

Supplementary tables for:

Connecting *HTT* intermediate alleles and microRNA dysregulation to enhanced tauopathy in Late-Onset Alzheimer's Disease

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Table S1. Clinical and neuropathological information from subjects with postmortem brain tissue (caudate) samples

Patient ID	Biobank	Gender	Onset age	Death age	Braak stage	APOE	Disease duration	HTT short allele	HTT long allele	P.M.I (h)
Control										
C1	BPA	M	N. A	82	N. A	3/3	N. A	18	21	5:30
C2	BPA	F	N. A	71	N. A	3/3	N. A	18	21	4:50
C3	BPA	M	N.A	77	N.A	3/4	N.A	17	17	N.A
C4	BPA	M	N. A	69	N. A	2/4	N. A	15	23	4:10
C5	BPA	M	N. A	68	N. A	3/3	N. A	17	26	4:00
C6	BPA	F	N. A	71	N. A	3/3	N. A	15	17	7:10
LOAD non-HTT IAs										
A1	BPA	M	N. A	68	VI	4/4	N. A	18	20	4:00
A2	IBIBAPS	M	73	87	VI	3/3	14	15	18	10:00
A3	IDIBAPS	M	78	87	V	3/4	9	16	18	15:00
A4	IDIBAPS	F	70	76	VI	3/4	6	17	18	10:00
A5	IDIBAPS	M	77	83	VI	3/3	6	17	17	8:45
A6	IDIBAPS	F	79	83	V	3/4	4	11	19	6:00
A7	IDIBAPS	F	82	89	V	3/3	7	17	17	13:00
A8	IDIBAPS	M	65	74	V	4/4	9	18	19	6:45
A9	IDIBAPS	F	71	85	V	3/4	14	16	17	5:00
A10	IDIBAPS	F	79	86	VI	3/4	7	16	17	4:30
A11	IDIBAPS	M	63	78	VI	2/3	15	17	19	7:00
A12	IDIBAPS	F	N. A	84	VI	2/4	N. A	15	17	16:30
A13	IDIBAPS	M	N. A	74	VI	4/4	N. A	17	17	8:00
A14	IDIBAPS	F	76	87	V	3/3	9	16	17	19:30
LOAD HTT IAs										
B1	BPA	M	N. A	89	III	3/3	N. A	19	27	N. A
B2	BPA	M	N. A	65	VI	N. A	N. A	17	29	5:00
B3	BPA	F	N. A	89	V	3/3	N. A	21	29	4:55
B4	IDIBAPS	F	N. A	86	VI	3/3	N. A	17	30	13:00
B5	IDIBAPS	F	78	81	V	3/4	3	17	34	5:30
B6	IDIBAPS	M	68	73	V	3/3	5	15	27	6:30
B7	IDIBAPS	F	87	94	V	3/3	7	15	39	12:30
B8	IDIBAPS	M	69	73	VI	3/3	4	20	30	14:30
B9	IDIBAPS	F	75	84	VI	3/3	9	18	27	5:00
B10	IDIBAPS	M	62	77	VI	2/3	15	17	29	5:00
B11	IDIBAPS	F	N. A	81	VI	3/3	N. A	17	27	5:00
B12	IDIBAPS	F	66	72	VI	4/4	6	17	29	14:00
B13	IDIBAPS	M	82	88	V	3/4	6	13	27	3:00
Abbreviations: N. A, not available; M, Male; F, Female; BPA, Biobanco del Principado de Asturias; IDIBAPS, Instituto de Investigaciones Biomédicas August Pi i Sunyer; APOE, Apolipoprotein E; HTT, Huntingtin gene; P.M.I, <i>post mortem</i> interval; HTT IAs, Huntingtin gene intermediate alleles.										

