Supplementary Material

A Candidate microRNA Profile for Early Diagnosis of Sporadic Alzheimer's Disease

Supplementary Table 1. Descriptive information of the 14 included studies for the selection of miRs. The Mini-Mental State Examination (MMSE) scores (mean (SD)), age (mean (SD)), sex (% women), and size of the study population, are provided.

	Study	Study size (cases/controls)	MMSE scores	Age (years)	Sex (%Women)
1	Kayano et al., 2016 [1]	30 MCI / 23 Controls	MCI: 24.3/ Controls: 28.6	MCI: 72.8 / Controls: 70.6	MCI: 52.2% / Controls: 60%
2	Cheng et al., 2014 [2]	Discovery: 3 MCI & 23 AD / 23 Controls and Validation: 8 MCI & 16 AD / 36 Controls	Discovery: MCI:23 (5.7) & AD: 15 (8.7) / Controls: 29 (1.2) Validation: MCI: 29 (2.0) & AD: 21 (8.1) / Controls: 30 (1.1)	Discovery: MCI:76.91 (4.4) & AD: 78.89 (7.33) / Controls: 73.07 (7.57) Validation: MCI: 78.91 (6.3) & AD: 78.29 (7.55) / Controls: 78.55 (6.52)	Discovery: MCI:33% & AD:57% / Controls: 44% Validation: MCI: 50% & AD: 63% / Controls: 58%
3	Leidinger et al., 2013 [3]	18 MCI / 23 Controls	MCI: 25.3 (1.4) / Controls: 29.3 (1.2)	MCI: 73.9 (6.2) / Controls: 67.1 (7.5)	MCI: 50% / Controls: 50%
4	Nagaraj et al., 2017 [4]	8 MCI / 6 Controls	MCI: 25.62 (3) / Controls: N/A	MCI: 64.3 (6.0) / Controls: 66 (5.0)	MCI: 43% / Controls: 67%
5	Kiko et al., 2014 [5]	10 MCI / 10 Controls	MCI: 21.1 (3.5) / Controls: 29.5 (0.7)	MCI: 80.7(5.8) / Controls: 73.0 (5.2)	MCI: 70% / Controls: 60%
6	Xie et al., 2017 [6]	330 aMCI & 128 AD (conversion group)	MCI: 24.3 (2.1) / Controls: N/A	MCI: 69.9 (4.0) & AD: 76.0 (4.8)	MCI: 53.6% / AD: 59.4%
7	Sheineerman et al., 2012 [7]	Pilot: 10 MCI /10 Controls & Main: 20 MCI / 20 Controls	Pilot: MCI: 25.8 (3.5) / Controls: 29.2 (1.3)	Pilot: MCI: 81.7 (75-87) / Controls: 77.4 (71-85) & Main: MCI: 79.9 (72-89) / Controls: 80.2 (76-86)	Pilot: MCI: 50% / Controls: 50% & Main: MCI: 25% / Controls: 40%
8	Geekiyanage et al., 2012 [8]	7 MCI & 7 AD / 7 Controls	MCI: 25.3(1.9) & AD: 15 (3.6) / Controls: 25.6 (0.5)	MCI: 85-94 & AD: 80-92 / Controls: 82-91	MCI: 43% & AD: 71% / Controls:43%
9	Kumar et al., 2013 [9]	9 MCI / 20 Controls	MCI: 24.7 (1.7) / Controls: 29.4 (1.1)	MCI: 63-84 / Controls: 60-77	MCI: 67% / Controls:40%
10	Dong et al., 2015 [10]	30 MCI & 127 AD/123 Controls	MCI: 25.6 (2.3) & AD: 11.5 (7.7) / Controls: 27.2(1.3)	MCI: 81.1 (6.8) & AD: 79.3 (8.9) / Controls: 79.5 (6.8)	MCI: 30% & AD: 43% / Controls: 47%
11	Kumar et al., 2017 [11]	Primary: 16 MCI & 10 AD / 14 controls & Validation: 1 AD & 4 MCI / 4 Controls	Primary: MCI: 25.3 (2.7) & AD: 25.3 (2.7 / Controls: 27.1 (3.1)	Primary: MCI: 56-88 & AD: 56-88 / Controls: 58-86	MCI: 62% & AD: 50% / Controls: 57%
12	Wang et al., 2015 [12]	116 MCI & 97 AD / 81 Controls	MCI: 23.9 (3.8) & AD: 13.8 (5.4)/ Controls: 26.5 (3.5)	MCI: 70.1 (4.6) & AD: 68.6 (5.3) / Controls: 71.7(5.4)	MCI: 65% & AD: 60% / Controls: 56%
13	Siedlecki-Wullich et al., 2019 [13]	26 MCI & 56 AD / 14 Controls	MCI: 26.9 (2.2) & AD: 16.1 (7.2)/ Controls: 29.2 (1.1)	MCI: 72.0 (8.5) & AD: 77.7 (6.7) / Controls: 68.3 (9.0)	MCI: 62% & AD: 73% / Controls: 50%
14	Al-Rawaf et al., 2021 [14]	70 MCI / 80 Controls	MCI: 21.3 (2.5) / Controls: 28.4 (3.3)	MCI: 64.9 (4.1) / Controls: 65.3 (3.5)	MCI: 43% / Controls: 38%

