy. PD, Parkinson's disease; miRNA, microRNA.

a pathological event directly associated with the formation of Lewy bodies (19,20).

Khoo *et al* (15) identified that miR-1826, miR-626, and miR-505 were upregulated and miR-450b-3p downregulated. miR-1826 was also observed to be upregulated in the plasma of patients with multiple sclerosis. This miRNA targets the neuronal PAS domain protein 3 gene and regulates neurogenesis, in particular in the hippocampus (21). miR-505 inhibits cell proliferation via induction of apoptosis (22) and regulates fibroblast growth factor (FGF)18, a pro-angiogenic factor (23).

However, dopamine depletion in PD is due to the apoptosis of dopaminergic neurons, an effect that may result from the increased apoptosis induction as a result of miR-505. Currently, no studies on miR-626 or miR-450b-3p have investigated their association with any disease or cell function, or have evaluated whether these biomarkers directly or indirectly function in PD pathogenesis (15).

When comparing patients with PD and healthy controls, Cardo *et al* (9) observed that miR-331-5p was significantly more elevated in the patients. The previous study also

Table II. Summary of characteristics of included studies.

First author, year	Location	Study design	Sample (n)	Gender	Mean age (years)	Disease stage (Hoehn and Yahr)	Mean duration (years)	Refs.
Martins, 2011	Portugal	Cross-sectional	PD, 19; control, 13	PD, 10M/9F; control, 5M/8F	PD, 65.10; control, 64.38	I-V	8.7	14
Margis, 2011	Brazil	Cross-sectional	UPD, 8; LOPD, 7; control, 8	50% male	UPD, 66; LOPD, 45; control, 67	I-III	UPD, 3.0; LOPD, 7.2	13
Khoo, 2012	USA	Cross-sectional	Detection: PD, 32; control, 32 Replication: PD, 20M/22F; PD, 42; control, 30 Validation: PD, 30; control, 8	Detection: PD, 16M/16F; control, 15M/17F Replication: PD, 20M/22F; control, 10M/20F Validation: PD, 16M/14F; control, 3M/5F	PD, 66M/67F; control, 65M/62F PD, 68M/72F control, 64M/59F	I-II	-	15
Soreq, 2013	Israel	Experimental	PD, 7; control, 6	Male	PD, 68M/71F; control, 71M/73F	-	-	17
Cardo, 2013	Spain	Cohort	PD, 31; control, 25	50% male	PD, 56; healthy control, 56.5 PD, 63.9; healthy control, 67.6	-	-	9
Botta-Orfila, 2014	Spain	Transversal	Pilot study: IPD, 10; PD LRRK2, 10; control, 10 Validation study 1: IPD, 20; PD LRRK2, 20; control, 20 Validation study 2: IPD, 65; control, 65	50% male	IPD, 61.10; PD LRRK2, 61.4; control, 65 Validation study 1: IPD, 69.75; PD LRRK2, 62.05; control, 71.3 Validation study 2: IPD, 68.09; control, 66.3	I-V	9.6	10
Vallelunga, 2014	Italy	Transversal	PD, 25; MSA, 25; control, 25	PD, 13M/12F; AMS, 12M/13F; control, 13M/12F	PD, 55; MSA-Parkinsonian, 63; MSA-cerebellar, 62; control, 59	III	-	11
Serafin, 2015	Italy	Transversal	PD L-DOPA, 36; control without PD, 36; PD without treatment, 10; control without PD, 10	PD L-DOPA 14M/22F; control without PD, 14M/22F; PD without treatment, 6M/4F; control without PD, 6M/4F	PD L-DOPA, 68 control without PD, 67; PD without treatment, 68; control without PD, 67	I-III	PD L-dopa, 7; PD without treatment, 4	12
Alieva, 2015	Russia	Transversal	PD without treatment, 20; PD with treatment, 18	50% male	55.6	I-II	-	16

PD, Parkinson's disease; M, male; F, female; UPD, untreated PD; LOPD, late onset PD; IPD, idiopathic PD; MSA, multiple system atrophy; LRRK2, leucine-rich repeat kinase 2; L-DOPA, levodopa.

