

Exosomal MicroRNAs modulate the cognitive function in fasudil treated APPswe/PSEN1dE9 transgenic (APP/PS1) mice model of Alzheimer's disease

Yuqing Yan^{1*#}, Ye Gao^{1*}, Gajendra Kumar^{3*#}, Qingli Fang¹, Hailong Yan¹, Nianping Zhang¹, Yuna Zhang¹, Lijuan Song², Jiehui Li¹, Yucheng Zheng¹, Nan Zhang¹, Peijun Zhang¹, Cungen Ma^{1, 2#}

1. Institute of Brain Science, Shanxi Key Laboratory of Inflammatory Neurodegenerative Diseases, Medical School of Shanxi Datong University, Datong, China.
2. The Key Research Laboratory of Benefiting Qi for Acting Blood Circulation Method to Treat Multiple Sclerosis of State Administration of Traditional Chinese Medicine, Research Center of Neurobiology, Shanxi University of Chinese Medicine, Taiyuan, China.
3. Department of Neuroscience, City University of Hong Kong, Kowloon, Hong Kong.

* Contributed equally.

Corresponding author (Yuqing Yan: 779734216@qq.com; Gajendra Kumar: gajendra_kumar@brown.edu, Cungen Ma: macungen@sxtcm.edu.cn).

Supplementary table 1: Sample validation using read counts and error rate.

Sample	Raw Reads	Bases	Error rate	Q20	Q30	GC_content	clean reads
WT_A	10114488	0.759G	0.09%	85.38%	74.90%	37.14%	3765627
WT_B	15649992	1.174G	0.14%	81.26%	71.29%	35.63%	3164192
ADNS_A	12170574	0.913G	0.10%	84.74%	73.66%	39.00%	3151328
ADNS_B	15584627	1.169G	0.14%	81.06%	70.73%	31.96%	2918508
ADF_A	12046496	0.903G	0.09%	84.91%	74.44%	38.65%	3587425
ADF_B	10480737	0.786G	0.09%	85.97%	75.40%	41.00%	3833080

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Supplementary table 2: Priority order of Small RNA (sRNA).

Types	ADF_A	ADF_A (percent)	ADF_B	ADF_B (percent)	ADNS_A	ADNS_A (percent)	ADNS_B	ADNS_B (percent)	WT_A	WT_A (percent)	WT_B	WT_B (percent)
total	2734952	100%	3008437	100%	2817263	100%	2606403	100%	3309916	100%	2630666	100%
known_miRNA	5631	0%	6721	0%	7077	0%	5565	0%	5235	0%	5358	0%
rRNA	1643733	60%	2019593	67%	2058486	73%	1937039	74%	989965	30%	1187153	45%
tRNA	10510	0%	11156	0%	10988	0%	10809	0%	10796	0%	16149	1%
snRNA	78310	3%	66380	2%	92660	3%	68786	3%	228357	7%	120080	5%
snoRNA	12926	0%	7089	0%	8572	0%	7824	0%	30872	1%	17806	1%
repeat	513503	19%	389576	13%	270555	10%	246434	9%	1486776	45%	794220	30%
novel_miRNA	955	0%	432	0%	688	0%	396	0%	701	0%	885	0%
exon	66573	2%	45438	2%	44744	2%	32146	1%	147210	4%	114127	4%
intron	49955	2%	39118	1%	29890	1%	30317	1%	121697	4%	88806	3%
other	352856	13%	422934	14%	293603	10%	267087	10%	288307	9%	286082	11%

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Supplementary table 3a: Differential miRNA was screened, based on fold change and significant level (p/q value) for WT_vs_ADNS.

sRNA_tpm	WT_A	WT_B	ADNS_A	ADNS_B	log2FoldChange	P value
novel_130	39462.86654	0	0	0	-9.5033	0.047063
novel_56	5755.00137	7638.732869	0	0	-7.448	0.0066963
mmu-miR-1903	25760.48232	14378.79128	4415.011038	1239.157373	-3.04	0.0058736
mmu-miR-7058-3p	58098.10907	40889.68771	7910.228109	11648.07931	-2.5302	0.0018204
mmu-miR-25-3p	24116.19622	36845.65266	53532.00883	120693.9281	1.512	0.038549
mmu-miR-144-3p	2192.381474	7638.732869	14900.66225	26517.96778	2.2458	0.025886
novel_131	0	224.6686138	2391.464312	10408.92193	5.7948	0.0283
mmu-miR-126a-3p	0	0	5334.805004	2230.483271	6.3615	0.048557
mmu-miR-142a-3p	0	0	5150.84621	3221.80917	6.505	0.037973
mmu-miR-142b	0	0	5150.84621	3221.80917	6.505	0.037973
mmu-miR-140-3p	0	0	4047.093451	4708.798017	6.5648	0.034056
mmu-miR-451a	0	0	3863.134658	5204.460967	6.6142	0.031333
mmu-let-7i-5p	0	0	2391.464312	6939.281289	6.6503	0.030465
mmu-miR-1a-3p	0	0	10853.5688	247.8314746	6.9224	0.026137
mmu-miR-1b-5p	0	0	10853.5688	247.8314746	6.9224	0.026137
mmu-miR-16-5p	0	0	919.7939662	12887.23668	7.2102	0.011791
mmu-miR-19a-3p	0	0	2207.505519	14374.22553	7.4763	0.0047744