31

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Table S2. Patients in each experiment according to demographic and neuropathological data										
Patient ID	Gender	Onset age	Death age	Braak stage	IHC	IF	PLA	WB	RT-qPCR	small RNA-sequencing
Control										
C1	M	N. A	82	N. A	+	-	-	-	+	+
C2	F	N. A	71	N. A	+	-	-	-	+	+
C3	M	N. A	77	N. A	+	-	-	-	+	+
C4	M	N. A	69	N. A	-	+	-	-	+	+
C5	M	N. A	68	N. A	+	+	+	-	-	+
C6	F	N. A	71	N. A	+	+	+	-	+	+
LOAD non-HTT IAs										
A1	M	N. A	68	VI	-	-	-	-	+	+
A2	M	73	87	VI	+	+	-	-	+	+
A3	M	78	87	V	+	-	-	+	+	+
A4	F	70	76	VI	+	+	-	+	+	+
A5	M	77	83	VI	+	-	-	+	+	+
A6	F	79	83	V	-	-	-	+	+	+
A7	F	82	89	V	+	-	-	+	+	+
A8	M	65	74	V	+	-	-	-	+	+
A9	F	71	85	V	+	+	-	+	+	+
A10	F	79	86	VI	+	-	-	-	+	+
A11	M	63	78	VI	-	-	+	+	+	+
A12	F	N. A	84	VI	-	-	+	-	+	+
A13	M	N. A	74	VI	+	-	-	-	+	+
A14	F	76	87	V	+	+	-	-	+	+
LOAD HTT IAs										
B1	M	N. A	89	III	-	-	-	-	+	+
B2	M	N. A	65	VI	-	-	-	-	+	+
B3	F	N. A	89	V	-	-	-	-	+	+
B4	F	N. A	86	VI	+	-	-	+	+	+
B5	F	78	81	V	-	+	-	+	+	+
B6	M	68	73	V	+	-	-	-	+	+
B7	F	87	94	V	+	-	-	+	+	+
B8	M	69	73	VI	+	+	+	+	+	+
B9	F	75	84	VI	+	+	-	-	+	+
B10	M	62	77	VI	+	+	-	+	+	+
B11	F	N. A	81	VI	+	-	+	+	+	+
B12	F	66	72	VI	+	-	-	+	+	+
B13	M	82	88	V	+	-	-	-	+	+
Abbreviations: N. A, not available; M, Male; F, Female; IHC, immunohistochemistry; IF, immunofluorescence; PLA, proximity ligation assay; WB, western blot; +, included for experiment; -, excluded for experiment; <i>HTT</i> IAs, Huntingtin gene intermediate alleles; RT-qPCR, reverse transcription quantitative polymerase chain reaction										

Table S3. Primary antibodies used in each experiment						
Experiment	Primary antibody	Clone	Source	Dilution	Vender	Reference
<i>IHC</i>	anti- tau RD3	8E6C11	Mouse-IgG	1:400	Merck Millipore	05-803
	anti-tau RD4	1E1A6	Mouse-IgG	1:100	Merck Millipore	05-804
	anti-HTT	EPR5526	Rabbit-IgG	1:100	Abcam	Ab109115
	anti- HTT	EM-48	Mouse-IgG	1:50	Merck Millipore	MAB5374
<i>IF</i>	anti-SFPQ	6D7	Mouse-IgG	1:100	Sigma Aldrich	WH0006421M2
	anti-FUS	-	Rabbit-IgG	1:100	Bethyl laboratories	A300-293A
<i>PLA</i>	anti-SFPQ	6D7	Mouse-IgG	1:100	Sigma Aldrich	WH0006421M2
	anti-FUS	-	Rabbit-IgG	1:300	Bethyl laboratories	A300-293A
<i>WB</i>	anti- tau RD3	8E6C11	Mouse-IgG	1:500	Merck Millipore	05-803
	anti-tau RD4	1E1A6	Mouse-IgG	1:500	Merck Millipore	05-804
	anti-FUS/TLS	4H11	Mouse-IgG	1:500	Santa Cruz Biotechnology	sc-47711
	anti- SFPQ	B92	Mouse-IgG	1:1000	Abcam	Ab11825
	anti-tau (total)	-	Mouse-IgG	1:400	Invitrogen	AHB0042
	anti-SRSF6	-	Rabbit-IgG	1:500	LSBio	LS-B5712
	anti- β -Actin (HRP)	-	Mose-IgG	1:4000	Santa Cruz Biotechnology	sc-47778
Abbreviations: IHC, immunohistochemistry; IF, immunofluorescence; PLA, proximity ligation assay; WB, western blot						

