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African Mitochondrial DNA Subhaplogroups and Peripheral Neuropathy during Antiretroviral Therapy

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Abstract

Susceptibility to peripheral neuropathy during antiretroviral therapy with nucleoside reverse transcriptase inhibitors (NRTIs) was previously associated with a European mitochondrial DNA (mtDNA) haplogroup among non-Hispanic white persons. To determine if NRTI-associated peripheral neuropathy was related to mtDNA variation in non-Hispanic black persons, we sequenced mtDNA of participants from AIDS Clinical Trials Group study 384. Of 156 non-Hispanic blacks with genomic data, 51 (33%) developed peripheral neuropathy. In a multivariate model, African mtDNA subhaplogroup L1c was an independent predictor of peripheral neuropathy (OR=3.7, 95% CI 1.1-12.0). An African mtDNA subhaplogroup is for the first time implicated in susceptibility to NRTI-associated toxicity.

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Introduction

Acquired immunodeficiency syndrome (AIDS) morbidity and mortality have been reduced by antiretroviral therapy (ART). Nucleoside reverse transcriptase inhibitors (NRTIs) were the first drugs approved to treat HIV and remain cornerstones of ART.[1] However, exposure to NRTIs has been associated with complications related to mitochondrial dysfunction. Distal sensory peripheral neuropathy, characterized by symmetric distal anesthesia and/or painful dysesthesia can develop in ART-treated persons exposed to NRTIs, especially didanosine (ddI) and stavudine (d4T).[2] Abnormal mitochondria and mitochondrial DNA (mtDNA) depletion are seen with dideoxycytidine (ddC)-associated peripheral neuropathy.[3] Peripheral neuropathies are also common findings in inherited mitochondrial diseases.

Mitochondrial DNA is distinct from nuclear DNA, encodes thirteen electron transport chain subunits, and exhibits abundant genetic variation across its >16,000 base pairs. Human mtDNA sequences have diverged over approximately the last 150,000 years due to natural selection and human migration, resulting in distinct patterns of single nucleotide polymorphisms (SNPs), called haplogroups.[4] In addition to their key role in cellular energy production, mitochondria also are involved in free radical generation and apoptosis. It is suspected that mtDNA variation leads to distinctive mitochondrial electron transport chains, each with perhaps slightly different capacities for energy production, free radical generation and apoptosis. Epidemiological evidence for functional differences among mitochondrial haplogroups has been demonstrated in studies of longevity[5] and neurodegenerative disorders.[6]

Similarities between clinical manifestations of inherited mtDNA diseases and NRTI toxicities have prompted us to look for variations in mtDNA that may explain susceptibility to peripheral neuropathy among HIV-infected persons. Previously, we examined non-Hispanic white participants exposed to NRTIs in a large clinical trial (AIDS Clinical Trials Group study 384 [ACTG 384]) and identified an association between peripheral neuropathy and a European mitochondrial haplogroup.[7] While persons of European descent can be assigned haplogroups in a fairly straightforward manner because of haplogroup-unique SNPs, African mtDNA generally have greater variation and thus more challenging classification.[8] We report here the results of an analysis of mitochondrial subhaplogroups among non-Hispanic black participants from ACTG 384. Because NRTI-associated peripheral neuropathy is believed to result in part from mitochondrial dysfunction, our hypothesis was that mtDNA variation in these non-Hispanic black subjects would be represented in African subhaplogroups, and would be associated with susceptibility to peripheral neuropathy during NRTI treatment.

Methods

Study Population and Ascertainment

ACTG 384 was a randomized, double-blinded, factorial design treatment strategy trial that enrolled over 800 individuals in the US in 1998-1999. Subjects were ART-naïve at the time of enrollment and were randomized to one of multiple study arms: ddI plus d4T or zidovudine plus lamivudine with nelfinavir, efavirenz, or both.[9] The median follow up was approximately two years. The clinical outcome relevant for this study was the development of peripheral neuropathy, which was defined as the development of a clinical diagnosis or first new sign or symptom at follow-up study visits as described previously.[7,9] Symptoms and/

or signs were graded using the DAIDS table for severity of adult adverse events (http://www3.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/PDF/DAIDSAEGradingTable.pdf). These analyses were limited to subjects self-identified as "non-Hispanic black" race/ethnicity. All participants in ACTG 384 provided written informed consent, and participants in this genetic study provided additional informed consent for inclusion of DNA and clinical data in the ACTG Human DNA Repository. The specific analysis of fully de-identified DNA and clinical data presented here was approved separately by the Vanderbilt University Institutional Review Board.

