frontiers

Supplementary Material

Circulating miRNAs as diagnostic biomarkers for Parkinson's disease

Anna-Elisa Roser#, Lucas Caldi Gomes#, Jonas Schünemann, Fabian Maass, Paul Lingor*

*** Correspondence:** Paul Lingor: plingor@gwdg.de

Supplementary Table 1: Studies using circulating miRNAs as biomarkers for PD or other Parkinsonian syndromes.

Author, year	source	method	study type (n° of centres)	deregulated miRNAs in PD	deregulated miRNAs in other Parkinsonian syndromes	Discovery cohort	validation cohort	reported relevant pathways
Margis et al., 2011	whole blood	microarrays/ qRT-PCR	Mono-centric	↑ miR-16-2-3p, miR-26a-2-3p and miR-30a-5p (in PD treated vs PD untreated); ↓ miR-1-3p, miR-22-5p, miR-29a-3p (PD vs Ctr)	n/a	8 non-treated PD, 4 treated PD, 7 early onset PD, 8 CTRL	-	- tubulin/microtubule system and αSyn aggregation - dopamine transport regulation - protein kinase C-mediated internalization of the dopamine transporter (DAT) - glutamatergic regulation - BDNF signalling
Khoo et al., 2012	plasma	microarrays/ qRT-PCR	Multi-centric (2)	↑ miR-1826, miR-222-3p, miR-626 and miR-505-3p	↑ miR-626, miR-505-3p	32 PD, 32 CTRL	30 PD, 8 CTRL, 5 PSP, 4 MSA (val. cohort); 42 treated PD, 30 CTRL (replication cohort)	- cell proliferation and survival - multiple sclerosis (MS)
Cardo et al., 2013	plasma	qRT-PCR	Mono-centric	↑ miR-331-5p	n/a	31 PD, 25 CTRL	-	- neurogenesis and neurodegeneration - axon guidance - MAPK signalling
Li et al., 2017	plasma	qRT-PCR	Mono-centric	↑ miR-137-3p; ↓ miR-124-3p	n/a	60 PD, 60 CTRL	-	- Parkin-induced mitochondrial autophagy - calpain/cdk5 pathway proteins in dopaminergic neurons - loss of dopaminergic neurons in MPTP-treatment - apoptosis and impaired autophagy of SNpc dopaminergic neurons - proliferation and differentiation of adult neural stem cells - depression

Schwienbacher et al., 2017	plasma	qRT-PCR	Mono-centric	↑ miR-30a-5p and miR-30b-5p *(trend)*	n/a	50 treated PD, 10 non-treated PD, 49 CTRL	-	- EGFR/PI3K/Akt pathway - PI3K/Akt/mTOR pathway - oxidative stress / increased susceptibility to neurotoxicity - mitochondrial dynamics
Botta-Orfila et al., 2014	serum	qRT-PCR	Mono-centric	↓ miR-29a-3p, miR-29c-3p, miR-19a-3p and miR-19b-3p	n/a	10 PD, 10 LRRK2 PD, 10 CTRL	20 PD, 20 LRRK2 PD, 20 CTRL (val. cohort 1); 65 PD, 65 CTRL (val. cohort 2)	- extracellular matrix reception (ECM) pathway / leucocyte recruitment - adipocytokines - focal adhesion - axon guidance - mTOR sig. pathway - MAPK sig. pathway
Vallelunga et al., 2014	serum	microarrays	Multi-centric (2)	↑ miR-24-3p, miR-324-3p and miR-223-5p; ↓ miR-30c-5p and miR-148b-3p	↑ miR-24-3p, miR-148b-3p, miR-223-3p, miR-324-3p; ↓ miR-339-5p	6 PD, 6 MSA-P, 3 MSA-C, 5 CTRL	25 PD, 25 MSA, 25 CTRL (val. cohort)	- cell cycle regulation - modulation of apoptosis - spinal cord injury - response to neuronal injury - demyelination in multiple sclerosis
Fernández-Santiago et al., 2015	serum	qRT-PCR	Mono-centric	n/a	↓ miR-19b-3p, miR-29a-3p and miR-29c-3p	RBD1 (disease-free), RBD2 (PD or DLB), 28 CTRL	-	- regulation of PD-associated genes
Ding et al., 2016	serum	Solexa-sequencing / qRT-PCR	Multi-centric (2)	↑ miR-195-5p; ↓ miR-185-5p, miR-15b-5p, miR-221-3p and miR-181a-5p	n/a	106 PD, 91 CTRL	-	- astrocyte dysfunction - dendritic and spine development deficits - neuron apoptosis, development, regeneration and growth - Alzheimer's disease / MS
Dong et al., 2016	serum	Solexa-sequencing / qRT-PCR	Mono-centric	↓ miR-141-3p, miR-214-3p, miR-146b-5p and miR-193a-3p	n/a	30 PD, 30 CTRL	92 PD, 74 CTRL	- regulation of PD-associated genes - selective dopaminergic neural cell death and absence of Lewy bodies by PARK2 regulation - neuron guidance, growth, polarity/axonal growth, neural