Table S4. RNA related aspects to analyzed samples				
	Control (N = 5)	LOAD non- <i>HTT</i> IAs (N = 14)	LOAD <i>HTT</i> IAs (N = 13)	<i>p</i> -value
RNA ng/μl				
Mean (SD)	319.61 (136.58)	231.01 (52.2)	322.87 (98.18)	<i>n. s</i>
Range	148.8-463.5	141.7-293.4	211.6-583.3	
RNA ratio 260/280				
Mean (SD)	1.95 (0.08)	1.97 (0.02)	1.97 (0.04)	<i>n. s</i>
Range	1.73-2.02	1.92-1.99	1.94-2.01	
RIN value				
Mean (SD)	3.65 (0.72)	3.2 (1.26)	3.73 (0.61)	<i>n. s</i>
Range	2.4-4.9	1.5-4.9	2.1-4.3	
28S/18S ratio				
Mean (SD)	2.55 (1.47)	6.76 (1.45)	2.9 (1.54)	< 0.001a <0.001b
Range	0.8-5.3	4.7-8.7	1.3-5.7	
PMI (h)				
Mean (SD)	7:49 (4.27)	5:08 (1.28)	9:34 (4.75)	<i>n. s</i>
Range	3:00-14:30	4:00-7:10	4:00-19:30	
Abbreviations: n.s, no significance; RIN, RNA integrity number; PMI, <i>post mortem</i> interval. Statistical analysis: One-way ANOVA followed by Tukey's test. ^a LOAD <i>HTT</i> IAs vs. Control. ^b LOAD non- <i>HTT</i> IAs vs. Control.				

Table S5. Genes validated for qPCR (Anygene)	
Genes	NM Code
<i>SRSF1</i>	NM_006924.5
<i>SRSF2</i>	NM_001195427.2
<i>SRSF3</i>	NM_003017.5
<i>SRSF4</i>	NM_005626.5
<i>SRSF7</i>	NM_005626.5
<i>SRSF9</i>	NM_003769.3
<i>SRSF11</i>	NM_001350605.2
<i>SFPQ</i>	NM_005066.3
<i>FUS</i>	NM_004960.3
<i>β-ACTIN</i>	NM_001101.5
<i>GAPDH</i>	NM_002046.7

Table S6. Pre-designed sequences used for qPCR		
Genes	Sequence	Amplification protocol
<i>Tau 4R</i> (forward)	5' GGTGCAGATAATTAATAAGAAGCTGGA 3'	10 min 95 °C (40x) 10 s 95 °C 30 s 60 °C 1 min 60 °C 30 s 65 °C
<i>Tau 4R</i> (reverse)	5' GTGTTTGATATTATCCTTTGAGCCAC 3'	
<i>Tau 3R</i> (forward)	5' GAAGAATGTCAAGTCCAAGATCGG 3'	
<i>Tau 3R</i> (reverse)	5' GACTATTTGCACCTTCCCGC 3'	
<i>MAPT</i> (forward)	5'AGAGTCCAGTCGAAGATTGGGTC 3'	
<i>MAPT</i> (reverse)	5' GGGTTTCAATCTTTTATTTCTCC 3'	

Table S7. Frequency and distribution of APOE isoforms in the studied cohorts			
APOE alleles	Control (<i>N</i> = 335)	LOAD (<i>N</i> = 323)	<i>p</i>-value^a
ε2, ε2	1 (0.30%)	1 (0.31%)	0.746
ε2, ε3	40 (12.01%)	4 (1.23%)	<0.001
ε2, ε4	9 (2.70%)	10 (3.09%)	0.484
ε3, ε3	221 (66.36%)	151 (46.74%)	<0.001
ε3, ε4	60 (18.01%)	127 (39.31%)	<0.001
ε4, ε4	2 (0.60%)	29 (8.97%)	<0.001
^a Data are shown as N (%). Statistical analysis: Fisher's test.			

