Poster # 465

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Mitochondrial DNA Haplogroups and Neurocognitive Impairment in the CHARTER Cohort

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CHARTER
CNS HIV Anti-Retroviral Therapy Effects Research
CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH

Objective

To determine associations between mitochondrial DNA haplogroups and neurocognitive impairment in CHARTER.

Background & Significance

- Neurocognitive impairment (NCI) remains an important complication in the combination antiretroviral therapy (CART) era.
- Host factors – including genetic variants – that influence NCI are not completely known.
- Mitochondrial DNA (mtDNA) haplogroups are ancestry-specific patterns of single nucleotide polymorphisms in mtDNA that have been associated with differential mitochondrial function and human disease risk.
- Haplogroups have been associated with HIV- and ART-associated outcomes (including peripheral neuropathy), and with neurodegenerative diseases in HIV-uninfected populations.
- To our knowledge, mtDNA haplogroups and NCI in HIV have not previously been studied.
- Understanding genetic factors associated with NCI can lead to better diagnostic, prevention, and therapeutic strategies.

Methods

- CHARTER is a U.S.-based observational study of ambulatory HIV-infected adults who underwent standardized neuromedical assessments between 2003 and 2007.
- CHARTER genetic studies excluded persons with confounding neurologic cormorbidities.
- mtDNA genotyping was obtained from whole blood using the GeneChip Human Mitochondrial Resequencing Array v2.0 (Affymetrix, Inc., Santa Clara, CA, USA). Array intensity data were processed using the MitoChip Filtering Protocol (MFP) under a haploid model, and variants called relative to the Revised Cambridge Reference Sequence (rCRS).
- Haplogroups were assigned using the HaploGrep program (http://haplogrep.uibk.ac.at/) based on full mtDNA sequences.
- Outcomes included: 1) Global deficit score (GDS) as a continuous measure; 2) GDS impairment (defined as GDS≥0.5); and 3) HIV-associated neurocognitive disorder (HAND; defined using Frascati Criteria).
- Primary analyses were stratified by self-reported race/ethnicity and limited to non-Hispanic blacks and whites and Hispanics. Additional analyses in a subgroup (N=1037) with available nuclear genome-wide genotype data were adjusted for ancestry markers using principal components (PC), and the results did not differ.
- Multivariable regression of associations between mtDNA haplogroups and GDS or HAND were performed adjusting for: comorbidity status (incidental vs. contributing), current CART status (yes vs. no), plasma HIV RNA, CHARTER site, IQ estimate (Wide-Range Achievement Test-III [WRAT] Reading), and nadir CD4 T cell count.

Results – Baseline Data & Univariable Analyses

Table 1. Characteristics of the overall CHARTER genetic study population, the Hispanic subgroup, and major mtDNA haplogroups within Hispanics

Variable	Overall (N=1046)	Hispanics (N=104)	Haplogroup A (N=34)	Haplogroup B (N=18)	Haplogroup C (N=17)	Other haplogroups (N=35)
Age (years)	43 (38-49)	41 (35-47)	43 (38-46)	39 (33-45)	42 (35-47)	40 (37-46)
Race/Ethnicity						
Black, non-Hispanic	498 (48)					
White, non-Hispanic	444 (42)					
Hispanic	104 (10)					
Female sex, N (%)	246 (24)	28 (27)	9 (26)	2 (11)	5 (29)	12 (34)
Nadir CD4 (per mm^3)	178 (50-308)	167 (51-271)	109 (53-219)	188 (169-325)	120 (21-187)	207 (45-342)
HIV RNA, plasma (log_{10} copies/mL)	2.29 (1.70-3.99)	1.91 (1.70-3.83)	1.98 (1.70-3.47)	1.70 (1.70-3.04)	1.88 (1.70-3.05)	2.45 (1.70-4.27)
On CART, N (%)	749 (72)	82 (79)	25 (74)	15 (83)	15 (88)	27 (77)
Comorbidity, N (%)						
Incidental	676 (65)	63 (61)	19 (56)	14 (78)	9 (53)	21 (60)
Contributing	370 (35)	41 (39)	15 (44)	4 (22)	8 (47)	14 (40)
WRAT score	96 (83-105)	94 (85-100)	96 (81-105)	99 (95-108)	88 (85-98)	94 (87-99)
GDS	0.32 (0.11-0.63)	0.58 (0.32-0.95)	0.68 (0.42-0.99)	0.21 (0.12-0.41)	0.63 (0.42-1.42)	0.58 (0.34-0.95)
Impaired GDS, N (%)	366 (35)	56 (54)	23 (68)	4 (22)	10 (59)	19 (54)
HAND						
Normal	562 (54)	29 (28)	8 (24)	9 (50)	3 (18)	9 (26)
Any impairment	483 (46)	75 (72)	26 (76)	9 (50)	9 (82)	26 (74)
ANI	357 (34)	52 (50)	17 (50)	6 (33)	8 (47)	21 (60)
MND	95 (9)	17 (16)	6 (18)	3 (17)	3 (18)	5 (14)
HAD	31 (3)	6 (6)	3 (9)	0 (-)	3 (18)	0 (-)

Data are median (IQR) or N (%). ANI=asymptomatic neurocognitive impairment; CART=combination antiretroviral therapy; GDS=global deficit score; HAD=HIV-associated dementia; HAND=HIV-associated neurocognitive disorder; MND=mild neurocognitive disorder; WRAT=wide-range achievement test