Supplementary Table 2. List of potential miRs implicated in early sAD based on the available data retrieved from the 14 included studies. These candidate circulating miRs have earlier been confirmed by literature and/or functional analysis for their link to Tau-driven AOP toward memory loss [15]. The human mature miRs, with their link to the starting point (SP) and/or key events (KEs) of the Tau-driven AOP, and the regulation of their expression in biofluids, as retrieved from literature, are provided.

miRs	Link to Tau-AOP	Regulation	Biofluids	References
hsa-let-7d-5p	KE7	Down	Plasma	[9]
hsa-let-7g-5p	KE8	Down	Plasma	[9]
hsa-miR-9-5p	KE2, KE3, KE4, KE7, KE8	Down	Serum & CSF	[5, 8]
hsa-miR-15a-5p	KE1, KE3, KE8	Down	Serum	[2]
hsa-miR-15b-5p	KE1, KE3, KE4	Up / Down	Serum / Plasma	[2, 9]
hsa-miR-26a-5p	KE3, KE7	Up	Blood	[3]
hsa-miR-26b-5p	KE3, KE7	Up	Blood	[3]
hsa-miR-29a-3p	SP_Glucose, KE7, KE8	Down	Serum & Plasma	[5, 8]
hsa-miR-29b-1-5p	SP_Glucose, KE1, KE7, KE8	Down	Serum & Plasma	[5, 8]
hsa-miR-30b-5p	KE7	Down	Plasma	[4]
hsa-miR-34a-5p	KE1, KE3, KE4, KE7, KE8	Down	Plasma & CSF	[5]
hsa-miR-93-5p	KE3, KE4	Up	Serum	[2]
hsa-miR-101-3p	KE3, KE4, KE8	Up	Serum	[1, 2]
hsa-miR-103a-3p	KE1, KE3, KE4	Down	Blood & Plasma	[3, 4]
hsa-miR-106a-3p	SP_Cholesterol	Up	Serum	[2]
hsa-miR-107	KE4, KE8	Down	Blood, Plasma & CSF	[3, 12]
hsa-miR-124-3p	KE1, K2, KE3, KE4, KE7, KE8	Up	Serum	[14]
hsa-miR-125b-5p	KE2, KE3, KE7, KE8	Up / Down	CSF / Serum	[5, 14]
hsa-miR-128-3p	SP_Glucose, SP_Cholesterol, KE2, KE3, KE5	Up	Plasma	[7]
hsa-miR-132-3p	KE2, KE3, KE4, KE7, KE8	Up	Serum & Plasma	[6, 7]
hsa-miR-134-5p	KE7	Up	Plasma	[7]
hsa-miR-143-3p	KE1, KE2, KE8	Up / Down	Serum	[2, 10]
hsa-miR-143-5p	KE1, KE2, KE8	Down	Serum	[10]
hsa-miR-146a-5p	KE2, KE3, KE4, KE7, KE8	Up / Down	Serum / Plasma & CSF	[5, 10]
hsa-miR-148a-3p	SP_Glucose, KE3, KE7, KE8	Down	Serum	[10]
hsa-miR-151a-3p	KE7	Up	Blood	[3, 4]

hsa-miR-151a-5p	KE7	Down	Plasma	[3, 4]
hsa-miR-181c-5p	SP_Cholesterol, KE7, KE8	Up / Down	Plasma / Serum	[13, 16]
hsa-miR-191-5p	KE7	Up/Down	Plasma / Serum & Plasma	[1, 9, 10]
hsa-miR-200a-3p	KE2, KE3	Up	Plasma	[4]
hsa-miR-210-3p	KE1, KE2, KE7	Up	Plasma	[13]
hsa-miR-301a-3p	KE7	Down	Plasma	[9]
hsa-miR-335-5p	SP_Cholesterol	Up	Serum	[2]
hsa-miR-483-5p	KE2	Up	Plasma & Serum	[4, 14]
hsa-miR-486-5p	KE2	Up	Plasma	[4]
hsa-miR-545-3p	SP_Cholesterol	Down	Plasma	[9]