Mitochondrial DNA Sequencing and Assignment of Subhaplogroups for African Mitochondria

DNA was isolated from whole blood of participants consenting to the ACTG Human DNA Repository using PUREGENE (Gentra Systems Inc., Minneapolis, MN, USA). Mitochondrial DNA from these samples was sequenced using GeneChip® Human Mitochondrial Resequencing Array v2.0 (Affymetrix, Inc., Santa Clara, CA, USA). Nine African mtDNA subhaplogroups were assigned based on an algorithm derived from published SNPs.[8]

Study Design and Statistical Analysis

The study design was a race-specific case control analysis. Cases were participants who developed any new clinical diagnosis or first signs or symptoms of at least mild peripheral neuropathy (≥grade 1) following randomization. Participants with any signs or symptoms of peripheral neuropathy at baseline (N=5) were excluded from analyses. Controls were participants who did not develop peripheral neuropathy during study follow-up. Intention-to-treat was maintained based on the ART regimen into which they were randomized. Mitochondrial subhaplogroup frequencies were compared between cases and controls using Fisher's exact test or χ^2 tests. Continuous variables were compared using Mann-Whitney U test. Multivariable logistic regression was used to assess the relationship between independent variables (African mtDNA subhaplogroups and potential confounding variables) and peripheral neuropathy. Effect size for the association is measured as odds ratio (OR) with 95% confidence intervals (CI). STATA 10.0 (College Station, Texas) was used for all analyses.

Results

Of a total of 526 participants from ACTG 384 with DNA available (59% of the total U.S. study population), 161 (31%) were self-identified non-Hispanic black. Five were excluded from the analysis because they either had a diagnosis, signs, and/or symptoms of peripheral neuropathy at randomization. Of the 156 remaining participants, 51 (33%) developed peripheral neuropathy of ≥grade 1 during study follow-up. Of these, 36 (71%) developed symptoms of peripheral neuropathy only; the remaining 15 (29%) had both symptoms and a diagnosis of peripheral neuropathy (which included those with clinical signs). Most peripheral neuropathy was graded as mild (52%) or moderate (39%) severity. Non-Hispanic blacks who developed peripheral neuropathy tended to have fewer baseline $CD4^+$ T lymphocytes, were significantly older at randomization, and were significantly more likely to have been randomized to ddI plus d4T-containing ART (Table 1). We have previously shown that participants from ACTG 384 included in the ACTG Human DNA Repository were not significantly different with respect to key confounding variables than those who were not.[7]

Mitochondrial DNA sequence was available from all subjects. The mean call rate for the 16,545 base positions covered by the sequencing array was 97%. All 3 major African mtDNA haplogroups (L1, L2 and L3) were represented as well as 9 subhaplogroups (L1a, L1b, L1c, L1/L2, L2a, L2b, L2e, L3, L3b, and L3e) and non-African haplogroups (Table 1).

Univariate analysis revealed that peripheral neuropathy was more frequent in the 16 persons with African mitochondrial subhaplogroup L1c than in those (N=140) with other subhaplogroups (56% vs. 30%; unadjusted OR 3.0, 95% CI 1.0-8.6; P=0.04). Subhaplogroup L1c accounted for 10.3% of mtDNA subhaplogroups. Following adjustment for potentially confounding baseline variables and ART randomization arms (Table 2), African subhaplogroup L1c remained independently associated with the development of peripheral neuropathy (OR=3.7, 95% CI 1.1-12.0; P=0.03). Older age and randomization to ddI plus d4T were independently associated with the development of peripheral neuropathy, but baseline CD4 T cell count was not after adjusting for subhaplogroup L1c. Peripheral neuropathy tended to be less frequent in the 16 persons having subhaplogroup L3b (13% vs. 35%; OR=0.3, 95% CI 0.1-1.2; P=0.09). In a separate model adjusted for the factors listed above, the trend toward association between subhaplogroup L3b and peripheral neuropathy was less apparent (OR=0.3, 95% CI 0.1-1.6; P=0.16).

