

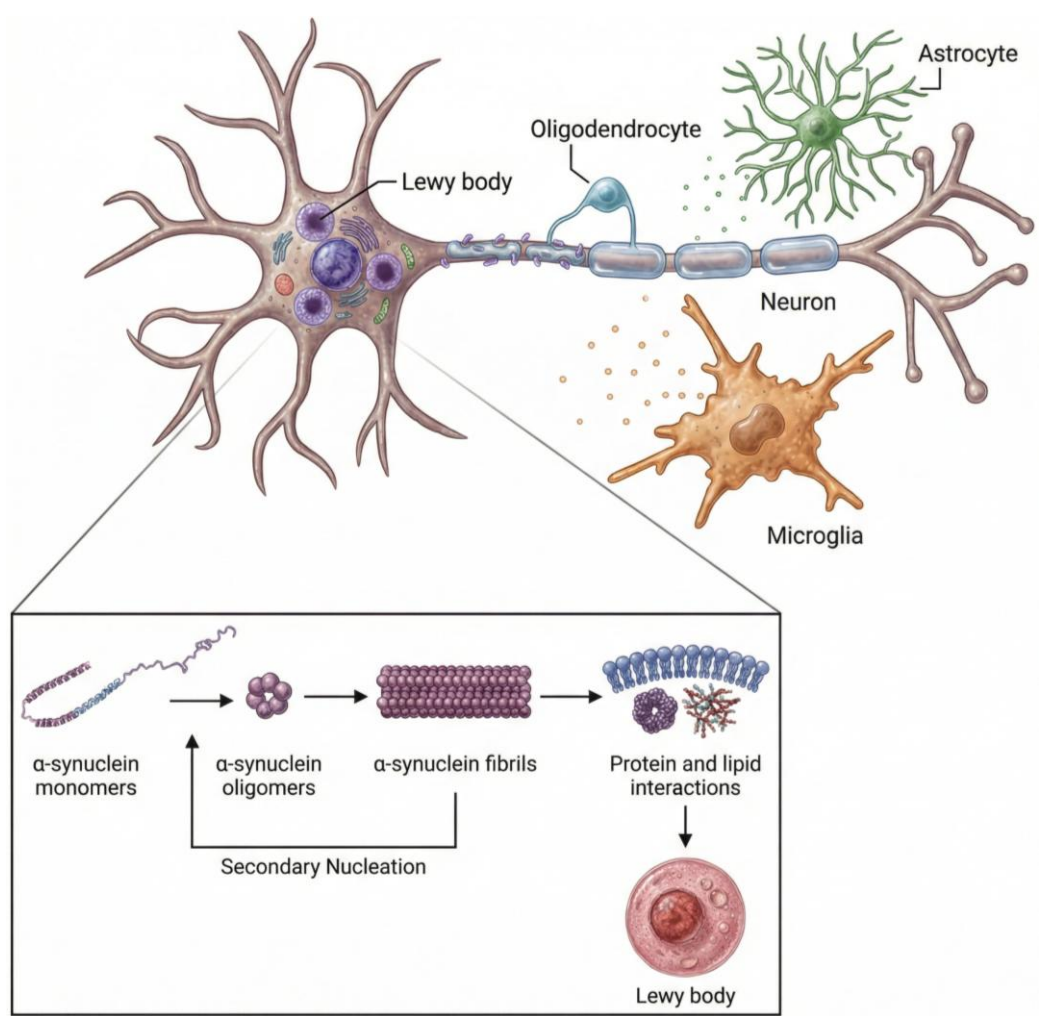
Profiling MicroRNA Signatures Reveals Neuropathological And Clinical Subtype Differences In Lewy Body Dementia