reported that this miRNA may be associated with neurogenesis and neurodegeneration and may be a useful biomarker of diagnosis, disease progression, and treatment response. Botta-Orfila *et al* (10) observed a downregulation of miR-29c, miR-29a and miR-19b when patients were compared with idiopathic PD and controls. Fernández-Santiago *et al* (24) indicated that miR-19b dysregulation occurs in the prodromal phase of synucleinopathies. The accumulation of α -synuclein in the form of intracellular filamentous aggregates is one of the pathological features of the neurodegenerative diseases designated synucleinopathies, which include PD (25). Vallelunga *et al* (11) observed a downregulation of miR-30c and miR-148b in patients with PD compared with patients with MSA. miR-148b is important in neurological development and apoptosis (26).

The levels of miR-1, miR-22* and miR-29a were lower in untreated patients than in healthy individuals, whereas the levels of miR-16-2a*, miR-26a2* and miR-30a were higher in patients treated with levodopa than in untreated patients (13). These miRNAs may be indirectly associated with the functioning of the α -synuclein gene, synuclein- α (SNCA), which is responsible for coding the α -synuclein protein (5). SNCA is one of the primary genes implicated in the development of PD (27). The specific role of this protein remains to be elucidated, however, data has suggested that it is a molecular chaperone that regulates protein-protein and protein-lipid interactions, and that it may be important in the metabolism of synaptic vesicles and the storage and compartmentalization of neurotransmitters, particularly dopamine (28). High SNCA expression is characteristic of PD (29).

miR-1 and miR-30a are involved in the regulation of dopamine transport and are therefore implicated in the pathogenesis of PD (5). Furthermore, miR-30 may bind FGF20, which is also associated with miR-16-2a* (13). FGF20 is preferentially expressed in the substantia nigra and stimulates dopaminergic neuron maturation (30). These results would explain the correlation observed between high SNCA expression and high FGF20 translation in cultures of brain cells and tissues from patients with PD (30).

Margis and Rieder (13) demonstrated miR-29a was the only miRNA which exhibited reduced expression following treatment with levodopa. The authors suggest that miR-29a expression may not be directly associated with the occurrence of motor symptoms given that downregulation was maintained following administration of the therapeutic agent. However, the authors highlighted the importance of miR-29a in PD.

Cell division cycle 42 is a protein associated with septin 4, and a target of miR-29a. Shehadeh *et al* (31) observed that in addition to increased septin 4 levels, α -synuclein levels were also increased in the substantia nigra *post mortem* in patients with PD. Decreased miR-29a expression also occurs in Alzheimer's disease in association with an increase in β -secretase (BACE1) (32,33). The levels of insulin-like growth factor 1 (IGF-1) are associated with the preservation and homeostasis of the nervous system, and IGF-1 is also a target of miR-29a. IGF-1 levels in the serum and brain differ in a number of human neurodegenerative diseases (34). A previous study demonstrated that blood IGF-1 levels were slightly elevated in treated patients with PD compared with controls, although this effect was not statistically significant (35).

Eacker *et al* (36) demonstrated a significant association between lower miR-29a expression and higher BACE1 expression in brain tissue. miR-29a is expressed in neurons and astroglia, suggesting that the specific reductions in its expression are not a secondary consequence of the death of specific neurons.

Serafin *et al* (12) observed that patients treated with levodopa exhibited decreased levels of miR-103a-3p, miR-30b-5p and miR-29a-3p. The results suggest a role of the treatment with levodopa for the expression of miR-103a-3p, indicating a potential association with the occurrence of motor symptoms. Other studies have demonstrated an association between miRNAs 103a-3p and 29a-3p and insulin resistance, a process that may be associated with neurodegeneration in PD (37,38).

Alieva *et al* (16) observed an upregulation of miR-7, miR-9-3p, miR-9-5p, miR-129 and miR-132 in treated patients with PD when compared with untreated patients. The authors hypothesize that miRNAs are sensitive to therapy and that an effect of treatment may be observed in changes in their levels as well as those of their target genes in patients with PD. In addition to administration of therapeutic agents, other factors may influence miRNA expression, such as the presence of comorbidities, disease severity, disease duration, and gender (10,15).

miR-7 is abundantly expressed in the brain and binds preferentially to the 3'UTR of the SNCA gene, which significantly decreases the synthesis of α -synuclein and inhibits α -synuclein-mediated cell death (6). miR-9-3p was identified as a tumor suppressor in hepatocellular carcinoma (39). miR-9-5p has an inhibitory effect on transforming growth factor beta receptor type II and on the expression of NADPH-oxidase 4 (40). The ectopic expression of miR-129 promoted apoptosis, cell proliferation and cell cycle inhibition in colorectal cancer cells (41). miR-132 is enriched in the central nervous system and may be involved in neuron development, maturation, and function (42).