Discussion

In this study, we observed that self-identified non-Hispanic black participants from ACTG 384 who belonged to mtDNA subhaplogroup L1c appeared to be at increased risk of developing peripheral neuropathy during ART. This excess risk was independent of receipt of ddI plus d4T, age at randomization, or HIV disease parameters ($CD4^+$ T cell count or HIV-1 RNA). By multivariate analysis, randomization to ddI plus d4T, older age, and belonging to mitochondrial subhaplogroup L1c were independent predictors of peripheral neuropathy. To our knowledge, this is the first study to identify a possible genetic predictor of peripheral neuropathy during ART among non-Hispanic black individuals.

At the end of 2007, estimates suggested that more than two million persons in sub-Saharan Africa were receiving ART, and seven million more needed ART. Aggressive ART “roll-out” in Africa has continued, often using NRTIs known to be associated with mitochondrial toxicities such as peripheral neuropathy. Although their use in combination is no longer recommended, d4T and ddI are still used individually, and have been associated with development of peripheral neuropathy in these settings.[10] Genetic predictors for NRTI-associated peripheral neuropathy have not previously been reported for persons of African descent, but could suggest novel approaches to optimize long-term ART management among these populations. In the U.S., rates of HIV and AIDS have risen in non-Hispanic blacks. Data from the U.S. have suggested a decreasing incidence of peripheral neuropathy,[11] but a study from a similar resource-abundant setting (Australia) did not find a decreased prevalence.[12] Regardless of current temporal trends, peripheral neuropathy remains one of the most common neurologic complications of ART throughout the world.

Because mtDNA haplogroup assignment in persons of European descent is less complex than in other racial/ethnic groups, the majority of clinical studies have been performed in this population. Several studies of mtDNA haplogroups and metabolic diseases have also been performed in Asian populations. Due in part to the greater complexity of mtDNA from persons of African descent, however, fewer association studies have been performed and less is known about functional differences in African mitochondria due to mtDNA variation. A study of African mitochondrial subhaplogroups in more than 1100 African-Americans found subhaplogroup frequencies that were similar to those we report here.[13]

Classification of L1c for this study followed the method of Herrnstadt, et al.[8] and included SNPs from 8 of 13 protein-coding regions in mtDNA, as well as rRNA-coding regions. Two of these SNPs (7146A>G in cytochrome C oxidase subunit I [Tyr-Ala] and 10321T>C in NADH dehydroxygenase subunit 3 [Val-Ala]) are non-synonymous. It is plausible that these SNPs have functional consequences, or that the L1c subhaplogroup is a marker for other SNPs

that are not L1c-defining *per se*, but influence susceptibility to NRTI-associated peripheral neuropathy.

The absence of published association studies with L1c and the lack of established biologic mechanisms are limitations of our results. Two studies examined African subhaplogroups in elite Kenyan[14] and Ethiopian[15] distance runners, finding that mtDNA variation may influence distance running in the former, but not the latter population. No associations were seen with L1 subhaplogroups. Approximately 10% of self-identified non-Hispanic black persons in our study group had non-African haplogroup classifications. We elected to take the most clinically relevant perspective and include these persons in analyses to determine effect sizes. When analyses were limited to only persons having an L subhaplogroup (i.e. persons having non-African haplogroups did not contribute data to the analyses), the results did not differ substantially and the L1c haplogroup remained statistically associated with development of peripheral neuropathy (data not shown).

Limitations of our study also include a small sample size, which may have limited our ability to detect smaller differences in some subhaplogroups (potential false negative associations), a relatively weak primary statistical association that would not withstand correction for multiple comparisons (potential false positive associations), and a phenotype that was not ascertained using invasive or objective confirmatory testing (e.g. nerve conduction velocity and/or intraepidermal nerve fiber density). With respect to the latter limitation, robust associations between peripheral neuropathy and well-recognized risk factors that have been observed in multiple studies (increasing age and exposure to “d-drug” NRTIs) provides some reassurance that case-control misclassification was not extreme in this study. Our sample size also precludes stratified analyses by type of neuropathy diagnosis (symptoms, signs, or both) or severity grade. Incidence of ≥grade 1 peripheral neuropathy among this clinical trial population was high (33%), and was similar to the non-Hispanic white population (29%).[7] The role of mtDNA variation in persons receiving more contemporary ART regimens with lower peripheral neuropathy risk is not yet known.

