Poster # 702

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

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The A5322 (HAILO) Study

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 HumanHap 650Y, Ilumina 1M duo array, or Illumina HumanCore Exome Chip. HAPLOGREP2 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

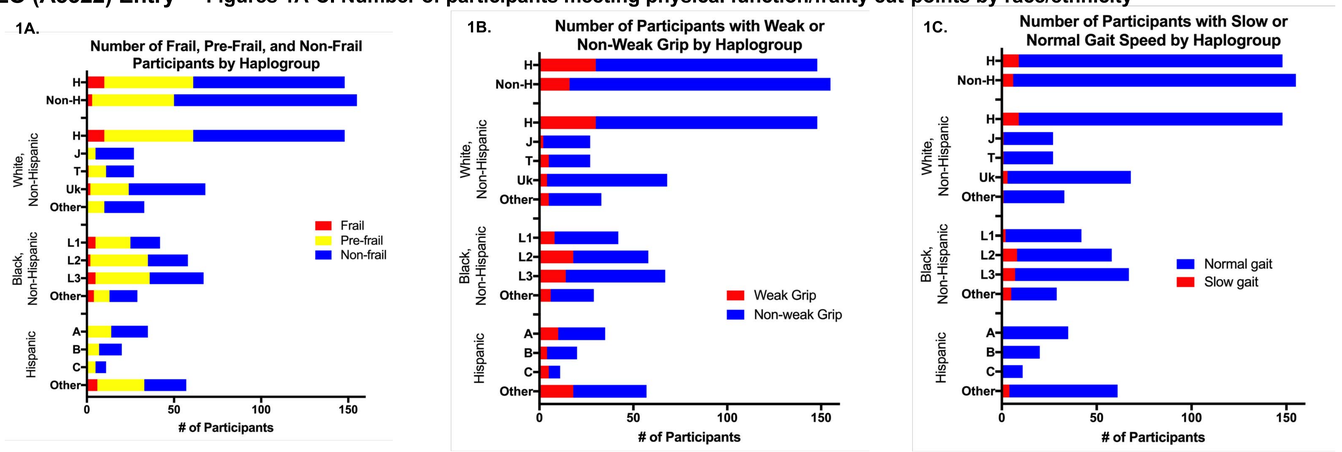
- Multivariable logistic and multinomial logistic regression models were fit for variables known to be associated with frailty, slow gait, or weak grip from our prior analyses.
- Variables significantly associated with at least 1 outcome were included in the final models and included age, sex, education,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

Results

Table. Participant Characteristics at HAILO (A5322) Entry

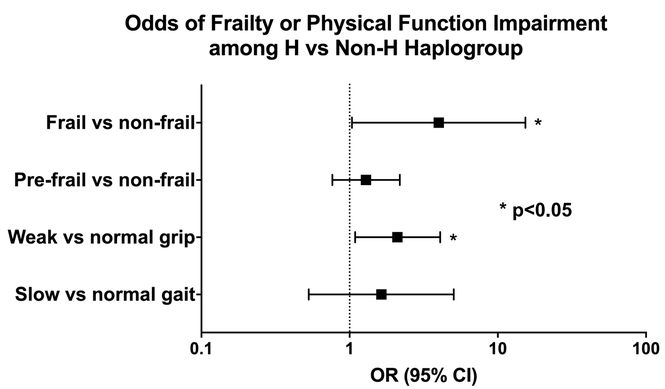
Characteristic	N=634
Age in years (mean, SD)	51.0 (7.5)
Sex (N, %)	
Male	511 (81)
Female	123(19)
Race/Ethnicity (N, %)	
Non-Hispanic White	310(49)
Non-Hispanic Black	199(31)
Hispanic	125(20)
Frailty (N, %)	
Non-frail	343 (55)
Pre-frail	244 (39)
Frail	35 (6)
Gait	
Normal (N, %)	581 (93)
Slow (N, %)	41 (7)
Mean (SD)	4.0 (0.96)
Grip	
Normal (%)	493 (79)
Weak (%)	129 (21)
Mean (SD)	36.0 (10.7)
Education in years (mean, SD)	13.8 (3.5)
Cigarette smoker (%)	
Current	175 (28)
Never	249 (39)
Prior	210 (33)
HCV antibody positive (%)	86 (14)
CD4 nadir (mean, SD)	218.5 (167.3)
Prior exposure to DDI or D4T (%)	55 (9)

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



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

Figure 2. Adjusted analyses demonstrating the effect of H vs non-H haplogroup on frailty, grip, and gait.



- 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=0.11); 20% of H and 11% of non-H haplogroup men (p=0.07) had weak grip.

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.

Acknowledgements

- We thank the A5322 study participants and site staff for their ongoing dedication.
- The study was supported by the NIH: R01 AG054366 and K23 AG 050260 (KME); AI077505 (YB, MR); R01 AI077505, UM1 AI069439, P30 AI110527 and TR 002243 (DWH); UM1 AI068636 (ACTG) and UM1 AI068634 (SDAC)
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