

### Supplementary Tables:

Table S1. Recent studies on the effects of miRNAs associated with ALS

miRNA	Disease	Expression change	Result	Reference
mi-R128	ALS	Increased	miR-218 has been shown to reflect the loss of motor neurons and respond to ALS treatment.	Hoye, Kaval et al. <sup>150</sup>
mi-R424 mi-R206	ALS	Increased	mi-R424 and mi-R206 were found to be overregulated in both skeletal muscle and plasma of ALS patients.	de Andrade, de Albuquerque et al. <sup>151</sup>
miR-338-3p	ALS	Increased	miR-338-3p was found to be significantly upregulated in sALS blood patients.	De Felice, Guida et al. <sup>152</sup>
miR-27a-3p	ALS	Decreased	miR-27a-3p was downregulated in ALS patients and may play a role in the development of ALS, and therefore has the potential to be a reference for ALS diagnosis in the clinic.	Xu, Zhao et al. <sup>153</sup>
hsa-miR-142-3p	ALS	Decreased	hsa-miR-142-3p is predicted to target TDP-43 and C9orf72 expression.	Matamala, Arias-Carrasco et al. <sup>154</sup>
mi-124a mi-R206 mi-R9 mi-R7b mi-r638	ALS	Decreased	Downregulation was detected in miRNAs miR-124a, miR-206, miR-9, let-7b, and miR-638. Additionally, significant upregulation of the AATK gene and downregulation of the DNMT2 gene were detected.	Vrabec, Boštjančič et al. <sup>155</sup>

Table S2. Recent studies on the effects of miRNAs associated with Multiple Sclerosis

miRNA	Disease	Expression change	Result	Reference
mi-R18a mi-R20b mi-R29a mi-R103 mi-R326	Multiple Sclerosis	Decreased	It was observed that miR-18a, miR-20b, miR-29a, miR-103, and miR-326 were suppressed in patients with MS, but the expression of these miRNAs returned to normal after 1 year or more of Natalizumab treatment.	Ingwersen, Menge et al. <sup>163</sup>
hsa-miR-320b hsa-miR-7	Multiple Sclerosis	hsa-miR-320b Increased & hsa-miR-7 Decreased	When the patients' white matter lesions were compared with the normal-appearing white matter ratios, the miRNA that increased the most pathogenically was hsa-miR-320b. The miRNA with the most negative pathogenic values was hsa-miR-7.	Tripathi, Volsko et al. <sup>164</sup>
miR-24-3p miR-128-3p	Multiple Sclerosis	Increased	miR-24-3p and miR-128-3p were found to tend to be associated with disability accumulation and disease activity, respectively.	Vistbakka, Sumelahti et al. <sup>165</sup>
hsa-miR-16-2-3p hsa-miR-20a-5p hsa-miR-7-1-3p	Multiple Sclerosis	hsa-miR-16-2-3p Increased & hsa-miR-20a-5p		Keller, Leidinger et al. <sup>166</sup>

		hsa-miR-7-1-3p Decreased	hsa-miR-16-2-3p was found to be significantly up-regulated, and hsa-miR-20a-5p and hsa-miR-7-1-3p were found to be down-regulated.	
miR-145 miR155	Multiple Sclerosis	Decreased	miRNA-145 and miRNA-155 were partially reduced in individuals with relapsing-remitting multiple sclerosis.	Ali Ashrafi, Asadi et al. <sup>167</sup>
miR-145	Multiple Sclerosis	Increased	miR-145 was found to be up-regulated three times.	Søndergaard, Hesse et al. <sup>168</sup>

Table S3. Recent studies on the effects of miRNAs associated with spinal cord injury

