# Converging peripheral blood micro-RNA profiles in idiopathic Parkinson's disease and progressive supranuclear palsy.

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## Background

- ✓ Micro-RNA (miRNA) acts via modification of gene expression via suppression of messenger RNA (mRNA) translation in the DNA-RNA-protein axis.
- ✓ MiRNAs were shown to be implicated in epigenetic dysregulation across neurodegenerative disorders including Parkinson's disease (PD) and atypical parkinsonism.

## Objectives

- ✓ To identify specific miRNA expression profiles in idiopathic PD (iPD) and progressive supranuclear palsy (PSP) in comparison to controls.
- ✓ Test miRNA subsets as dignostic biomarker between iPD (n=367), PSP (n=35) and controls (HC, n=416).

## Methods

- ✓ Individuals identified with PD-linked mutation were excluded (screened by Neurochip and resequencing of GBA gene).
- ✓ Differential miRNA expression analysis testing the effects of (i) iPD vs. controls, (ii) PSP vs controls and (iii) PSP vs iPD on miRNA expression adjusting for age and sex, using the moderated t-test implemented in the R package limma.
- ✓ Logistic lasso regression was fitted to model binary disease status based on age, sex and miRNAs to acquire cross-validated area under the curve (AUC).
- ✓ Additional inquiry into an early-stage (iPD and PSP) miRNA dysregulation and predictive power of miRNAs in this initial phase (early-stage defined by disease duration since diagnosis ≤ 5 years).

## Results

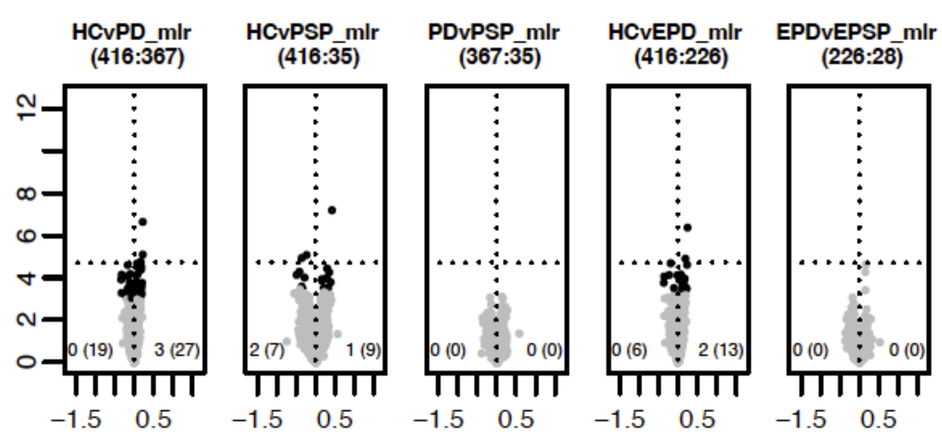


**Figure 1**. Volcano plots showing minus log10 transformed p-values (significance, y-axis) against log2 fold change (effect size, x-axis) of miRNA in multiple linear regression (mlr) adjusted for age and sex.

- ✓ Number of significantly dysregulated miRNA(s) in bottom of each plot at Bonferroni and at Benjamini-Hochberg in brackets (left corner: negative effect size, right corner: positive effect size).
- ✓ **Abbreviations:** PD: idiopathic Parkinson's disease; EPD: early-stage PD; EPSP: early-stage PSP; HC: controls; PSP: progressive supranuclear palsy; AAA: age at assessment; sex female:male.