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Supplementary table 3b: Differential miRNA was screened, based on fold change and significant level (p/q value) for ADNS_vs_ADF.

sRNA_tpm	ADNS_A	ADNS_B	ADF_A	ADF_B	log2FoldChange	pval
mmu-miR-130b-3p	5334.805004	15613.3829	0	0	-7.8612	0.0020358
novel_63	9197.939662	5700.123916	0		-7.5538	0.0062166
mmu-miR-19a-3p	2207.505519	14374.22553	0	0	-7.4565	0.0092767
mmu-miR-451a	3863.134658	5204.460967	0	0	-6.7432	0.049054
mmu-miR-423-5p	7726.269316	8426.270136	258.8661662	0	-6.1866	0.015919
mmu-miR-574-5p	36975.71744	19578.68649	10354.64665	5743.243243	-2.2644	0.025623
mmu-miR-466i-5p	310154.5254	158116.4808	105099.6635	51013.51351	-2.0394	0.017422
mmu-let-7i-5p	2391.464312	6939.281289	24851.15195	29391.89189	2.2615	0.044319

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Supplementary table 3c: Differential miRNA for WT_vs_ADNS and ADNS_vs_ADF.venn.

	WT_vs_ADNS							ADNS_vs_ADF				
sRNA_tpm	WT_A	WT_B	ADNS_A	ADNS_B	log2FoldC hange	pval	ADNS_A	ADNS_B	ADF_A	ADF_B	log2FoldC hange	P value
mmu-let-7i- 5p	0	0	2391.46 4312	6939.28 1289	6.6503	0.0304 65	2391.46 4312	6939.28 1289	24851.1 5195	29391.8 9189	2.2615	0.0443 19
mmu-miR-1 9a-3p	0	0	2207.50 5519	14374.2 2553	7.4763	0.0047 744	2207.50 5519	14374.2 2553	0	0	-7.4565	0.0092 767
mmu-miR-4 51a	0	0	3863.13 4658	5204.46 0967	6.6142	0.0313 33	3863.13 4658	5204.46 0967	0	0	-6.7432	0.0490 54

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Supplement table 4a: Prediction and analysis of target genes for WT_vs_ADNS.