miRNA	Disease	Expression change	Result	Reference
miR-21	Spinal cord injury	Increased	miR-21 was found to be significantly upregulated, and when miR-21 was suppressed with Antagomir-21, motor functions decreased, lesions enlarged, and tissue preservation and apoptosis control were impaired in spinal cord injured rats. While the expression of FasL and PTEN genes increased, PDCD4 was not affected.	Hu, Huang et al. <sup>176</sup>
miR-223	Spinal cord injury	Decreased	Suppression of miR-223 led to decreased apoptosis in neurons after SCI and increased motor recovery.	Shi, Zhou et al. <sup>177</sup>
miR-21	Spinal cord injury	Increased	Increasing miR-21 reduces astrocyte growth and may limit scar formation.	Shi, Zhou et al. <sup>177</sup>
miR-9*, miR-219 miR-384-5p	Spinal cord injury	-	These miRNAs can be used as biomarkers for diagnosis and follow-up. They can also be used to determine the severity of SCI.	Shi, Zhou et al. <sup>177</sup>
miRNA-29b	Spinal cord injury	Increased	Injection of miRNA-29b exosomes accelerated the motor function of SCI rats, alleviated histopathological damage in spinal cord tissues, and the injection promoted neuronal regeneration.	Yu, Zhao et al. <sup>178</sup>
miR-20a miR-29b	Spinal cord injury	Increased	These miRNAs may protect neurons by suppressing BH3-only genes and increasing the expression of the anti-apoptotic Mcl-1 gene. However, overexpression of miR-20a in particular may increase neuronal cell death, leading to damage similar to traumatic SCI.	Pinchi, E., Frati et al. <sup>179</sup>
miR-223	Spinal cord injury	Increased	It particularly suppresses the NLRP3 inflammasome and reduces Bax and caspase-3 expression with antagomir-223 application. The increase in miR-223 is associated with neutrophil activation and inflammatory processes. In addition, miR-223 has been shown to be associated with neurotoxicity by suppressing NMDA and AMPA receptors.	Pinchi, E., Frati et al. <sup>179</sup>

miR-21	Spinal cord injury	Increased	It prevents cell death by suppressing many proapoptotic genes such as PDCD4, RECK, TPM1, PTEN, and APAF1. In addition, the expression of miR-21 in astrocytes contributes to recovery by suppressing hypertrophic responses after trauma. Its silencing leads to increased apoptosis and activation of death-related genes such as the Fas ligand.	Pinchi, E., Frati et al. <sup>179</sup>
miR-15 miR-16	Spinal cord injury	Increased	Upregulation of miR-15b and miR-16 has been associated with uppression of Bcl-2	Pinchi, E., Frati et al. <sup>179</sup>
miR-124a miR-223	Spinal cord injury	miR-124a Decreased & miR-223 Increased	In situ hybridization showed the presence of miR-223 around the injured area. However, miR-124a, which is found in the standard spinal cord, was not observed in the injured area. In conclusion, they demonstrated a time-dependent expression pattern of miR-223 and miR-124a in a mouse model of SCI.	Nakanishi, Nakasa et al. <sup>180</sup>
miR-486	Spinal cord injury	Increased	This miRNA suppresses the expression of the NeuroD6 gene, resulting in the accumulation of reactive oxygen species. Overexpression of miR-486 inhibits this defense, increasing apoptosis and motor impairment.	Jee, Jung et al. <sup>181</sup>

Table S4. Clinical findings of Huntington's disease

Stage	Type of Symptom	Symptoms
Early	Psychiatric symptoms	Clumsiness, Irritability, Apathy, Anxiety, Depression, Disinhibition, Delusions, Hallucinations
	Neurological Symptoms	Agitation, Abnormal eye movements, Olfactory disturbance
Middle	Motor Symptoms	Dystonia, Involuntary movements (chorea, writhing, shaking, unconnected gait), Balance and walking problems, Decreased manual dexterity
	Motor Planning Problems	Slow voluntary movement, Difficulty initiating movement, Poor speed/force control, Slow reaction time
	Systemic and Other	General weakness, Weight loss, Difficulty speaking, Stubbornness
Late	Motor Symptoms	Rigidity, Bradykinesia, Severe chorea (less), Inability to walk
	Communication & Swallowing Problems	Inability to speak, Difficulty swallowing, Risk of choking
	Daily Living Ability	Inability to care for oneself, significant weight loss

Table S5. Expression changes and functional roles of miRNAs associated with Huntington's disease

miRNA	Disease	Expression change	Result	Reference
AAV5-miHTT	Huntington	-	AAV5-miHTT was administered to the humanized mouse model of HD, Hu128/21, suppressing the expression of the HTT gene. This treatment resulted in behavioral and neuropathological improvements.	Caron, Southwell et al. <sup>189</sup>
miR-132-3p	Huntington	Increased	Some miRNAs, especially miR-132-5p and miR-132-3p, were similarly differentiated in both HD CSF and other neurodegenerative diseases such as Alzheimer's and Parkinson's.	Reed, Latourelle et al. <sup>190</sup>
miR29B-3p	Huntington	Increased	Striatal medium spiny neurons derived from HD patients had increased chromatin accessibility near the host gene MIR29B-3p, and this miRNA was found to be upregulated compared to MSNs derived from younger pre-symptomatic patients.	Oh, Lee et al. <sup>191</sup>
miR-137 miR-214 miR-148a	Huntington	Decreased	Real-time PCR performed 48 h after miR-137, miR-214, or miR-148a transfection showed a strong decrease in HTT mRNA (messenger Rna) level.	Kozłowska, Krzyżosiak et al. <sup>192</sup>

