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POSTER PRESENTATION

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Association of mitochondrial DNA copy number with brain MRI and cognitive function in the TOPMed Program

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Abstract

Background: Mitochondria are the main energy source for normal neuronal functions. Mitochondrial DNA (mtDNA) copy number (CN), a measure of mtDNA levels in the cell, correlates with cellular energy generating capacity and metabolic status. Previous studies have observed a significant decrease of circulating cell-free mtDNA content in the cerebrospinal fluid of patients with Alzheimer's disease (AD). However, it is unknown whether mtDNA CN circulating in the blood is related to AD endophenotypes. We aimed to investigate the cross-sectional association of mtDNA CN with MRI markers of abnormal brain aging and cognitive function.

Method: We included dementia-free, multiethnic participants from seven population-based cohorts with whole-genome sequencing as part of the Trans-Omics for Precision Medicine (TOPMed) program. The average mtDNA CN in whole blood was estimated as twice the ratio of the average coverage of mtDNA to the average coverage of the nuclear DNA using fastMitoCalc from mitoAnalyzer. Brain MRI markers included total brain volume, hippocampal volume, and white matter hyperintensities. General cognitive function was derived from at least three distinct cognitive domains using principal component analysis. We related mtDNA CN to AD endophenotypes assessed within 5 years of blood draw per cohort and further performed random-effects or sample size-weighted meta-analyses. Models were adjusted for demographics and vascular risk factors.

Result: Higher mtDNA CN was significantly associated with better general cognitive function (P-values<0.05) in four cohorts after adjusting for age, sex, batch effect, self-reported race/ethnicity, the time between blood draw and MRI/Cognitive evaluation, cohort-specific variables, and education (Figure 1). Meta-analysis across all

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cohorts confirmed and strengthened the significant association between mtDNA CN and general cognitive function (n=11,021, Beta=0.046, SE=0.01, P-value=0.0002). Additional adjustment for diabetes, hypertension, hyperlipidemia, and obesity led to similar results (Beta=0.043, SE=0.01, P-value=0.002). We observed no significant associations between mtDNA CN and brain MRI markers.

Conclusion: This study suggests that higher mtDNA CN is cross-sectionally associated with better general cognitive function in a large sample from diverse communities across the US, providing novel findings that support the role of mtDNA in healthy brain aging. Additional analyses are underway to relate mtDNA CN to AD endophenotypes prospectively and to incident dementia.

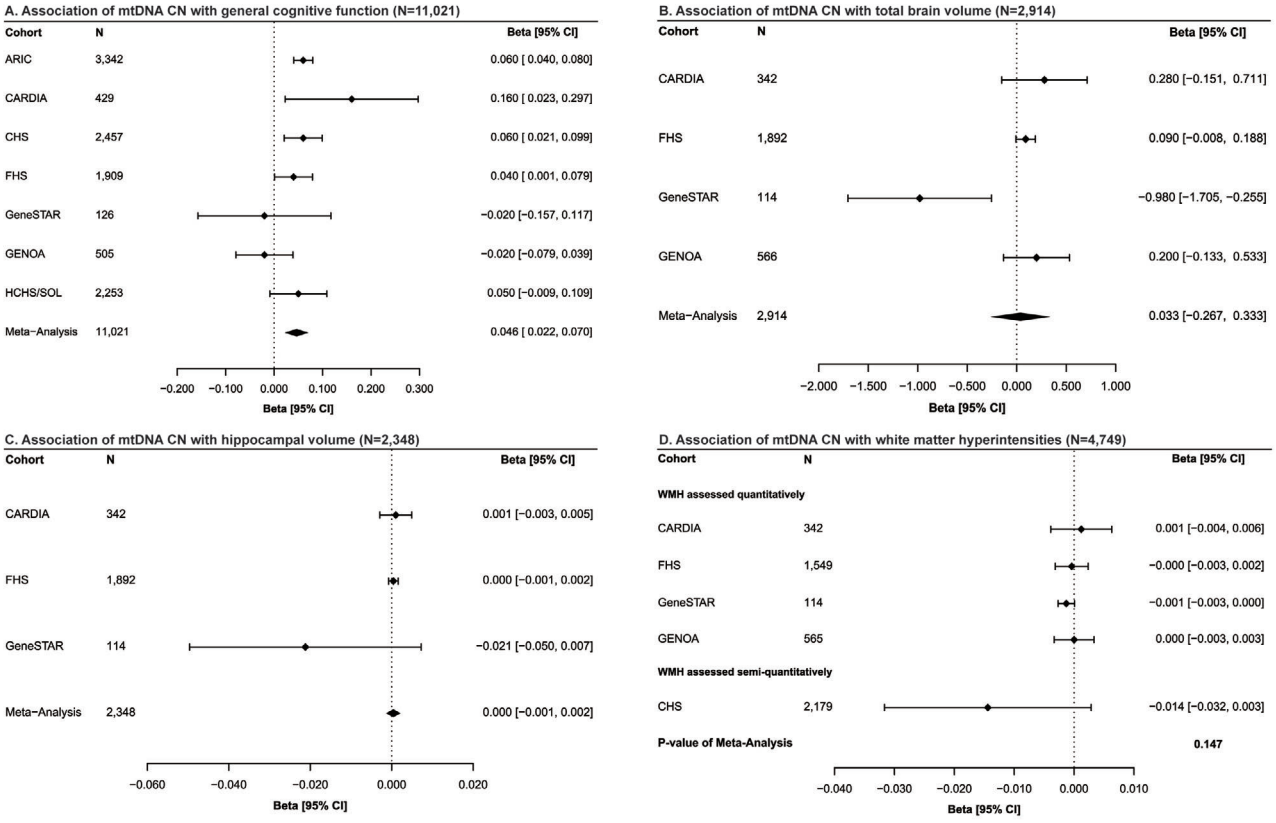

Figure 1. Association analyses of mtDNA copy number with general cognitive function and MRI markers of brain aging.
The random-effects inverse variance method was applied in Meta-Analysis in (A), (B), and (C). Because white matter hyperintensity was assessed semi-quantitatively in CHS and quantitatively in other cohorts, the optimally weighted Z-test method was applied to combine p-values in Meta-Analysis in (D).

FIGURE 1