S. no	miRNA	Gene list
1	mmu-let-7i-5p	Apc2, Armc2, Atp2b2, Col1a2, Cts8, Fbxl14, Gnl3l, Ifnar1, Il6, Lins1, Meis2, Msi2, Mup11, Mup17, Nf2, Nup214, Tnfrsf26, Zfp444
2	mmu-miR-126a-3p	Adam9, Dnmt1, Errf1, Fzd7, Hoxa9, Irs1, Itga11, Pik3r2, Runx1, Sfpi1, Spred1, Ston1, Tal1, Vegfa
3	mmu-miR-140-3p	Fn1, Pou3f3, Smad2
4	mmu-miR-142a-3p	Adcy9, Akr1d1, Arntl, AW549877, Cd2ap, Egfl6, Hmgbl, Homez, Il6, Il6st, Irak1, Lnpk, Olr1, Sema6a, Shc4, Smarca2, Zfp949
5	mmu-miR-144-3p	4930539E08Rik, Abca1, Bsn, Cab39, Car10, Cdc42ep3, Cebpa, Enpp6, Gja5, Hdglf3, Hif1a, Lifr, Lrig2, Map7d1, Mapre1, Prkaa1, Pten, Ptp4a3, Rcor3, Spred1, Sptbn1, Traf6, Uba1y, Unc5c, Zbtb34
6	mmu-miR-16-5p	Angell1, App, Arl2, Armcx6, Bcl11b, Bcl2, Bcl2l2, Bicl1, Bri3bp, Cadm1, Ccnd1, Ccne1, Cent2, Cd274, Cd40, Creb5, Ddx19b, Dhhdh, Erlin2, Fbxo21, Fgd4, Fgf2, Idua, Irgq, Itgav, Jag1, Jun, Klc1, Lpcat2b, Mapkap1, Mdm4, Ncl, Pacsin2, Plpp3, Pomk, Rnf168, Slc6a4, Sorcs2, Spsb4, Tacc1, Tifab, Trim2, Vegfa, Wnt3a
7	mmu-miR-1903	A830018L16Rik, Agl, Baz1b, Btbd9, Cplx2, Dcc, Dgkg, Dusp26, Emp2, Gcm1, Gpnmb, Gpr146, Htr3b, Iigp1, Lpin1, Metap2, Nab1, Nbl1, Nhlh2, Ntm, Pbx2, Pigr, Prlr, Ptpro, Rab3c, Rgs17, Rsl, Sec14l3, Serpinb1c, Sh2d4a, Slc22a12, Slc7a13, Steap4, Synj2bp, Tango6, Tmprss11e, Tnfrsf15, Trab2b, Ttl17, Unc5d, Vash1, Zfp300
8	mmu-miR-19a-3p	Acadm, Akap2, Atp10a, Atxn1, Chrna7, Chrnd, Fam104a, Fam83d, Fgfr1op2, Fzd4, Gja3, Ilf3, Kdm2a, Lrp6, Map3k12, Nat8f2, Nat8f4, Nhs1l, Pten, PTEN, Rnf11, Slc35f1, Snap25, Snx27, Tet2, Timp2, Tmem25, Tnf, Ttc39b, Ubap2l, Zfpm2
9	mmu-miR-1a-3p	Acta1, Adar, Anxa5, Bdnf, Calm1, Calm2, Cdc42, Cdk9, Clcn3, Cpeb1, Ets1, Fn1, Fzd7, Gata4, Gja1, GTF2B, Hand2, Hdac4, Hes1, Hspa1b, Hspd1, Igf1, Igf1r, Irx5, Klf4, Map4k3, Mef2a, Meox2, Mkl1, Mup10, Mup11, Mup12, Mup14, Mup17, Mup19, Myh6, Myocd, Nfat5, Nppa, Pax3, Pax7, Pola1, Rarb, Rasa1, Rheb, Rnf170,

		Rps6, Sh3bgrl, Smarcb1, Smarcd2, Srf, Tgoln1, Tlx2, Ucp2
10	mmu-miR-1b-5p	1110059G10Rik, A630001G21Rik, Acot11, Acvr2a, Ado, AI429214, Akap7, Arl15, Atf2, Atp7a, B3gnt2, BC003965, Bpifc, Bsn, Casp8, Ccdc138, Ccdc169, Ccna2, Ccpg1, Cd28, Cds2, Chek1, Chic1, Cisd2, Csnk1g3, Csrnp3, Cwf1912, Cysltr1, Dtna, Dzank1, E2f1, Ephb3, Etfbkmt, Fam169b, Fbxl14, Fbxo45, Foxk1, Frmd6, Gabpb2, Gabra2, Gfod1, Haus2, Hist1h1d, Hoxd1, Htt, Iars2, Il15ra, Iws1, Lhfpl4, Lin28b, Loxl3, Lrrc75b, Mavs, Mtf1, Nacc2, Nras, Nxpe3, Oip5, Pdxk, Pgm2l1, Pik3ca, Pitpnb, Piwil2, Plag1, Plxna1, Pofut1, Prl5a1, Prmt8, Prpf18, Psd3, Ptdss1, Rasa2, Rbbp9, Rbm41, Rbm47, Rgl1, Rps3, Rsbn11, Rufy2, Sass6, Satb2, Sept3, Slc16a10, Slc16a9, Slc25a46, Slc41a3, Snx27, Srgap3, Ss18l1, St6galnac1, Strbp, Stxbp6, Tas1r3, Tbc1d13, Tbc1d22b, Tdrd1, Tfcp2l1, Tigd5, Tlr4, Tmem161b, Tmem200a, Tnrc6b, Tpte, Trhr, Ubac1, Unc5b, Uty, Wfdc12, Zbtb39, Zfp354a, Zfp446, Zfp462, Zfp874b, Zfp941, Zfp963, Zscan4c, Zscan4d
11	mmu-miR-25-3p	Btg2, Cd69, Chm, Cpeb1, Fam136a, Fbxw7, Gm5148, Il5ra, Ncam2, Rhbdl3, Stk10, Tagap, Tagap1, Uba1y, Wwp2, Xylt2, Zfp300, Zfp970, Zpbp
12	mmu-miR-451a	Abhd17b, Acc, Akt3, Ankrd17, Ankrd46, Arnt2, Atf2, Avl9, AW549877, Cab39, Clstn1, D14Abb1e, Ddx19b, Gdap1, Gm2a, Gnai3, Grin3a, Hey1, Ik, Ints10, Irf8, Klhl5, Limch1, Lonrf2, Lphn2, Lsm14a, Megf9, MIF, Myc, Nsmaf, Nucks1, Pom121, Ppm1l, Prkaa1, Rnf103, Scn8a, Setd5, Shank2, Sidt2, Snrk, Sptssa, Syp, Tenm2, Thbd, Thrsp, Trim33, Trpc3, Vezt, Xiap, Ywhaz, Zfp644