SP-Glucose, starting point-Glucose dysmetabolism; SP-Cholesterol, starting point-cholesterol dysmetabolism; KE1, mitochondrial dysfunction; KE2, oxidative stress; KE3, hyperphosphorylation of tau; KE4, dysfunctional autophagy; KE7, synaptic dysfunction; KE8, neuroinflammation; CSF, cerebrospinal fluid.

Supplementary Table 3. The ID assays, mature sequences, miRBase accession number, and genomic coordinates of the measured mature miRs.

Unique miRs	ID miR assay	Mature miR Sequence	miRBase Accession Number	Chromosome Location
hsa-let-7g-5p	478580_mir	UGAGGUAGUAGUUUGUACAGUU	MIMAT0000414	Chr.3: 52268278 - 52268361 [-]
hsa-miR-101-3p	477863_mir	UACAGUACUGUGAUAACUGAA	MIMAT0000099	Chr.1: 65058434 - 65058508 [-]
hsa-miR-103a-3p	478253_mir	AGCAGCAUUGUACAGGGCUAUGA	MIMAT0000101	Chr.5: 168560896 - 168560973 [-]
hsa-miR-107	478254_mir	AGCAGCAUUGUACAGGGCUAUCA	MIMAT0000104	Chr.10: 89592747 - 89592827 [-]
hsa-miR-124-3p	480901_mir	UAAGGCACGCGGUGAAUGCCAA	MIMAT0000422	Chr.8: 9903388 - 9903472 [-]
hsa-miR-125b-5p	477885_mir	UCCCUGAGACCCUAACUUGUGA	MIMAT0000423	Chr.11: 122099757 - 122099844 [-]
hsa-miR-128-3p	477892_mir	UCACAGUGAACCGGUCUCUUU	MIMAT0000424	Chr.2: 135665397 - 135665478 [+]
hsa-miR-132-3p	477900_mir	UAACAGUCUACAGCCAUGGUCG	MIMAT0000426	Chr.17: 2049908 - 2050008 [-]
hsa-miR-134-5p	477901_mir	UGUGACUGGUUGACCAGAGGGG	MIMAT0000447	Chr.14: 101054687 - 101054759 [+]
hsa-miR-143-3p	477912_mir	UGAGAUGAAGCACUGUAGCUC	MIMAT0000435	Chr.5: 149428918 - 149429023 [+]
hsa-miR-143-5p	478713_mir	GGUGCAGUGCUGCAUCUCUGGU	MIMAT0004599	Chr.5: 149428918 - 149429023 [+]
hsa-miR-146a-5p	478399_mir	UGAGAACUGAAUUCCAUGGGUU	MIMAT0000449	Chr.5: 160485352 - 160485450 [+]
hsa-miR-151a-3p	477919_mir	CUAGACUGAAGCUCCUUGAGG	MIMAT0000757	Chr.8: 140732564 - 140732653 [-]
hsa-miR-15a-5p	477858_mir	UAGCAGCACAUAAUGGUUUGUG	MIMAT0000068	Chr.13: 50049119 - 50049201 [-]
