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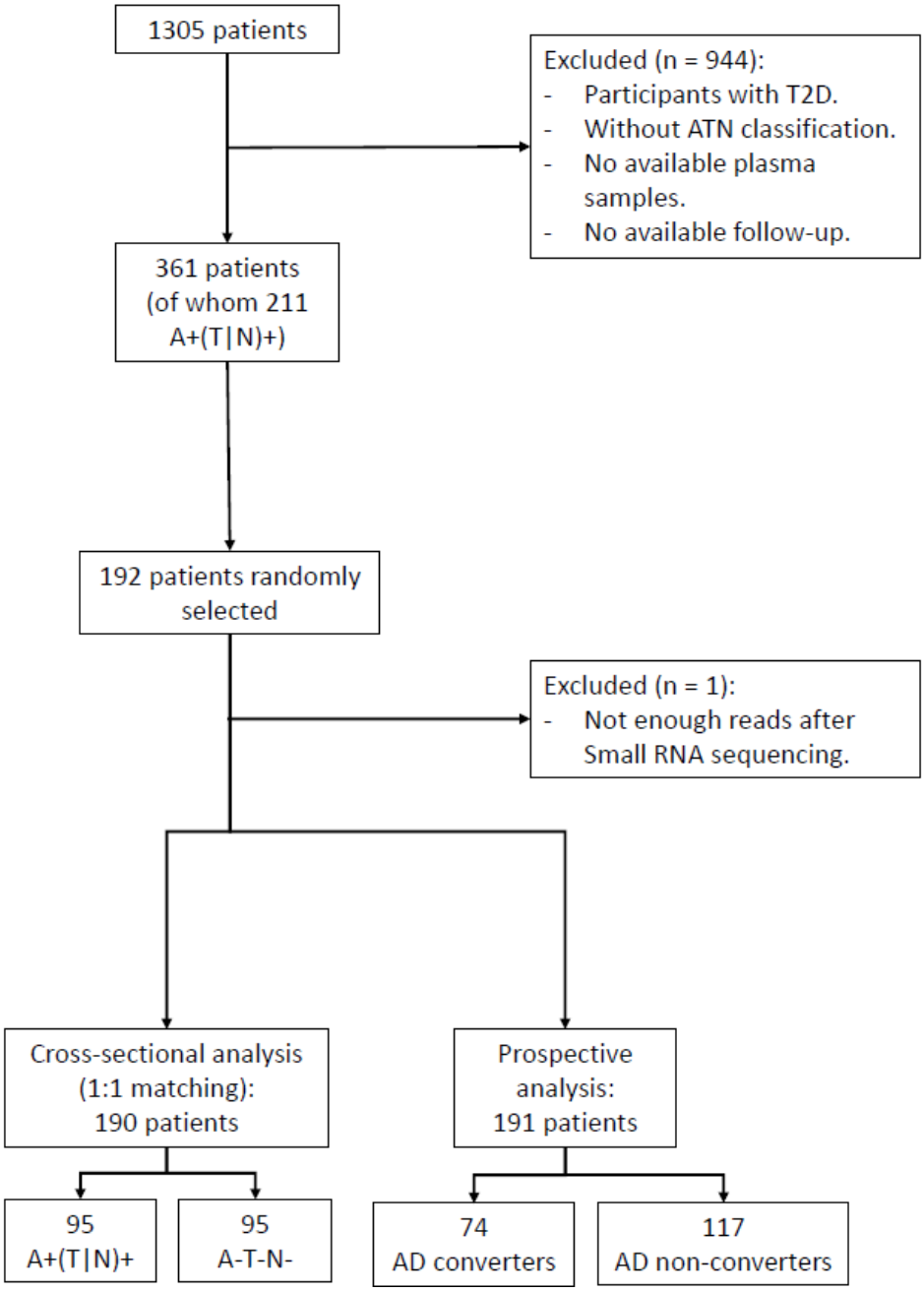


eFigure 1 | Flowchart of patient inclusion.

Abbreviations: T2D, type 2 diabetes; AD, Alzheimer's disease.

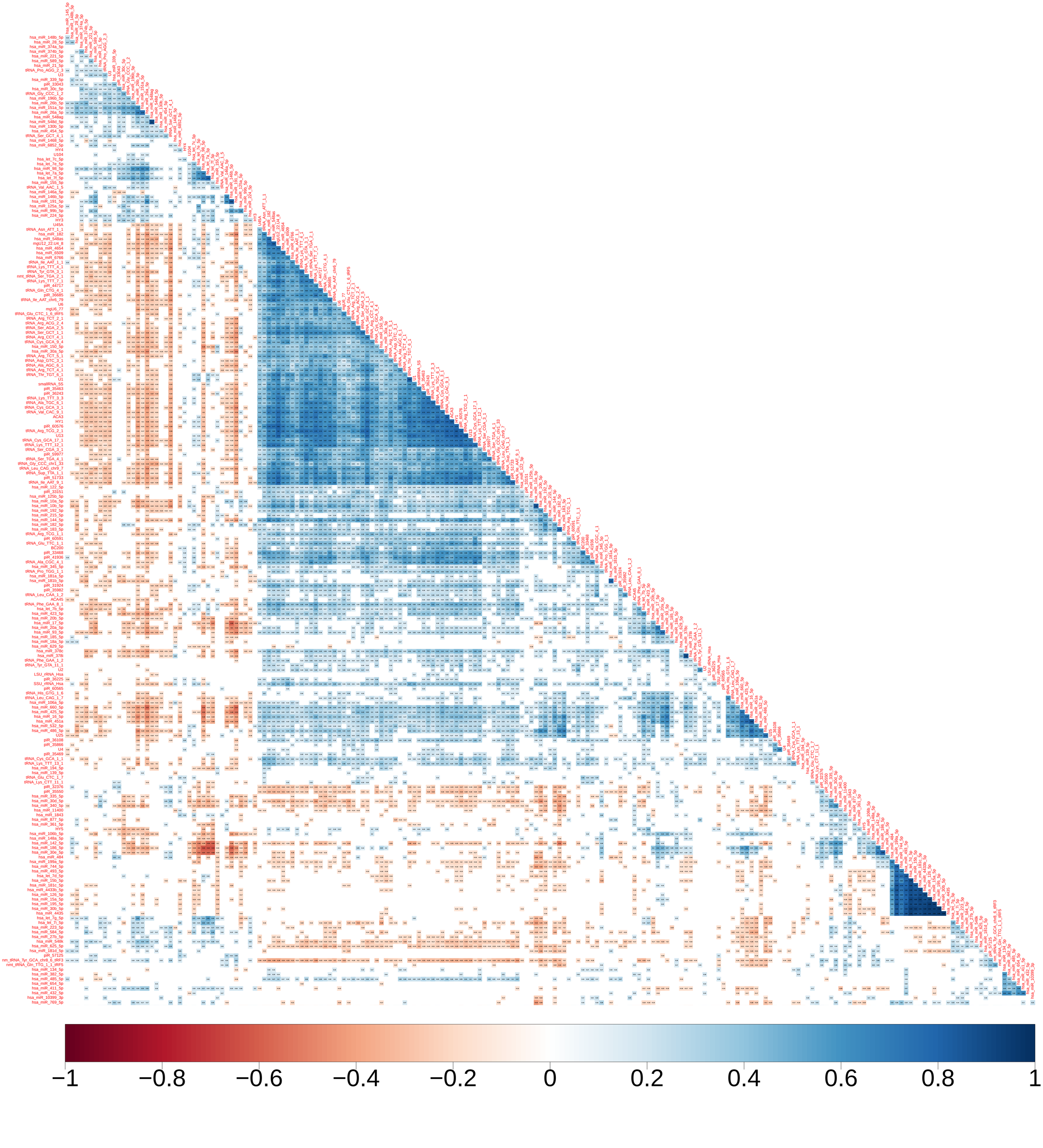
eMethods | Sequencing and processing of sncRNA.

Total RNA was isolated from 400 µL of plasma using the Plasma/Serum RNA Purification Midi Kit (Norgen Biotek, Canada) and quantified with the Qubit RNA HS Assay Kit (Life Technologies, USA) on a Qubit fluorometer (Life Technologies, USA). Since the concentration of RNA was below the lower standard, the entire volume was concentrated in vacuo using the Savant SPD2010 Speedvac Concentrator (ThermoScientific, USA) and resuspended in 5 µL of DNase/RNase-free water. SncRNAs were analyzed using Illumina TruSeq SncRNA Library Prep Kit (Illumina, USA), following the manufacturer's instructions. Briefly, RA5 and RA3 RNA oligonucleotides were ligated to 5' and 3' ends of RNA, respectively. Adapter-ligated RNA was reverse-transcribed using an RT Primer and the resulting cDNA was amplified in a 15-cycle PCR that used RP1 and indexed RP1 primers. A gel purification step was used to isolate PCR products of 145-160 bp through a 5% Mini-Protean TBE Gel (Biorad, USA). The integrity of the generated sncRNA sequencing library was confirmed using High Sensitivity D1000 Screen Tape Assay on 4200 TapeStation System (Agilent, USA), and it was quantified with the Qubit 1X dsDNA HS Assay Kit (Life Technologies, USA). The sncRNA expression profiling was generated from the NextSeq 2000 Sequencing System (Illumina, USA). Leftover RNA and cDNA were stored at -80ºC.

The Illumina DRAGEN Bio-IT Platform was used for the generation of raw, demultiplexed sequencing data. Quality control was performed using the FastQC (v0.11.9) software. Reads with a quality score of 20 or higher were filtered using Trim Galore tool (v0.6.7), which implements the Cutadapt tool for adapter trimming.