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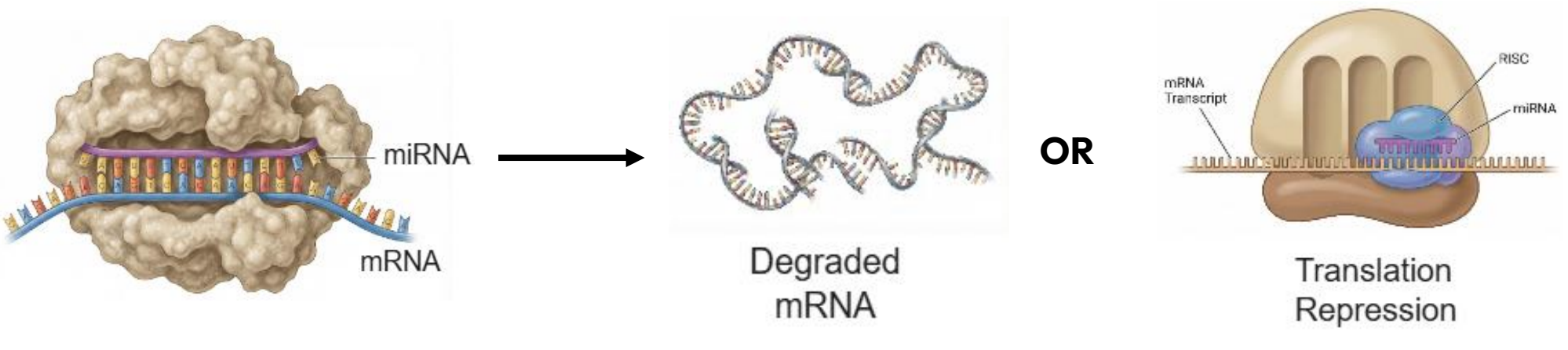
Introduction

- Lewy body dementias (LBD) are progressive neurodegenerative disorders that exhibit **cognitive decline, motor deficits, and behavioural fluctuations**.
- Accumulation of **α -synuclein** within neurons can lead to the formation of intracellular inclusions referred to as **Lewy bodies (LB)**, which can cause neuronal cell death and dysfunction.
- Distinguishing LBD subtypes is challenging due to overlapping clinical and neuropathological features.

