

Supplementary data:

Supplementary Table 1: Attribute Weighted Brain Derived Extracellular Vesicles (BDEVs) miRNA

BDEV 3 was removed as it was an outlier as determined by PCA.

Supplementary Table 2: Attribute Weighted serum EV miRNA

Serum EV 2 was removed as it was an outlier as determined by PCA.

Supplementary Table 3: Reads RPM for miRNA in Brain Derived Extracellular Vesicles (BDEVs)

Supplementary Table 4: Reads RPM for miRNA in Serum EVs

Supplementary Table 5: TargetScan of Common Significant miRNA in Brain Derived Extracellular Vesicles (BDEVs) and Serum EVs

Supplementary Table 6: Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway of Significant miRNA in Brain Derived extracellular vesicles (BDEVs)

KEGG pathway	p-value	#genes	#miRNAs
Prion diseases	9.21E-15	13	7
Fatty acid biosynthesis	3.25E-08	3	4
Proteoglycans in cancer	7.54E-08	76	13
Thyroid hormone signaling pathway	2.35E-07	51	10
Renal cell carcinoma	3.29E-06	33	13
FoxO signaling pathway	4.18E-06	55	14
Glioma	6.03E-05	27	12
Hippo signaling pathway	9.52E-05	55	14
AMPK signaling pathway	0.000107	54	10
Lysine degradation	0.000152	19	6
ErbB signaling pathway	0.000152	33	9
Acute myeloid leukemia	0.000655	24	10
Insulin signaling pathway	0.000655	54	13
Hepatitis B	0.000655	50	13
Pathways in cancer	0.001541	121	13
mTOR signaling pathway	0.001681	27	11
Endocytosis	0.001814	74	11
Prostate cancer	0.001814	37	12
GnRH signaling pathway	0.002285	35	9
Ubiquitin mediated proteolysis	0.002475	55	10
Cell cycle	0.002684	43	11
MAPK signaling pathway	0.002684	79	13
Oocyte meiosis	0.003935	40	10
Long-term potentiation	0.003993	28	8
Steroid biosynthesis	0.004857	7	6
Protein processing in endoplasmic reticulum	0.004966	55	10
Colorectal cancer	0.005463	24	10

Sphingolipid metabolism	0.005657	19	9
Non-small cell lung cancer	0.007676	23	11
Primary bile acid biosynthesis	0.008328	5	4
Adrenergic signaling in cardiomyocytes	0.008328	45	9
N-Glycan biosynthesis	0.008861	16	6
TGF-beta signaling pathway	0.008861	27	13
Chronic myeloid leukemia	0.008861	28	13
Dorso-ventral axis formation	0.00992	13	10
Regulation of actin cytoskeleton	0.009932	67	12
Neurotrophin signaling pathway	0.01053	41	9
HIF-1 signaling pathway	0.010565	40	10
Starch and sucrose metabolism	0.011223	20	7
Glycosaminoglycan biosynthesis - keratan sulfate	0.013589	5	4
PI3K-Akt signaling pathway	0.016303	100	14
Focal adhesion	0.016408	65	10
Axon guidance	0.020772	43	11
Viral carcinogenesis	0.023323	59	14
Estrogen signaling pathway	0.027082	33	10
Adherens junction	0.03038	28	8
Other glycan degradation	0.032139	4	4
p53 signaling pathway	0.032915	23	9
Sphingolipid signaling pathway	0.032915	40	10
Glycosaminoglycan biosynthesis - chondroitin sulfate / dermatan sulfate	0.033118	7	6
Small cell lung cancer	0.03416	29	10
Progesterone-mediated oocyte maturation	0.043474	31	10
2-Oxocarboxylic acid metabolism	0.045544	7	4

Supplementary Table 7: Gene Ontology analysis of Significant miRNA in Brain Derived extracellular vesicles (BDEVs)