The mapping and quantification of sncRNAs were done in two different protocols: miRNA and other sncRNAs. For the identification of miRNAs, reads were mapped to the human genome(1) and quantified using mature and hairpin miRNA database references(2) using the miRDeep2 tool (v2.0.1.2). Duplicates were removed. For the identification of other sncRNAs, a BLAST (v.2.5.0) against the miRNA database was performed(2), kept the non-miRNA reads and a new BLAST against the sncRNA database(3) was performed.

eFigure 2 | Heatmap of sncRNAs correlations. Spearman's rank correlation coefficient is shown for each correlation. Only significant correlations are shown (P value < .05).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tRNA_Pro_AGG_2_3
U13
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piR_33043
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tRNA_Gly_CCC_1_2
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hsa_miR_26b_5p
hsa_miR_151a_5p
hsa_miR_26a_5p
hsa_miR_548ag
hsa_miR_548d_5p
hsa_miR_130b_5p
hsa_miR_454_5p
tRNA_Ser_GCT_4_1
hsa_miR_1468_5p
hsa_miR_6852_5p
HY4
U104
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hsa_let_7e_5p
hsa_miR_98_5p
hsa_let_7a_5p
hsa_let_7f_5p
hsa_miR_155_5p
tRNA_Val_AAC_1_5
hsa_miR_146a_5p
hsa_miR_146b_5p
hsa_miR_191_5p
hsa_miR_125a_5p
hsa_miR_99b_5p
hsa_miR_224_5p
HY3
U45A
tRNA_Asn_ATT_1_1
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hsa_miR_548as
mgU12_22.U4_8
hsa_miR_4654
hsa_miR_6509
hsa_miR_6766
tRNA_Ile_AAT_1_1
tRNA_Lys_TTT_4_1
tRNA_Tyr_GTA_3_1
nmt_tRNA_Ser_TGA_2_1
tRNA_Lys_TTT_7_1
piR_44717
tRNA_Gln_CTG_4_1
piR_36685
tRNA_Ile_AAT_chr6_79
U6
mgU6_77
tRNA_Glu_CTC_1_6_tRF5
tRNA_Arg_TCT_2_1
tRNA_Arg_ACG_2_4
tRNA_Ser_AGA_2_5
tRNA_Ser_GCT_1_1
tRNA_Arg_CCT_4_1
tRNA_Cys_GCA_9_4
hsa_miR_150_5p
hsa_miR_30a_5p
tRNA_Arg_TCT_5_1
tRNA_Asp_GTC_3_1
tRNA_Ala_AGC_6_1
tRNA_Arg_TCT_4_1
tRNA_Thr_TGT_6_1
U1
smallRNA_5S
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HY1
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piR_33468
piR_41936
tRNA_Ala_CGC_4_1
hsa_miR_345_5p
tRNA_Pro_TGG_1_1
hsa_miR_181a_5p
hsa_miR_181b_5p
piR_31924
piR_35982
tRNA_Leu_CAA_1_2
ACA45
tRNA_Phe_GAA_8_1
hsa_let_7b_5p
hsa_miR_423_5p
hsa_miR_20b_5p
hsa_miR_17_5p
hsa_miR_20a_5p
hsa_miR_93_5p
hsa_miR_185_5p
hsa_miR_18a_5p
hsa_miR_629_5p
hsa_miR_378c
hsa_miR_378i
tRNA_Phe_GAA_1_2
tRNA_Tyr_GTA_11_1
U2
LSU_rRNA_Hsa
piR_36225
SSU_rRNA_Hsa
piR_60565
tRNA_His_GTG_1_6
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hsa_miR_106a_5p
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U4
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tRNA_Glu_CTC_1_7
tRNA_Lys_CTT_11_1
piR_32376
piR_35550
hsa_miR_335_5p
hsa_miR_30d_5p
hsa_miR_340_5p
hsa_miR_11400
hsa_miR_1843
hsa_miR_877_5p
hsa_miR_361_5p
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hsa_miR_142_5p
hsa_miR_186_5p
hsa_miR_30e_5p
hsa_miR_484
hsa_miR_199a_5p
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hsa_let_7d_5p
hsa_miR_15b_5p
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hsa_let_7g_5p
hsa_let_7i_5p
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hsa_miR_27b_5p
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0.8
1

eFigure 3 | A literature search was carried out using the MEDLINE-PubMed database from inception through 10 April 2023. For the database searches, terms related to “miRNA” or “gene” were combined with terms related to Alzheimer’s disease, cognition and brain. In each run, the miRNA’s and the gene name were changed.

((mir-224-5p) OR (SKIL)) AND ((alzheimer) OR (MCI) OR (mild cognitive impairment) OR (brain) OR (neuron) OR (neurodegeneration) OR (cognitive decline) OR (memory) OR (aging))

eTable 1 | Characteristics of the A+(T|N)+ study participants according to their A, T and N profile.

Variable	A+T+N+ participants	A+T+N- and A+T-N+ participants	P value
n	65	31	
Age (years)	77.3 (72.4, 80.2)	74.9 (69.8, 79.9)	0.343
Women [N (%)]	36 (55.4)	11 (35.5)	0.423
Body mass index (kg/m^2)	25.4 (23.4, 28.7)	25.5 (23.7, 28.4)	0.641
APOE ε4 carriers [N (%)]	43 (66.2)	16 (51.6)	0.171
Education (years)	8 (6, 10)	8 (6, 12)	0.849
Smoking [N (%)]			
Never	48 (73.8)	20 (64.5)	0.053
Former	12 (18.5)	10 (32.3)	0.024*
Current	5 (7.7)	1 (3.2)	0.770
Medication [N (%)]			
Antidepressant and anxiolytic	24 (36.9)	9 (29.0)	0.447
Antihypertensive	26 (40.0)	14 (45.2)	0.632
Statins	16 (24.6)	12 (38.7)	0.155
Other lipid-lowering drugs	4 (6.2)	2 (6.5)	0.978
MMSE at baseline (score)	25 (24, 27)	26 (24, 28)	0.402
A [N (%)]	65 (100.0)	31 (100.0)	1.000
T [N (%)]	65 (100.0)	28 (90.3)	0.011*
N [N (%)]	65 (100.0)	3 (9.7)	<0.001***
Follow-up (years)	1.7 (1.0, 2.7)	1.7 (1.0, 2.9)	0.896
Conversion to AD [N (%)]	47 (72.3)	22 (71.0)	0.891

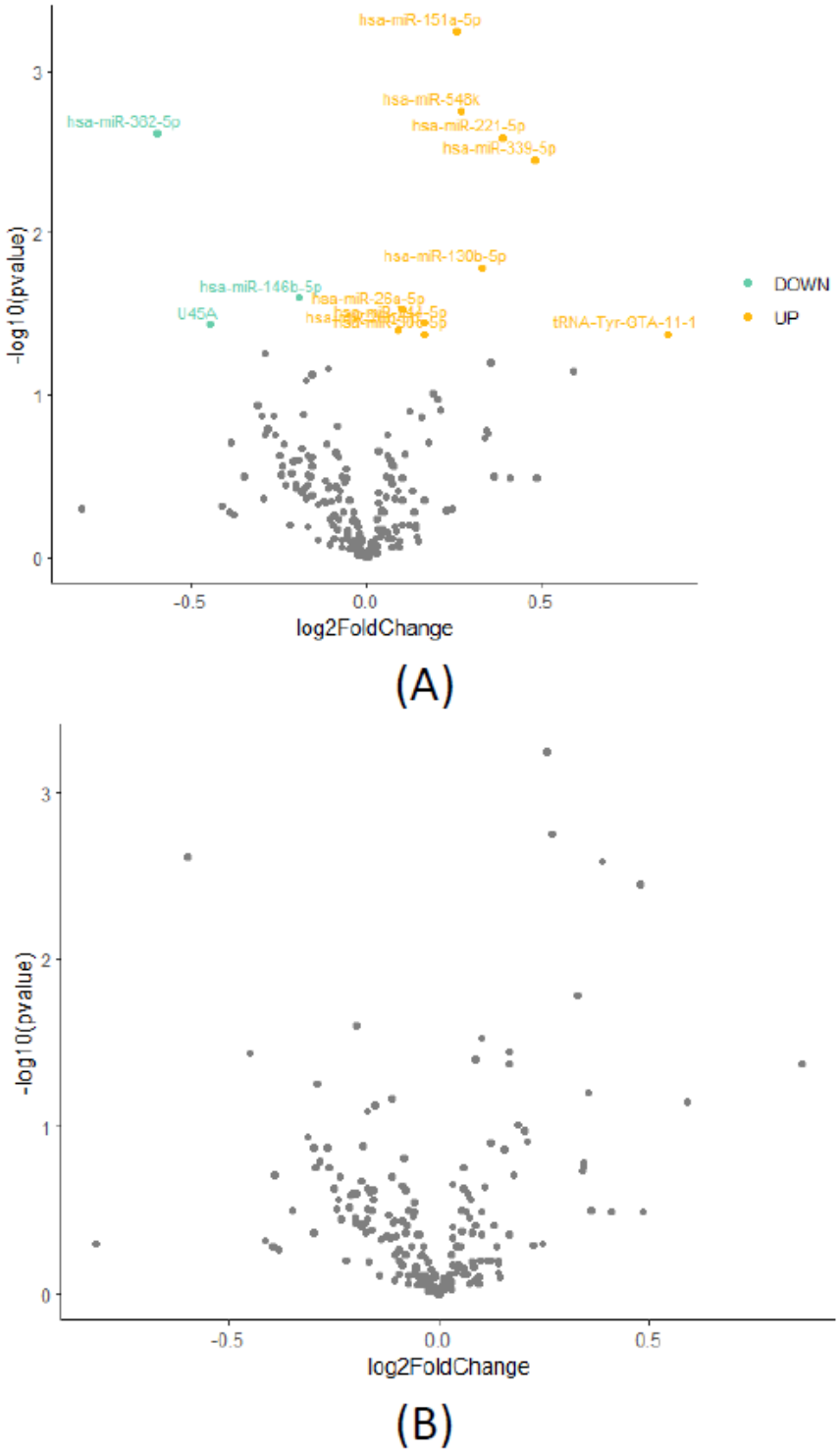
Abbreviations: MMSE, Mini-mental state examination; AD, Alzheimer's disease.