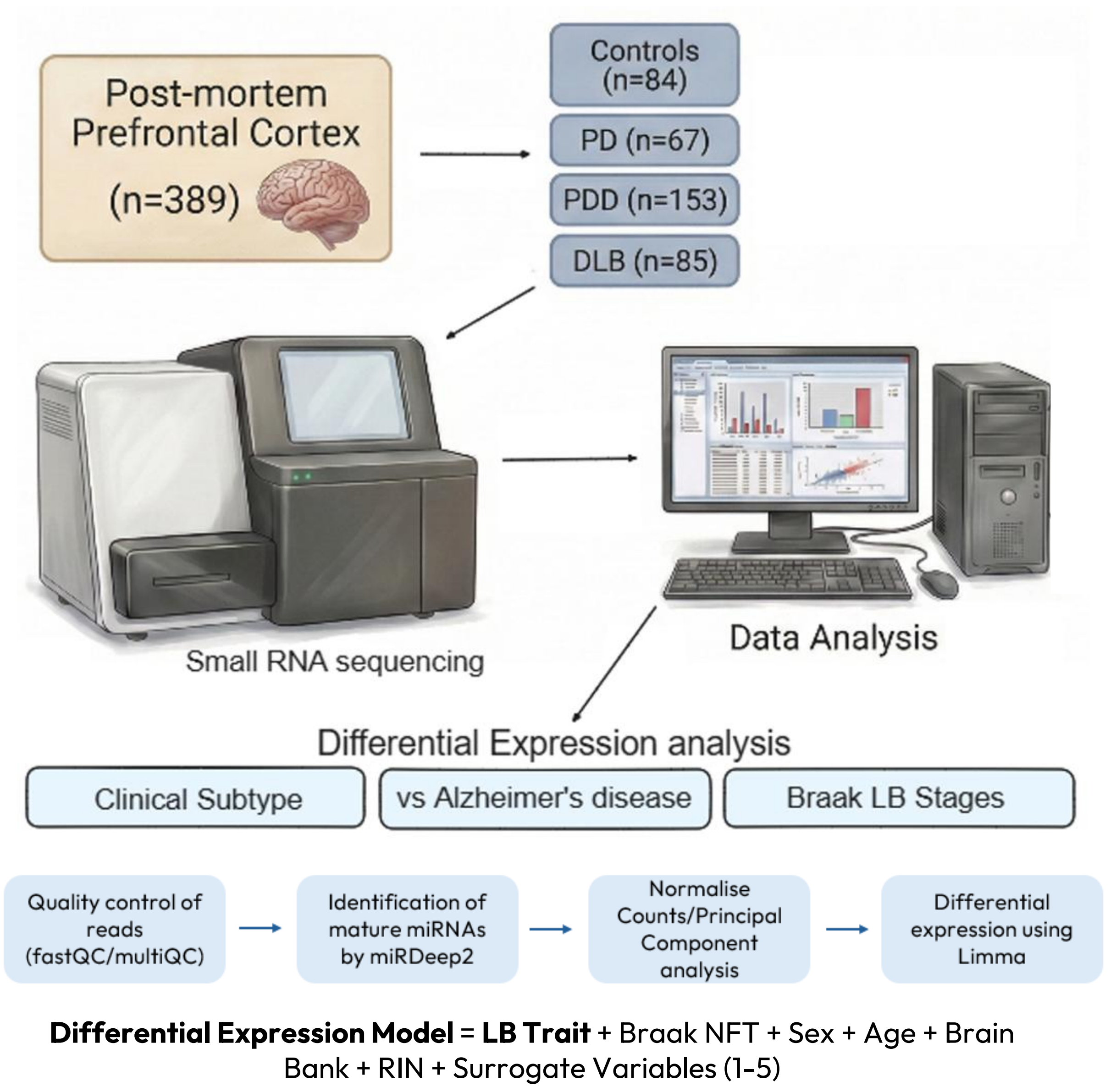


MicroRNAs

- MicroRNAs **regulate gene expression** by binding to the 3' untranslated region of target messenger RNAs¹.
- Dysregulation in microRNA expression** has been shown to play a major role in gene dysregulation and the pathogenesis of neurodegenerative and psychiatric disorders².



Methodology



References

1. He, L., Hannon, G.J. MicroRNAs: small RNAs with a big role in gene regulation. *Nat Rev Genet.* 2004;5(7):522-31.
2. Vattathil, S. M., Gerasimov, E. S., Canon, S. M. *et al.* Mapping The MicroRNA Landscape In The Older Adult Brain And Its Genetic Contribution To Neuropsychiatric Conditions. *Nature Aging.* 2025; 5, 306-319.
3. Labuza, A., Alldred, M.J., Pidkitt, H., *et al.* Frontal cortex pyramidal neuron expression profiles differentiate the prodromal stage from progressive degeneration across the Alzheimer's disease spectrum. *Alzheimer's Dement.* 2025; 21:e70395.
4. Sekilide, R. *et al.* Application of microRNA In Situ Hybridization on Long-term Stored Human Formalin-fixed Paraffin-embedded Brain Samples from Psychiatric Patients. *Mol. Neurobiol.* 1-11 (2025).

Figures made in <https://illustrator.co/> or BioRender.com

Results

- Median sequence length of **22bp** with a mean number of **5.62M reads** across samples.
- Technical replicates (for 93 samples) displayed a correlation of **> 0.99**.
- 595 mature miRNAs** were identified for **353 samples**, following outlier removal.