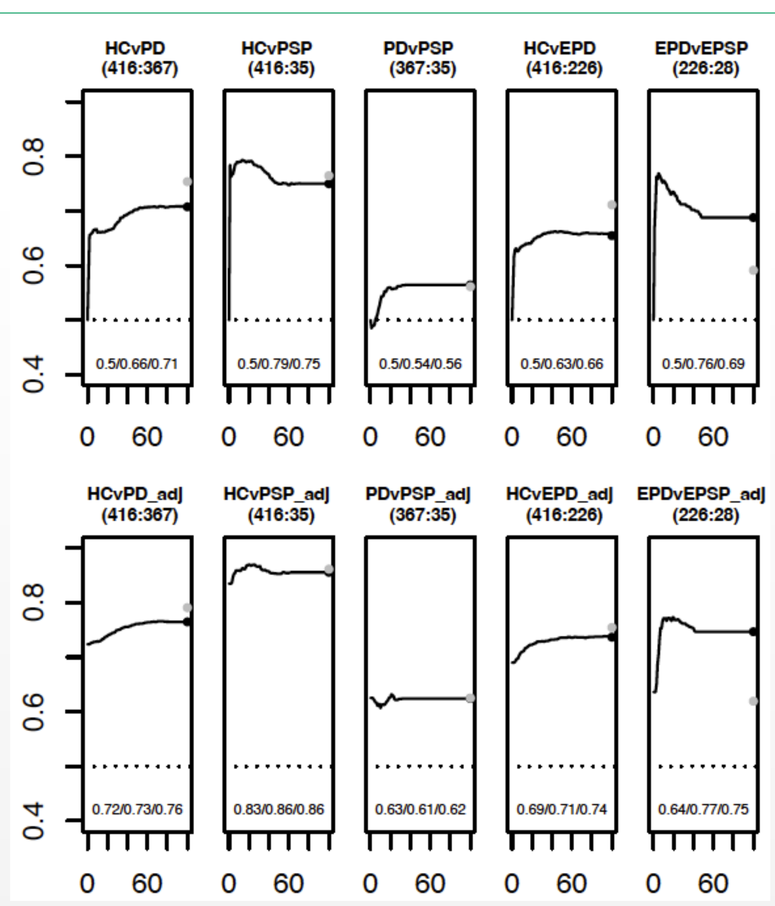


**Figure 2**. Cross-validated area under the ROC curve (AUC) from logistic lasso regression on the y-axis against maximum number of miRNAs on the x-axis for intergroup prediction of iPD, PSP and controls. **First row:** not including age/sex in the prediction model; **second row**: including unpenalized age/sex in the models (adj: adjusted).

- ✓ The numbers at the bottom indicate the cross-validated loss of lasso regression with at most 0, 10 and 100 miRNAs (non-zero coefficients other than intercept, AAA and sex).
- ✓ The black and grey dots show the predictive performance of standard lasso and ridge regression, respectively.

### Differential miRNA expression analysis

- ✓ 46 significantly dysregulated miRNA iPD vs controls
- ✓ 16 significantly dysregulated miRNAs in PSP vs controls
- ✓ No miRNA significantly dysregulated in PD vs PSP
- ✓ Overlap in 4 miRNAs direction between PD vs. controls dysregulated and PSP vs controls:

*miR-197-3p*

*let-7d-3p*

*miR-1225-5p*

*miR-505-3p*

(all 4 up-regulated)

### Predictive modelling of disease group using miRNAs

**iPD vs controls:**

- ✓ AUC of 0.72/0.73/0.76 when using at most 0/10/100 miRNAs and unpenalized variables age/sex

**PSP vs controls:**

- ✓ AUC 0.83/0.86/0.86 with at most 0/10/100 miRNAs and unpenalized age/sex.

**PSP vs iPD:**

- ✓ AUC 0.63/0.61/0.62 with at most 0/10/100 miRNAs and unpenalized age/sex.

**Early-stage iPD (EPD) vs early PSP (EPSP):**

- ✓ AUC 0.64/0.77/0.75 in the model using at most 0/10/100 miRNAs and unpenalized age/sex.

## Conclusion

- ✓ Predictive power of miRNA subset was relatively modest in predicting iPD or PSP from controls and low in *PSP vs. iPD*. Most of the AUC is due to the age/sex with little contribution when adding miRNAs in the models.
- ✓ We determined 4 overlapping significantly up-regulated miRNAs between *PSP vs controls* and *PD vs controls* (*miR-197-3p, let-7d-3p, miR-1225-5p, miR-505-3p*). These findings could point to partially convergent pathways in the *pathogenesis* or *disease progression* across different classes of neurodegenerative disorders.
- ✓ We replicated 3 out of 13 significantly dysregulated microRNAs from a previous systematic meta-analysis of microRNAs (*miR-141-3p, miR-451a, miR-185-5p*) by *Schulz J et al 2019* [1].
- ✓ *miR-141-3p* to be implicated in the mitochondrial dysfunction, apoptosis and oxidative stress in 1-methyl-4-phenylpyridinium treated induced cell model of PD.
- ✓ *miR-451a* was recently found dysregulated in the prodromal stage of PD in idiopathic Rapid-Eye-Movement (REM) sleep behaviour disorder (iRBD) [2] as well as consistently dysregulated in non-manifesting LRRK2 mutation carriers and iPD individuals [3].

miRNAs might be useful in unravelling the epigenetic processes behind the neurodegenerative processes.

[1] Schulz J et al (2019) Meta-analyses identify differentially expressed microRNAs in Parkinson's disease. *Ann Neurol* **85**, 835–851.
[2] Soto M et al (2022) Serum MICRORNAs Predict Isolated Rapid Eye Movement Sleep Behavior Disorder and Lewy Body Diseases. *Mov Disord* **37**, 2086–2098.
[3] Soto M et al (2023) Differential serum microRNAs in premotor LRRK2 G2019S carriers from Parkinson's disease. *Npj Park Dis* **9**, 15.