Continuous data are presented as median (interquartile range), and categorical variables are presented as number (%). The Mann-Whitney test was used for comparison of non-normally distributed continuous variables, and the X^2 was used for comparison of categorical variables. Only three participants were A+T-N+ and consequently were joined with the A+T+N- group. *P value < .05, **P value < .01, ***P value < .001.

eTable 2 | Upregulated and downregulated Differentially Expressed sncRNAs comparing A+(T|N)+ with A-T-N-.

sncRNA	baseMean	log_2FC	lfcSE	stat	P value	Padj	Regulation
hsa-miR-130b-5p	5.420	0.330	0.137	2.402	0.016	0.565	Up
hsa-miR-146b-5p	1886.588	-0.194	0.087	-2.241	0.025	0.674	Down
hsa-miR-151a-5p	204.766	0.259	0.075	3.447	0.001	0.118	Up
hsa-miR-221-5p	6.494	0.389	0.129	3.014	0.003	0.134	Up
hsa-miR-26a-5p	10699.047	0.103	0.047	2.174	0.030	0.674	Up
hsa-miR-26b-5p	1836.808	0.088	0.043	2.062	0.039	0.674	Up
hsa-miR-30c-5p	96.306	0.167	0.082	2.033	0.042	0.674	Up
hsa-miR-339-5p	5.368	0.480	0.164	2.917	0.004	0.147	Up
hsa-miR-382-5p	6.025	-0.597	0.197	-3.035	0.002	0.134	Down
hsa-miR-548k	15.239	0.269	0.086	3.127	0.002	0.134	Up
hsa-miR-744-5p	88.619	0.167	0.080	2.099	0.036	0.674	Up
tRNA-Tyr-GTA-11-1	21.284	0.862	0.424	2.032	0.042	0.674	Up
U45A	108.560	-0.447	0.214	-2.089	0.037	0.674	Down

Padj using FDR. Padj < .05 was considered significant.



eFigure 4 | Volcano plot of upregulated and downregulated Differentially Expressed sncRNAs comparing A+(T|N)+ with A-T-N-. (A) sncRNAs with P value < .05, (B) sncRNAs with Padj < .05 after FDR.

eTable 3 | Conditional logistic regression analysis examining the individual associations between sncRNAs expression and A+(T|N)+.

	Unadjusted model			Model 1		
sncRNA	**OR (95% CI)**	**P value**	**Padj**	**OR (95% CI)**	**P value**	**Padj**
hsa-miR-130b-5p	1.389 (1.0334, 1.8669)	0.029	0.705	1.3243 (0.8367, 2.096)	0.231	0.994
hsa-miR-146b-5p	0.7328 (0.5452, 0.9851)	0.040	0.705	0.73 (0.4741, 1.1239)	0.153	0.994
hsa-miR-151a-5p	1.7397 (1.251, 2.4193)	0.001	0.208	1.6678 (0.9703, 2.8666)	0.064	0.994
hsa-miR-221-5p	1.5214 (1.1103, 2.0848)	0.009	0.312	1.1617 (0.7714, 1.7496)	0.473	0.994
hsa-miR-26a-5p	1.3664 (1.0166, 1.8367)	0.039	0.705	1.2099 (0.7566, 1.935)	0.426	0.994
hsa-miR-27b-5p	1.3263 (0.9915, 1.7742)	0.057	0.792	1.7286 (1.0805, 2.7653)	0.022	0.994
hsa-miR-30c-5p	1.3559 (1.0007, 1.8372)	0.049	0.781	1.3398 (0.7999, 2.2441)	0.266	0.994
hsa-miR-339-5p	1.6316 (1.1752, 2.2653)	0.003	0.236	1.7428 (1.0193, 2.98)	0.042	0.994
hsa-miR-382-5p	0.6456 (0.4729, 0.8814)	0.006	0.304	0.7356 (0.4657, 1.162)	0.188	0.994
hsa-miR-548ag	1.3584 (1.0131, 1.8215)	0.041	0.705	1.6379 (1.0379, 2.5846)	0.034	0.994
hsa-miR-548k	1.6149 (1.1846, 2.2014)	0.002	0.236	1.3953 (0.8811, 2.2097)	0.156	0.994
piR-31924	0.8858 (0.6534, 1.201)	0.435	0.984	0.6519 (0.4366, 0.9735)	0.037	0.994
piR-33043	1.3754 (1.0181, 1.858)	0.038	0.705	1.1593 (0.7557, 1.7784)	0.499	0.994
tRNA-Pro-AGG-2-3	1.5231 (1.1198, 2.0715)	0.007	0.304	1.3558 (0.8687, 2.1162)	0.180	0.994
LSU-rRNA-Hsa	1.0853 (0.8101, 1.4541)	0.583	0.984	0.6615 (0.4547, 0.9623)	0.031	0.994
U3	1.3709 (1.0234, 1.8364)	0.034	0.705	1.0957 (0.7138, 1.6819)	0.676	0.994
U4	1.2717 (0.9455, 1.7103)	0.112	0.984	1.631 (1.0302, 2.5822)	0.037	0.994

Abbreviations: OR, odds ratio; CI, confidence interval; MMSE, Mini-mental state examination.

Model 1 was adjusted for age, BMI, APOE ε4, smoking habit, education, use of anxiolytic or antidepressants, antihypertensive drugs, statins, and other lipid-lowering medication, and baseline MMSE. *Padj < .05, **Padj < .01, ***Padj < .001.

eTable 4 | Sensitivity analysis using logistic regression analysis to examine the individual associations between sncRNAs expression and A+(T|N)+.

	Unadjusted model			Model 1		
sncRNA	**OR (95% CI)**	**P value**	**Padj**	**OR (95% CI)**	**P value**	**Padj**
hsa-miR-130b-5p	1.392 (1.040, 1.888)	0.029	0.614	1.329 (0.842, 2.136)	0.227	0.990
hsa-miR-146b-5p	0.728 (0.537, 0.973)	0.035	0.614	0.726 (0.463, 1.114)	0.148	0.990
hsa-miR-151a-5p	1.713 (1.259, 2.390)	0.001	0.159	1.686 (0.999, 3.013)	0.061	0.990
hsa-miR-221-5p	1.530 (1.128, 2.131)	0.009	0.295	1.165 (0.768, 1.776)	0.469	0.990
hsa-miR-26a-5p	1.376 (1.030, 1.862)	0.034	0.614	1.215 (0.760, 1.977)	0.420	0.990
hsa-miR-26b-5p	1.364 (1.021, 1.843)	0.038	0.614	1.048 (0.649, 1.706)	0.850	0.990
hsa-miR-27b-5p	1.326 (0.994, 1.785)	0.058	0.806	1.742 (1.104, 2.870)	0.022	0.990
hsa-miR-30c-5p	1.354 (1.013, 1.836)	0.044	0.660	1.352 (0.810, 2.315)	0.257	0.990
hsa-miR-339-5p	1.675 (1.220, 2.371)	0.002	0.159	1.775 (1.060, 3.185)	0.040	0.990
hsa-miR-382-5p	0.638 (0.460, 0.830)	0.005	0.250	0.731 (0.451, 1.143)	0.182	0.990
hsa-miR-548ag	1.366 (1.022, 1.846)	0.038	0.614	1.651 (1.059, 2.676)	0.032	0.990
hsa-miR-548k	1.616 (1.197, 2.225)	0.002	0.159	1.401 (0.887, 2.256)	0.153	0.990
piR-31924	0.881 (0.619, 1.179)	0.415	0.994	0.647 (0.423, 0.992)	0.035	0.990
piR-33043	1.402 (1.045, 1.918)	0.028	0.614	1.167 (0.759, 1.830)	0.487	0.990
tRNA-Pro-AGG-2-3	1.525 (1.133, 2.095)	0.007	0.283	1.362 (0.868, 2.145)	0.177	0.990
LSU-rRNA-Hsa	1.082 (0.809, 1.502)	0.598	0.994	0.657 (0.441, 0.980)	0.029	0.990
U3	1.390 (1.041, 1.876)	0.028	0.614	1.100 (0.714, 1.706)	0.665	0.990
U4	1.264 (0.946, 1.721)	0.122	0.994	1.640 (1.053, 2.686)	0.036	0.990

Abbreviations: OR, odds ratio; CI, confidence interval; MMSE, Mini-mental state examination.

Model 1 was adjusted for age, sex, BMI, APOE ε4, smoking habit, education, use of anxiolytic or antidepressants, antihypertensive drugs, statins, and other lipid-lowering medication, and baseline MMSE. *Padj < .05, **Padj < .01, ***Padj < .001.

eTable 5 | Sensitivity analysis of sncRNAs associated with A+(T|N)+ in a logistic regression analysis. SncRNA are ranked from the highest to the lowest elastic net positive and negative regression coefficients for A+(T|N)+.