								differentiation, proliferation and apoptosis by PDDC1 and DGKQ regulation - neuroinflammation - fibrosis
Ma et al., 2016	serum	qRT-PCR	Mono-centric	↓ miR-29c-3p, miR-146a-5p, miR-214-3p and miR-221-3p	n/a	138 PD, 112 CTRL	-	- extracellular matrix (ECM)-receptor interaction - focal adhesion MAPK, Wnt and mTOR signalling - neuronal projection - regulation of αSyn - neuroinflammation initiation - iron accumulation - apoptosis / fibrosis
Kume et al., 2017	serum	microarrays	Mono-centric	n/a	↑ 50 miRNAs; ↓ 17 miRNAs *no significance for selected species by qRT-PCR validation*	10 MSA, 6 CTRL	-	- αSyn aggregation / neuronal apoptosis by HSP70 regulation - regulation of immune response - autophagy - inflammation - cell proliferation and apoptosis by IGF-1 regulation - neurodegeneration - Alzheimer's disease
Martins et al., 2011	PBMCs	microarrays	Mono-centric	↓ miR-335-5p, miR-374a-5p, miR-199a-3p, miR-199b-3p, miR-126-5p, miR-151a-3p, miR-199a-5p, miR-151a-5p, miR-126-3p, miR-29b-3p, miR-147a, miR-28-5p, miR-30b-5p, miR-374b-5p, miR-19b-3p, miR-30c-5p, miR-29c-3p, miR-301a-3p and miR-26a-5p	n/a	19 PD, 13 CTRL	-	- protein ubiquination pathway - DNA methylation and transcriptional repression signalling - semaphorin signalling in neurons - retinoic acid receptor activation - glycosphingolipid biosynthesis - synaptic long-term potentiation
Pasinetti, 2012	PBMCs	NGS	Mono-centric	↑ miR-29c-3p, miR-424-5p and miR-30e-5p	n/a	13 PD, 10 CTRL	-	- PD pathophysiology / cellular dopamine metabolism and release