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	APOE		Onset age		Death age		Braak stage		Disease duration		CAG size	
miRNA ID	Spearman R	p-value	Spearman R	p-value	Spearman R	p-value	Spearman R	p-value	Spearman R	p-value	Spearman R	p-value
miR-218-5p	-0.22	0.39747	-0.20	0.45736	-0.12	0.56470	0.06	0.75510	-0.16	0.55893	0.52	0.00573
miR-99b-5p	-0.20	0.44655	-0.18	0.50973	-0.30	0.12547	0.18	0.37153	-0.53	0.03555	0.59	0.00114
miR-128-3p	-0.30	0.23975	-0.09	0.73956	-0.06	0.74793	-0.09	0.66710	-0.37	0.15974	0.48	0.01133
miR-9-3p	-0.30	0.24703	-0.25	0.344	0.03	0.89996	0.07	0.73932	-0.13	0.62834	0.58	0.00158
miR-487b-3p	-0.46	0.06461	0.06	0.81126	0.21	0.29490	-0.16	0.41467	-0.12	0.66831	0.36	0.06626
miR-9-5p	-0.37	0.1432	-0.18	0.50612	-0.07	0.73644	0.02	0.92827	-0.03	0.91873	0.45	0.01728
miR-30d-5p	-0.66	0.00491	-0.17	0.51693	0.18	0.37932	-0.28	0.16083	0.02	0.93185	0.38	0.04858
miR-151a-5p	-0.12	0.6445	-0.12	0.66196	-0.08	0.68772	0.02	0.92001	0.05	0.84038	0.39	0.04366
miR-23b-3p	-0.18	0.49208	-0.36	0.16744	-0.33	0.09397	0.02	0.91726	-0.40	0.13000	0.38	0.04799
miR-191-5p	-0.45	0.07193	-0.26	0.33542	0.09	0.66988	-0.14	0.49756	-0.01	0.98458	0.26	0.18698
miR-27b-3p	-0.10	0.70713	-0.14	0.59904	-0.34	0.08137	0.06	0.77896	-0.38	0.14269	0.46	0.01547
miR-30a-5p	-0.35	0.16235	0.02	0.94098	0.10	0.60247	-0.22	0.26176	-0.05	0.86200	0.40	0.04032
miR-100-5p	-0.25	0.34116	-0.28	0.29689	-0.18	0.36027	0.10	0.60739	-0.37	0.15447	0.40	0.03816
miR-126-3p	-0.19	0.46661	0.07	0.80275	0.08	0.69220	-0.04	0.83536	-0.44	0.08607	0.31	0.11414

Table S9. Detailed data for KEGG enrichment analysis for neurodegeneration-related pathways targeted by differentially expressed miRNAs between controls and LOAD subgroups							
KEGG term ID	Term name	Term genes	Target genes	miRNAs	miRNA names	P-value	FDR
HSA04120	Ubiquitin mediated proteolysis	142	112	26	let-7a-5p, miR-100-5p, miR-103a-3p, miR-124-3p, miR-125a-5p, miR-125b-5p, miR-126-3p, miR-128-3p, miR-139-5p, miR-151a-3p, miR-181a-5p, miR-191-5p, miR-218-5p, miR-221-3p, miR-23b-3p, miR-24-3p, miR-27b-3p, miR-29a-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99a-3p, miR-99b-5p	2.9E-19	9.89E-17
HSA04140	Autophagy	146	105	25	let-7a-5p, miR-100-5p, miR-103a-3p, miR-124-3p, miR-125a-5p, miR-125b-5p, miR-126-3p, miR-128-3p, miR-139-5p, miR-151a-3p, miR-181a-5p, miR-191-5p, miR-218-5p, miR-221-3p, miR-23b-3p, miR-24-3p, miR-27b-3p, miR-29a-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99a-3p, miR-99b-5p	2.46E-13	1.4E-11
HSA05022	Pathways of neurodegeneration	539	296	26	let-7a-5p, miR-100-5p, miR-103a-3p, miR-124-3p, miR-125a-5p, miR-125b-5p, miR-126-3p, miR-128-3p, miR-139-5p, miR-151a-3p, miR-181a-5p, miR-191-5p, miR-218-5p, miR-221-3p, miR-23b-3p, miR-24-3p, miR-27b-3p, miR-29a-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99a-3p, miR-99b-5p	6.98E-10	1.46E-08
HSA04810	Regulation of actin cytoskeleton	224	139	26	let-7a-5p, miR-100-5p, miR-103a-3p, miR-124-3p, miR-125a-5p, miR-125b-5p, miR-126-3p, miR-128-3p, miR-139-5p, miR-151a-3p, miR-181a-5p, miR-191-5p, miR-218-5p, miR-221-3p, miR-23b-3p, miR-24-3p, miR-27b-3p, miR-29a-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99a-3p, miR-99b-5p	1.19E-09	2.03E-08