By comparing gene expression in patients with PD and healthy controls prior to and following DBS and 1 h after stimulus cessation, Soreq *et al* (17) observed that miR-1249, miR-20a, miR-18b, miR-378c and miR-4293 were reduced following electrical stimulation, and 1 h after stimulus cessation, miR-423, miR-365, miR-486, miR-1260 and miR-218 were increased and miR-652, miR-15a*, miR-29c, miR-29a, miR-376c and miR-143 were decreased.

miR-365 is a negative regulator of interleukin-6 (IL-6) (43). A cohort study involving 53 patients with PD demonstrated that high levels of IL-6 may be a marker of mortality in patients with PD (44). Scalzo *et al* (45) demonstrated that high levels of IL-6 may be involved in the acceleration of muscle catabolism, leading to sarcopenia, and thus may contribute to weakness and fatigue and be associated with functional impairment in PD.

Previous studies have associated miR-20a, miR-18b, miR-365, miR-486, miR-218, miR-652, miR-15a*, miR-29c, miR-376c, and miR-143 with hepatocellular carcinoma (46,47), breast cancer (48), liver disease (49), lung cancer (50), and melanoma (51), but these miRNAs were not associated with PD.

The miRNAs in the reviewed previous studies were extracted from mononuclear cells, leukocytes, plasma, serum and peripheral blood. Thus, it has been demonstrated that blood

Table III. MicroRNAs involved in PD.

miRNA					
First author, year	Upregulated in PD	Downregulated in PD	Sample	Analysis method	Refs.
Martins, 2011		miR-29c, miR-30c, miR-335, miR-374a, miR-199a-3p/199b-3p, miR-126*, miR-151-3p, miR-199a-5p, miR-151-5p, miR-126, miR-29b, miR-147, miR-28-5p, miR-30b, miR-374b, miR-301a, miR-26a, miR-19b miR-1, miR-22*, miR-29a miR-450b-3p	PBMCs	RT-qPCR to validate the microarray results (TaqMan) Exiqon (miRCURY) LNA array v.10.0	14
Margis, 2011	miR-16-2a*, miR-26a2*, miR-30a		PB	RT-qPCR (SYBR Green)	13
Khoo, 2012	miR-1826, miR-626, miR-505		Plasma	TRI Reagent RT (Agilent miRNA microarray v.3.0), RT-qPCR (TaqMan)	15
Soreq, 2013	miR-199b, miR-1274b, miR-21, miR-150, miR-671, miR-1249, miR-20a, miR-18b*, miR-4317, miR-143, miR-424 (DBS)	miR-320a, miR-320b, miR-320c, miR-769, miR-92b, miR-16, miR-378c, miR-4293 (PD vs. healthy control); miR-1249, miR-20a, miR-18b*, miR-378c, miR-4293, miR-424*, miR-210, miR-93 (DBS); miR-423, miR-365, miR-486, miR-1260, miR-218, miR-652, miR-15a*, miR-29c, miR-29a, miR-376c, miR-143 (after 1 h DBS)	Venous blood leukocytes	Small RNA Expression Kit (Applied Biosystems; Thermo Fisher Scientific, Inc., Foster City, CA, USA)	17
Cardo, 2013	miR-181c, miR-331-5p, miR-196b, miR-454, miR-125a-3p, miR-137		Plasma	TaqMan low density miRNA array on ABI 7990 (Applied Biosystems); Thermo Fisher Scientific, Inc.)	9
Botta-Orfila, 2014		miR-29c, miR-19b, miR-92a, miR-16, miR-100, miR-21, miR-29a, miR-181a, miR-484, miR-134, miR-532-5p, miR-223 (pilot study, PD), miR-19a, miR-19b, miR-16, miR-451, miR-532-5p (pilot study, LRRK2); miR-19b, miR-29c (Validation 1, PD); miR-19a, miR-21, miR-29a, miR-29c (Validation 1, LRRK2); miR-29c, miR-29a, miR-19b (PD vs. control) miR-30c, miR-339-5p, miR-148b (PD vs. healthy control) miR-339-5p (PD vs. MSA) miR-30b-5p, miR-29a-3p, miR-103a-3p	Serum	RT-qPCR (TaqMan), TaqMan low density miRNA array v.2.0.A	10
Valllunga, 2014	miR-223*, miR-324-3p, miR-24 (PS vs. healthy control) miR-223*, miR-324-3p, miR-24 (PD vs. MSA)		Serum	TaqMan low density miRNA v.3.0, validated by RT-qPCR (TaqMan)	11
Serafin, 2015	miR-7, miR-9-3p, miR-9-5p, miR-129, miR-132, miR-133b, miR-153, miR-191, miR-346, miR-433, miR-598, miR-7, miR-9-3p, miR-9-5p, miR-129, miR-132 (PD treated vs. control)		PB	RT-qPCR	12
Alieva, 2015			PB	RT-qPCR	16

