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Mitochondrial DNA Haplogroups and Domain-Specific Neurocognitive Performance in Adults with HIV

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Abstract

Neurocognitive (NC) impairment (NCI) is an important cause of morbidity in persons with HIV (PWH). In the high-energy environment of the central nervous system, mitochondria contribute to neuroinflammation and aging, which may ultimately drive the pathogenesis of neurodegenerative diseases. Mitochondrial DNA (mtDNA) haplogroups are associated with health outcomes in persons with HIV (PWH). For example, we previously observed less global NCI in Hispanic ancestry PWH having mtDNA haplogroup B. Another study reported increased NCI among PWH having African subhaplogroup L2a. We therefore analyzed NC domains in relation to these haplogroups in CHARTER, a multi-site observational neuro-HIV study. Haplogroups were assigned using mtDNA sequence in 1,016 PWH. Outcomes were NCI, defined by domain deficit score and mean T-scores (TS) for seven NC domains. Ancestry-stratified analyses of NC performance included Wilcoxon rank sum, χ^2, and Fisher's exact tests. Multivariable regression adjusted for NC comorbidity, ART use, and nadir $CD4^+$ T-cells. Among 98 Hispanic ancestry PWH, executive function, learning, and recall performance were better with haplogroup B (N=17) than other haplogroups. With adjustment for covariates, haplogroup B remained associated with better executive function (p=0.04) and recall TS (p=0.03). PWH with haplogroup B had fewer impaired domains than other haplogroups (p<0.01). Subhaplogroup L2a (N=89) was associated with greater NCI in learning, recall and working memory among 478 PWH of African ancestry, and had more impaired domains than other subhaplogroups (p<0.01). These findings may inform risk stratification for NCI and studies to define mechanisms by which mtDNA variation may influence NCI in PWH.

Keywords

HIV; neurocognitive disorders; DNA; mitochondrial; Hispanic Americans; African Americans

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INTRODUCTION

Neurocognitive (NC) impairment (NCI) remains an important cause of morbidity in persons with HIV (PWH) and impacts both quality of life and functional status (Clifford and Ances, 2013). Despite advances in HIV care and the widespread use of combination antiretroviral therapy (ART), up to half of all treated PWH have some degree of NCI, a proportion similar to the pre-ART era (Clifford and Ances, 2013; Heaton *et al*, 2011). While the biological mechanisms are likely heterogeneous, possible contributors include persistent inflammation, drug toxicity, and aging-related neurodegeneration (Eggers *et al*, 2017; Hong and Banks, 2015).

The role of mitochondria in the pathogenesis of common metabolic and neurodegenerative diseases, cancer and aging has gained increasing recognition (Gomez-Duran *et al*, 2010; Khusnutdinova *et al*, 2008; Wallace, 2013; Wallace and Lott, 2013). Mitochondria produce approximately 90% of the body's energy via oxidative phosphorylation. In addition to energy production, mitochondria also generate reactive oxygen species (ROS), control cellular redox levels, modulate cytosolic calcium dynamics, modulate several cellular signal-transduction pathways and the epigenome, and regulate the intrinsic pathway of apoptosis (Wallace, 2013). Thus, mitochondria function in diverse aspects of cellular health and bioenergetics, and are key mediators of cellular damage in response to environmental stressors.

The critical role of mitochondria is perhaps most evident within the central nervous system (CNS). Of all organs, the human brain has the highest energy requirements, using ~20% of the total mitochondrial energy production despite accounting for only 2–3% of the body's weight (Wallace, 2013). In this high-energy environment, mitochondria are vital to brain health and function. Additionally, through modulation of inflammatory, apoptotic, and cellular signaling pathways, mitochondria contribute to neuroinflammation, which may ultimately drive the pathogenesis of neurodegenerative diseases (Di Filippo *et al*, 2010).

The mitochondrial genome consists of 13 protein-coding genes, which encode electron transport chain proteins. Mitochondrial DNA (mtDNA) is maternally inherited, and patterns of mtDNA variants called haplogroups define maternal ancestry and have been associated with common human diseases (Wallace and Lott, 2013), including neurodegenerative diseases (Chinnery and Gomez-Duran, 2018). For example, European ancestry mtDNA haplogroups appear to alter the risk of Alzheimer's and Parkinson's diseases (Chagnon *et al*, 1999; Hutchin and Cortopassi, 1995; Santoro *et al*, 2010; Shoffner *et al*, 1993; van der Walt *et al*, 2004).

Since ART drugs, particularly older nucleoside reverse-transcriptase inhibitors (Gardner *et al*, 2014) and HIV itself (Rozzi *et al*, 2017) can affect mitochondria, mtDNA haplogroups may be associated with health outcomes in PWH (Hart *et al*, 2013). Our group previously reported that mtDNA haplogroups influenced the development and severity of NCI in PWH (Hulgan *et al*, 2015). Specifically, NCI (defined by the Global Deficit Score [GDS], indicating HIV-associated neurocognitive disorder [HAND]), was less frequent among Hispanic ancestry PWH having mtDNA haplogroup B than among those having

other haplogroups. Another group found significant differences in NC performance by haplogroup among PWH of African ancestry (Azar *et al*, 2016). Specifically, individuals with subhaplogroup L2a had worse executive/working memory composite performance than the rest of the cohort, although this relationship did not remain significant in further analyses (Azar *et al*, 2016). Persons having subhaplogroup L3e had better performance on psychomotor speed and dexterity tasks compared to the remainder of the cohort.

