Mitochondrial DNA Variation and Physical Function among Men with and without HIV

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Introduction

- Mitochondrial DNA variation is associated with multiple aging-related comorbidities among people with HIV (PWH).
- Mitochondrial DNA variation have been linked to mitochondrial function, which is crucial for cellular energy production and plays a central role in aerobic metabolism and physical function.
- Data on the impact of inherited mitochondrial DNA variants on physical function in PWH remain limited.
- Investigating the genetic contribution of mtDNA variation could provide novel insights into personalized approaches for mitigating physical function decline in PWH.

Methods

Study Population and Data Collection

- We included men with ≥2 visits from the Multicenter AIDS Cohort Study.
- Gait speed and grip strength were evaluated twice annually using standard methods beginning in 2006.

Measurements

- Gait speed (m/s) was defined as the fastest of 2 attempts over a 4-meter distance. Grip strength (kg) was the average across three measures with the dominant hand.
- Definition of mtDNA variation
  - mtDNA information was extracted based genotyping data from MEGA Array (the expanded Multi-Ethnic Genotyping Arrary).
  - mtDNA haplotypes:
    - Haplotypes are validated in the UK Biobank from European ancestry population based on chronic disease and mortality outcomes.
    - Seven distinct functionally informed mitochondrial DNA (mtDNA) haplotypes were annotated based on mtDNA SNPs: MT73, MT7028, MT10238, MT12612, MT1317, and MT15257.
  - mtDNA haplogroups:
    - mtDNA haplogroups are inferred based on Phylotree using HaploGrep.
    - Common European (H, JT, UK) and African haplogroups (L0, L1, L2, L3) were extracted.

Statistical Analyses

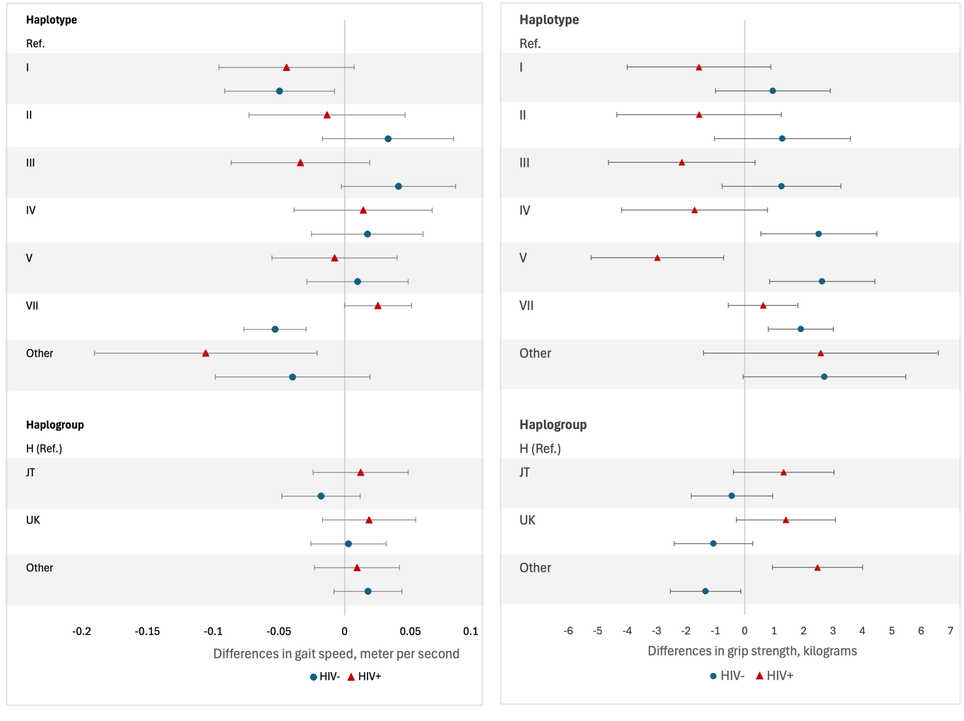
- We compared gait speed and grip strength outcomes by mtDNA variation groups using multivariable mixed-effects linear regression.
- Analyses were stratified by genetic ancestry (European or African ancestry) groups.
- Models were controlled for demographics, follow up year, genetic ancestry principal components (PC1-PC5). BMI, income, education, smoking status, alcohol consumption, injection drug use, multi-morbidities.
- Models were adjusted for multiple testing using Bonforroni correction.

Mitochondrial DNA genetic variations are associated with physical function in men with and without HIV. The direction of these associations may vary based on HIV status.

Results

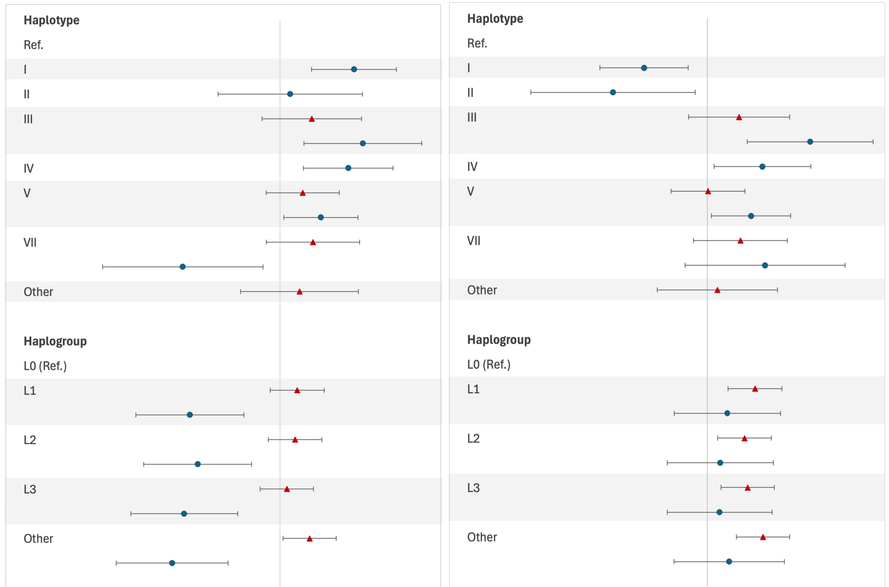
- Total N=2314 (1277 PWH) with 38,913 person-years of follow-up.
- 26% Black, 59% White
- Median age at baseline: 47 (IQR: 40-54)

Figure 1. Gait speed and grip strength by mtDNA haplogroups and haplotypes in European ancestry men with and without HIV.



Results (cont.)

Figure 2. Gait speed and grip strength by mtDNA haplogroups and haplotypes in African ancestry men with and without HIV.



Conclusions

- mtDNA genetic variation is associated with gait speed and grip strength in men.
- Among European men without HIV, mtDNA haplotypes IV, and VII are associated with greater grip strength. The association between haplotype V and grip strength differs by HIV serostatus.
- African mtDNA haplogroup L1, L2, and L3 are associated with slower gait speed in men without HIV.
- African men without HIV carrying mtDNA haplotype III, IV, and V exhibit greater grip strength and faster gait speed.
- These findings suggested that mtDNA genetic variation may play a role in physical function among aging men.
- Further investigation is warranted to understand the functional implication of mitochondrial genetic variation.
- Next steps:
  - Extend the investigation to include women with and without HIV.
  - Explore the interaction between HIV serostatus and mtDNA genetic variation on physical function.

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