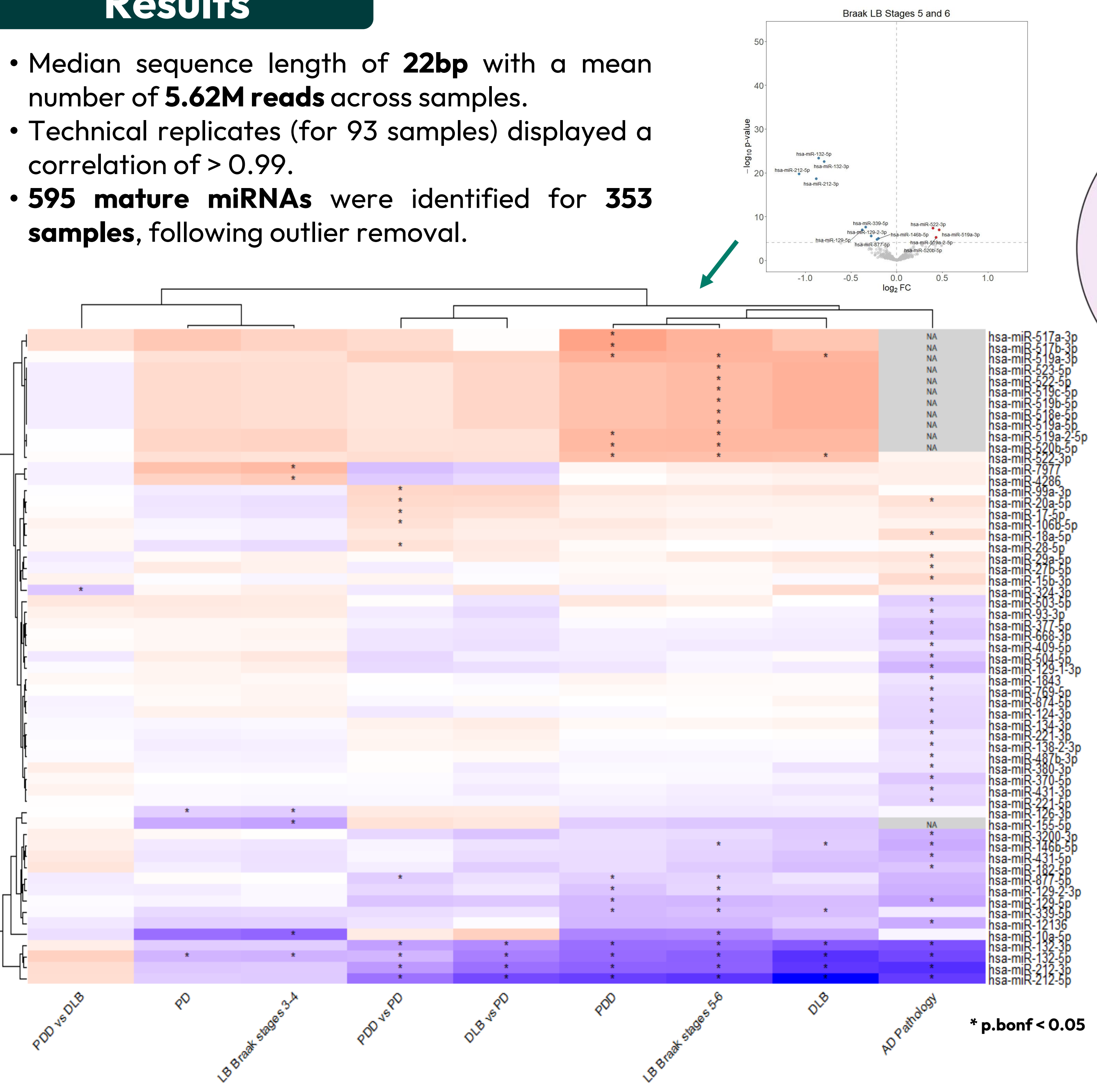


Figure 1. Heatmap of significant microRNAs for 9 differential expression analyses. Upregulated microRNAs shown in red and downregulated microRNAs shown in blue. Differential expression analysis clustered by hierarchy based on similarities. * indicates microRNAs of Bonferroni significance where $p.bonf < 0.05$.