					30c-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99a-3p, miR-99b-5p		
HSA05016	Huntington disease	339	197	26	let-7a-5p, miR-100-5p, miR-103a-3p, miR-124-3p, miR-125a-5p, miR-125b-5p, miR-126-3p, miR-128-3p, miR-139-5p, miR-151a-3p, miR-181a-5p, miR-191-5p, miR-218-5p, miR-221-3p, miR-23b-3p, miR-24-3p, miR-27b-3p, miR-29a-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99a-3p, miR-99b-5p	1.51E-09	2.46E-08
HSA05017	Spinocerebellar ataxia	145	96	26	let-7a-5p, miR-100-5p, miR-103a-3p, miR-124-3p, miR-125a-5p, miR-125b-5p, miR-126-3p, miR-128-3p, miR-139-5p, miR-151a-3p, miR-181a-5p, miR-191-5p, miR-218-5p, miR-221-3p, miR-23b-3p, miR-24-3p, miR-27b-3p, miR-29a-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99a-3p, miR-99b-5p	3.86E-09	5.26E-08
HSA05014	Amyotrophic lateral sclerosis	408	228	26	let-7a-5p, miR-100-5p, miR-103a-3p, miR-124-3p, miR-125a-5p, miR-125b-5p, miR-126-3p, miR-128-3p, miR-139-5p, miR-151a-3p, miR-181a-5p, miR-191-5p, miR-218-5p, miR-221-3p, miR-23b-3p, miR-24-3p, miR-27b-3p, miR-29a-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99a-3p, miR-99b-5p	9.71E-09	1.23E-07
HSA04211	Longevity regulating pathway	105	72	24	let-7a-5p, miR-100-5p, miR-103a-3p, miR-124-3p, miR-125a-5p, miR-125b-5p, miR-126-3p, miR-128-3p, miR-139-5p, miR-151a-3p, miR-181a-5p, miR-191-5p, miR-218-5p, miR-221-3p, miR-23b-3p, miR-24-3p, miR-27b-3p, miR-29a-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	3.85E-08	3.86E-07

HSA05010	Alzheimer disease	426	234	26	let-7a-5p, miR-100-5p, miR-103a-3p, miR-124-3p, miR-125a-5p, miR-125b-5p, miR-126-3p, miR-128-3p, miR-139-5p, miR-151a-3p, miR-181a-5p, miR-191-5p, miR-218-5p, miR-221-3p, miR-23b-3p, miR-24-3p, miR-27b-3p, miR-29a-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99a-3p, miR-99b-5p	4.54E-08	4.43E-07
HSA05012	Parkinson disease	282	159	25	let-7a-5p, miR-100-5p, miR-103a-3p, miR-124-3p, miR-125a-5p, miR-125b-5p, miR-126-3p, miR-128-3p, miR-139-5p, miR-151a-3p, miR-181a-5p, miR-191-5p, miR-218-5p, miR-221-3p, miR-23b-3p, miR-24-3p, miR-27b-3p, miR-29a-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99a-3p, miR-99b-5p	8.36E-07	6.06E-06
HSA03013	RNA transport	199	113	26	let-7a-5p, miR-100-5p, miR-103a-3p, miR-124-3p, miR-125a-5p, miR-125b-5p, miR-126-3p, miR-128-3p, miR-139-5p, miR-151a-3p, miR-181a-5p, miR-191-5p, miR-218-5p, miR-221-3p, miR-23b-3p, miR-24-3p, miR-27b-3p, miR-29a-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99a-3p, miR-99b-5p	2.08E-05	9.44E-05
HSA03015	mRNA surveillance pathway	108	67	24	let-7a-5p, miR-100-5p, miR-103a-3p, miR-124-3p, miR-125a-5p, miR-125b-5p, miR-126-3p, miR-128-3p, miR-139-5p, miR-151a-3p, miR-181a-5p, miR-191-5p, miR-218-5p, miR-221-3p, miR-23b-3p, miR-24-3p, miR-27b-3p, miR-29a-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99a-3p	2.4E-05	0.000106
HSA03018	RNA degradation	101	55	26	let-7a-5p, miR-100-5p, miR-103a-3p, miR-124-3p, miR-125a-5p, miR-125b-5p, miR-126-3p, miR-128-3p, miR-139-5p, miR-151a-3p, miR-181a-5p, miR-191-5p, miR-218-5p, miR-221-3p, miR-23b-3p, miR-24-3p, miR-27b-3p, miR-29a-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99a-3p	0.008542	0.020512

