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NUCLEAR-MITOCHONDRIAL INTERACTIONS AND NEUROCOGNITIVE IMPAIRMENT IN HIV+ ADULTS

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

Objective

To identify and characterize interactions between mitochondrial DNA (mtDNA) haplogroups and nuclear genes found to be associated with neurocognitive impairment and HAND phenotypes in the CHARTER cohort.

Background & Significance

- HIV-Associated Neurocognitive Disorder (HAND) is a term established to capture a spectrum of neurocognitive (NC) deficits associated with HIV infection; the genetic underpinnings of HAND are poorly understood.
- CHARTER is a U.S.-based observational study of neuro-HIV outcomes in ambulatory, HIV+ adults who underwent comprehensive assessment and were assigned a Global Deficit Score (GDS) **[Heaton et al.]**
- Mitochondrial function has long been thought to play a role in neurodegeneration, along with iron metabolism and transport.
- Genetic variation in mitochondrial DNA is classified into haplogroups (H, T, J, and Uk in Europeans) which alter mitochondrial function through oxidative phosphorylation.
- A recent GWAS of GDS in the CHARTER cohort also revealed SNPs with p-values below 1x10-7 **[Jia et al.]**

Hypotheses

- **We hypothesize that mitochondrial haplogroups and previously-associated nuclear SNPs statistically interact to influence Global Deficit Scores in the CHARTER study**
- **We hypothesize that specific SNP-haplogroup combinations within ancestry groups drive associations to GDS, and that these combinations may point to specific molecular mechanisms influencing neurocognitive impairment in HIV-infected populations**

Table 1. CHARTER Study Overview (European Subset)

	All (N=403)	Haplogroup H (N = 218)	Haplogroup T (N = 48)	Haplogroup J (N = 47)	Haplogroup Uk (N = 90)
Comorbidity status Contributing/Incidental	127/276	68/150	19/28	12/36	28/62
Current cART On/Off	284/119	155/63	34/14	30/17	65/25
Plasma HIV RNA (log10)	2.76 (1.29)	2.78 (1.29)	2.63 (1.13)	2.85 (1.39)	2.74 (1.28)
Wide-Range Achievement Test-III (WRAT) Reading	101.00 (12.05)	101.28 (11.27)	100.50 (11.87)	103.23 (9.32)	99.41 (14.72)
Nadir CD4+	227.98 (195.53)	222.89 (192.70)	227.08 (267.91)	226.19 (144.48)	241.73 (178.39)
rs12460243 Genotypes	11/108/284	6/58/154	1/14/33	3/15/29	1/21/68
GDS	0.51 (0.55)	0.51 (0.50)	0.63 (0.77)	0.53 (0.63)	0.44 (0.43)

Method

We first performed mixed-model analysis to assess the cumulative significance and phenotypic variance explained for the top 10 SNPs associated to continuous GDS and the top 10 SNPs associated to dichotomous GDS (20 SNPs total) based on prior CHARTER GWAS [Jia et al.]. We fit each model separately within each of the three genomically-defined ancestry groups (European-descent, African-descent, and Admixed Hispanic).

MT Haplogroup Effect; Interaction Effect; Cumulative SNP Effect

$$y = \alpha + \beta g + \beta m + \beta gm + \text{covars}$$

Mixed Linear Model (MLM)

Additive Effect of all SNPs for person i; Allele Frequency Weight; Estimate of SNP Effect

$$g_i = \sum_{i=1}^{20} z_{ij} u_j$$

Mixed Effect for top 20 GWAS-significant SNPs

This model includes three terms dummy-encoding the possible MT haplogroups, and three interaction terms for each dummy-encoded MT variable by the cumulative genetic effect. This full model was compared to a reduced model with no interaction terms via likelihood ratio test. This analysis revealed a significant cumulative SNP-Haplogroup interactions within African descent (p = 0.02) and European descent (p = 0.05) individuals.

We proceeded to examine individual SNP-Haplogroup interactions within European- and African-descent groups using linear regression with continuous GDS as the outcome. All models were adjusted for comorbidity status (incidental vs contributing); current cART use (yes vs no); plasma HIV RNA; reading ability (by Wide-Range Achievement Test-III [WRAT] Reading subtest score); and self-reported nadir CD4+ T-cell count and first 3 PCs, consistent with prior CHARTER studies. Only SNP-Haplogroup interactions in the European subset were significant after correction from multiple testing (Bonferroni $\alpha = 0.0025$). Table 1 shows demographics of the CHARTER study for the European subset.