We hypothesized that previously seen differences in the African subhaplogroups L2a and L3e would again be present in African ancestry PWH, with better performance testing in psychomotor speed for individuals with subhaplogroup L3e but worse performance in working memory and executive function for individuals with L2a. Furthermore, we hypothesized that Hispanic ancestry PWH with Haplogroup B would have better performance in specific NC domains, which would account for the better global NC performance seen previously (Hulgan *et al*, 2015).

METHODS

Study Design and Participants

This study was a cross-sectional analysis of baseline data from the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study (Heaton *et al*, 2010). CHARTER is a prospective, observational study of neurologic outcomes in PWH conducted at 6 US locations: Baltimore, MD; New York, NY; San Diego, CA; Galveston, TX; Seattle, WA; and St Louis, MO. Institutional review boards at each site approved this research, and each participant provided written informed consent. Data were collected between 2003 and 2007, and included comprehensive neuromedical, neurobehavioral, and laboratory assessments that were standardized across all sites.

Mitochondrial and Nuclear DNA Sequencing, Haplogroup and Ancestry Determination

Isolation of DNA from whole blood samples was performed using PUREGENE (Gentra Systems Inc, Minneapolis, Minnesota). Full mtDNA sequence was determined using the GeneChip Human Mitochondrial Resequencing Array v2.0 (Affymetrix, Inc, Santa Clara, California). Array intensity data were processed using the MitoChip Filtering Protocol (Xie *et al*, 2011), and variants were called relative to the Revised Cambridge Reference Sequence (Andrews *et al*, 1999). Haplogroups were assigned using HaploGrep (Kloss-Brandstatter *et al*, 2011).

Most participants also underwent nuclear DNA genotyping using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Inc, Santa Clara, California). Ancestry-informative markers were analyzed using EIGENSTRAT software to generate principal components (PC). Model-based clustering on the top 3 PCs, using the *mclust* R package, was used to assign individuals to genetic ancestry clusters using an ellipsoidal model. Genetic ancestry clusters showed 97.4% agreement with self-reported race and ethnicity. All analyses used PC-based ancestry stratifications (European, African, or admixed Hispanic).

Assessments of Neurocognitive Impairment

Participants underwent a comprehensive NC test battery, which was designed to assess seven domains affected by HIV: executive function, learning, delayed recall, speed of information processing, working memory, verbal fluency, and motor performance. Individual tests used for each domain have been described previously (Heaton *et al*, 2010). Raw test scores were converted into T-scores (TS; standard scores with a mean of 50 and standard deviation [SD] of 10) using demographic normative data to control for the effects of age, education, sex, and race/ethnicity. For self-reported Hispanics, three of the 15 tests were corrected for English-speaking Hispanics normative standards (WAIS-III Digit Symbol, Symbol Search and Letter-Number Sequencing); these are the only tests that have corrections for English-speaking Hispanics. For all other tests, Hispanics were normed as White, which is the closest available normative group as determined in the WAIS-III national normative study (Heaton, 2003). There were no Spanish-speakers in this study. Adjusted T-scores were then converted into deficit scores using a 0- to 5-point deficit scale (Blackstone *et al*, 2012). Domain deficit scores (DDS) and the GDS were derived by dividing the sum of the deficit points of each contributing test by the number of tests per domain or over the entire battery. Test scores also were corrected for practice effects using an approach that adjusts for the number of prior testings (Cysique *et al*, 2011). Domain deficit scores >0.5 defined domain-specific NCI; GDS ≥0.5 defined global NCI (Blackstone *et al*, 2012).

Comorbidities for participants were classified as incidental, contributing, or confounding, based on the estimated influence of comorbid conditions on performance (Antinori *et al*, 2007; Heaton *et al*, 2010). Examples of contributing conditions included developmental learning disorder and traumatic brain injury. Individuals with confounding neurocognitive comorbidities that precluded assessment of the contribution of HIV to their NCI were excluded from CHARTER genetic analyses.

Statistical Analyses

Outcomes included: a) domain TS as a continuous measure; b) binary impairment status for each domain (DDS >0.5 = impaired; DDS ≤0.5 = non-impaired/normal performance); and c) median number of impaired domains. We also assessed global NC performance as continuous mean TS and as dichotomized GDS-defined impairment status. Both continuous (TS) and dichotomous (DDS) outcome measures were included in analyses as they provide separate but related measures of normed performance and normed impairment status. Analyses were stratified by PC-derived genetic ancestry. Univariate analyses included the nonparametric Wilcoxon Rank Sum test for continuous TS and Fisher's exact test for impairment status. Multivariable linear and logistic regression were performed to obtain coefficients and odds ratios (OR) for mtDNA haplogroup associations with domain TS and impairment status, respectively, and were adjusted for: comorbidity status (incidental vs. contributing); current ART use (yes vs. no); and nadir $CD4^+$ T-cell count. Formal corrections for multiple comparisons were not performed because of the limited number of targeted haplogroups within each ancestry group. Statistical analyses were conducted using R version (1.1.453) and Stata Statistical Software, Release 13 (College Station, TX: StataCorp LP).