GO Category	p-value	#genes	#miRNAs
Cell	0	3067	20
Intracellular	0	2801	20
Organelle	1.52E-162	2405	19
anatomical structure development	3.43E-153	958	19
biological_process	7.96E-152	3911	20
ion binding	2.68E-82	1475	19
molecular_function	1.21E-77	3810	20
cell differentiation	1.58E-77	700	18
embryo development	7.54E-60	295	19
cellular protein modification process	2.17E-53	642	19
Cytoplasm	7.76E-48	2297	20
chromosome organization	9.11E-35	187	17
cellular nitrogen compound metabolic process	1.45E-34	1013	20
biosynthetic process	7.85E-32	897	20

cellular_component	4.53E-30	3708	20
anatomical structure formation involved in morphogenesis	2.13E-26	216	16
cell morphogenesis	7.73E-22	187	14
homeostatic process	8.65E-19	239	14
protein complex	2.73E-16	841	20
cell death	7.82E-16	241	17
cell division	6.72E-15	148	12
Cytoskeleton	3.51E-14	378	14
cell cycle	4.03E-13	263	16
nuclear chromosome	7.38E-13	77	12
cytoskeleton organization	1.88E-12	189	16
catabolic process	5.37E-12	418	16
cell motility	6.45E-12	159	15
cytoplasmic membrane-bounded vesicle	3.69E-11	144	15
Growth	1.73E-10	119	17
Chromosome	1.85E-10	174	15
cytoskeletal protein binding	1.41E-09	187	16
cellular component assembly	4.34E-07	273	17
Endosome	6.89E-07	172	14
protein binding transcription factor activity	1.70E-06	110	14
in utero embryonic development	4.29E-06	103	13
nucleic acid binding transcription factor activity	5.21E-06	207	16
developmental maturation	8.68E-06	42	10
Nucleoplasm	1.01E-05	248	17
response to stress	1.73E-05	453	16
enzyme binding	0.000121478	257	12
endoplasmic reticulum	0.000299717	375	15
Vacuole	0.000311825	77	11
ligase activity	0.0005797	150	14
cofactor metabolic process	0.005444081	57	9
circulatory system process	0.005610098	39	9
small molecule metabolic process	0.007069404	414	17
peptidyl-threonine phosphorylation	0.012510811	25	7
enzyme regulator activity	0.016359561	163	10
Golgi apparatus	0.016359561	332	15
ribonucleoprotein complex assembly	0.025437908	36	11
nuclear envelope	0.03794573	64	10
vesicle-mediated transport	0.040989097	211	13

Supplementary Table 8: Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of Significant miRNA in serum extracellular vesicles (EVs)

KEGG pathway	p-value	#genes	#miRNAs
Lysine degradation	2.17E-05	9	2
Porphyrin and chlorophyll metabolism	7.64E-05	13	2

Hippo signaling pathway	0.000159	23	2
Steroid biosynthesis	0.000339	2	1
TGF-beta signaling pathway	0.006718	10	1
Drug metabolism - other enzymes	0.013213	10	2
FoxO signaling pathway	0.013213	18	2
Thyroid hormone signaling pathway	0.018594	20	2
Drug metabolism - cytochrome P450	0.023957	8	2
Glycosaminoglycan degradation	0.029001	4	1
Sulfur relay system	0.035561	2	2
Pathways in cancer	0.046221	40	2