					30c-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99a-3p, miR-99b-5p		
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81

82

Table S10. Detailed data for KEGG enrichment analysis for neurodegeneration-related pathways targeted by differentially expressed miRNAs between LOAD subgroups.							
KEGG term ID	Term name	Term genes	Target genes	miRNAs	miRNA names	P-value	FDR
HSA04120	Ubiquitin mediated proteolysis	142	88	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	1.78E-16	6.06E-14
HSA04140	Autophagy	146	81	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	1.28E-11	8.72E-10
HSA04211	Longevity regulating pathway	105	60	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	1.23E-09	2.8E-08
HSA03015	mRNA surveillance pathway	108	61	12	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p	1.69E-09	3.59E-08
HSA04810	Regulation of actin cytoskeleton	224	104	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	1.49E-08	2.2E-07
HSA05017	Spinocerebellar ataxia	145	70	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p	5.57E-07	5.43E-06

					3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p		
HSA03013	RNA transport	199	88	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	2.53E-06	2.01E-05
HSA05014	Amyotrophic lateral sclerosis	408	159	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	5.22E-06	3.87E-05
HSA05016	Huntington disease	339	133	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	2.1E-05	0.000117
HSA05022	Pathways of neurodegeneration	539	199	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	2.2E-05	0.000119
HSA05010	Alzheimer disease	426	158	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	0.00012	0.00048
HSA05012	Parkinson disease	282	108	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	0.000363	0.001318
HSA03018	RNA degradation	101	45	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	0.000565	0.001945

Table S11. Detailed data for REACTOME enrichment analysis for RNA-related pathways/processes targeted by differentially expressed miRNAs between LOAD subgroups

Reactome term ID	Term name	Term genes	Target genes	miRNAs	miRNA names	P-value	FDR
R-HSA-74160	Gene expression (Transcription)	1661	717	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	5.57E-31	1.34E-27
R-HSA-73857	RNA Polymerase II Transcription	1509	642	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	2.03E-25	2.44E-22
R-HSA-72172	mRNA Splicing	200	106	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	3.38E-11	3.12E-09
R-HSA-159231	Transport of Mature mRNA transcript	43	30	10	miR-100-5p, miR-128-3p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	1.51E-07	5.75E-06
R-HSA-8953854	Metabolism of RNA	790	301	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	2.93E-06	6.78E-05
R-HSA-109688	mRNA 3'-end processing	64	35	12	miR-100-5p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	5.57E-05	0.000806

R-HSA-8868773	Metabolism of non-coding RNA	57	31	11	miR-100-5p, miR-128-3p, miR-151a-3p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	0.000168	0.001805
R-HSA-191859	snRNP Assembly	57	31	11	miR-100-5p, miR-128-3p, miR-151a-3p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	0.000168	0.001805
R-HSA-211000	Gene Silencing by RNA	141	63	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	0.000311	0.002919
R-HSA-429947	Deadenylation of mRNA	35	18	10	miR-100-5p, miR-128-3p, miR-151a-3p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p	0.008329	0.043759

Table S12. GO-Cellular Component enrichment analysis of predicted target genes of differentially expressed miRNAs between LOAD subgroups

GO term ID	Term name	Term genes	Target genes	miRNAs	miRNA names	P-value	FDR
GO:0005634	Nucleus	7177	2725	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	1.3E-143	2.4E-140
GO:0005829	Cytosol	5614	2190	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	1.1E-119	6.5E-117

GO:003299 1	Protein-containing complex	785	359	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	8.38E-31	2.98E-28
GO:001660 7	Nuclear speck	472	208	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	4E-16	5.47E-14
GO:199090 4	Ribonucleoprotein complex	182	94	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	1.04E-12	1.09E-10
GO:001660 4	Nuclear body	360	155	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	2.05E-11	1.46E-09
GO:007100 7	U2-type catalytic step 2 spliceosome	31	17	10	miR-128-3p, miR-151a-3p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	0.000913	0.012595

Table S13. *GO-Molecular Function* enrichment analysis of predicted target genes of differentially expressed miRNAs between LOAD subgroups

GO term ID	Term Name	Term genes	Target genes	miRNAs	miRNA names	P-value	FDR
GO:000372 3	RNA binding	1707	759	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	2.8E-54	6.09E-51