RESULTS

Participant Characteristics

Major haplogroups and neurocognitive domain data were available for 1016 participants. Median age (Table 1) was 43 years (interquartile range [IQR] 38–49) and 234 (23%) were women. Median CD4+ T cell nadir was 209 cells/mm^3 and 728 participants (72%) were on ART at the time of baseline assessment. Of 725 on ART with plasma HIV RNA measured, 419 (58%) had HIV RNA in plasma below the lower limit of quantification. Of the 1016 persons included in analyses, 657 (65%) had incidental (minimal) comorbidities and 359 (35%) had contributing comorbidities. Haplogroup frequencies within each ancestry group were consistent with U.S. population-based data (Mitchell *et al*, 2014).

Out of the 1016 total participants, there were 98 participants of Hispanic ancestry, including 17 participants (17.3%) with haplogroup B (Table 2). The median age of haplogroup B participants was 40 years (IQR 34–45) and they were predominantly male, with only 2 (12%) women. Median CD4+ T cell nadir was 180 cells/mm^3 (IQR 168–342 cells/mm^3), 14 (82%) were on ART at the time of baseline assessment, and 10 (59%) had HIV RNA in plasma below the lower limit of quantification. Median years of education was 12 (IQR 10–13), and 13 (77%) had incidental (minimal) neurologic comorbidities.

There were a total of 478 participants in African ancestry haplogroups, including 89 (19%) in subhaplogroup L2a with a median age of 43 years; and 86 (18%) in subhaplogroup L3e with a median age of 45 years (Table 2). Women comprised 29 (33%) of participants in subhaplogroup L2a and 27 (31%) of participants in subhaplogroup L3e. Participants had a median CD4+ T cell nadir of 129 cells/mm^3 (IQR 20–251 cells/mm^3) and 110 cells/mm^3 (IQR12–249 cells/mm^3) in subhaplogroups L2a and L3e, respectively, with 66 (74%) in subhaplogroup L2a and 67 (78%) in subhaplogroup L3e on ART at the time of baseline assessment. Only 35 (39%) and 40 (47%) had plasma HIV RNA below the lower limit of quantification in subhaplogroups L2a and L3e, respectively. Median years of education was 12 (IQR 11–13) for participants of both L2a and L3e, and 57 (64%) in L2a and 47 (55%) in L3e had incidental (minimal) neurologic comorbidities (Table 2). Demographic comparisons between analyzed haplogroups are shown in the Supplemental Table.

Major mtDNA Haplogroups and Neurocognitive Performance

Major mtDNA haplogroups in European and African ancestry groups were not statistically significantly associated with NC domain-specific TS or impairment (data not shown). Within the Hispanic ancestry group, the 17 participants with haplogroup B had better global NC performance by both outcome measures, with less impairment (18% vs 61%, p=0.002) and better performance by global TS (47.9 vs 43.5, p=0.009). In the domain-specific analysis, these differences were found to be driven by significantly higher TS (better performance) in executive function (median 45.5 vs. 39.5; p=0.02), learning (46.0 vs. 38.0; p=0.04) and recall memory (49.5 vs. 43.5; p=0.01); and less impairment in executive function by DDS cutoffs compared to individuals with other haplogroups (29% vs 61%; p=0.03) (Table 3 and Figure 1). While impairment in learning (35% vs. 56%) and recall memory (18% vs. 41%) as measured by DDS were also less frequent among

individuals with haplogroup B, these differences were not statistically significant (p=0.18 and p=0.10, respectively). Persons with haplogroup B had a median of one impaired NC domain, compared with a median of three impaired domains of non-B-haplogroup individuals (p=0.005; Table 3).

With adjustment for comorbidity status, current ART use, and nadir $CD4^+$ T-cell count, haplogroup B had better global performance by TS (p=0.05), which was driven by better executive function TS (β=4.72 [95% CI 0.19, 9.25]; p=0.04) and recall TS (β=4.58 [95% CI 0.53, 8.64]; p=0.03). The association with learning TS weakened (p=0.22; Table 3). PWH with haplogroup B were significantly less likely to have global impairment (adjusted OR [aOR] 0.16 [95% CI 0.04, 0.62]; p =0.008) or impairment in executive function (aOR 0.29 [95% CI 0.09, 0.91]; p=0.04). Learning and recall memory impairment also were less likely to be impaired (aOR 0.57 and 0.39, respectively), but these associations were not statistically significant (Table 3).

Selected subhaplogroup analysis in African-ancestry population

Based on published data (Azar *et al*, 2016), we also examined domain-specific NC performance among persons of African ancestry for whom mtDNA haplogroup data were available. African subhaplogroups L2a and L3e comprised 89 (19%) and 86 (18%) of African-ancestry participants, respectively.

Compared with other persons of African ancestry, those with subhaplogroup L2a had more frequent impairment in global neurocognitive performance (40% vs 29%, p=0.04), which persisted after adjustment for the covariates noted above (aOR 1.74 [1.07, 2.83]; p=0.03). There was no significant difference in mean TS for global NC performance in subhaplogroup L2a.