PD, Parkinson's disease; PB, peripheral blood; PBMC, PB mononuclear cells; miR, microRNA; PCR, polymerase chain reaction; RT-qPCR, reverse transcription-quantitative PCR; DBS, deep brain stimulation; MSA, multiple system atrophy.

samples are a useful source in the identification of miRNAs associated with PD. Lawrie *et al* (52) were the first to investigate the presence of miRNAs in serum, comparing patients with diffuse lymphoma and healthy individuals. Another study has demonstrated the presence of miRNAs in other biological fluids, including urine, saliva, amniotic fluid, and pleural fluid (53).

An ideal biomarker must be specific, sensitive, minimally invasive, quantifiable, cost-effective and reproducible. Therefore, blood analysis may provide an ideal resource for the development of biomarkers that fit these requirements and enable patient monitoring over time. By contrast, a biopsy for PD is almost impossible, and neuroimaging every three months is financially prohibitive (15). The use of miRNAs as biomarkers has certain advantages. miRNAs are easy to detect, and the methods are extremely specific. Furthermore, as reliable data analysis is essential to the outcome of a given study, it is important to select adequate normalization methods to remove variations and to increase precision in miRNA quantification (54).

The miRNA analysis used in the majority of the reviewed studies was RT-qPCR. The RT-qPCR technique is the gold standard in nucleic acid quantification, due to its sensitivity and specificity (55). Briefly, the procedure involves four major steps: i) Sample collection and preparation; ii) the generation of global miRNA profiles using RT-qPCR; iii) data normalization and analysis; and iv) miRNA biomarker selection and validation (56).

In summary, there is a general lack of studies that confirm the involvement in PD of the majority of miRNAs presented in the reviewed studies. Novel analyses are important to establish the expression profile of miRNAs in PD in order to more accurately determine the ideal treatment strategy and to improve the role of miRNAs as biomarkers in clinical practice.

In conclusion, this systematic review of literature from the past 10 years analyzed the expression of 91 different miRNAs in the context of PD, with the expression of 39 of these miRNAs differing significantly between individuals with PD and healthy controls and/or between treated and untreated patients with PD. The downregulated miRNAs were as follows: miR-30b, miR-30c, miR-26a, miR-450b-3p, miR-148b, miR-1, miR-22*, miR-29a, miR-103a-3p, miR-30b-5p, miR-29a-3p, miR-1249, miR-20a, miR-18b, miR-378c, miR-4293, miR-652, miR-15a*, miR-29c, miR-376c, miR-143, and miR-19b. The upregulated miRNAs were as follows: miR-1826, miR-626, miR-505, miR-16-2a*, miR-26a2*, miR-30a, miR-7, miR-9-3-p, miR-9-5p, miR-129, miR-132, miR-423, miR-365, miR-486, miR-1260, miR-218, and miR-331-5p. The miRNAs were extracted from mononuclear cells, leukocytes, plasma, serum and peripheral blood, and the majority of the studies used RT-qPCR, considered to be the gold standard, for miRNA analysis.

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