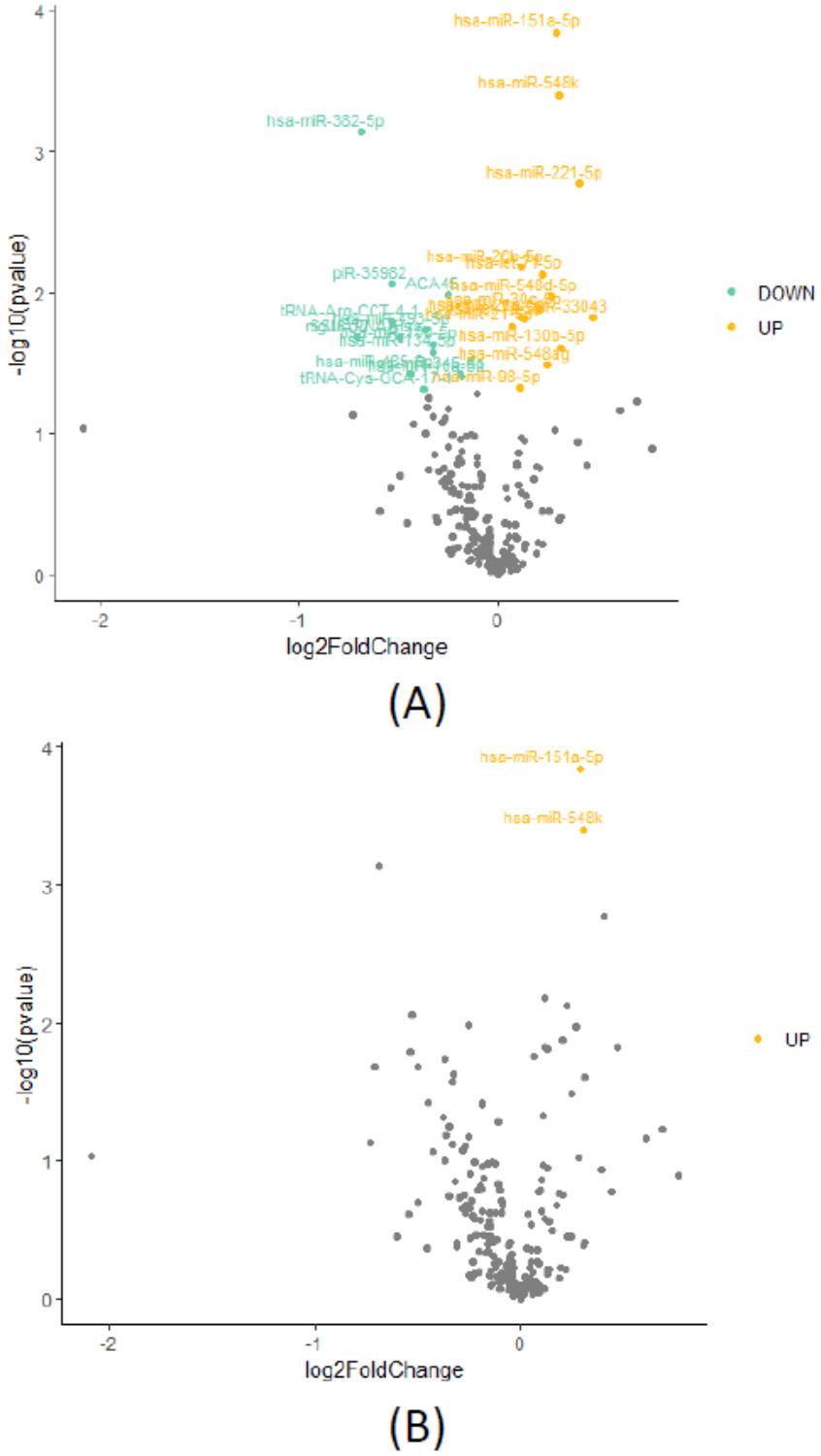
sncRNA	#a	β (95% CI)	sncRNA	#a	β (95% CI)
hsa-miR-339-5p	100	0.145 (0.136, 0.153)	hsa-miR-382-5p	100	-0.179 (-0.188, -0.170)
hsa-miR-548k	100	0.143 (0.131, 0.154)	hsa-miR-146b-5p	100	-0.131 (-0.141, -0.122)

Abbreviations: #a, Occurrence of metabolites (out of 100) in the elastic net conditional logistic regression; sncRNA, small non-coding RNA; hsa, Homo sapiens; CI, confidence interval.

eTable 6 | Upregulated and downregulated Differentially Expressed sncRNAs between AD-converters and AD non-converters.

sncRNA	baseMean	log_2FC	lfcSE	stat	P value	Padj	Regulation
hsa-let-7a-5p	3023.850	0.134	0.055	2.422	0.015	0.239	Up
hsa-let-7f-5p	12233.306	0.227	0.085	2.677	0.007	0.239	Up
hsa-miR-10a-5p	2344.771	-0.183	0.089	-2.056	0.040	0.331	Down
hsa-miR-130b-5p	5.420	0.316	0.141	2.250	0.024	0.255	Up
hsa-miR-134-5p	33.236	-0.331	0.149	-2.221	0.026	0.261	Down
hsa-miR-150-5p	62.127	-0.324	0.143	-2.266	0.023	0.255	Down
hsa-miR-151a-5p	204.766	0.293	0.077	3.801	0.000	0.030*	Up
hsa-miR-21-5p	6795.002	0.070	0.029	2.381	0.017	0.239	Up
hsa-miR-221-5p	6.494	0.410	0.131	3.136	0.002	0.089	Up
hsa-miR-26a-5p	10699.047	0.119	0.049	2.434	0.015	0.239	Up
hsa-miR-26b-5p	1836.808	0.119	0.044	2.712	0.007	0.239	Up
hsa-miR-30c-5p	96.306	0.209	0.084	2.474	0.013	0.239	Up
hsa-miR-345-5p	29.522	-0.186	0.090	-2.077	0.038	0.327	Down
hsa-miR-382-5p	6.025	-0.690	0.204	-3.376	0.001	0.051	Down
hsa-miR-485-5p	4.928	-0.445	0.214	-2.082	0.037	0.327	Down
hsa-miR-493-5p	56.626	-0.364	0.155	-2.357	0.018	0.239	Down
hsa-miR-548ag	7.793	0.249	0.117	2.136	0.033	0.309	Up
hsa-miR-548d-5p	9.170	0.273	0.107	2.551	0.011	0.239	Up
hsa-miR-548k	15.239	0.310	0.088	3.541	0.000	0.042*	Up
hsa-miR-98-5p	496.171	0.110	0.055	1.985	0.047	0.372	Up
piR-33043	51.833	0.478	0.197	2.427	0.015	0.239	Up
piR-35982	36.664	-0.530	0.202	-2.621	0.009	0.239	Down
tRNA-Arg-CCT-4-1	23.134	-0.534	0.222	-2.401	0.016	0.239	Down
tRNA-Cys-GCA-17-1	31.848	-0.373	0.189	-1.974	0.048	0.372	Down
SSU-rRNA-Hsa	42.313	-0.496	0.215	-2.311	0.021	0.241	Down
ACA45	40.174	-0.248	0.097	-2.563	0.010	0.239	Down
mgU6-77	11.710	-0.710	0.308	-2.310	0.021	0.241	Down

NOTE. Padj using FDR. Padj < 0.05 was considered significant.



eFigure 5 | Volcano plot of upregulated and downregulated Differentially Expressed sncRNAs comparing AD-converters and AD non-converters. **(A)** sncRNAs with P value < .05, **(B)** sncRNAs with Padj < .05 after FDR.

eTable 7 | Cox regression analysis examining the individual associations between sncRNAs expression and risk of progression from MCI to AD.

	Unadjusted model			Model 1		
sncRNA	**HR (95% CI)**	**P value**	**Padj**	**HR (95% CI)**	**P value**	**Padj**
hsa-let-7a-5p	1.286 (1.030, 1.605)	0.026	0.361	1.157 (0.911, 1.470)	0.233	0.964
hsa-let-7f-5p	1.348 (1.056, 1.721)	0.017	0.270	1.306 (1.036, 1.646)	0.024	0.677
hsa-miR-106b-5p	0.880 (0.691, 1.122)	0.303	0.853	0.670 (0.454, 0.987)	0.043	0.677
hsa-miR-146b-5p	0.946 (0.744, 1.203)	0.653	0.899	1.378 (1.047, 1.814)	0.022	0.677
hsa-miR-15a-5p	0.659 (0.295, 1.471)	0.308	0.853	0.206 (0.066, 0.639)	0.006	0.645
hsa-miR-151a-5p	1.508 (1.214, 1.872)	<0.001	0.042*	1.086 (0.860, 1.371)	0.491	0.964
hsa-miR-181c-5p	0.821 (0.542, 1.245)	0.354	0.853	0.449 (0.211, 0.958)	0.038	0.677
hsa-miR-191-5p	0.969 (0.766, 1.227)	0.795	0.949	1.370 (1.036, 1.813)	0.028	0.677
hsa-miR-20a-5p	0.893 (0.701, 1.136)	0.357	0.853	0.707 (0.510, 0.978)	0.037	0.677
hsa-miR-21-5p	1.288 (1.027, 1.616)	0.029	0.361	1.178 (0.861, 1.611)	0.307	0.964
hsa-miR-221-5p	1.310 (1.084, 1.581)	0.005	0.152	1.179 (0.918, 1.513)	0.197	0.964
hsa-miR-26a-5p	1.293 (1.026, 1.631)	0.030	0.361	1.051 (0.823, 1.34)	0.692	0.999
hsa-miR-26b-5p	1.348 (1.055, 1.722)	0.017	0.270	1.127 (0.863, 1.471)	0.382	0.964
hsa-miR-30c-5p	1.321 (1.060, 1.647)	0.013	0.270	1.043 (0.837, 1.298)	0.709	0.999
hsa-miR-30e-5p	1.064 (0.847, 1.335)	0.596	0.899	0.742 (0.551, 0.999)	0.049	0.677
hsa-miR-339-5p	1.357 (1.109, 1.661)	0.003	0.152	1.004 (0.795, 1.269)	0.970	0.999
hsa-miR-382-5p	0.670 (0.508, 0.884)	0.005	0.152	0.803 (0.598, 1.078)	0.144	0.841
hsa-miR-493-5p	0.582 (0.352, 0.961)	0.034	0.396	0.772 (0.481, 1.238)	0.282	0.964
hsa-miR-548ag	1.315 (1.048, 1.648)	0.018	0.270	1.199 (0.933, 1.54)	0.156	0.841
hsa-miR-548d-5p	1.351 (1.070, 1.705)	0.011	0.261	1.311 (1.012, 1.700)	0.041	0.677
hsa-miR-548k	1.514 (1.194, 1.921)	0.001	0.062	1.215 (0.927, 1.593)	0.158	0.841
hsa-miR-584-5p	1.207 (0.960, 1.516)	0.107	0.853	1.851 (1.375, 2.491)	<0.001	<0.001***

hsa-miR-99b-5p	1.159 (0.918, 1.463)	0.216	0.853	1.321 (1.012, 1.724)	0.041	0.677
piR-33043	1.398 (1.132, 1.72)	0.002	0.125	1.258 (0.995, 1.592)	0.056	0.722
piR-33151	1.330 (1.090, 1.624)	0.005	0.152	1.164 (0.907, 1.494)	0.234	0.964
piR-44717	1.129 (0.922, 1.384)	0.241	0.853	1.223 (1.008, 1.487)	0.042	0.677
tRNA-Asp-GTC-3-1	1.141 (0.916, 1.421)	0.238	0.853	1.275 (1.009, 1.611)	0.042	0.677
tRNA-Glu-CTC-1-7	0.985 (0.794, 1.221)	0.889	0.974	1.339 (1.005, 1.783)	0.046	0.677
tRNA-Gly-CCC-1-2	1.331 (1.077, 1.645)	0.008	0.213	1.113 (0.878, 1.412)	0.377	0.964
tRNA-Pro-AGG-2-3	1.261 (1.040, 1.528)	0.018	0.270	0.970 (0.736, 1.278)	0.827	0.999
tRNA-Ser-GCT-4-1	1.130 (0.909, 1.404)	0.271	0.853	1.364 (1.019, 1.825)	0.037	0.677

Abbreviations: HR, hazard ratio; CI, confidence interval; MMSE, Mini-mental state examination.