hsa-miR-15b-5p	478313_mir	UAGCAGCACAUCAUGGUUUACA	MIMAT0000417	Chr.3: 160404588 - 160404685 [+]
hsa-miR-181c-5p	477934_mir	AACAUUCAACCUGUCGGUGAGU	MIMAT0000258	Chr.19: 13874699 - 13874808 [+]
hsa-miR-200a-3p	478490_mir	UAACACUGUCUGGUAACGAUGU	MIMAT0000682	Chr.1: 1167863 - 1167952 [+]
hsa-miR-210-3p	477970_mir	CUGUGCGUGUGACAGCGGCUGA	MIMAT0000267	Chr.11: 568089 - 568198 [-]
hsa-miR-26a-5p	477995_mir	UUCAAGUAAUCCAGGAUAGGCU	MIMAT0000082	Chr.3: 37969404 - 37969480 [+]
hsa-miR-26b-5p	478418_mir	UUCAAGUAAUUCAGGAUAGGU	MIMAT0000083	Chr.2: 218402646 - 218402722 [+]
hsa-miR-29a-3p	478587_mir	UAGCACCAUCUGAAAUCGGUUA	MIMAT0000086	Chr.7: 130876747 - 130876810 [-]
hsa-miR-335-5p	478324_mir	UCAAGAGCAAUAACGAAAAAUGU	MIMAT0000765	Chr.7: 130496111 - 130496204 [+]
hsa-miR-34a-5p	478048_mir	UGGCAGUGUCUUAGCUGGUUGU	MIMAT0000255	Chr.1: 9151668 - 9151777 [-]
hsa-miR-483-5p	478432_mir	AAGACGGGAGGAAAGAAGGGAG	MIMAT0004761	Chr.11: 2134134 - 2134209 [-]
hsa-miR-486-5p	478128_mir	UCCUGUACUGAGCUGCCCCGAG	MIMAT0002177	Chr.8: 41660441 - 41660508 [-]
hsa-miR-93-5p	478210_mir	CAAAGUGCUGUUCGUGCAGGUAG	MIMAT0000093	Chr.7: 100093768 - 100093847 [-]
hsa-miR-9-5p	478214_mir	UCUUUGGUUAUCUAGCUGUAUGA	MIMAT0000441	Chr.1: 156420341 - 156420429 [-]
hsa-miR-301a-3p	477815_mir	CAGUGCAAUAGUAUUGUCAAAGC	MIMAT0000688	Chr.17: 59151136 - 59151221 [-]
hsa-let-7d-5p	478439_mir	AGAGGUAGUAGGUUGCAUAGUU	MIMAT0000065	Chr.9: 94178834 - 94178920 [+]
hsa-miR-545-3p	479002_mir	UCAGCAAACAUUUAUUGUGUGC	MIMAT0003165	Chr.X: 74287104 - 74287209 [-]
hsa-miR-106a-3p	478623_mir	CUGCAAUGUAAGCACUUCUUAC	MIMAT0004517	Chr.X: 134170198 - 134170278 [-]
hsa-miR-148a-3p	477814_mir	UCAGUGCACUACAGAACUUUGU	MIMAT0000243	Chr.7: 25949919 - 25949986 [-]
hsa-miR-151a-5p	478505_mir	UCGAGGAGCUCACAGUCUAGU	MIMAT0004697	Chr.8: 140732564 - 140732653 [-]
hsa-miR-191-5p	477952_mir	CAACGGAAUCCCAAAAGCAGCUG	MIMAT0000440	Chr.3: 49020618 - 49020709 [-]