In the domain-specific analysis, subhaplogroup L2a had worse NC performance (median TS 42.5 vs. 46.5, p=0.02) and more frequent impairment (35% vs. 24%, p=0.04) in working memory (Table 4 and Figure 2). These associations remained significant in analyses after adjustment for the covariates (β=−2.38 [95% CI −4.40, −0.36]; p=0.02 and aOR for impairment 1.72 [95% CI 1.05, 2.83]; p=0.03; Table 4).

Subhaplogroup L2a was also associated with more recall impairment (45% vs. 29%; p=0.005; aOR 2.12 [95% CI 1.31, 3.44]; p=0.002; Table 4 and Figure 2B), but not recall memory TS (p=0.48; Figure 2A). Additionally, participants of subhaplogroup L2a had worse learning TS (41.0 vs 43.5, p=0.048), with a trend towards more learning impairment (44% vs 33%, p=0.07; Table 4 and Figure 2). With adjustment for covariates, the association with learning impairment persisted (aOR 1.61 [95% CI 1.00, 2.59], p=0.050), although the association with learning TS was no longer significant. Finally, persons with subhaplogroup L2a had a median of two impaired domains compared with a median of one impaired domain in African persons not belonging to L2a (p=0.004; Table 4). Subhaplogroup L3e was not significantly associated with global or domain-specific NC performance (Table 5).

DISCUSSION

These analyses further characterize a previously observed association between mtDNA haplogroup B and NCI in PWH of Hispanic ancestry. Persons having haplogroup B had better global NC performance and less NCI than Hispanic-ancestry persons with other haplogroups (Hulgan *et al*, 2015). Here we report that differences in global performance appear to be driven by differences in executive function and delayed recall. Performance was generally better across all domains but was statistically significantly better in adjusted models of these specific domains.

In addition, we confirmed published findings linking subhaplogroup L2a to NC performance in a study of 157 predominantly African American PWH with comprehensive NC evaluations (Azar *et al*, 2016). In that study, subhaplogroup L2a was also associated with poorer executive function/working memory scores and lower global mean TS, and African subhaplogroup L3e was associated with better performance on measures of psychomotor speed and dexterity. In our analysis, subhaplogroup L2a was associated with poorer NC performance/NCI in domains related to memory and learning. We did not see differences in motor performance among persons with African subhaplogroup L3e. Differences in some associations may reflect population differences, measurement variations, or, potentially, either spurious associations or underpowered analyses. We found no significant associations between major European and African haplogroups and neurocognitive impairment.

We focused on two measures of performance in each domain: TS and impairment status determined by DDS. We did not analyze outcomes of clinical performance rating, or the categorical DDS. Measurements were corrected for practice effects. We also explored differences in the total number of impaired domains by mtDNA haplogroups. Despite small sample sizes, particularly within Hispanic-ancestry PWH, mtDNA haplogroup B was associated with fewer impaired domains (median of one vs. three impaired domains out of seven), and subhaplogroup L2a with significantly more impaired domains (median of two vs. one impaired domain) compared with other haplogroups in the respective ancestry groups. Consistent findings and direction of associations across a range of NC measures and in total number of domains impaired, and in the case of L2a, consistency across more than one cohort, suggests robustness of results.

Strengths of these analyses include the large and ancestrally diverse population. The NC assessments used are well established and were administered in rigorous and uniform fashion, providing a very strong dataset of validated NC outcome measures. A thorough review process also determined the likely contribution of comorbid factors (other than HIV) to NCI; persons with confounding comorbidities were excluded from genetic analyses, and multivariable models were adjusted for comorbid conditions that may have affected NC performance. While the exclusion of participants with confounding comorbidities is a strength, we acknowledge that this may reduce generalizability, especially among communities with higher comorbidity rates and confounding neurologic conditions. Limitations of these analyses include the cross-sectional design and the lack of a control population of persons without HIV. Another potential limitation was the relatively young age of the participants, with median ages between 40 and 45 years in CHARTER overall and in

haplogroups B, L2a, and L3e. These results may not be generalizable to older populations and further studies in these populations are needed. Additionally, despite the overall large sample size, and the relatively large sample (almost 100) of PWH having Hispanic ancestry, the primary results are based on 17 with mtDNA haplogroup B. While a small subgroup of the overall population, haplogroup B represents almost 20% of Hispanic-ancestry persons, and African haplogroup L2a almost 20% of African Americans, proportions that could be substantial as the U.S. HIV epidemic includes growing numbers of persons of color (Hess *et al*, 2017). While we cannot definitively exclude unmeasured confounders related to haplogroup and NC performance, we previously addressed questions about country of origin and language in this cohort (Hulgan *et al*, 2015), which did not differ by haplogroup in the Hispanic-ancestry group. Because our analyses focused on replication of prior associations in a limited number of haplogroups and NC domain performance are not wholly independent measures, we did not formally adjust our analyses for multiple comparisons. A conservative Bonferroni-corrected p-value of 0.00625 (0.05/8 domains plus global performance) would have yielded fewer, but would not have eliminated all significant associations in ancestry-stratified analysis. Finally, we acknowledge that participants were assessed prior to the integrase inhibitor era and mostly used either protease inhibitor- or non-nucleoside reverse transcriptase inhibitor-based regimens. We adjusted for use of ART but elected not to limit analyses to only those with suppressed HIV RNA due to sample size and power considerations.