Table S6. Studies on the effect of temperature on exosome stability

Cell	Storage Condition	Conclusion	Reference
HEK293 cell culture	Room temperature 4 °C -70 °C	Exosomes were structurally disrupted within 30 minutes at room temperature. After 10 days of incubation at 4°C, a greater than 70% decrease in CD63 protein was observed. Protein loss was minimal in those stored at -70°C.	Lee, M et al. <sup>198</sup>
M-Exos	-80 °C	Exosomes stored at -80 °C did not show any change in size, structure and protein content over a long time. They were found to be quite stable in terms of shelf life.	Agrawal, A et al. <sup>199</sup>
Human cells	-20 °C 4 °C 37 °C	Exosomes stored at 4 °C and 37 °C decreased in size over time, indicating weakened membrane integrity and the onset of structural losses.	Sokolova et al. <sup>200</sup>
Lung cancer cells	-80 °C (25 mM trehalose + PBS)	Trehalose-containing PBS long-term preserved the zeta potential, size distribution, protein content, and morphology of exosomes. It stood out as the most effective cryoprotectant.	Ruzycka-Ayoush et al. <sup>201</sup>
Neutrophilic granulocyte EVs	4 °C -20 °C	At both temperatures, the size of EVs changed significantly. Furthermore, losses in antimicrobial effects were observed, especially more pronounced at -20 °C.	Lőrincz et al. <sup>202</sup>
Grapefruit-derived nanovesicles	Mouse gastrointestinal fluid	Nanovesicles remained stable in GI fluid regarding particle size and zeta potential. Structural dissolution was minimal in the gastric environment.	Wang, B. et al. <sup>203</sup>

Table S7. Isolation methods employed for exosomes

Method	Basic Principle	Advantages	Disadvantages	Productivity	Purity
Differential Centrifuge	Separation by size (centrifugation at increasing speeds)	-Simple equipment -Suitable for large volumes -Gold standard -No special reagents required -High sample volumes can be processed	-Low yield and purity -Long term processing -Large equipment investment -Risk of mechanical damage -Aggregate risk	%20-40	Middle
Filtration + Ultracentrifuge	Physical separation by size and molecular weight	-Medium efficiency -Fast -Easy -Low equipment requirement	-Filter may become clogged -Protein contamination may occur	%60	Middle
Density Gradient Centrifuge	Separation based on density difference	-Highest purity -Subfractionation possible -Higher purity -Separates from protein aggregates	-Lowest efficiency -Time and labor intensive -Gradient preparation difficulties are experienced	%10	High
PEG Precipitation	Precipitation with polymer	-Highest efficiency -Easy and fast -Requires low technical expertise	- Low purity -Polymer residue -Contamination risk	%80-90	Low
Immunoaffinity Capture	Specific binding of surface markers by antibodies	-High specificity -Subtype selection possible -High purity	- Expensive - Low yield - Dependent on surface markers - Antibody cost yüksek	Low	High
Nano-DLD	Filtration at certain intervals at nano scale	-Can separate particles of 20–100 nm precisely -Compatible with microfluidic systems.	-Need for advanced devices -Limited prevalence	Unspecified	High
Microfluidic Systems	Size, density, surface antigens	-Fast -Suitable for small samples	-Scalability is limited -System is complex	Middle	High
Field Flow Fractionation	Balance of flow and diffusion	-Subpopulation separation -Scalable	-Must be optimized for clinical use	Middle-High	Middle - High
Size Exclusion Chromatography (SEC)	Chromatographic separation according to particle size	-High structural integrity -Biological activity is preserved	-Low throughput - Not scalable -Long processing time	Middle	Middle - High
Flow Field-Flow Fractionation (FFFF)	Separation under laminar flow according to flow rate and particle size	-High resolution -Size-based precision separation	-New technology - High cost -Requires technical expertise	Middle	High

Hydrostatic Filtration Dialysis (HFD)	Physical retention and separation by hydrophobic membranes	-Cheap -Easy -Compatible with large volumes	-Subsequent purification may be required -Low purity	Middle	Middle
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