Model 1 was adjusted for ATN at baseline, age, sex, BMI, *APOE* ε4, smoking habit, education, use of anxiolytic or antidepressants, antihypertensive drugs, statins, and other lipid-lowering medication, and baseline MMSE. *Padj < .05, **Padj < .01, ***Padj < .001.

eTable 8 | Genes regulated by the ATN-related sncRNA signature.

Gene Symbol	Gene Name	miRNA regulation	Functions related to AD	References
ILF3	Interleukin enhancer binding factor 3	↑ hsa-miR-221-5p ↓ hsa-miR-382-5p	Transcriptional suppressor of the LOAD risk gene *HLA-DQA1*, which has been found upregulated in AD patient's hippocampus.	(4,5)
CTNNB1	Catenin Beta 1	↑ hsa-miR-221-5p	When the Wnt/β-catenin (*CTNNB1*) is activated, β-catenin facilitates gene transcription, while when this pathway is inactivated, β-catenin is degraded. Mutations of *CTNNB1* disturb synaptic plasticity, neuronal apoptosis, and neurogenesis.	(6,7)
FAM98B	Family with sequence similarity 98 member B	↓ hsa-miR-146b-5p ↓ hsa-miR-382-5p	It shuttles between the nucleus and the cytoplasm, transporting RNAs, and modulates the translation of specific neuronal mRNAs.	(1,2)
DDX6	DEAD-box helicase 6	↑ hsa-miR-548k ↑ hsa-miR-144-5p	Tau binds directly to DDX6 and increases miRNAs miR-21, miR-124 and let-7 silencing activity, which have been related to AD pathology.	(8)
CARHSP1	Calcium regulated heat stable protein 1	↑ hsa-miR-548k ↑ hsa-miR-144-5p	Oligodendrogenic transcription factor downregulated in the brain of Ulk4$^{tm1a/tm1a}$ mice, characterized by impaired myelination.	(3)
DDX21	DExD-box helicase 21	↓ hsa-miR-146b-5p ↑ hsa-miR-339-5p	RNA helicase which coordinates ribosomal RNA transcription and processing, RNA editing, RNA transport, and nuclear and mitochondrial splicing. Downregulated in the anterior cingulate of bipolar disorder patients.	(4)

RNF19A	Ring finger protein 19A	↑ hsa-miR-221-5p ↑ hsa-miR-339-5p	Rnf19a-deficient mice have been found to have reduced adult neurogenesis and enhanced long-term potentiation in the dentate gyrus. Also implicated in amyotrophic lateral sclerosis and Parkinson's disease.	(9)
SKIL	SKI like proto-oncogene	↑ hsa-miR-548k ↓ hsa-miR-382-5p	Promotes the expression of cell proliferation genes and concomitantly represses the differentiation genes in granule neuron precursors of mice cerebellum. It also plays a dual role as a corepressor or coactivator of *TGFβ*-induced transcription in postmitotic neurons and drives axonal growth.	(10,11)
CBX6	Chromobox 6	↑ hsa-miR-221-5p ↓ hsa-miR-146b-5p	Causative gene associated with *Nbg15* for the development of T2D, a risk factor for AD.	(12)
HNRNPA1	Heterogeneous nuclear ribonucleoprotein A1	↑ hsa-miR-221-5p ↑ hsa-miR-339-5p ↓ hsa-mir-382-5p	Affects the alternative splicing of an exon of *CD33*. This gene is an immune receptor on the membrane of microglia and macrophages, have been found increased in human AD brains and correlated with plaque burden as well as insoluble $A\beta_{42}$ levels. Mice lacking Cd33 showed a reduced burden of amyloid plaques and insoluble $A\beta_{42}$. Regulation of *CD33* splicing through *HNRNPA1* is associated with reduced risk of AD and decreased suppressive signaling on microglial activity.	(13–15)
CUL3	Cullin 3	↑ hsa-miR-144-5p ↑ hsa-miR-339-5p	Downregulation of the ubiquitin ligase (E3) gene *CUL3* in brain exacerbates AD through *NRF2* aggregation and impaired oxidative stress protection.	(16,17)
SMAD4	SMAD family member 4	↑ hsa-miR-144-5p ↑ hsa-miR-221-5p ↑ hsa-miR-339-5p	Tgfb1(-/-) mice with *Smad4* inhibition exhibit highly increased neuronal apoptosis. Mice with *Smad4* blockage exhibited *BACE* upregulation, *APP* degradation, tangle formation and Aβ generation in the brain.	(18,19)

MYLIP	Myosin regulatory light chain interacting protein	↑ hsa-miR-548k ↑ hsa-miR-221-5p ↑ hsa-miR-339-5p	Promotes the ubiquitylation and subsequent lysosomal degradation of LDLR. Genetic ablation of *MYLIP* increases LDLR, which facilitates Aβ uptake and clearance by microglia in the brains of APP/PS1 mice. Also, *MYLIP* inhibition upregulates lysosomal/phagocytic genes in microglia.	(7)
SOD2	Superoxide dismutase 2	↑ hsa-miR-144-5p ↑ hsa-miR-221-5p ↑ hsa-miR-339-5p ↓ hsa-miR-382-5p	Antioxidant enzyme that maintains the control of ROS. *SOD2* polymorphisms have been associated with increased susceptibility to oxidative stress. The relationship between *SOD2* rs4880 polymorphism and AD have yielded inconsistent results, but in combination with *APOε4* allele carriage it increases the risk for MCI and AD.	(20,21)
PRPF8	Pre-mRNA processing factor 8	↑ hsa-miR-144-5p ↑ hsa-miR-221-5p ↓ hsa-miR-146b-5p ↓ hsa-miR-382-5p	Regulation of glutamatergic neurotransmission in brain cortex. Homozygous mice expressing the aberrant Prpf8 variants developed atrophy pf the cerebellum because of extensive granule cell loss.	(22,23)

Abbreviations: LOAD, Late Onset Alzheimer's disease; AD, Alzheimer's disease; T2D, type 2 diabetes; ROS, reactive oxygen species; LDLR, low density lipoprotein receptor; MCI, mild cognitive impairment.

eTable 9 | Genes regulated by the AD-related sncRNA signature.

Gene Symbol	Gene Name	miRNA Regulation	Function related to AD	References
B2M	Beta-2-microglobulin	↑ hsa-miR-548d-5p ↓ hsa-miR-224-5p	*B2M* is part of the MHC I complex, which exhibits increased expression in samples from AD patients, and impairs neuronal plasticity, neurite growth, and neurite regeneration. It is a membrane marker of senescence and blood biomarker of AD. The increase in *B2M* is related to a decline in cognitive scores, to the pathological changes of Aβ (low CSF Aβ1-42), but not to neurodegeneration or tau pathology. Compared with young mice, old mice experience elevated *B2M* levels in their hippocampus and plasma.	(24–27)
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	↓ hsa-miR-224-5p ↑ hsa-miR-221-5p	Interaction between *GAPDH* and AD proteins through oxidative stress in brain. Specimens of AD, including Aβ, Aβ precursor protein and Tau, leads to impairment of the *GAPDH* glycolytic function in AD and thus in apoptosis. Proapoptotic factor abundant in the blood of AD patients.	(28–31)
SEC24C	SEC24 homolog C, COPII coat complex component	↑ hsa-miR-877-5p ↓ hsa-miR-224-5p ↑ hsa-miR-221-5p	The family of SEC24p oversee vesicle trafficking, including shaping vesicle, cargo selection and concentration, of subunits of the γ-secretase (involved in Aβ production). *SEC24C* transports the γ-subunit nicastrin.	(32)
ARIH2	Ariadne RBR E3 ubiquitin protein ligase 2	↓ hsa-miR-224-5p ↓ hsa-miR-382-5p	In spinal cord injury, *ARIH2* overexpression promotes neurotrophic growth factor expression, brain-derived neurotrophic factor expression, astrocyte and neuronal viability, neuroprotective cytokine pleiotrophin, neurite outgrowth, and suppressed astrocyte apoptosis. Knockdown of *ARIH2*-derived Triad1 protein has the opposite effects.	(33)