The relationship of mtDNA variation to NCI is supported by frequent NCI in inherited mtDNA diseases as well as associations between mtDNA haplogroups and neurodegenerative diseases (Chinnery and Gomez-Duran, 2018). An unanswered question is the mechanism for these potential associations. Mitochondrial genetic variation may have arisen through evolutionary pressures on the mitochondrial genome to provide advantages in different environmental niches, potentially related to bioenergetics, oxidative phosphorylation, and heat production (Wallace, 2013). This variation may alter disease vulnerability, conferring either beneficial or detrimental effects in different settings through regulation of mitochondrial energy output, inflammation, or apoptosis. Recognition of the importance of mitochondria in innate and adaptive immune responses is growing, which could influence CNS health in chronic HIV infection (Fields and Ellis, 2019). Our group found differences in levels of cerebrospinal fluid (CSF) tumor necrosis factor-*alpha* by European mtDNA haplogroups H and J in a subgroup of CHARTER participants, but the Hispanic-ancestry subgroup was too small to assess (Samuels *et al*, 2016). We are unaware of other data on the relationship between mtDNA haplogroup and neuroinflammatory biomarkers in Hispanic persons and this is another important future research direction.

Differential performance in functional domains could inform studies of targeted brain regions with greater or less susceptibility to neuroinflammation and potentially guide neuroimaging assessments. The combination of associations with measures of executive function, memory, and learning could point to specific mitochondrial function deficits in relevant brain regions, including the hippocampus, prefrontal cortex, and cerebellum (O'Shea *et al*, 2016; Vikbladh *et al*, 2019). Prospective studies assessing hippocampal structure and function in persons having certain mtDNA haplogroups could yield mechanistic information about how mtDNA genetic variation influences NC performance.

These findings could also provide guidance toward precision medicine approaches and targeted interventions to prevent NC decline or improve NC performance in specific domains, such as working memory in persons of African ancestry and subhaplogroup L2a.

In summary, these results demonstrate novel mtDNA haplogroup associations with domain-specific NC performance in African- and Hispanic-ancestry PWH in the U.S. These findings could inform our understanding of the biological bases for disparities in NCI among PWH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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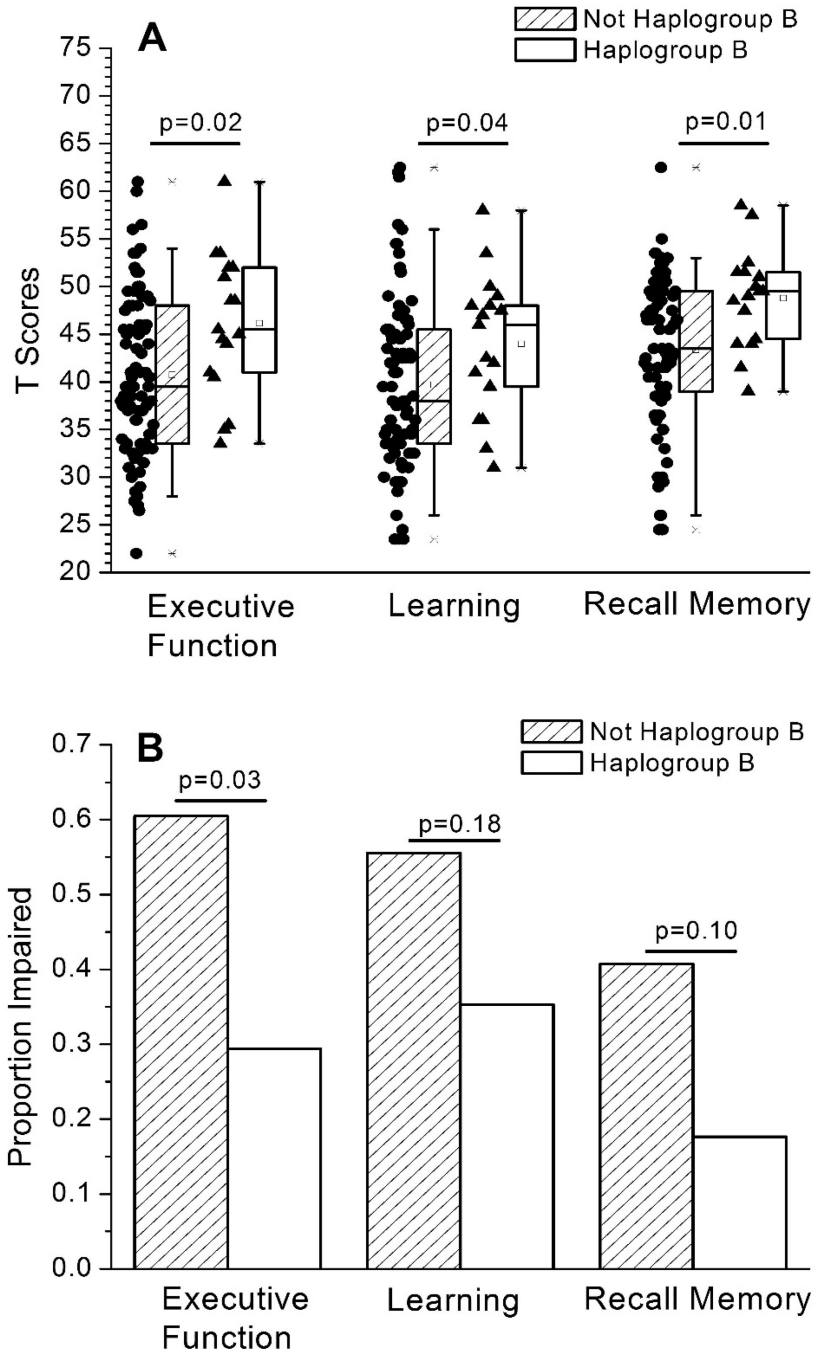

