Mt-AD: Cell-type & Sex-specific Mitochondrial Remodeling in Alzheimer's Disease

Objective

Map how mitochondrial (mt) pathways relate to AD pathology across brain cell types and sexes and nominate robust gene drivers.

Data & Methods

Data structure

- Single-nucleus expression aggregated to pseudo-bulk per donor×cell-type×sex (Ast, Exc, Inh, Mic, Oli, OPC, Vas, T cells).
- QC covariates available: pct_counts_mt (and where available: total_counts, doublet_score, batch).
- Donor-level phenotypes: amyloid, NFT/tangles, global pathology (gPath), neuritic/diffuse plaques, cognition measures (global score and domain-specific slopes), and cognitive resilience (CR_score).

Pathway scoring

- Curated mt catalogs (Reactome/GO/WP; OXPHOS/ETC, mt-translation, mitophagy/autophagy, TCA/β-oxidation, mtRNA processing).
- Pathway activity derived per sample (one score per pathway).

Modeling

- For each cell type, pathway, and pathology axis. Estimates (Œ≤) are signed and converted to ±log10(FDR). BH FDR correction was applied within each pathology predictor.

$$score \sim scale\ (pathology) + QC + (1|projid)$$

- Sex effects: Fisher's exact tests comparing numbers of significant mt genes in females vs males per cell type. Besides, mixed model with interaction. Interaction terms summarized as signed ±log10(FDR).

$$score \sim sex \times scale\ (pathology) + QC + (1|projid)$$

- Gene-level drivers: from DREAM results, agreement (fraction of pathology axes where a gene's sign matches the focal pathway's sign) and sample support (n). Leading genes ranked within cell type × sex × pathway.

- Visualization: heatmaps of pathway×pathology (signed strength), sex-stratified contrasts, interaction heatmaps (top pathways per panel), recurrent-gene barplots, and per-pathway leading-gene lollipop plots.

Results

- **Neurons dominate. inhibitory >> excitatory**. Inhibitory neurons show the largest and broadest mt associations across amyloid/NFT/gPath and cognition. Balance heatmaps indicate **down-shift of OXPHOS/mt-translation** with higher pathology.

- **Female bias in neurons**. Fisher tests show strong female enrichment of significant mt genes in Inh and Exc. Interactions indicate steeper pathology effects in females for neuronal OXPHOS/translation/mitophagy modules.

- **Oligodendrocyte adaptation with male lean**. Oli signals concentrate in fatty-acid oxidation (FAO) and mitophagy, often positive with pathology. Sex analyses favor males and interactions suggest stronger male slopes.

- **Other cell types are modest**. Microglia and Vas exhibit smaller, pathway-limited patterns (Vas: mtRNA processing/ATP synthase). OPC shows a single cognition-related peak.

- **Compact, repeated gene drivers**

  • **Neurons**: ETC subunits and assembly (MT-ND, COX, ATP5).

  • **Oli:** lipid/FAO & mitophagy genes (ACADM, ACSL1, ACOT9/11, AMACR, ALDH2/3, ATP5 family).

  • **Ast/Vas**: BNIP3/BCL2 (mitophagy regulation), SESN2/GTPBP3/HSPA (mtRNA processing).

These recur across pathology axes and explain pathway signals.

AD pathology is coupled to neuron-centric bioenergetic failure (female-biased OXPHOS/translation/mitophagy disruption). Oligodendrocytes mount a lipid-centric, mitophagy-linked adaptation (male-leaning). The convergence on a small driver roster makes the biology testable and suggests cell-type- and sex-aware therapeutic angles.