ELAVL1	ELAV like RNA binding protein 1	↓ hsa-miR-625-5p ↑ hsa-miR-221-5p	Downregulated *ELAVL1* may reduce the abundance and type of mRNA in AD patients through modulation of mRNA stability and promotion of variable cleavage of precursor RNA.	(34,35)
TNRC6A	Trinucleotide repeat containing adaptor 6A	↑ hsa-miR-548d-5p ↓ hsa-miR-769-5p ↓ hsa-miR-224-5p	*TNRC6A* promotes dendritic growth, both in the hippocampus and cerebellum, by regulating global somatodendritic translation and actin cytoskeletal dynamics of developing neurons. Perturbation of this protein results in reduced dendritic growth of cultured hippocampal neurons.	(36)
EPAS1	Endothelial PAS domain protein 1	↓ hsa-miR-625-5p ↓ hsa-miR-224-5p	This oxygen-dependent transcription factor is the major regulator of *EPO*, which has neuroprotective and pro-angiogenesis effects, and triggers responses to hypoxia including metabolic adaptation and angiogenesis.	(37)
TNRC6B	Trinucleotide repeat containing adaptor 6B	↓ hsa-miR-625-5p ↓ hsa-miR-224-5p ↑ hsa-miR-221-5p ↓ hsa-miR-454-5p	Inhibits translation. In ADHD, heterozygous pathogenic variant in *TNRC6B* have been found.	(38,39)
AGO2	Argonaute RISC catalytic component 2	↑ hsa-miR-548d-5p ↑ hsa-miR-548k ↓ hsa-miR-625-5p	It cleaves mRNA to regulate gene expression. Astrocytes exposed to $A\beta_{1-42}$ oligomers show loss of Ago2 phosphorylation, which leads to uncontrolled production of pro-inflammatory cytokines and neuroinflammation, leading to loss of neurons. *BACE1* and *APP* protein levels are significantly elevated following *AGO2* silencing in cultured human brain cells.	(40,41)
ATXN1L	Ataxin 1 like	↑ hsa-miR-548k ↑ hsa-miR-877-5p	*ATXN1* may help to shuttle *ATXN1L* into the nucleus where they interact in a large protein complex. Therefore, it is related to Aβ pathology mediated by *BACE1* expression. Also related to progressive non-fluent aphasia.	(42)

CSNK1E	Casein kinase 1 epsilon	↑ hsa-miR-221-5p ↓ hsa-miR-382-5p	Involved in circadian rhythms during early AD development. The expression of Csnk1E was higher in AD mice compared to control mice after light induction.	(43)
ATXN1	Ataxin 1	↑ hsa-miR-877-5p ↓ hsa-miR-625-5p ↓ hsa-miR-224-5p ↓ hsa-miR-454-5p ↓ hsa-miR-382-5p	Knockout of Atxn1 increases *BACE1* levels and enhances amyloidogenic cleavage of APP, exacerbating Aβ deposition and gliosis in AD mouse models, and impaired hippocampal neurogenesis and olfactory axonal targeting.	(44)
GAB1	GRB2 associated binding protein 1	↑ hsa-miR-548d-5p ↑ hsa-miR-877-5p	Promotes hippocampal LTP. In AD patients and in a mouse model of AD it is decreased, inhibiting septal cholinergic neurons projecting to the hippocampus.	(45)
CRKL	CRK like proto-oncogene, adaptor protein	↑ hsa-miR-877-5p ↓ hsa-miR-769-5p	Some of the neurotoxic effects of Aβ peptides may be mediated via the activation of proteins belonging to the Abl family, that regulate actin cytoskeleton structure through *CRKL* and phosphorylate microtubule-associated Tau protein, thus weakening synaptic transmission.	(46)
NF2	Moesin-ezrin-radixin like (MERLIN) tumor suppressor	↓ hsa-miR-769-5p ↑ hsa-miR-221-5p	Loss of function of the gene lead to the development of schwannomas, meningiomas and juvenile cataracts.	(47)
AKT1	AKT serine/threonine kinase 1	↑ hsa-miR-548k ↓ hsa-miR-382-5p	The PI3K/Akt signaling pathway is anti-apoptotic, and *AKT1* inhibits Akt phosphorylation (activation), which in turn upregulates the activity of *GSK3β*, a kinase implicated in the pathogenesis of AD. ROS-mediated oxidative modification of Akt1 leads to reduced synaptic Akt1-mTOR signaling which contributes to synaptic dysfunction in AD. It is rescued by overexpression of Akt1 in APP/PS1 mice.	(48,49)

HSP90AA1	Heat shock protein 90 alpha family class A member 1	↑ hsa-miR-548d-5p ↑ hsa-miR-548k ↓ hsa-miR-625-5p ↓ hsa-miR-224-5p	Regulates the stabilization and function of p-tau in AD. Inhibition of Hsp90 in AD mouse models reduced Aβ toxicity and normalizes synaptic function. In another study, *HSP90AA1* was decreased in the blood from MCI and AD and was negatively correlated with α and β secretase activities.	(50,51)
RICTOR	RPTOR independent companion of MTOR complex 2	↓ hsa-miR-769-5p ↓ hsa-miR-625-5p	Regulates transcription of multiple genes involved in oxidative phosphorylation and other mitochondrial functions. Inhibits nuclear mitochondrial expression. It also controls the actin cytoskeleton polymerization. Some studies find it not altered in AD. Other studies find that Rictor conditional knockout impairs long-term memory and late long-term potentiation, involved in spatial memory.	(52,53)
CTNNB1	Catenin Beta 1	↑ hsa-miR-548d-5p ↑ hsa-miR-548k	When the Wnt/β-catenin (*CTNNB1*) is activated, β-catenin facilitates gene transcription, while when this pathway is inactivated, β-catenin is degraded. Mutations of *CTNNB1* disturb synaptic plasticity, neuronal apoptosis, and neurogenesis.	(6,7)
OLA1	Obg like ATPase 1	↓ hsa-miR-769-5p ↓ hsa-miR-382-5p	Antioxidant suppressor. Downregulated *OLA1* preserves neuronal components.	(54)
AP3S2	Adaptor related protein complex 3 subunit sigma 2	↑ hsa-miR-548d-5p ↑ hsa-miR-548k ↓ hsa-miR-769-5p	Encodes a protein involved in protein transport whose variants are associated with the risk of T2D (which is a risk factor for AD).	(55)

YWHAG	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein gamma	↑ hsa-miR-548d-5p ↓ hsa-miR-224-5p ↓ hsa-miR-454-5p	Involved in signal transduction. Expression levels are increased in CSF specimens from AD patients and in the hippocampus of 5XFAD mice compared to controls. Recurrent distal deletion of *YWHAG* has been identified in patients with intellectual disability and neurobehavioral problems.	(56,57)
MAPK1	Mitogen-activated protein kinase 1	↓ hsa-miR-769-5p ↓ hsa-miR-454-5p ↓ hsa-miR-382-5p	The AKT-MAPK1-MTORC1 pathways is activated in 5XFAD mice (which has Aβ pathology). *MAPK1* phosphorylates the transcription factor EB, a master regulator of the autophagy-lysosomal pathway, thus inactivating it and promoting the development of AD.	(58)
NUDT21	Nudix hydrolase 21	↑ hsa-miR-548k ↓ hsa-miR-625-5p ↓ hsa-miR-454-5p	Elevated *NUDT21* results in an enrichment of inefficiently translated long mRNA isoforms, which is associated with intellectual disability and neuropsychiatric disease. Contrary, other studies indicate that reduce *NUDT21* function, such as in *Nudt21*$^{+/-}$ mice, cause learning deficits, cortical hyperexcitability, and misregulated alternative polyadenylation in the hippocampi.	(59,60)
ARL6IP1	ADP ribosylation factor like GTPase 6 interacting protein 1	↑ hsa-miR-548d-5p ↑ hsa-miR-548k ↓ hsa-miR-224-5p ↓ hsa-miR-382-5p	Elevated in the brain of AD Tg2576 mice and AB_{1-42} treated brain CECs. Promotes apoptosis through interaction with *ASK1*.	(61)

Abbreviations: *EPO*, Erytrhopoietin; ADHD, Attention aeficit and hyperactivity disorder; LTP, Long-term potentiation; Abl, Abelson non-receptor tyrosine kinase; PNC, Peripheral nervous system; NSC, neural stem cells; CEC, Cerebral microvascular endothelial cells; *ASK1*, Apoptosis signal-regulating kinase 1.

eTable 10 | Significantly enriched KEGG pathways for the ATN-related sncRNA signature.

KEGG ID	KEGG term	Gene Set Size	Counts	Padj	Genes
hsa05200	MicroRNAs in cancer	150	44	<0.001	*ABCC1, ABL1, BAK1, BCL2L11, BCL2L2, BMI1, BRCA1, CASP3, CCND1, CCND2, CCNG1, CDCA5, CDK6, CDKN1A, COMMD3-BMI1, CRKL, CYP1B1, DICER1, FZD3, HDAC4, HOXD10, KRAS, MAP2K1, MDM4, MMP16, MTOR, NFKB1, NOTCH1, PDGFRA, PDGFRB, PLCG2, PRKCA, PTEN, RHOA, SHC4, SLC7A1, SOS1, SOS2, STAT3, TGFB2, TNC, TP63, ZEB1, ZEB2*
hsa04722	Neurotrophin signaling pathway	119	27	0.029	*ABL1, AKT3, ARHGDIA, CALM1, CALML4, CAMK4, CRKL, GAB1, IRAK1, IRAK4, KRAS, MAP2K1, NFKB1, NTF3, NTRK2, PDPK1, PLCG2, RAP1A, RAP1B, RAPGEF1, RHOA, SHC4, SORT1, SOS1, SOS2, TRAF6, YWHAE, NOTCH1, PDGFRA, PDGFRB, PLCG2, PRKCA, PTEN, RHOA, SHC4, SLC7A1, SOS1, SOS2, STAT3, TGFB2, TNC, TP63, ZEB1, ZEB2*
hsa04550	Signaling pathways regulating pluripotency of stem cells	139	31	0.021	*ACVR1B, AKT3, BMI1, BMPR1A, COMMD3-BMI1, DLX5, DVL1, FZD1, FZD10, FZD2, FZD3, FZD5, FZD7, ID4, IGF1, IL6ST, JARID2, KAT6A, KRAS, MAP2K1, MEIS1, NEUROG1, PCGF5, SKIL, SMAD1, SMAD3, SMAD5, STAT3, WNT16, WNT5A, WNT9B, PRKCA, PTEN, RHOA,*