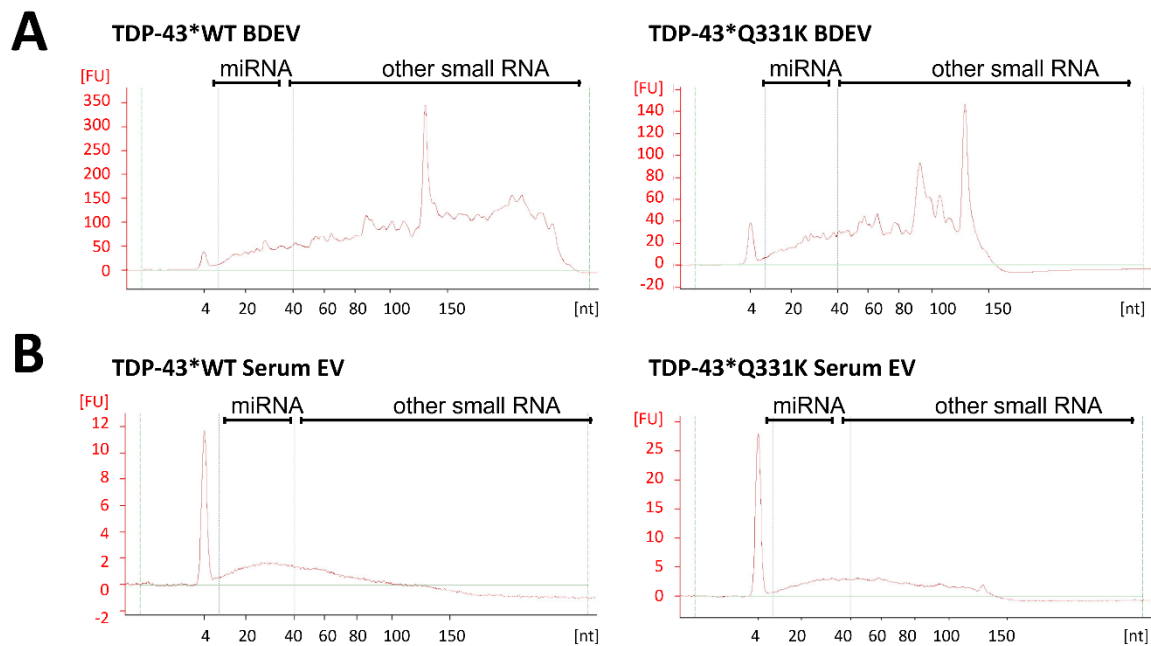
Supplementary Table 9: Gene Ontology analysis of Significant miRNA in Serum extracellular vesicles (EVs)

GO Category	p-value	#genes	#miRNAs
Cell	1.88E-242	872	2
Intracellular	3.43E-143	812	2
Organelle	2.70E-43	698	2
anatomical structure development	4.42E-42	282	2
biological_process	1.57E-41	1137	2
ion binding	6.10E-27	446	2
cell differentiation	4.83E-22	208	2
embryo development	1.19E-19	94	2
molecular_function	8.34E-19	1102	2
biosynthetic process	1.74E-16	295	2
Cytoplasm	2.35E-13	671	2
cellular protein modification process	6.03E-13	183	2
cellular nitrogen compound metabolic process	1.06E-12	311	2
chromosome organization	3.99E-10	57	2
cofactor metabolic process	7.15E-09	36	2
anatomical structure formation involved in morphogenesis	1.53E-07	65	2
homeostatic process	9.34E-07	76	2
cellular amino acid metabolic process	9.68E-05	43	2
Growth	0.000122	41	2
protoporphyrinogen IX biosynthetic process	0.00045	7	1
cell morphogenesis	0.0005	50	2
response to stress	0.000557	151	2
in utero embryonic development	0.000957	38	2
sulfur compound metabolic process	0.001244	28	2
cell death	0.00184	68	2
cytoskeleton organization	0.004526	55	2
cellular_component	0.00891	1050	2
protein complex	0.01226	233	2
catabolic process	0.014422	119	2
cytoplasmic membrane-bounded vesicle	0.017902	41	2
small molecule metabolic process	0.025585	136	2

cellular component assembly	0.02668	83	2
protein binding transcription factor activity	0.0268	35	2
cell division	0.029894	38	2
positive regulation of fibroblast proliferation	0.046663	12	2
Cytoskeleton	0.046663	101	2

Supplementary Table 10: TargetScan of Significant miRNA in Brain Derived Extracellular Vesicles (BDEVs)

Supplementary Table 11: TargetScan of Significant miRNA in serum EVs



Supplementary Fig. 1: Small RNA is present in Brain Derived Extracellular Vesicles (BDEVs) and serum EVs. (A). A small RNA assay was run using the Agilent Bioanalyser on the small RNA isolated from the BDEVs and serum EVs. The initial peaks at 4 nt represent the marker. The BDEVs isolated from the TDP-43*WT and TDP-43*Q331K mice appear to contain miRNA indicated by peaks in the 10-40 nt region, in addition to other small non-coding RNAs due to peaks in the ≥ 40 nt region. **(B).** The serum EVs isolated from the TDP-43*WT and TDP-43*Q331K mice appear to contain miRNA indicated by peaks in the 10-40 nt region. These results are from TDP-43*WT and TDP-43*Q331K mice of n=12 (from the BDEVs), and n=12 (from the serum EVs).