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2	mmu-miR-130b-3p	Acbd5, Arrdc3, Chrna7, Fgfr1op2, Homez, Inpp5e, Irf1, Kdm2a, Map3k12, Meox2, Mup13, Mup7, Nfia, Rhod, Snx27, Tgfb1, Timp2, Tmem25, Ubap2l
3	mmu-miR-19a-3p	Acadm, Atp10a, Atxn1, Chrna7, Chrnd, Fam104a, Fam83d, Fgfr1op2, Fzd4, Gja3, Ilf3, Kdm2a, Lrp6, Map3k12, Nat8f2, Nat8f4, Nhsl1, Pakap, PTEN, Pten, Rnf11, Slc35f1, Snap25, Snx27, Tet2, Timp2, Tmem25, Tnf, Ttc39b, Ubap2l, Zfp62
4	mmu-miR-451a	Abhd17b, Acc, Akt3, Ankrd17, Ankrd46, Arnt2, Atf2, Avl9, AW549877, Cab39, Clstn1, D14Abb1e, Ddx19b, Gdap1, Gm2a, Gnai3, Grin3a, Hey1, Ik, Ints10, Irf8, Klhl5, Limch1, Lonrf2, Lphn2, Lsm14a, Megf9, MIF, Myc, Nsmaf, Nucks1, Pom12l, Ppm1l, Prkaa1, Rnf103, Scn8a, Setd5, Shank2, Sidt2, Snrk, Sptssa, Syp, Tenm2, Thbd, Thrsp, Trim33, Trpc3, Vezt, Xiap, Ywhaz, Zfp644
5	mmu-miR-466i-5p	4921509C19Rik, Abcc9, Ackr4, Acot2, Acsn2, Acss1, Adamts14, Adamts17, Adarb2, Adgra1, Ado, Adra1b, Agrap, Akap10, Akap2, Akap7, Ank2, Aplar, Apba1, Aplnr, Appl1, Aptx, Asah2, Asap3, Asb13, Ascl4, Asxl2, Atp2b3, Atxn1, B4galt6, Barhl2, Baz2b, Bcl2, Bcl2l11, Bend3, Bnc2, C5ar2, Cacna2d2, Calcoco1, Calcr, Camk1d, Cap2, Car10, Casc4, Cask, Casp8, Ccdc85a, Ccna2, Ccpg1, Cd1d1, Cd274, Cd28, Cd2ap, Cd33, Cd4, Cdh12, Cdh20, Cdk13, Cdk7, Cds2, Ceacam1, Ceacam18, Cer1, Chrnb4, Chrnd, Chst2, Clec7a, Clvs1, Cnih3, Cnksr2, Cntn3, Commd7, Cox15, Cradd, Creg2, Csf2ra, Cxcl15, D430042O09Rik, D630003M21Rik, D630045J12Rik, Ddx6, Dgkg, Dhhdh, Dhfr, Dmd, Dmrta1, Dnaaf5, Dnase1l3, Dnlz, Draxin, Drp2, Dzank1, E2f8, Ebf3, Ece1, Efcab14, Egfl6, Ehd3, Ehhdh, Elfn1, Elovl6, Entpd1, Eogt, Epas1, Epha4, Epha7, Etv3, Evi2b, Fam107a, Fam169b, Fam198a, Fam213a, Fblim1, Fbrs, Fbxl17, Fech, Flnb, Flrt1, Foxk1, Frk, Frmd5, Fsd1l, Gabpb2, Gatac, Gata4, Gdpgp1, Gfod1, Gfpt1, Gfra2, Gm14137, Gm14326, Gm4841, Gm5615, Gna13, Gnal, Gnb4, Gramd1c, Grasp, Greb1, Gria3, Grid1, Grik3, Grk3, Gtf2h2, Has2, Havcr2, Hif1an, Hoxc8, Hpcap