GO:000016 6	Nucleotide binding	2030	765	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	4.47E-25	4.87E-22
GO:000367 7	DNA binding	2466	900	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	1.94E-24	1.41E-21
GO:000368 2	Chromatin binding	513	243	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	6.92E-22	4.31E-19
GO:000372 9	mRNA binding	229	123	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	7.2E-17	2.09E-14
GO:000373 0	mRNA 3'-UTR binding	103	47	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p	7.38E-05	0.003912
GO:004815 6	Tau protein binding	45	25	10	miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p	7.63E-05	0.003957
GO:007088 3	Pre-miRNA binding	6	6	10	miR-126-3p, miR-128-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p	0.000451	0.016624

GO:004802 7	mRNA 5'-UTR binding	27	16	12	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	0.00057 4	0.02053 8
GO:003519 8	miRNA binding	36	19	12	miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	0.00127 1	0.04069 8

Table S14. GO-Biological process enrichment analysis of predicted target genes of differentially expressed miRNAs between LOAD subgroups

GO term ID	Term Name	Term genes	Target genes	miRNAs	miRNA names	P-value	FDR
GO:000639 7	mRNA processing	436	201	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR- 99b-5p	7.24E- 17	7.60E- 14
GO:000838 0	RNA splicing	333	157	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR- 99b-5p	1.70E- 14	1.34E- 11
GO:000039 8	mRNA splicing (spliceosome)	283	127	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR- 99b-5p	3.19E- 10	1.12E- 07
GO:000640 6	mRNA export from nucleus	111	61	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p,	1.16E- 09	3.86E- 07

					miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p		
GO:0051028	mRNA transport	117	62	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	5.78E-09	1.66E-06
GO:0006396	RNA processing	100	55	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	7.22E-09	1.98E-06
GO:0006405	RNA export from nucleus	62	33	12	miR-100-5p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	1.80E-05	0.001649
GO:0010586	miRNA metabolic process	16	12	13	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	0.000111	0.006454
GO:0070918	Pre-miRNA processing	14	11	12	miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p, miR-99b-5p	0.000108	0.006454
GO:0043488	Regulation of mRNA stability	138	57	14	miR-100-5p, miR-126-3p, miR-128-3p, miR-151a-3p, miR-191-5p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-487b-3p, miR-9-3p, miR-9-5p, miR-99b-5p	0.000353	0.016367
GO:0006376	mRNA splice site selection	23	14	8	miR-128-3p, miR-218-5p, miR-23b-3p, miR-27b-3p, miR-30a-5p, miR-30d-5p, miR-9-3p, miR-9-5p	0.000854	0.031781

Table S15. Spearman correlation coefficient and <i>p-value</i> between miRNA expression, CAG expansion number and histopathological hallmarks analyzed						
	Pretangles		Ghost tangles		Soluble HTT signal	
	Rho Spearman	<i>p-value</i>	Rho Spearman	<i>p-value</i>	Rho Spearman	<i>p-value</i>
miR-218-5p	-0.75	0.0003	0.57	0.0131	0.73	0.0002
miR-99b-5p	-0.35	0.1608	0.38	0.1221	0.55	0.0122
miR-128-3p	-0.72	0.0008	0.45	0.0615	0.56	0.0105
miR-9-3p	-0.45	0.0594	0.33	0.1762	0.58	0.0071
miR-487b-3p	-0.67	0.0024	0.36	0.1468	0.51	0.0212
miR-9-5p	-0.58	0.0112	0.43	0.0745	0.54	0.0143
miR-30d-5p	-0.75	0.0004	0.26	0.2892	0.42	0.0666
miR-151a-5p	-0.43	0.0713	0.33	0.1805	0.58	0.0072
miR-23b-3p	-0.32	0.2013	0.18	0.4679	0.49	0.0265
miR-191-5p	-0.50	0.0329	0.17	0.4886	0.45	0.0492
miR-27b-3p	-0.31	0.2060	0.32	0.2000	0.64	0.0024
miR-30a-5p	-0.26	0.2909	0.49	0.0402	0.47	0.0362
miR-100-5p	0.07	0.7724	0.14	0.5812	0.38	0.0937
miR-126-3p	-0.12	0.6416	0.32	0.1969	0.43	0.0613
CAG size	-0.59	0.0101	0.58	0.0119	0.70	0.0006