					SHC4, SLC7A1, SOS1, SOS2, STAT3, TGFB2, TNC, TP63, ZEB1, ZEB2
hsa04390	Hippo signaling pathway	154	34	0.019	*ACTG1, BMP2, BMP8B, BMPR1A, CCND1, CCND2, CSNK1D, CTNNA3, DVL1, FZD1, FZD10, FZD2, FZD3, FZD5, FZD7, LIMD1, MPP5, NF2, PARD6B, PRKCZ, SMAD1, SMAD3, TEAD1, TGFB2, TGFBR1, WNT16, WNT5A, WNT9B, WWTR1, YAP1, YWHAB, YWHAE, YWHAQ, YWHAZ, SHC4, SLC7A1, SOS1, SOS2, STAT3, TGFB2, TNC, TP63, ZEB1, ZEB2*
hsa04120	Ubiquitin mediated proteolysis	136	29	0.041	*BRCA1, CBL, CBLB, CUL3, CUL4A, HERC2, KLHL13, KLHL9, NEDD4L, PIAS2, RHOBTB1, SKP1, SMURF2, TRAF6, UBE2A, UBE2B, UBE2E1, UBE2E3, UBE2G1, UBE2H, UBE2J1, UBE2K, UBE2QL1, UBE3A, UBE4A, UBR5, VHL, WWP1, XIAP, YAP1, YWHAB, YWHAE, YWHAQ, YWHAZ, SHC4, SLC7A1, SOS1, SOS2, STAT3, TGFB2, TNC, TP63, ZEB1, ZEB2*
hsa05205	Proteoglycans in cancer	198	42	0.014	*ACTG1, AKT3, CASP3, CBL, CCND1, CDKN1A, CTTN, DDX5, ERBB4, FZD1, FZD10, FZD2, FZD3, FZD5, FZD7, GAB1, GPC1, HOXD10, IGF1, ITGAV, ITGB1, ITPR1, KRAS, MAP2K1, MSN, MTOR, PDPK1, PLCG2, PRKCA, RHOA, RRAS2, SDC2, SDC4, SOS1, SOS2, STAT3, TGFB2, TIAM1, TLR4, WNT16, WNT5A, WNT9B, ZEB1, ZEB2*

hsa05202	Transcriptional misregulation in cancer	186	39	0.019	*BAK1, BCL11B, BCL6, BMI1, CCND2, CCNT1, CDK14, CDKN1A, COMMD3-BMI1, DDX5, ELK4, EWSR1, HDAC2, HIST1H3F, HIST1H3G, IGF1, IL6, KLF3, KMT2A, MEF2C, MEIS1, MLLT1, MYCN, NCOR1, NFKB1, NSD2, PAX5, POLK, RUNX1T1, RUNX2, RXRA, SIN3A, SMAD1, SP1, SPI1, SS18, TLX3, WNT16, ZEB1, WNT16, WNT5A, WNT9B, ZEB1, ZEB2*
hsa05414 1	Protein processing in endoplasmic reticulum	165	34	0.037	*ATXN3, BAG2, BAK1, CKAP4, DAD1, DDOST, DNAJC10, DNAJC3, EDEM3, EIF2AK3, ERLEC1, ERO1A, HERPUD1, HSP90AA1, HSPA1B, HYOU1, MARCH6, NFE2L2, NSFL1C, P4HB, SAR1A, SAR1B, SEC62, SEC63, SKP1, SSR2, STT3A, TUSC3, UBE2G1, UBE2J1, UBQLN2, UGGT1, XBP1, YOD1, SPI1, SS18, TLX3, WNT16, ZEB1, WNT16, WNT5A, WNT9B, ZEB1, ZEB2*
hsa04010	MAPK signaling pathway	295	55	0.025	*AKT3, ANGPT4, ATF2, CACNA2D3, CASP3, CRKL, DUSP7, EFNA5, ELK4, ERBB4, FGF7, GNG12, HSPA1B, IGF1, IL1B, IL1RAP, IRAK1, IRAK4, KIT, KITLG, KRAS, MAP2K1, MAP3K2, MAP4K3, MAP4K4, MAPK8IP1, MAPKAPK5, MECOM, MEF2C, NFATC1, NFATC3, NFKB1, NTF3, NTRK2, PDGFRA, PDGFRB, PLA2G4A, PPM1A, PPP3CA, PPP3CB, PRKCA, PTPRR, RAP1A, RAP1B*
hsa05200	Pathways in cancer	524	97	0.001	*ABL1, ADCY2, AKT3, APPL1, AR, BAK1, BCL2L11, BMP2, CALM1, CALML4, CASP3, CBL, CCDC6, CCND1, CCND2,*

	CDK6, CDKN1A, COL4A1, CRKL, CTBP2, CTNNA3, DLL1, DVL1, F2R, F2RL3, FGF7, FZD1, FZD10, FZD2, FZD3, FZD5, FZD7, GNA13, GNG12, GSTA1, GSTM2, HDAC2, HHIP, HSP90AA1, IFNA21, IFNA4, IGF1, IL23A, IL6

eTable 11 | Significantly enriched KEGG pathways for the AD-related sncRNA signature.

KEGG ID	KEGG term	Gene Set Size	Counts	Padj	Genes
hsa05206	MicroRNA in cancer	150	67	<0.001	*ABCC1, ABL1, ATM, BAK1, BCL2, BCL2L2, BMF, BMI1, BMPR2, BRCA1, CASP3, CCND1, CCND2, CCNG1, CD44, CDC25C, CDCA5, CDK6, CDKN1B, COMMD3-BMI1, CREBBP, CRKL, CYP1B1, DDIT4, DICER1, DNMT3B, EFNA3, ERBB2, FZD3, HDAC4, HNRNPK, HOXD10, IGF2BP1, IRS1, KRAS, MAP2K1, MAP2K2, MAPK1, MARCKS, MCL1, MDM4, MMP16, MTOR, NFKB1, NOTCH1, NOTCH2, PDCD4, PDGFB, PDGFRA, PDGFRB, PLCG2, PRKCA, PTEN, RPS6KA5, SHC4, SIRT1, SLC7A1, SOS1, SOS2, STAT3, TGFB2, TNC, TP63, TPM1, TRIM71, ZEB1, ZEB2*
hsa03015	mRNA surveillance pathway	91	38	<0.001	*ACIN1, BCL2L2-PABPN1, CASC3, CPSF2, CPSF6, CPSF7, CSTF2, CSTF2T, ETF1, GSPT1, GSPT2, MSI2, NCBP2, NUDT21, NXF1, PABPC1, PABPC1L2A, PABPC1L2B, PABPC4, PABPC5, PABPN1, PAPOLA, PAPOLG, PNN, PPP1CA, PPP2CA, PPP2R1A, PPP2R2C, PPP2R2D, RBM8A, SAP18, SMG1, SMG5, SRRM1, UPF2, UPF3B, WDR33, WDR82*
hsa04550	Signalling pathways regulating pluripotency of stem cells	139	58	<0.001	*ACVR1B, ACVR2A, ACVR2B, AKT2, AKT3, AXIN2, BMI1, BMPR2, COMMD3-BMI1, DLX5, DUSP9, DVL3, FZD10, FZD2, FZD3, FZD5, FZD6, FZD7, GSK3B, HAND1, IGF1, IGF1R, IL6ST, INHBA, INHBC, ISL1, JAK3, JARID2, KAT6A, KLF4, KRAS, LEFTY2, MAP2K1, MAP2K2, MAPK1, MEIS1, NEUROG1, OTX1, PAX6, PCGF3, PCGF5, PIK3CB, PIK3R3, REST, RIF1, SKIL, SMAD2, SMAD3, SMAD4, SMAD5, SMAD9, SOX2, STAT3, TBX3, WNT16, WNT5A, WNT7B, WNT9B*

hsa04390	Hippo signaling pathway	154	57	<0.001	*ACTB, ACTG1, AMOT, AXIN2, BBC3, BMP8B, BMPR2, CCND1, CCND2, CDH1, CSNK1D, CTNNA3, DVL3, FZD10, FZD2, FZD3, FZD5, FZD6, FZD7, GDF6, GSK3B, LATS1, LATS2, LEF1, LIMD1, MOB1A, MOB1B, NKD1, PARD3, PARD6B, PPP1CA, PPP2CA, PPP2R1A, PPP2R2C, PPP2R2D, PRKCI, PRKCZ, SERPINE1, SMAD2, SMAD3, SMAD4, SOX2, TCF7L2, TEAD1, TGFB2, TGFBR1, TP73, WNT16, WNT5A, WNT7B, WNT9B, WWTR1, YAP1, YWHAE, YWHAG, YWHAQ, YWHAZ*
hsa04218	Cellular senescence	160	59	<0.001	*AKT2, AKT3, ATM, CACNA1D, CALM1, CALML3, CALML4, CAPN2, CCNB1, CCND1, CCND2, CDK1, CDK4, CDK6, CHEK2, ETS1, FOXM1, HIPK1, HIPK2, HIPK3, HLA-A, HLA-G, ITPR1, KRAS, MAP2K1, MAP2K2, MAPK1, MTOR, NBN, NFATC1, NFATC3, NFKB1, PIK3CB, PIK3R3, PPP1CA, PPP3CA, PPP3CB, PPP3R1, PTEN, RAD1, RASSF5, RBL2, RELA, RRAS2, SERPINE1, SIRT1, SLC25A5, SMAD2, SMAD3, SQSTM1, TGFB2, TGFBR1, TRAF3IP2, TRPM7, TSC1, VDAC1, VDAC2, ZFP36L1, ZFP36L2*
hsa04141	Protein processing in endoplasmic reticulum	165	56	0.002	*ATXN3, BAK1, BCAP31, BCL2, CALR, CAPN2, DAD1, DDIT3, DDOST, DERL1, DNAJC10, DNAJC3, EDEM3, EIF2AK2, EIF2AK3, ERO1A, GANAB, HERPUD1, HSP90AA1, HSPA8, HSPH1, HYOU1, MAN1A1, MAN1A2, MAPK8, MAPK9, MARCH6, NFE2L2, NSFL1C, P4HB, SAR1A, SAR1B, SEC23A, SEC24A, SEC24C, SEC62, SEC63, SEL1L, SKP1, SSR1, SSR3, STT3A, SVIP, SYVN1, TRAM1, TUSC3, UBE2D1, UBE2D2, UBE2D3, UBE2G1, UBE2J1, UBQLN2, UBQLN4, UGGT1, XBP1, YOD1*
hsa04120	Ubiquitin mediated proteolysis	136	46	<0.011	*ANAPC1, BRCA1, CBL, CBLB, CDC27, CUL4A, CUL5, DDB1, FBXW8, HERC2, HERC4, HUWE1, KLHL13, KLHL9, NEDD4L, PIAS1, PIAS2, PIAS3, RHOBTB1, SIAH1, SKP1, SMURF2, SYVN1, TRIM37, UBA6, UBE2A, UBE2B, UBE2D1, UBE2D2, UBE2D3, UBE2E1, UBE2F, UBE2G1, UBE2H, UBE2J1, UBE2K, UBE2N, UBE2QL1, UBE2R2, UBE2Z, UBE4A, UBOX5, UBR5, VHL, WWP1, XIAP*

