**Supplementary Materials**

**Supplementary Figure 1. UMAP plots coloured by disease for leave-one-out dataset.** Data was pre-processed and batch corrected with the indicated dataset removed. Clustering was then performed using the resultant consensus exmiRNA common to all datasets included. UMAP plots were then regenerated (n\_neighbours = 30, n\_epochs = 2500) and showed similar clustering as the full super-series, suggesting that no one dataset significantly skewed UMAP results.

Map

Description automatically generated

**Supplementary Figure 2. UMAP plots coloured by disease category for leave-one-out datasets.** As in Supplementary Figure 1, data were pre-processed and batch-corrected with the indicated dataset removed. As in the full super-series, exmiRNA were again restricted to those common between all datasets included, and clustering with UMAP was performed in two dimensions (n\_neighbours = 30, n\_epochs = 2500), and points coloured by disease category. Again, similar clustering as in the full super-series is observed, suggesting that there is no strong driving influence by any one dataset in the UMAP analysis.

Map

Description automatically generated

**Supplementary Figure 3. Expression of key exmiRNA differentiating disease states from healthy CSF samples.** (a) hsa-miR-767-5p is statistically significantly detected at a higher level in CSF of patients with Alzheimer’s disease (AD) as compared to healthy patients. (b) hsa-miR-142-5p is detected at a lower level in CSF of patients with amyotrophic lateral sclerosis (ALS) compared to healthy controls. (c) hsa-miR-361-3p is detected at a lower level in the CSF of patients with Huntington’s disease compared to healthy controls. (d) hsa-miR-885-5p is detected at higher levels of patients with low clinical probability of Huntington’s disease (HD-Pre-Low), as defined by the PREDICT-HD study, as compared to healthy control populations. (e, f) When comparing patients with degenerative conditions more generally to healthy controls, hsa-miR-142-5p and hsa-miR-361-3p show statistically significant decrease in expression.

Diagram, engineering drawing, schematic

Description automatically generated

**Supplementary Figure 4. UMAP plot for patients with selected degenerative conditions.** UMAP (Universal Manifold Approximation) plots computed for consensus miRNA profiles among patients with Alzheimer’s disease (AD), Parkinson disease (PD), and Parkinson disease dementia (PDD). UMAP settings with n\_epochs = 10000 and n\_neighbors = 5.

Chart, scatter chart

Description automatically generated