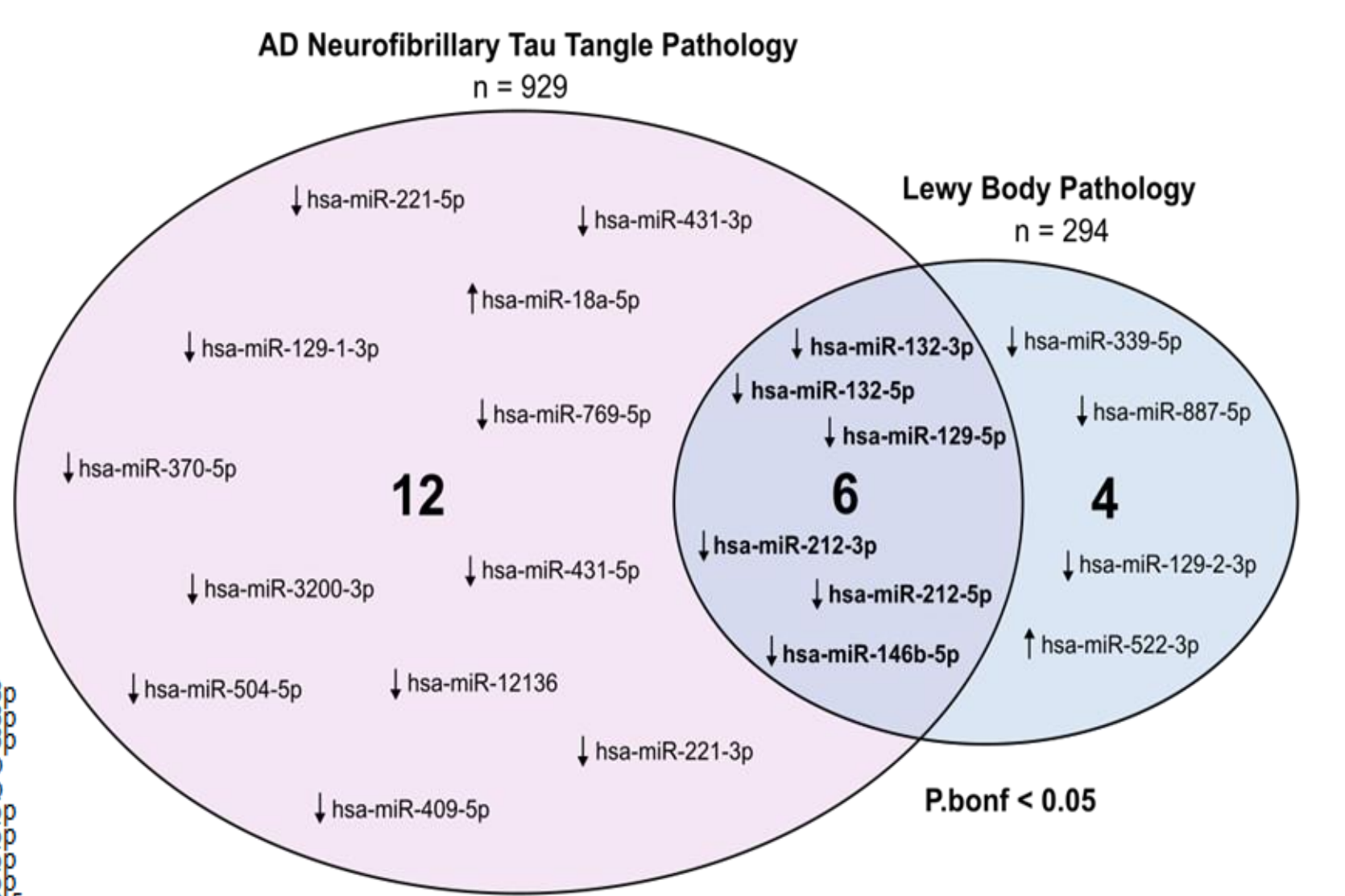


Figure 2. Comparison of Bonferroni significant microRNAs expressed in Braak Lewy body stages 5-6 and an independent meta-analysis Alzheimer's disease cohort at Braak Neurofibrillary Tau Tangle Stages 5-6 (n=929) (Pishva *et al.*, in preparation).