hsa05202	Transcriptional misregulation in cancer	186	62	<0.001	*AFF1, ATM, BAK1, BCL11B, BMI1, CCND2, CCNT1, CCNT2, CD40, CDKN1B, COMMD3-BMI1, DDIT3, DDX5, ELK4, ETV1, ETV6, EWSR1, EYA1, FEV, FLI1, H3F3B, HDAC2, HIST1H3B, HIST1H3F, HIST1H3G, HOXA10, HPGD, IGF1, IGF1R, KLF3, KMT2A, MAF, MEF2C, MEIS1, MEN1, MITF, MLLT1, MLLT3, MYCN, NCOR1, NFKB1, PAX5, PAX7, PLAT, POLK, PPARG, PRCC, PROM1, RELA, RUNX1, RUNX2, RXRA, SIN3A, SIX4, SP1, SS18, SUPT3H, TFE3, TLX3, TRAF1, WNT16, ZEB1*
hsa04010	MAPK signaling pathway	295	91	<0.001	*AKT2, AKT3, ANGPT2, ANGPT4, ARRB1, CACNA1D, CACNA1E, CACNA2D3, CACNB1, CACNB4, CACNG7, CASP3, CDC42, CHUK, CRKL, DDIT3, DUSP10, DUSP7, DUSP8, DUSP9, EFNA3, EFNA5, ELK1, ELK4, ERBB2, ERBB4, EREG, FAS, FGF7, GNG12, HSPA8, IGF1, IGF1R, IGF2, IL1B, IRAK4, JUND, KIT, KITLG, KRAS, MAP2K1, MAP2K2, MAP2K4, MAP3K2, MAP4K3, MAP4K4, MAPK1, MAPK8, MAPK8IP1, MAPK9, MAPKAPK5, MAPT, MECOM, MEF2C, MKNK2, NF1, NFATC1, NFATC3, NFKB1, NLK, NTF3, NTRK2, PAK2, PDGFB, PDGFRA, PDGFRB, PPM1A, PPP3CA, PPP3CB, PPP3R1, PPP5C, PRKACA, PRKCA, PTPRR, RAC1, RAP1A, RAP1B, RASA2, RASGRF1, RASGRP1, RELA, RPS6KA4, RPS6KA5, RPS6KA6, RRAS2, SOS1, SOS2, TAOK1, TAOK2, TGFB2, TGFBR1*

hsa05200	Pathways in cancer	524	153	<0.001	*ABL1, ADCY2, ADCY3, AGTR1, AKT2, AKT3, APPL1, AR, AXIN2, BAK1, BBC3, BCL2, CALM1, CALML3, CALML4, CAMK2A, CASP3, CASP7, CBL, CCND1, CCND2, CDC42, CDH1, CDK4, CDK6, CDKN1B, CHUK, COL4A1, COL4A3, CREBBP, CRKL, CSF2RB, CTNNA3, CXCR4, DVL3, EDNRA, EGLN1, ELK1, EPO, ERBB2, ESR1, ETS1, F2RL3, FAS, FGF7, FZD10, FZD2, FZD3, FZD5, FZD6, FZD7, GNA13, GNAI1, GNAI2, GNAQ, GNB4, GNG11, GNG12, GNG7, GSK3B, GSTA1, GSTM2, GSTM3, HDAC2, HEY1, HEYL, HSP90AA1, IFNA21, IFNGR2, IGF1, IGF1R, IGF2, IL12RB2, IL13RA1, IL23A, IL5, IL6R, IL6ST, IL7R, ITGA6, ITGAV, ITGB1, JAK3, KIT, KITLG, KRAS, LAMC1, LEF1, LPAR1, MAP2K1, MAP2K2, MAPK1, MAPK8, MAPK9, MECOM, MITF, MTOR, NCOA3, NFE2L2, NFKB1, NOS2, NOTCH1, NOTCH2, NQO1, PDGFB, PDGFRA, PDGFRB, PIK3CB, PIK3R3, PLCB1, PLCB4, PLCG2, POLK, PPARG, PRKACA, PRKCA, PTEN, PTGER3, RAC1, RAD51, RALA, RALBP1, RASGRP1, RASSF5, RELA, RPS6KA5, RPS6KB1, RUNX1, RXRA, SKP1, SMAD2, SMAD3, SMAD4, SOS1, SOS2, SP1, STAT1, STAT2, STAT3, SUFU, TCF7L2, TGFB2, TGFBR1, TPM3, TPR, TRAF1, TRAF4, VHL, WNT16, WNT5A, WNT7B, WNT9B, XIAP*

eTable 12 | Significantly enriched GO terms in the ATN-related sncRNA signature.

GO ID	GO Term	Gene Set Size	Counts	Padj
Biological process				
GO: 0022008	Neurogenesis	1551	264	<0.001
GO: 0033554	Cellular response to stress	1867	311	<0.001
GO: 0010629	Negative regulation of gene expression	1733	285	<0.001
GO: 0070727	Cellular macromolecule localization	1825	296	<0.001
GO: 0045935	Positive regulation of nucleobase-containing compound metabolic process	1847	298	<0.001
GO: 0009719	Response to endogenous stimulus	1595	253	<0.001
GO: 0007267	Cell-cell signaling	1575	249	<0.001
GO: 0051049	Regulation of transport	1765	276	<0.001
GO: 0006928	Movement of cell or subcellular component	1967	299	<0.001
GO: 0009888	Tissue development	1925	288	<0.001
Molecular function				
GO: 0019904	Protein domain specific binding	684	142	<0.001
GO: 0019787	Ubiquitin-like protein transferase activity	416	79	<0.001
GO: 0019900	Kinase binding	711	124	<0.001
GO: 0008134	Transcription factor binding	638	111	<0.001
GO: 0003700	DNA-binding transcription factor activity	1700	269	<0.001
GO: 0051020	GTPase binding	646	102	0.008
GO: 0003723	RNA binding	1603	248	<0.001
GO: 0008092	Cytoskeletal protein binding	940	140	0.009
GO: 0046914	Transition metal ion binding	1058	153	0.016
GO: 0017076	Purine nucleotide binding	1865	261	0.002
Cellular component				
GO: 0030054	Cell junction	1268	220	<0.001
GO: 0044451	Nucleoplasm part	1087	178	<0.001
GO: 0005694	Chromosome	1014	162	<0.001
GO: 0097458	Neuron part	1690	269	<0.001
GO: 0005730	Nucleolus	939	144	<0.001
GO: 1902494	Catalytic complex	1346	202	<0.001
GO: 0005794	Golgi apparatus	1516	226	<0.001
GO: 0098805	Whole membrane	1630	229	<0.001
GO: 0005783	Endoplasmic reticulum	1861	250	<0.001
GO: 0005887	Integral component of plasma membrane	1596	213	<0.001

Abbreviations: GO, Gene ontology.

eTable 13 | Significantly enriched GO terms in the AD-related sncRNA signature.

GO ID	GO Term	Gene Set Size	Counts	Padj
Biological process				
GO: 0010629	Negative regulation of gene expression	1733	546	<0.001
GO: 0022008	Neurogenesis	1551	462	<0.001
GO: 0070647	Protein modification by small protein conjugation or removal	1028	303	<0.001
GO: 0009719	Response to endogenous stimulus	1595	470	<0.001
GO: 0070727	Cellular macromolecule localization	1825	533	<0.001
GO: 2000026	Regulation of multicellular organismal development	1908	552	<0.001
GO: 0009891	Positive regulation of biosynthetic process	1949	557	<0.001
GO: 0046907	Intracellular transport	1803	508	<0.001
GO: 0033554	Cellular response to stress	1867	520	<0.001
GO: 0008283	Cell proliferation	1986	537	<0.001
Molecular function				
GO: 0019787	Ubiquitin-like protein transferase activity	416	139	<0.001
GO: 0019904	Protein domain specific binding	684	217	<0.001
GO: 0019901	Protein kinase binding	631	187	<0.001
GO: 0003700	DNA-binding transcription factor activity	1700	500	<0.001
GO: 0003723	RNA binding	1603	449	<0.001
GO: 0051020	GTPase binding	646	169	<0.001
GO: 0032553	Ribonucleotide binding	1865	466	<0.001
GO: 0046914	Transition metal ion binding	1058	264	<0.001
GO: 0042802	Identical protein binding	1696	413	<0.001
GO: 0005102	Signalling receptor binding	1538	363	<0.001
Cellular component				
GO: 0044451	Nucleoplasm part	1087	329	<0.001
GO: 0097458	Neuron part	1690	479	<0.001
GO: 0005694	Chromosome	1014	278	<0.001
GO: 0005730	Nucleolus	939	255	<0.001
GO: 1902494	Catalytic complex	1346	365	<0.001
GO: 0005794	Golgi apparatus	1516	403	<0.001
GO: 0098805	Whole membrane	1630	416	<0.001
GO: 0005783	Endoplasmic reticulum	1861	454	<0.001
GO: 0031226	Intrinsic component of plasma membrane	1673	381	<0.001
GO: 0044430	Cytoskeletal part	1620	364	<0.001

Abbreviations: GO, Gene Ontology.

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