Title: Mitochondrial PRSs Uncover Shared Genetics in Neurodegeneration Diseases

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Abstract:

Mitochondrial dysfunction is a unifying biological hallmark of ageing, yet its contribution to various ageing-related neurodegenerative disorders remains incompletely characterised. In this study, we evaluated mitochondrial pathway-specific polygenic risk scores (mtPRSs) to quantify genetically mediated mitochondrial liability for four major neurodegenerative conditions in the UK Biobank: glaucoma, age-related hearing loss, Alzheimer's disease (AD), and Parkinson's disease (PD). Nuclear mtPRSs were constructed using curated mitochondrial pathway gene sets and tested for association with each disease.

mtPRSs showed significant associations across all conditions, with the strongest effect observed for AD (OR: 1.84, 95% CI: 1.81–1.89, with ApoE included), followed by glaucoma (OR: 1.18, 95% CI: 1.16–1.20), PD (OR: 1.13, 95% CI: 1.10–1.18), and hearing loss (OR: 1.11, 95% CI: 1.08–1.13). These results indicate shared mitochondrial-related genetic architecture contributing to neurodegenerative disease susceptibility, potentially reflecting underlying subclinical or pathway-level processes.

Our findings support the utility of pathway-specific PRSs for interpreting disease biology and identifying individuals whose neurodegeneration risk may be driven by mitochondrial mechanisms. Ongoing work will examine pathway-level mechanisms and assess whether mtPRSs can stratify patient subgroups most likely to benefit from mitochondrial-targeted treatments.