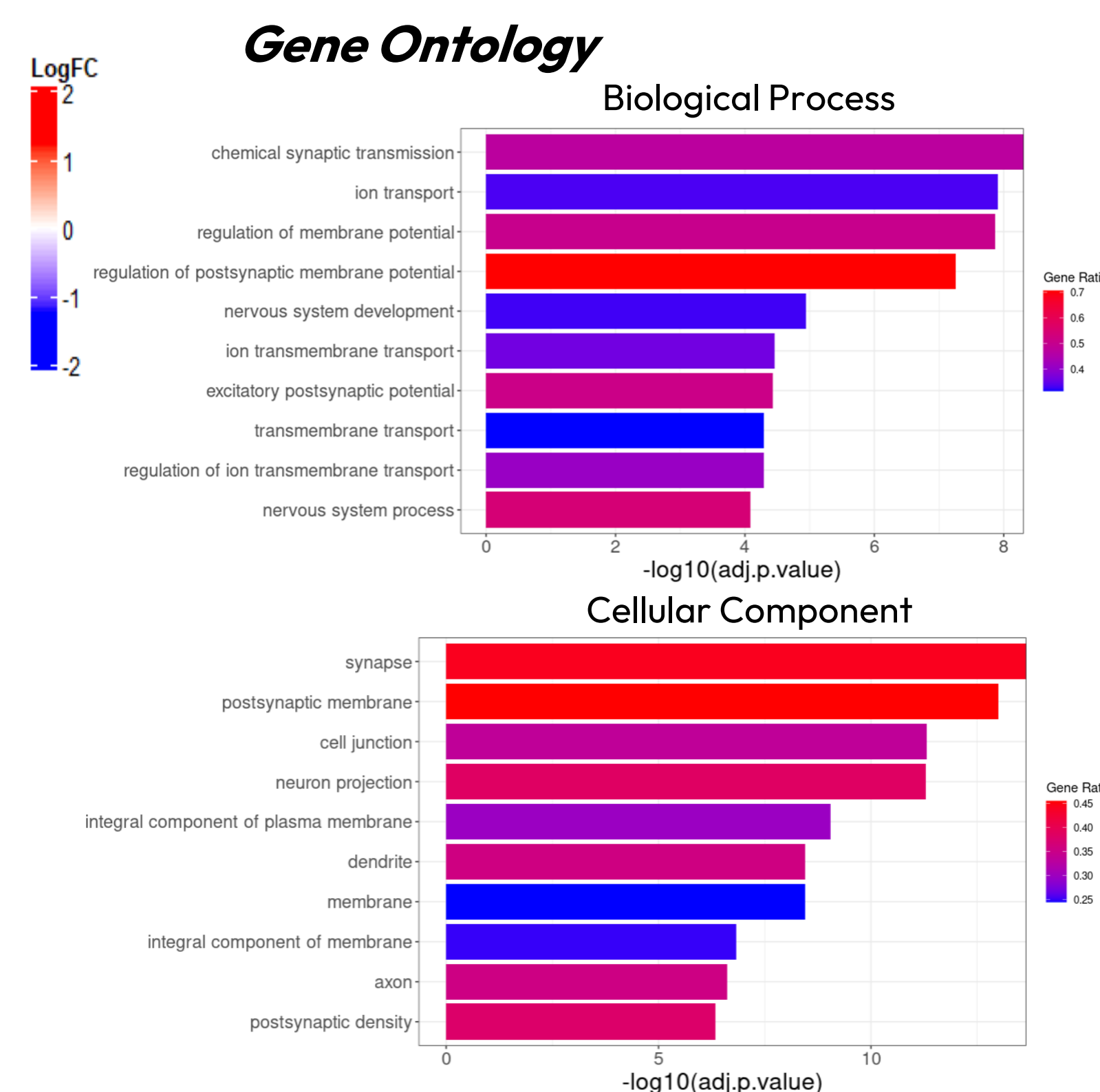


Figure 3. Gene Ontology analysis of significant microRNAs expressed in Braak Lewy body stages 5-6. MiRinGO was used to predict target mRNA and perform GO analysis.

