

eTable 1. List of diagnoses of OND subjects.

Diagnosis	Number of subjects (n=27)
Alzheimer's disease	3
Parkinson's disease	3
Migraines	4
Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy	2
Dementia	2
Vertiginous syndrome	1
Functional neurological disorder	1
Pshychotic disorder	1
Non-MS lesions	5
Paraparesis	1
Spinal myelopathy	1
Alteration in sensitivity	1
Idiopathic intracranial hypertension	1
Tremor and altered walking	1

eTable 2. Differential miRNA expression among groups in CSF samples in the screening phase.

miRNA	Comparison	OND Median (Q1-Q3)	RRMS Median (Q1-Q3)	PPMS Median (Q1-Q3)	<i>p</i> value
miR-125a-5p		0.981 (0.752-1.307)	1.487 (1.090-1.712)	1.549 (0.924-1.666)	0.070
	OND vs RRMS				0.139
	OND vs PPMS				0.110
	RRMS vs PPMS				1.000
miR-125b-5p		0.746 (0.408-1.000)	1.196 (1.054- 1.883)	0.947 (0.595-1.818)	0.052
	OND vs RRMS				0.045
	OND vs PPMS				0.540
	RRMS vs PPMS				0.788
miR-143-3p		2.400 (1.340-5.419)	3.075 (2.536-4.669)	1.043 (0.923-2.934)	0.035
	OND vs RRMS				1.000
	OND vs PPMS				0.309
	RRMS vs PPMS				0.043
miR-29a-3p		0.693 (0.521-0.880)	0.575 (0.382-0.822)	1.219 (0.781-1.567)	0.077
	OND vs RRMS				0.936
	OND vs PPMS				0.829
	RRMS vs PPMS				0.071
miR-451a		2.798 (1.355-5.473)	2.954 (2.345-6.053)	6.237 (3.586-20.244)	0.078
	OND vs RRMS				1.000
	OND vs PPMS				0.090
	RRMS vs PPMS				0.385
miR-9-5p		1.894 (1.760-2.331)	1.062 (1.020-1.513)	0.658 (0.622-1.252)	0.009
	OND vs RRMS				0.216
	OND vs PPMS				0.007
	RRMS vs PPMS				0.737

OND: other neurological diseases individuals; RRMS: relapsing-remitting multiple sclerosis individuals; PPMS: primary progressive multiple sclerosis individuals. Q1-Q3: First quartile-Third quartile. Statistical differences were determined by Kruskal-Wallis test.

eTable 3. Differential miRNA expression among groups in CSF and serum samples.

miRNA	Comparison	OND Median (Q1-Q3)	RRMS Median (Q1-Q3)	Non-inflammatory PPMS Median (Q1-Q3)	Inflammatory PPMS Median (Q1-Q3)	<i>p</i> value
let-7b-5p (CSF)		0.126 (0.061-0.605)	0.083 (0.036-0.296)	0.030 (0.014-0.074)	0.073 (0.055-0.139)	0.018
	OND vs RRMS					1.000
	OND vs NonI-PPMS					0.010
	OND vs I-PPMS					1.000
	RRMS vs NonI-PPMS					0.128
	RRMS vs I-PPMS					1.000
	NonI-PPMS vs I-PPMS					0.437
miR-186-5p (Serum)		0.233 (0.195-0.362)	0.253 (0.186-0.273)	0.259 (0.183-0.343)	0.180 (0.142-0.235)	0.015
	OND vs RRMS					1.000
	OND vs NonI-PPMS					1.000
	OND vs I-PPMS					0.053
	RRMS vs NonI-PPMS					1.000
	RRMS vs I-PPMS					0.048
	NonI-PPMS vs I-PPMS					0.047
miR-20a-5p (Serum)		0.261 (0.174-0.361)	0.341 (0.260-0.455)	0.449 (0.308-0.554)	0.457 (0.344-0.638)	0.007
	OND vs RRMS					0.879
	OND vs NonI-PPMS					0.024
	OND vs I-PPMS					0.018
	RRMS vs NonI-PPMS					0.588
	RRMS vs I-PPMS					0.494
	NonI-PPMS vs I-PPMS					1.000