Figure 1.

Executive function, learning, and delayed recall domain performance by T-scores (**Panel A**) and proportion with domain-specific impairment (**Panel B**), by mtDNA haplogroup B within persons of Hispanic ancestry.

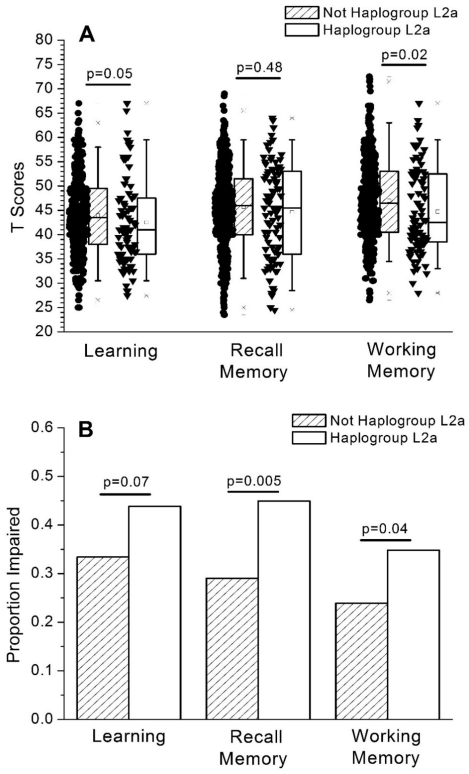

Figure 2.

Learning, recall memory, and working memory domain performance by T-scores (**Panel A**) and proportion with domain-specific impairment (**Panel B**), by mtDNA haplogroup L2a within persons of African ancestry.

Table 1.

Demographics and Other Characteristics of Participants by Genetic Ancestry

	Overall (n=1016)	European Ancestry (n=440)	African Ancestry (n=478)	Hispanic Ancestry (n=98)
Age, years	43 (38–49)	43 (38–49)	44 (39–49)	43 (38–49)
Female sex (%)	234 (23%)	49 (11%)	158 (33%)	27 (28%)
Nadir CD4+ T-cells, /mm^3	176 (50–306)	176 (67–324)	160 (30–287)	175 (50–301)
Plasma HIV RNA (log$_{10}$ copies/mL)	2.3 (1.7–4.0)	2.1 (1.7–4.0)	2.4 (1.7–4.0)	2.3 (1.7–4.0)
Estimated duration of HIV infection (months)	120 (57–184)	116 (45–187)	126 (73–180)	120 (57–185)
On ART (%)	728 (72%)	309 (70%)	342 (72%)	77 (79%)
Minimal comorbidity (%) [1]	657 (65%)	306 (70%)	293 (61%)	58 (59%)
Education (years)	12 (11–14)	13 (12–16)	12 (11–13)	12 (11–13)

Values are listed as N (%) or median (interquartile range); ART=antiretroviral therapy.

[1] Neurologic comorbidity status (incidental vs. contributing; see METHODS).

Table 2.

Demographics and Other Characteristics of Participants by Ancestry-specific Haplogroups

	Overall (n=1016)	African Haplogroup L2a (n=89)	African Haplogroup L3e (n=86)	Hispanic Haplogroup B (n=17)
Age, years	43 (38–49)	43 (39–48)	45 (40–48)	40 (34–45)
Female sex (%)	234 (23%)	29 (33%)	27 (31%)	2 (12%)
Nadir CD4+ T-cells, /mm ^{3}	176 (50–306)	129 (20–251)	110 (12–249)	180 (168–342)
Plasma HIV RNA (log_{10} copies/mL)	2.3 (1.7–4.0)	2.6 (1.7–4.1)	2.0 (1.7–4.0)	1.7 (1.7–3.1)
Estimated duration of HIV infection (months)	120 (57–184)	113 (53–169)	135 (89–173)	108 (52–128)
On ART (%)	728 (72%)	66 (74%)	67 (78%)	14 (82%)
Minimal comorbidity (%) [1]	657 (65%)	57 (64%)	47 (55%)	13 (77%)
Education (years)	12 (11–14)	12 (11–13)	12 (11–13)	12 (10–13)

Values are listed as N (%) or median (interquartile range); ART=Antiretroviral Therapy.