Future Directions

Explore microRNA-mRNA binding partners, microRNA-quantitative trait loci, relationship between DNA methylation and microRNA expression and cell-type enrichment.

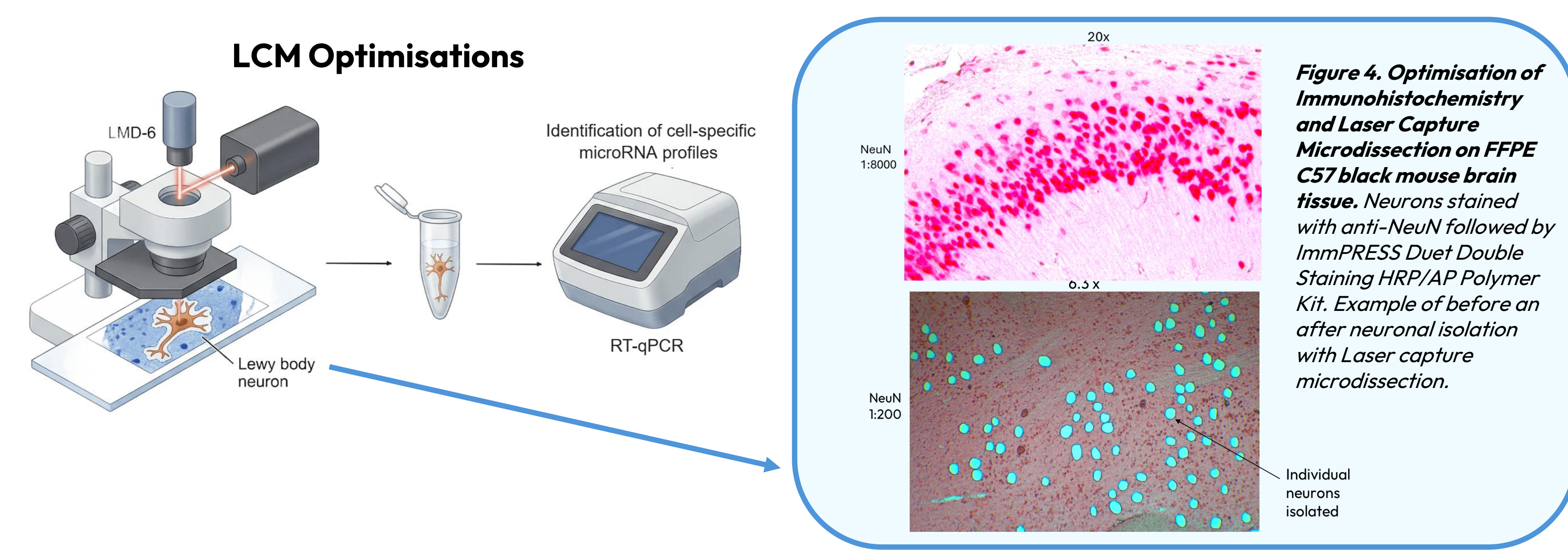


Figure 4. Optimisation of Immunohistochemistry and Laser Capture Microdissection on FFPE C57 black mouse brain tissue. Neurons stained with anti-NeuN followed by ImmPRESS Duet Double Staining HRP/AP Polymer Kit. Example of before and after neuronal isolation with Laser capture microdissection.

MicroRNAScope

Detects small RNAs at a **single-cell** resolution with **spatial** and **morphological** information⁴.

Aim: Explore the spatial and cellular profiles of **miR-132-5p**, **miR-129-5p** and **miR-339-5p**.