Weak Grip and Frailty are Associated with MtDNA Haplogroup in Adults with HIV

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Background

- Single nucleotide polymorphisms (SNPs) in mitochondrial DNA (mtDNA) define mitochondrial haplogroups that may represent susceptibility to diseases, and may be markers of longevity or underlying mitochondrial function.
- Among persons with HIV (PWH), mtDNA haplogroup has been associated with outcomes including AIDS progression, neuropathy, and cognitive impairment.
- Recently mtDNA haplogroup was also linked to gait speed decline among white men with HIV in the Multicenter AIDS Cohort Study.
- We sought to determine if haplogroup is associated with frailty and its components (slow gait or weak grip) among a diverse population of older men and women with HIV.

Methods

- Participants from ACTG A5322, an observational study of PWH aged ≥40 years who received initial ART regimen through an ACTG randomized clinical trial were included.
- Genome-wide genotype data were available from Illumina HumanCore Exome Chip. HAPLOGRP2P was used to assign mtDNA haplogroups.
- Outcomes: Frailty assessment at A5322 entry included 4 meter walk, grip strength, and self-reported weight loss, exhaustion, and low physical activity.
- Participants meeting previously-defined thresholds in 3-5 categories were considered frail, 1-2 pre-frail, and 0 non-frail.
- Gait speed and grip strength were dichotomized per frailty criteria.

Data Analysis

- Multivariable logistic and multinomial logistic regression models were fit for variables known to be associated with frailty, slow gait, or weak grip from our prior analyses.
- Variables significantly associated with at least 1 outcome were included in the final models and included age, sex, education, smoking, hepatitis C antibody positivity, and any prior use of didanosine (DDI) or stavudine (D4T).

Conclusions

- mtDNA haplogroup H was independently associated with frailty and weak grip compared with non-H haplogroups, among persons of non-Hispanic white race/ethnicity.
- This association has not been reported among people without HIV, and could represent a unique contribution of HIV to weakness and frailty, particularly among women.
- mtDNA haplogroup may be a relatively easily obtainable genetic risk factor that could inform targeted preventive or therapeutic interventions in an aging population of PWH.
- Longitudinal analyses of observational studies, analyses of existing frailty clinical trials, and new clinical trials are needed to validate these findings and explore biologic mechanisms and potential interventions.

Acknowledgments

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References


Figure 1A. Number of participants meeting physical function/frailty cut-points by race/ethnicity

Table. Participant Characteristics at HAILO (A5322) Entry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=634</th>
</tr>
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<tbody>
<tr>
<td>Age in years (mean, SD)</td>
<td>51.0 (7.5)</td>
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<tr>
<td>Sex (N, %)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>343 (55)</td>
</tr>
<tr>
<td>Female</td>
<td>291 (45)</td>
</tr>
<tr>
<td>Race/Ethnicity (N, %)</td>
<td></td>
</tr>
<tr>
<td>Hispanic Black</td>
<td>125 (20)</td>
</tr>
<tr>
<td>Hispanic White</td>
<td>199 (31)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>310 (49)</td>
</tr>
<tr>
<td>Education in years (mean, SD)</td>
<td>13.8 (3.5)</td>
</tr>
<tr>
<td>Prior exposure to DDI or D4T (% )</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>210 (33)</td>
</tr>
<tr>
<td>Current</td>
<td>175 (28)</td>
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<tr>
<td>CD4 nadir (mean, SD)</td>
<td>493 (79)</td>
</tr>
<tr>
<td>Grip (N, %)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>343 (55)</td>
</tr>
<tr>
<td>Weak</td>
<td>129 (21)</td>
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<tr>
<td>Mean (SD)</td>
<td>86 (14)</td>
</tr>
<tr>
<td>Pre-frail (N, %)</td>
<td></td>
</tr>
<tr>
<td>Non</td>
<td>36.0 (10.7)</td>
</tr>
<tr>
<td>Frail</td>
<td>13.8 (3.5)</td>
</tr>
<tr>
<td>Frailty (N, %)</td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>244 (39)</td>
</tr>
<tr>
<td>Non</td>
<td>206 (32)</td>
</tr>
<tr>
<td>Frail</td>
<td>581 (93)</td>
</tr>
</tbody>
</table>
| Figure 2. Adjusted analyses demonstrating the effect of H vs non-H haplogroup on frailty, grip, and gait.

Odds of Frailty or Physical Function Impairment among H vs Non-H Haplogroup

- In stratified analyses, women with H haplogroup were more likely to be frail (13%) or pre-frail (75%) than women with non-H haplogroups (0 and 40%, respectively); p=0.046.
- These differences were not seen among men, where frailty or pre-frailty were seen in 6 and 32% of H haplogroup or 2 and 30% of non-H haplogroups (p=0.15).
- In contrast, 25% of women with H and no women with non-H haplogroup had weak grip (p=0.01); 22% of H and 11% of non-H haplogroup men (p=0.07) had weak grip.

- The proportions of frailty and physical function impairment were not significantly different across Black or Hispanic haplogroups.

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