Mt-AD Proposal

Title

Cell-type and sex-specific mitochondrial pathway remodeling across Alzheimer's disease pathology (mt-AD)

Summary

We will systematically map how mitochondrial pathways change with AD pathologies across brain cell types and sexes, identify sex × pathology interaction patterns, and trace pathway signals back to concrete gene-level drivers. The goal is generating mechanistic, testable hypothesis for neuron- and glia-specific mitochondrial remodeling in AD.

Significance

Mitochondrial dysfunction is a hallmark of neurodegeneration, yet effects are heterogeneous across cell types and may differ by sex.

Defining where (cell type), in whom (sex), and along which axes of disease (amyloid, NFT, gPath, plaques, cognition) mt biology shifts will sharpen therapeutic targets and experimental follow-ups.

Specific Aims

Baseline mapping. Quantify associations of mt pathways with AD pathologies within each major cell type (Ast, Exc, Inh, Mic, Oli, OPC, Vas, T cells).

Sex effects. Test sex differences in pathway pathology associations (female vs male) and estimate sex×pathology interactions.

Drivers and replication. Link pathway hits to leading genes (agreement across pathologies) and validate robustness via alternative pathway catalogs and sensitivity analyses.

Data and Features

Expression / meta-data:

Single-nucleus data summarized to pseudo-bulk per donor×cell-type×sex;

QC covariates (pct_counts_mt, depth, doublet_score, batch), donor-level phenotypes (amyloid, NFT, gPath, plaques, cognitive slopes, CR_score).

Pathway catalogs: Reactome/GO/KEGG mt sets (OXPHOS/ETC, mito-translation, mitophagy/autophagy, TCA/β-oxidation, mtRNA processing).

Scoring: ssGSEA/GSVA or mean-z (confirm consistency).

Primary Modeling

Core model: pathway_score ~ scale(pathology) + covariates + (1|projid) per cell type; BH FDR within predictor.

Sex-stratified & interaction: run by sex; plus ~ sex*scale(pathology) to quantify slope differences.

Leading genes: For significant pathways, compute “agreement” (fraction of pathologies where a gene’s sign matches pathway sign) and list top drivers per cell type/sex.