Soreq et al., 2013	PBMCs	NGS	Mono-centric	↑ miR-21-5p, miR-671-5p, miR-150-5p, miR-1274b and miR-199b-5p; ↓ miR-320a-3p, miR-92b-3p, miR-769-5p, miR-320b-1/miR-320b-2, miR-320c-1/miR-320c-2, miR-16-1/miR-16-2 (precursors), ↑miR-1249-3p, miR-20a-5p, miR-18b-3p, miR-378c, miR-4293 *(the last 5 on the list had inverted expression after DBS)*	n/a	7 PD, 6 CTRL	-	- mitochondrion organization and metabolism - ubiquitin homeostasis / ligase complex - leukocyte/disease related pathways - regulation of translation - MAPK phosphatase export from nucleus - neuroinflammation - regulation of NK cell cytotoxicity - regulation of amyloid precursor protein - neurodegenerative disorders including prion-induced neurodegeneration, PD, AD and Huntington's disease
Serafin et al., 2015	PBMCs	qRT-PCR	Mono-centric	↑ miR-103a-3p, miR-30b-5p, and miR-29a-3p	n/a	36 treated PD, 10 non-treated PD, 46 CTRL	-	- neurodegenerative disorders including PD - AKT/PTEN pathway regulation - dopaminergic neuron development by regulation of BCL2 - cell death and oxidative stress by DJ-1 regulation - neurotoxicity related to GPR37 regulation - neuronal death related to CDC42 regulation
Burgos et al., 2014	CSF/ serum *post-mortem*	NGS	Mono-centric	↑ miR-19a-3p, miR-19b-3p and let-7g-3p; ↓ miR-132-5p, miR-485-5p, miR-127-3p, miR-128, miR-409-3p, miR-433-3p, miR-370, miR-431-3p, miR-873-3p, miR-136-3p, miR-212-3p,	n/a	67 PD patients, 78 CTRL	-	- regulation of αSyn levels / accumulation - regulation of amyloid precursor protein - memory consolidation - synaptic plasticity by SIRT1 regulation - cognitive decline

				miR-10a-5p, miR-1224-5p, miR-4448 *in CSF*; ↑ miR-338-3p, miR-30e-3p and miR-30a-3p; ↓ miR-16-2-3p, miR-1294-5p, *in serum*				- regulation of mitochondrial function - neuronal cell death, oxidative stress and αSyn aggregation by DJ-1 regulation - neuroinflammation - dopaminergic cell development / differentiation - neurodegenerative diseases including PD and AD
Gui et al., 2015	CSF	qRT-PCR	Multi-centric (2)	↑ miR-153-3p, miR-409-3p, miR-10a-5p and let-7g-3p; ↓ miR-1-3p, miR-19b-3p,	n/a	47 PD, 27 CTRL	78 PD, 35 CTRL	- neurotrophin signaling pathway - mTOR signaling pathway - ubiquitin mediated proteolysis - long-term potentiation - Axon guidance - cholinergic, glutamatergic and dopaminergic synapsis
Mo et al., 2016	CSF	qRT-PCR	Mono-centric	↑ miR-200a-3p, miR-542-3p and miR-144-5p	n/a	44 PD, 42 CTRL	-	- regulation of neuronal differentiation and proliferation - ischemic stroke and intracerebral hemorrhage - Huntington's and Alzheimer's disease
Müller et al., 2016	CSF	qRT-PCR	Mult-centric (3)	n/a	↓ miR-125b-5p	37 DLB, 40 CTRL	-	n/a
Marques et al., 2017	CSF	qRT-PCR	Mono-centric	↑ miR-205-5p; ↓ miR-24-3p	↓ miR-24-3p, miR-19a-3p, miR-19b-3p, miR-34c-5p	28 PD, 17 MSA, 28 CTRL	-	- involvement with idiopathic rapid eye movement sleep behavior disorder - regulation of Parkinson's disease related genes including LRRK2, DJ1, parkin and αSyn
Jurjević et al., 2017	CSF	qRT-PCR	Multi-centric (2)	n/a	↓ miR-4274 in the PS group	81 iNPH (28 with a possible	-	- involvement in dopaminergic signalling pathway: regulation of active transport of dopamine into

						Parkinsoni-an syndrome – PS), 6 CTRL		synaptic vesicles and other types of secretory vesicles for dopamine exocytotic release (by SLC18A2 regulation)
dos Santos et al., 2018	CSF	NGS	Mono-centric	↑ miR-151a-3p and let-7f-5p; ↓ miR-27a-3p, miR-125a-5p and miR-423-5p	n/a	40 PD, 40 CTRL	-	- prion disease - TGF-beta signalling - cell cycle regulation -ubiquitin-mediated proteolysis - neurotrophin signalling - mTOR signalling - AMPK signalling - FoxO signalling - fatty acid biosynthesis - Huntington's disease