

A Joint Single-Cell Transcriptomic Analysis of Alzheimer’s and Parkinson’s Disease

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AD and PD share convergent, cell-type-resolved molecular signatures: metabolic suppression (GAPDH, COX4I1), translational dysregulation, and stress-response induction conserved across all 5 major brain cell types in 144,956 nuclei from 47 donors.

INTRODUCTION

Background

Alzheimer's (AD) and Parkinson's (PD) disease are the two most prevalent neurodegenerative diseases. Despite being studied as distinct entities, they share overlapping GWAS risk loci and co-occurring neuropathology (amyloid, tau, α -synuclein).

Gap

Single-disease transcriptomic studies miss molecular programs conserved across neurodegenerative conditions. Joint cross-disease analysis is therefore needed.

Hypothesis

AD and PD engage shared cellular stress programs detectable via joint snRNA-seq integration, pointing to pan-neurodegenerative therapeutic targets.

METHODS

Datasets

AD: GSE174367 (n=24 donors, prefrontal cortex)
PD: GSE243639 (n=23 donors, substantia nigra + frontal cortex)
Total: 144,956 nuclei | 47 donors

5 cell types: astrocytes, microglia, neurons, oligodendrocytes, OPCs

Statistical Model

- NB mixed-effects (Nebula) | donor as random effect
- Age + sex as fixed covariates
- Pan-ND contrast: AD+PD vs. Control

Study Design: Joint snRNA-seq Analysis of AD & PD

RESULTS

- 4,357 unique DEGs across 5 cell types (AD+PD vs. Control)**
- In neurons we found 3,668 DEGs (3,556 up, 112 down), the largest response of any cell type**
- Known disease genes recovered: LINGO1, PICALM, LRRK2 (neurons); CTSB, HSPB1 (microglia); MAPT (oligos/OPCs); LAMP1 (astrocytes)**
- 7 genes significant in ALL 5 cell types with concordant direction**

DEGs per Cell Type (Pan-Neurodegeneration, AD+PD vs. Control)

Genes Dysregulated Across All 5 Cell Types (Concordant direction in all cell types)

Gene	Astrocytes	Microglia	Neurons	OPCs	Oligodendrocytes
GAPDH	-0.71***	-0.81***	-0.40**	-0.66***	-0.78***
CIRBP	-0.65***	-0.52**	-0.43**	-0.39**	-0.64***
COX4I1	-0.40**	-0.33**	-0.38**	-0.48***	-0.63***
SRP14	-0.46**	-0.42**	-0.41**	-0.35**	-0.52***
ANAPC16	+0.46**	+0.33**	+0.52**	+0.28**	+0.32**
BANP	+0.56***	+0.34**	+0.62***	+0.40***	+0.44***
SEM1	+0.60***	+0.68***	+0.73***	+0.68***	+0.47***

Pathway Enrichment by Cell Type (GO-BP GSEA NES: blue=down, red=up)

Neurons: Pan-Neurodegeneration DEGs (3556 up, 112 down; n=18,527 nuclei)

Cross-Cell Type DEG Overlap (Pan-Neurodegeneration)

CONCLUSIONS

- GAPDH and COX4I1 downregulated across all 5 cell types; ribosomal/ER dysregulation, UPR induction, and 119/127 cross-cell-type DEGs concordant**
- Pathway enrichment shows: translational/ribosomal suppression in oligos/OPCs, metabolic suppression in astrocytes, interferon and NMD pathway downregulation in microglia; astrocytes and neurons share the most cross-disease DEGs.**
- Shared signatures invisible to single-disease analyses point to convergent therapeutic targets; next steps include expanding to ALS and HD cohorts.**

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