[1] Neurologic comorbidity status (incidental vs. contributing; see METHODS).

Table 3.

Univariate and Multivariable Analyses of Impaired Domain and Global Performance and T Scores in Persons of Admixed Hispanic Ancestry, Stratified by mtDNA Haplogroup B

Domains		B haplogroup (N=17)	Non-B (N=81)	p-value[1]	Adjusted Odds Ratio or β-Coefficient (95% CI)[2]	p-value
Executive Function						
	Impaired	5 (29%)	49 (61%)	**0.03**	0.29 (0.09, 0.91)	**0.04**
	T-score	45.5 (41.0–52.0)	39.5 (33.5–48.0)	**0.02**	4.72 (0.19, 9.25)	**0.04**
Learning						
	Impaired	6 (35%)	45 (56%)	0.18	0.57 (0.18, 1.81)	0.34
	T-score	46.0 (39.5–48.0)	38.0 (33.5–45.5)	**0.04**	2.88 (−1.76, 7.52)	0.22
Recall						
	Impaired	3 (18%)	33 (41%)	0.10	0.39 (0.10, 1.55)	0.18
	T-score	49.5 (44.5–51.5)	43.5 (39.0–49.5)	**0.01**	4.58 (0.53, 8.64)	**0.03**
Speed of Information Processing						
	Impaired	3 (18%)	24 (30%)	0.39	0.65 (0.15, 2.71)	0.56
	T-score	50.0 (47.7–57.7)	45.3 (41.3–53.0)	0.13	3.44 (−1.27, 8.15)	0.15
Working memory						
	Impaired	4 (24%)	29 (36%)	0.41	0.52 (0.15, 1.80)	0.30
	T-score	45.0 (40.5–52.5)	42.5 (38.0–48.0)	0.22	2.25 (−2.27, 6.77)	0.33
Verbal fluency						
	Impaired	3 (18%)	15 (19%)	1.0	1.19 (0.29, 4.89)	0.81
	T-score	46.0 (42.5–50.5)	44.5 (40.5–51.5)	0.42	0.81 (−4.16, 5.79)	0.75
Motor						
	Impaired	2 (12%)	28 (35%)	0.08	0.28 (0.06, 1.37)	0.12
	T-score	47.5 (44.5–57.5)	45.0 (36.5–52.0)	0.23	2.02 (−3.48, 7.52)	0.47
# of Impaired Domains						
		1 (0–2)	3 (2–4)	**0.005**	−0.99 (−1.83, −0.15)	**0.02**
Global Performance						
	Impaired GDS	3 (18%)	49 (61%)	**0.002**	0.16 (0.04, 0.62)	**0.008**
	Global T-score	47.9 (46.1–50.1)	43.5 (40.1–46.8)	**0.009**	3.01 (−0.01, 6.04)	**0.05**

CI=Confidence Interval; GDS = Global deficit score.

[1] p-values by Fisher's exact (impairment status) or Wilcoxon ranksum (T scores) tests. Values shown are N (%) for impaired domain deficit score or median (IQR) for T-scores and impaired domains.

[2] Results shown are adjusted odds ratios (95% confidence interval) for mtDNA haplogroup B vs. all non-B Hispanic persons by logistic regression for impairment status, or adjusted coefficient (95% confidence interval) by linear regression for T-scores. All models are adjusted for neurologic comorbidity status (incidental vs. contributing), ART status at time of assessment (off vs. on), and nadir CD4 (per cell/mm^3 increase).

Table 4.

Univariate and Multivariable Analyses of Impaired Domain-Specific and Global Neurocognitive Performance and T-Scores in Persons of African Ancestry, Stratified by mtDNA Haplogroups L2a

Domains		L2a (N=89)	Non-L2a (N=389)	p-value[1]	Adjusted Odds Ratio or β-Coefficient (95% CI)[2]	p-value
Executive Function			(N=388)			
	Impaired	21 (24%)	89 (23%)	0.89	1.03 (0.60, 1.78)	0.91
	T-score	46.0 (41.5–51.0)	46.5 (41.8–52.5)	0.39	−1.31 (−3.25, 0.62)	0.18
Learning						
	Impaired	39 (44%)	130 (33%)	0.07	1.61 (1.00, 2.59)	**0.05**
	T-score	41.0 (36.0–47.5)	43.5 (38.0–49.5)	**0.0478**	−1.53 (−3.41, 0.35)	0.11
Delayed Recall						
	Impaired	40 (45%)	113 (29%)	**0.005**	2.12 (1.31, 3.44)	**0.002**
	T-score	45.5 (36.0–53.0)	46.0 (40.0–51.5)	0.48	−1.08 (−3.09, 0.94)	0.30
Speed of Information Processing						
	Impaired	15 (17%)	60 (15%)	0.75	1.10 (0.59, 2.06)	0.76
	T-score	49.7 (44.3–55.0)	50.0 (45.0–56.3)	0.67	−0.59 (−2.44, 1.26)	0.53
Working Memory						
	Impaired	31 (35%)	93 (24%)	**0.04**	1.72 (1.05, 2.83)	**0.03**
	T-score	42.5 (38.5–52.5)	46.5 (40.5–53.0)	**0.02**	−2.38 (−4.40, −0.36)	**0.02**
Verbal fluency						
	Impaired	11 (12%)	37 (10%)	0.44	1.34 (0.65, 2.76)	0.42
	T-score	50.5 (46.5–55.5)	52.0 (46.0–56.5)	0.64	−0.64 (−2.63, 1.35)	0.53
Motor		(N=88)	(N=388)			
	Impaired	15 (17%)	45 (12%)	0.21	1.60 (0.84, 3.05)	0.16
	T-score	48.3 (43.5–53.0)	48.0 (43.0–54.0)	0.96	−0.63 (−2.75, 1.48)	0.56
# of Impaired Domains						
		2 (1–3)	1 (0–2)	**0.004**	0.48 (0.14, 0.84)	**0.006**
Global Performance						
	Impaired GDS	36 (40%)	112 (29%)	**0.04**	1.74 (1.07, 2.83)	**0.03**
	Global T-score	46.0 (42.7–52.0)	48.0 (43.6–52.1)	0.12	−1.10 (−2.45, 0.24)	0.11