OND: other neurological diseases individuals; RRMS: relapsing-remitting multiple sclerosis individuals; NonI-PPMS: non-inflammatory primary progressive multiple sclerosis individuals. Q1-Q3: First quartile-Third quartile. Statistical differences were determined by Kruskal-Wallis.

eTable 4. Differential miRNA expression among groups in serum samples in the screening phase.

miRNA	Comparison	OND Median (Q1-Q3)		RRMS Median (Q1-Q3)		PPMS Median (Q1-Q3)		<i>p</i> value
miR-142-5p		4.992	(2.788-7.162)	8.192	(5.364-13.513)	8.532	(6.582-10.454)	0.051
	OND vs RRMS							0.123
	OND vs PPMS							0.073
	RRMS vs PPMS							1.000
miR-148a-3p		1.723	(1.363-2.431)	1.716	(1.281-2.131)	2.592	(1.763-3.166)	0.043
	OND vs RRMS							1.000
	OND vs PPMS							0.155
	RRMS vs PPMS							0.085
miR-186-5p		1.136	(1.020-1.361)	1.217	(0.844-1.538)	0.636	(0.472-0.937)	0.044
	OND vs RRMS							1.000
	OND vs PPMS							0.079
	RRMS vs PPMS							0.179
miR-20a-5p		5.264	(4.059-9.843)	6.102	(4.796-7.026)	9.584	(6.379-12.256)	0.075
	OND vs RRMS							1.000
	OND vs PPMS							0.218
	RRMS vs PPMS							0.142
miR-26a-5p		1.409	(0.875-4.312)	6.310	(3.299-10.798)	5.941	(2.092-9.896)	0.059
	OND vs RRMS							0.056
	OND vs PPMS							0.316
	RRMS vs PPMS							0.988
miR-320b		7.049	(4.384-9.896)	8.164	(5.918-8.915)	2.660	(2.088-3.367)	0.005
	OND vs RRMS							1.000
	OND vs PPMS							0.038
	RRMS vs PPMS							0.013
miR-326		0.427	(0.230-0.907)	0.697	(0.573-0.880)	0.259	(0.125-0.304)	0.007
	OND vs RRMS							1.000
	OND vs PPMS							0.113
	RRMS vs PPMS							0.008
miR-421		0.117	(0.091-0.136)	0.103	(0.089-0.151)	0.185	(0.144-0.227)	0.005
	OND vs RRMS							1.000
	OND vs PPMS							0.026
	RRMS vs PPMS							0.017
miR-502-3p		0.298	(0.248-0.455)	0.413	(0.341-0.455)	0.570	(0.436-0.637)	0.024
	OND vs RRMS							1.000
	OND vs PPMS							0.050
	RRMS vs PPMS							0.095
miR-652-3p		5.899	(5.703-6.333)	6.984	(6.523-7.798)	3.686	(5.519-5.680)	0.033
	OND vs RRMS							1.000
	OND vs PPMS							0.365
	RRMS vs PPMS							0.034

OND: other neurological diseases individuals; RRMS: relapsing-remitting multiple sclerosis individuals; PPMS: primary progressive multiple sclerosis individuals. Q1-Q3: First quartile-Third quartile. Statistical differences were determined by Kruskal-Wallis.

eFigure 1. Schematic workflow for characterizing miRNA signatures in PPMS.



Demographic, clinical and radiological data of the different sub-cohorts used in the study. CSF: cerebrospinal fluid; OND: other neurological diseases individuals; RRMS: relapsing-remitting multiple sclerosis individuals; PPMS: primary progressive multiple sclerosis individuals; M: male; F: female; Md: Median; OCGB: oligoclonal IgG bands; A: absence; P: presence; NI-PPMS: non-inflammatory PPMS; I-PPMS: inflammatory PPMS.