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Mitochondrial DNA Haplogroup B is Associated with Executive Function and Recall in Hispanic PLWH

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CHARTER
CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH

Objective

To determine relationships between mitochondrial DNA (mtDNA) haplogroups and neurocognitive (NC) performance domains in persons living with HIV (PLWH).

Background & Significance

- Neurocognitive impairment (NCI) is common among PLWH and impacts quality of life and functional status.
- Mitochondrial function has long been thought to play a role in neurodegeneration, and PLWH may be particularly vulnerable due to factors related to chronic neuroinflammation and exposure to antiretroviral therapy (ART).
- Prior research has described associations between mitochondrial DNA (mtDNA) haplogroups and HIV-related outcomes, including NCI.
- NCI (by Global Deficit Score and HAND) was less frequent among Hispanic PLWH having mtDNA haplogroup B than among those having other haplogroups.[1]
- We hypothesized that better global NC performance in PLWH with Hispanic mtDNA haplogroup B is due to improvements in specific NC domains.

Methods

- Study design: Cross-sectional analysis of baseline data from CHARTER, a prospective observational study of neurologic outcomes in PLWH.[2]
- Haplogroups were assigned using mtDNA genetic sequence data from the Affymetrix MitoChip v2.0 and HaploGrep.[1]
- Genetic ancestry was determined from Affymetrix Array 6.0 ancestry-informative genetic markers and principle components analysis.[3]
- Outcomes: **age-, sex-, and education-corrected domain deficit (DDS) and mean T scores (TS) for seven domains**: motor, working memory, verbal, executive function, processing speed, learning and delayed recall.[4]
- Statistical analyses:
  - Genetic ancestry-stratified univariate analyses of baseline DDS and domain TS (Wilcoxon rank sum, χ^2 tests).
  - Linear regression models were adjusted for nadir CD4+ T cell count, NC comorbidity status[4] (see Table 1 footnotes), and current ART use.
- Persons with potentially confounding NC comorbidities were excluded from genetic analyses.

Citations: [1]Hulgan, et al. *Clin Infect Dis* 2015; [2]Heaton, et al. *Neurology* 2010; [3]Jia, et al. *Am J Med Genet B* 2017; [4]Antinori, et al. *Neurology* 2007.

Results

- Major haplogroups and NC domain data were available for 1016 adults (median age 43 years, 23% female; **Table 1).**
- Haplogroup frequencies were as expected within genetic ancestry groups (**Figure 1**).
- Among 98 Hispanic PLWH, executive function, learning, and recall mean TS and DDS were better among 17 with **haplogroup B** compared to other haplogroups (Wilcoxon p<0.05; **Figure 2**).
- **With adjustment for covariates, haplogroup B remained significantly associated with executive function DDS and TS (p≤0.05 for both), and recall TS (p=0.03)** but was no longer associated with learning DDS and TS or recall DDS (**Figure 3**).
- Major haplogroups in other ancestry groups were not significantly associated with NC domain TS or DDS.

Table 1. Demographics and Other Characteristics of CHARTER participants, by Genetic Ancestry

	Overall (n = 1016)	European Ancestry (n = 440)	African Ancestry (n = 478)	Admixed Hispanic Ancestry (n = 98)
Age, years	43 (8)	43 (9)	43 (8)	41 (8)
Female Sex (%)	234 (23.0%)	49 (11.1%)	158 (33.1%)	27 (27.6%)
Genetic Ancestry (%)				
African	478 (47.0%)	-	478 (100%)	-
Admixed Hispanic	98 (9.6%)	-	-	98 (100%)
European	440 (43.3%)	440 (100%)	-	-
Haplogroup B (%)	17 (1.67%)	-	-	17 (17%)
Nadir CD4	209 (193)	228 (203)	194 (184)	197 (187)
Plasma HIV RNA (log10)	2.82 (1.28)	2.80 (1.29)	2.87 (1.28)	2.70 (1.28)
AIDS Status = non-AIDS (%)	387 (38.1%)	189 (43.0%)	171 (35.8%)	27 (27.6%)
Estimated Duration of HIV Infection, Months	122.5 (76.6)	120 (82.2)	126.2 (70.9)	115.97 (76.7)
On ART (%)	728 (71.7%)	309 (70.2%)	342 (71.5%)	77 (78.6%)
Minimal Comorbidity (%)*	657 (64.7%)	306 (69.5%)	293 (61.3%)	58 (59.2%)
Hepatitis C Virus (%)	255 (25.1%)	74 (16.8%)	169 (35.4%)	12 (12.2%)