CI=Confidence Interval; GDS = Global deficit score.

[1] p-values by Fisher's exact (impairment status) or Wilcoxon ranksum (T scores) tests. Values shown are N (%) for impaired domain deficit score or median (IQR) for T-scores and impaired domains.

[2] Results shown are adjusted odds ratio (95% confidence interval) for mtDNA haplogroup L2a vs. all non-L2a African American persons by logistic regression for impairment status, or adjusted coefficient (95% confidence interval) by linear regression for T-scores. All models are adjusted for neurologic comorbidity status (incidental vs. contributing), ART status at time of assessment (off vs. on), and nadir CD4 (per cell/mm^3 increase).

Table 5.

Univariate and Multivariable Analyses of Impaired Domain-Specific and Global Neurocognitive Performance and T-Scores in Persons of African Ancestry, Stratified by mtDNA Haplogroup L3e

Domains		L3e (N=86)	Non-L3e (N=392)	P-value[1]	Adjusted Odds Ratio or β-Coefficient (95% CI)[2]	P-value
Executive Function		(N=85)				
	Impaired	22 (26%)	88 (22%)	0.48	1.19 (0.69, 2.04)	0.54
	T-score	46.0 (41.0–53.5)	46.5 (42.0–51.5)	0.82	0.37 (−1.62, 2.35)	0.71
Learning						
	Impaired	29 (34%)	140 (36%)	0.80	0.87 (0.53, 1.44)	0.60
	T-score	43.5 (38.0–49.0)	43.0 (37.5–49.0)	0.94	0.22 (−1.71, 2.14)	0.83
Delayed Recall						
	Impaired	32 (37%)	121 (31%)	0.25	1.28 (0.78, 2.11)	0.33
	T-score	44.5 (37.5–50.0)	46.0 (40.0–52.0)	0.12	−1.16 (−3.21, 0.90)	0.27
Speed of Information Processing						
	Impaired	14 (16%)	61 (16%)	0.87	0.96 (0.50, 1.82)	0.89
	T-score	49.7 (45.0–57.3)	50.0 (45.0–55.7)	0.54	0.85 (−1.04, 2.73)	0.38
Working Memory						
	Impaired	21 (24%)	103 (26%)	0.79	0.89 (0.52, 1.54)	0.67
	T-score	46.8 (39.5–53.5)	45.5 (40.0–52.5)	0.57	1.13 (−0.94, 3.20)	0.29
Verbal fluency						
	Impaired	6 (7%)	42 (11%)	0.43	0.59 (0.24, 1.45)	0.25
	T-score	52.5 (44.5–57.0)	51.5 (46.0–56.5)	0.75	0.11 (−1.92, 2.14)	0.92
Motor			(N=390)			
	Impaired	13 (15%)	47 (12%)	0.47	1.17 (0.59, 2.30)	0.65
	T-score	48.0 (41.0–51.5)	48.0 (43.0–54.0)	0.27	−1.03 (−3.17, 1.12)	0.35
# of Impaired Domains						
		1 (0–3)	1 (0–2)	0.64	0.003 (−0.35, 0.36)	0.99
Global Performance						
	Impaired GDS	26 (30%)	122 (31%)	0.90	0.89 (0.53, 1.49)	0.66
	Global T-score	47.9 (42.9–52.5)	47.6 (43.5–51.7)	0.95	0.11 (−1.27, 1.48)	0.88

CI-Confidence Interval; GDS = Global deficit score.

[1] p-values by Fisher's exact (impairment status) or Wilcoxon ranksum (T scores) tests. Values shown are N (%) for impaired domain deficit score or median (IQR) for T-scores and impaired domains.

[2] Results shown are adjusted odds ratio (95% confidence interval) for mtDNA haplogroup L3e vs. all non-L3e African American persons by logistic regression for impairment status, or adjusted coefficient (95% confidence interval) by linear regression for T-scores. All models are adjusted for neurologic comorbidity status (incidental vs. contributing), ART status at time of assessment (off vs. on), and nadir CD4 (per cell/mm^3 increase).