Results

Table 2. European-descent SNP-Haplogroup Regression Results (GDS)

SNP	β (SNP)	β (MT)	Interaction P
rs17160128	**0.3353**	**0.0268**	**0.00152**
rs12460243	**0.3324**	**0.03294**	**0.00211**
rs17038463	0.5041	0.144	0.01999
rs876084	0.008842	0.1305	0.1068
rs1076546	0.2474	0.1334	0.1713
rs12437004	0.248	0.1396	0.1923
rs6723162	-0.03417	-0.1229	0.2266
rs11681615	-0.1184	-0.03199	0.2464
rs978490	0.3237	0.2019	0.2579
rs2293731	0.2518	0.1474	0.2691
rs795943	-0.1168	-0.02345	0.3423
rs9814567	-0.141	-0.07142	0.3939
rs2915495	0.08236	0.1751	0.399
rs17154702	-0.1892	-0.1189	0.4305
rs4772857	0.1444	0.08426	0.4368
rs11157436	0.2578	0.1892	0.4679
rs6542826	-0.1017	-0.06286	0.6197
rs7840128	0.2039	0.09352	0.6417
rs11915964	-0.1279	-0.09742	0.7081
rs829418	0.2453	0.211	0.7812

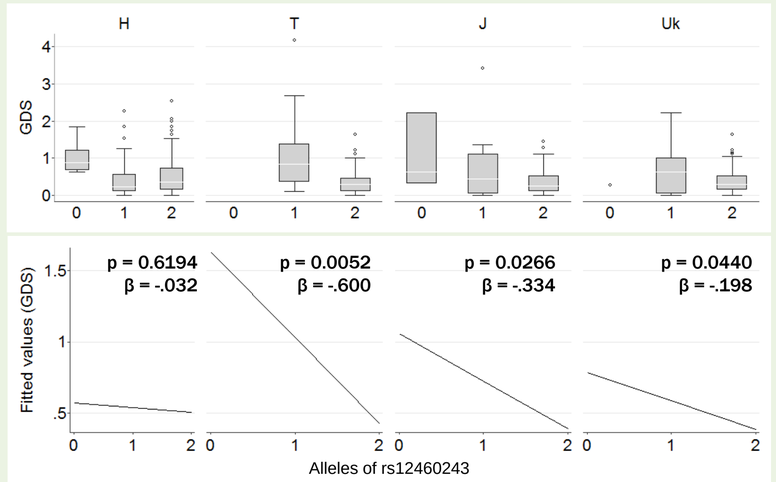


Figure 1. Box Plots and Fitted Regressions of rs12460243 to GDS by Haplogroup

Two SNPs, rs17160128 and rs12460243, in strong LD (r-squared =~ 1.0) in the *FBN3* gene region showed significant haplogroup interactions for continuous GDS within European-descent individuals. Figure 1 illustrates the effect of rs12460243, showing a non-significant effect in the H haplogroup, with progressively more significant additive effects in the Uk, J, and T haplogroups. Analysis of Variance (ANOVA) for GDS within H haplogroup individuals showed a significant effect (p = 0.028), indicating that the effect of this SNP is recessive for H but additive for the other haplogroups; this effect drives the observed statistical interaction.

Conclusions

We see evidence of interaction between previously-associated SNPs *en masse* and MT haplogroups within European-descent and African-descent individuals for continuous GDS. We further detected significant interactions between two nuclear SNPs (rs17160128 and rs12460243) and European haplogroups (J, H, T, and Uk). These associations point to *FBN3*, an extracellular matrix protein that assembles into microfibrils in many connective tissues, they potently regulate pathways of the immune response, inflammation and tissue homeostasis and are involved in impairing the blood brain barrier integrity when impaired.

References

Heaton RK, Clifford DB, Franklin DR Jr. et al. *Neurology* 2010; 75:2087–96.

Jia P, Zhao Z, Hulgan T, et al. *Am J of Med Gen.* 2017 (in press)

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CHARTER NEUROAIDS DATA RESOURCE

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