hsa-miR-29b-1-5p	478794_mir	GCUGGUUUCAUAUGGUGGUUUAGA	MIMAT0004514	Chr.7: 130877459 - 130877539 [-]
hsa-miR-30b-5p	478007_mir	UGUAAACAUCCUACACUCAGCU	MIMAT0000420	Chr.8: 134800520 - 134800607 [-]
cel-miR-39-3p	478293_mir	UCACCGGGUGUAAAUCAGCUUG	MIMAT0000010	
hsa-miR-24-3p	477992_mir	UGGCUCAGUUCAGCAGGAACAG	MIMAT0000080	Chr.9: 95086021 - 95086088 [+]
hsa-miR-484	478308_mir	UCAGGCUCAGUCCCUCCCGAU	MIMAT0002174	Chr.16: 15643294 - 15643372 [+]

Supplementary Table 4. The relative miR expression (log2) in serum presented as *mean* with *SD* in the measured samples (*N*) by both experiments (Experiment 1 and 2).

miRs	Experiment 1			Experiment 2		
	N	Mean	SD	N	Mean	SD
let-7d-5p	39	-0.445	1.823	39	-3.196	0.561
let-7g-5p	39	-0.771	1.216	39	-1.524	0.602
miR-15a-5p	39	-0.122	1.362	39	1.006	0.937
miR-26a-5p	38	-0.509	0.930	39	-0.749	0.536
miR-26b-5p	38	-0.050	0.992	39	-0.977	0.642
miR-29a-3p	38	-0.402	1.721	39	-0.941	0.520
miR-30b-5p	38	-0.561	1.171	39	-2.462	0.489
miR-93-5p	39	0.085	1.304	39	0.266	0.805
miR-101-3p	39	-0.339	1.520	39	1.150	0.848
miR-103a-3p	39	0.411	1.602	39	-0.957	0.729
miR-125b-5p	39	-0.123	0.916	39	-3.872	0.588
miR-128-3p	38	-0.078	0.950	39	-5.679	0.803
miR-132-3p	39	-0.022	1.869	39	-6.162	0.693
miR-143-3p	39	-0.302	1.493	39	-2.772	0.549
miR-146a-5p	39	0.379	1.139	39	-1.578	0.551
miR-148a-3p	38	-0.042	1.210	39	-1.714	0.634
miR-151a-5p	37	-0.537	0.858	39	-3.414	0.611
miR-181c-5p	38	0.048	1.017	39	-8.579	1.281
miR-191-5p	38	0.042	1.156	39	-1.306	0.553
miR-210-3p	32	-0.090	1.975	39	-4.446	0.900
miR-335-5p	39	0.366	1.449	39	-4.367	0.678
miR-484	38	-0.710	1.932	39	-1.969	0.742
miR-486-5p	39	0.024	1.354	39	2.229	1.161

Supplementary Table 5. Changes (%) in odds of having MCI (versus Control), per each doubling in relative miR expression in serum, using the most updated re-assessed cognitive data retrieved during the follow-up. Models were corrected for sex, age, and years of education. Odds ratio (OR), 95% confidence intervals (95% CI; lower to upper limit) and p-values are provided for both Experiment 1 and 2. When p-value<0.2, the miRs are indicated in bold and underlined.

miRs	Experiment 1		Experiment 2	
	OR (95%CI)	p	OR (95%CI)	p
let-7d-5p	0.83 (0.55 to 1.24)	0.36	3.04 (0.74 to 12.52)	*0.124*
let-7g-5p	0.96 (0.57 to 1.63)	0.89	2.36 (0.53 to 10.51)	0.26
miR-15a-5p	0.72 (0.37 to 1.39)	0.32	0.84 (0.38 to 1.82)	0.65
miR-26a-5p	0.74 (0.35 to 1.58)	0.44	0.81 (0.20 to 3.19)	0.76
miR-26b-5p	1.37 (0.67 to 2.77)	0.38	2.54 (0.75 to 8.56)	*0.132*
miR-29a-3p	0.75 (0.44 to 1.29)	0.30	1.04 (0.31 to 3.51)	0.95
miR-30b-5p	0.52 (0.24 to 1.12)	*0.094*	2.04 (0.44 to 9.49)	0.36
miR-93-5p	0.68 (0.36 to 1.30)	0.24	0.81 (0.33 to 1.96)	0.64
miR-101-3p	1.22 (0.70 to 2.15)	0.48	1.07 (0.45 to 2.54)	0.64
miR-103a-3p	0.63 (0.35 to 1.13)	*0.122*	0.59 (0.16 to 2.16)	0.42
miR-125b-5p	1.37 (0.61 to 2.88)	0.47	3.02 (0.79 to 11.48)	*0.105*
miR-128-3p	0.36 (0.12 to 1.08)	*0.068*	1.32 (0.56 to 3.11)	0.53
miR-132-3p	1.11 (0.75 to 1.65)	0.60	1.08 (0.44 to 2.68)	0.86
miR-143-3p	1.19 (0.60 to 2.33)	0.62	6.14 (1.18 to 32.00)	*0.031*
miR-146a-5p	1.05 (0.63 to 1.76)	0.85	0.55 (0.15 to 2.04)	0.37
miR-148a-3p	1.08 (0.57 to 2.03)	0.97	0.85 (0.30 to 2.43)	0.76
miR-151a-5p	0.65 (0.27 to 1.57)	0.34	1.34 (0.41 to 4.40)	0.63
miR-181c-5p	1.01 (0.56 to 1.81)	0.97	1.15 (0.73 to 1.82)	0.54
miR-191-5p	0.91 (0.54 to 1.54)	0.73	1.18 (0.34 to 4.15)	0.79
miR-210-3p	0.74 (0.40 to 1.35)	0.32	0.82 (0.38 to 1.74)	0.59
miR-335-5p	0.84 (0.54 to 1.30)	0.44	1.22 (0.46 to 3.20)	0.68
miR-484	0.48 (0.21 to 1.11)	*0.088*	0.63 (0.21 to 1.86)	0.40
miR-486-5p	0.88 (0.52 to 1.47)	0.62	0.74 (0.40 to 1.37)	0.34

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