		Hspb7, Htt, Iars, Iffo2, Ifi44, Igflr, Igf2, Iglon5, Igsf11, Il18r1, Ildr2, Insig2, Insr, Iqgap2, Itga11, Itga9, Jarid2, Kank2, Kenc1, Kenip3, Kenj1, Kenj16, Kif1a, Klhl13, Klhl23, Kmt5b, Krt222, L1cam, Lbp, Lcp2, Lhx6, Lifr, Lin7a, Lnpk, Lpp, Lrrc32, Lrrc61, Lrrn4cl, Lrtm2, Ltf, Ly6g6c, Ly96, Maf, Mafb, Magee2, Man1c1, Man2a2, Map3k7, Mapk11, Mapkbp1, Mavs, Mbnl3, Mcidas, Mdm2, Mfap3l, Micall1, Mlec, Mocs1, Mon1b, Mrgpre, Ms4a5, Mtmr12, Muc13, Mup18, Mylk4, Nab1, Nab2, Napb, Nat8f2, Nat8f4, Nat8l, Nbeal1, Ncam1, Ncan, Nedd4l, Neu1, Neurod2, Nfat5, Nfatc1, Ngfr, Nid1, Nkap, Nkx2-9, Nmnat2, Npr3, Nqo2, Nr4a2, Nrbp2, Nsun3, Nwd1, Nxpe3, Oacyl, Onecut2, Opcml, Oprm1, Oxsm, Oxtr, P4ha3, Pacsin2, Palm2, Pappa2, Pcdh10, Pcdh17, Pclo, Pcd4, Pdxk, Pgm5, Phactr3, Pik3r5, Pirt, Plcb1, Pld5, Podn, Pogk, Ppp1r16b, Ppp1r1c, Prdm12, Prdm8, Prelid3a, Prex2, Prkcd, Prkci, Proser3, Prrc2b, Prss42, Psd2, Psd3, Pstpip2, Ptgdr, Ptprb, Ptpre, Pura, Rab11fip1, Rab3c, Rab6b, Rab9b, Rabgap1, Rara, Rasa2, Rasal2, Rassf2, Reps2, Rfx3, Rgs9bp, Rhobtb1, Rhou, Rnasel, Rorb, Rpusd2, Rsph4a, Runx1, Runx1t1, Runx3, Saa4, Samd7, Scd3, Scn2a, Sema5a, Sema5b, Sema6a, Sfrp1, Sh2d2a, Shisa6, Shroom3, Sike1, Sim1, Six4, Ski, Slc17a5, Slc1a2, Slc22a8, Slc24a2, Slc25a12, Slc25a21, Slc30a10, Slc31a2, Slc39a14, Slc4a4, Slc5a8, Slc6a17, Slc6a6, Slc7a1, Slc8a1, Slc8a3, Smarca2, Smo, Smpd4, Snai2, Snap23, Snap25, Snx12, Sox1, Sp9, Srgap3, Ssr1, St18, St8sia1, Steap2, Stk10, Stxbp4, Stxbp5l, Supt7l, Syn3, Synj2bp, Syt15, Tacr1, Tacr2, Tbc1d30, Tbx15, Tbx22, Terf2ip, Tet2, Tfap2b, Tgfb2, Thsd4, Tiprl, Tmco1, Tmem132b, Tmem151b, Tmem236, Tmem245, Tmem26, Tmem47, Tmod2, Tnfrsf13c, Tns4, Trim65, Trp53i11, Trpc7, Trpm3, Tspan18, Tyw3, Ubtf, Uhrf1bp11, Unc13b, Unc5d, Unc93a, Uncx, Urb2, Vdr, Vprbp, Vps33b, Vps37a, Vsnl1, Wars2, Wdr46, Wrn, Xk, Xpr1, Xrcc3, Zeb2, Zfand2a, Zfhx3, Zfp169, Zfp248, Zfp329, Zfp39, Zfp449, Zfp46, Zfp488, Zfp607b, Zfp641, Zfp68, Zfp691, Zfp74, Zfp92, Zfp931, Znrfl3, Zscan29
6	mmu-miR-574-5p	A830018L16Rik, Asb7, Cdh12, Cpm, Cpne1, Ctsb, Dhdh, Fam213a, Fndc1, Gm5615, Gria3, Iffo2, Ifi44, Maoa, Mrap2, Mylk4, Piezo2, Ppp1cb, Rnasel, S1pr3, Sox1, Stxbp4, T2, Tbc1d5, Trim65, Tyw3, Ubac1, Zdhhc3, Zfp74, Zfp994