Figure 1. Global Deficit Score (GDS) impairment (GDS≥0.5), by race/ethnicity

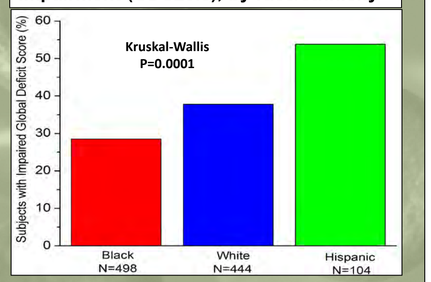


Figure 2. GDS impairment, by mtDNA haplogroups (Inset: simplified phylogenetic tree of haplogroups included in these analyses)

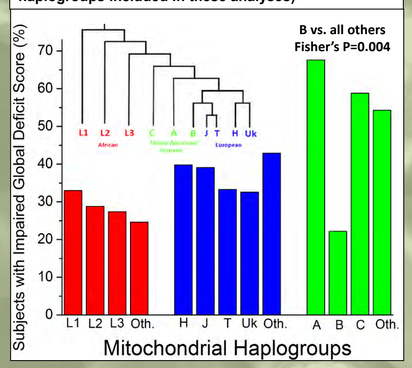
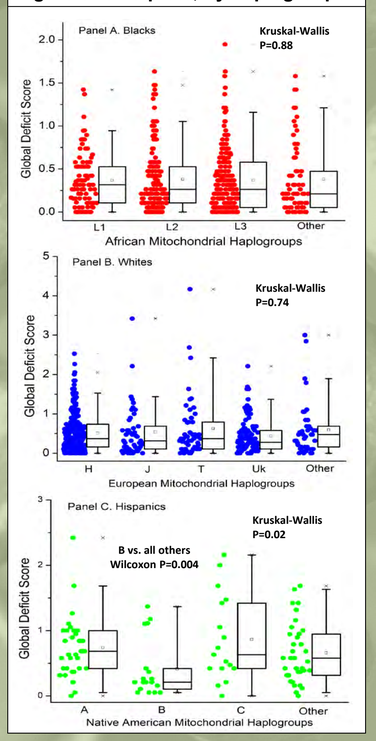


Figure 3. GDS plots, by haplogroups



Results – Multivariable Analyses

Table 2. Multiple Regression- GDS (continuous) within Hispanics

Variable	Coefficient	95% Confidence Interval	P-value
Haplogroup B (vs. all others)	**-0.262**	**-0.532, 0.007**	**0.06**
Nadir CD4 (per cell/mm^3)	**-0.001**	**-0.001, -0.0002**	**0.02**
Comorbitity (incidental vs. contributing)	-0.150	-0.361, 0.061	0.16
IQ estimate/WRAT-III	-0.002	-0.010, 0.006	0.60
On CART	0.033	-0.299, 0.366	0.84
HIV RNA, plasma (per log_{10} copies/mL)	-0.013	-0.106, 0.080	0.79
N = 97, Model P-value = 0.0027, R^2 = 0.20			

Table 3. Multiple Logistic Regression- GDS Impairment within Hispanics

Variable	Odds Ratio	95% Confidence Interval	P-value
Haplogroup B (vs. all others)	**0.19**	**0.05, 0.77**	**0.02**
Nadir CD4 (per cell/mm^3)	**0.995**	**0.992, 0.999**	**0.01**
Comorbitity (incidental vs. contributing)	0.54	0.20, 1.47	0.23
IQ estimate/WRAT-III	1.00	0.96, 1.04	0.99
On CART	1.15	0.23, 5.73	0.86
HIV RNA, plasma (per log_{10} copies/mL)	1.12	0.70, 1.79	0.65
N = 97, Model P-value = 0.0004, Pseudo R^2 = 0.18			

Results Summary

- Persons of Hispanic ethnicity in CHARTER were more likely to have GDS impariment.
- Within Hispanics, a relatively common Native American mtDNA haplogroup was associated with lower risk of GDS impairment, independent of nadir CD4, CART, and comorbidity.
- Associations persisted in stratified analyses of Hispanics with undetectable plasma HIV RNA and those with incidental comorbidities only, and with adjustment for genetic ancestry by PC (data not shown).
- The same mtDNA haplogroup was associated with lower likelihood of HAND in univariate analyses, but not in adjusted analyses (data not shown).
- Major African or European mtDNA haplogroups were not associated with NCI in Black or White non-Hispanic CHARTER participants.

Conclusions

- In this cohort of mostly CART-treated subjects, a common Native American mtDNA haplogroup was associated with lower prevalence of impaired GDS within Hispanics after adjustment for other risk factors, including nadir CD4 and plasma HIV RNA.
- Mitochondrial genetic variation may be an ancestry-specific host factor explaining variability in NCI in chronically HIV-infected persons.
- Hypotheses of neuroprotective mech anisms might include more efficient OXPHOS/ATP production, and/or more limited oxidative stress, neuroinflammation, or apoptosis.
- Validation in other cohorts and in vitro studies are needed. Future directions may also include exploring targeted genetic testing for risk-stratification, and personalized preventive and/or therapeutic interventions.

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CHARTER NEUROAIDS DATA RESOURCE

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