Values are listed as mean (standard deviation), except where denoted with (%), in which case values are N (%).
*Comorbidities were classified as either *incidental* secondary (or minimal) or potentially contributing, based on the likelihood that NCI was due to HIV-related effects on the brain rather than the comorbid condition. Examples of contributing comorbidities include developmental learning disorder and traumatic brain injury with mild educational or functional sequelae with subsequent decline in the context of HIV (Antinori, et al. *Neurology* 2007).

Figure 1. Haplogroup Prevalence by Genetic Ancestry

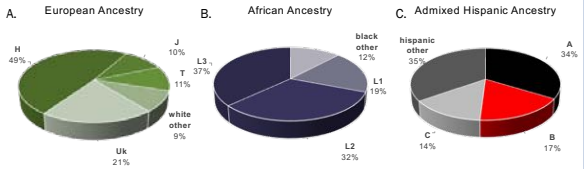


Figure 1. Pie charts displaying the prevalence of mitochondrial haplogroups within each genetic ancestry group. There were 17 Hispanic PLWH who had haplogroup B (prevalence 17%; Figure 1C).

Figure 2. Dot and Box Plots of Executive Function, Learning and Recall TS by Haplogroups in Hispanics

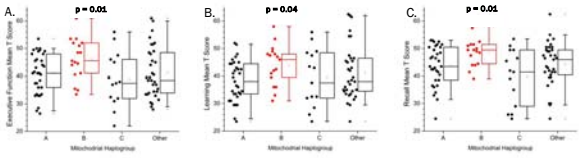


Figure 2. Dot and Box-whisker plots showing mean T scores for the selected neurocognitive domains of executive function (**Panel A**), learning (**Panel B**), and recall (**Panel C**) for patients with Hispanic haplogroup B. P-values are by Wilcoxon rank-sum tests of haplogroup B vs. all others. **Executive function and recall mean T scores remained significant following adjustment for covariates (see Figure 3B).** Boxes depict medians, IQR, and 95th percentiles of mean T scores.

Figure 3. Adjusted Linear Regression Haplogroup B Coefficients for Neurocognitive Domain Scores

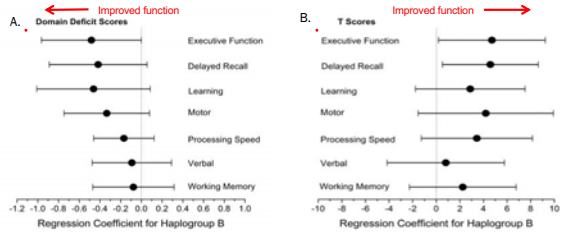


Figure 3. Forest plots of adjusted coefficients for Haplogroup B association with domain deficit (Panel A) and T scores (Panel B) for all neurocognitive domains tested. Coefficients were adjusted for nadir CD4 cell count, neurocognitive comorbidity status, and current ART use. Boxes denote statistically significant results (p≤ 0.05).

Limitations and Conclusions

- **Limitations include the cross-sectional design, small sample size of the mtDNA haplogroup B, and lack of mechanistic outcomes.**
- **Hispanic CHARTER participants with mtDNA haplogroup B had significantly better NC performance in delayed recall and executive function domains.**
- **These findings may inform future studies to define mechanisms by which mtDNA variation influences NC performance in PLWH, and studies of prevention and treatment of NCI.**

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