These results should be considered preliminary until they are replicated in other cohorts and/or clinical trials, ideally based on more thorough phenotype ascertainment. In addition, mechanistic studies are needed to assess for functional differences between African subhaplogroups at the cellular and tissue level. Mitochondrial DNA variation is an attractive target for pharmacogenomic investigation in HIV infection and treatment complications. Investigation in this area may ultimately increase understanding of the role of mtDNA variation in human disease and drug toxicity, and foster improved pre-ART risk assessment and targeted prescribing.

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Table 1

Baseline demographic and clinical characteristics and mitochondrial subhaplogroups in the overall ACTG Human DNA Repository (HDR) population and by non-Hispanic black case and control study groups

Baseline Characteristic	HDR subjects (N = 526)	Non-Hispanic black subjects (N=156[a])		P-value[b]
		Controls (n=105)	Cases (n=51)	
Age in years, median (range)	36 (17-72)	34 (17-66)	42 (19-64)	<0.001
Female sex	92 (17)	34 (32)	12 (24)	0.35
Race/ethnicity				-
Non-Hispanic white	257 (49)	-	-	
Non-Hispanic black	161[a] (31)	-	-	
Hispanic	95 (18)	-	-	
Other[c]	13 (2)	-	-	
HIV RNA (log_{10} copies/mL)	5.0 (4.3-5.5)	4.8 (4.0-5.4)	5.0 (4.2-5.6)	0.09
$CD4^+$ T lymphocytes/mm^3	274 (85-429)	271 (136-428)	149 (45-353)	0.07
NRTI at randomization				
Didanosine + stavudine	277 (53)	45 (43)	40 (78)	<0.001
Zidovudine + lamivudine	249 (47)	60 (57)	11 (22)	-
Any nelfinavir at randomization[d]	360 (68)	68 (65)	34 (67)	0.86
Mitochondrial subhaplogroup, N (% of non-Hispanic blacks[a])				
L1a	9 (5.8)	5 (4.8)	4 (7.8)	0.48
L1b	16 (10.3)	11 (10.5)	5 (9.8)	1.0
L1c	16 (10.3)	7 (6.7)	9 (17.7)	0.048
L1/L2	2 (1.3)	2 (1.9)	0 (0)	1.0
L2a	33 (21.2)	24 (22.9)	9 (27)	0.53
L2b	17 (10.9)	11 (10.5)	6 (11.8)	0.79
L3	20 (12.8)	13 (12.4)	7 (13.7)	0.80
L3b	16 (10.3)	14 (13.3)	2 (3.9)	0.09
L3e	10 (6.4)	7 (6.7)	3 (5.9)	1.0
Non-African[e]	17 (10.9)	11 (10.5)	6 (11.8)	0.79

Values shown are median (IQR) or N (%) except where noted.

HDR= ACTG Human DNR Repository; NRTI= nucleoside reverse transcriptase inhibitor

[a] Analyses excluded five non-Hispanic black persons with symptoms and/or signs of peripheral neuropathy at baseline

[b] Univariate P-value for case-control comparison by Fisher's exact or Wilcoxon rank-sum tests

[c] Other race/ethnicity included "Asian" (N=11) and "Native American" (2)

[d] Includes participants randomized to nelfinavir alone (N=171) or nelfinavir plus efavirenz (189).

[e] Non-African haplogroups included A (N=3); H (1); H2 (5); I (1); J1 (2); T1 (1); T2b (1); U6 (2); and U9 (1).

Table 2

Univariate and multivariate logistic regression of factors potentially associated with development of peripheral neuropathy after randomization in ACTG study 384

Covariate	Unadjusted OR (95% CI)	P-value	Adjusted[a] OR (95% CI)	P-value
Antiretroviral therapy at randomization				
Didanosine + stavudine vs. zidovudine + lamivudine	4.8 (2.2-10.5)	<0.001	6.0 (2.5-14.2)	<0.001
Any nelfinavir vs. efavirenz	1.1 (0.5-2.2)	0.82	1.2 (0.5-2.6)	0.74
Age at randomization (per year increase)	1.1 (1.0-1.1)	0.003	1.1 (1.0-1.1)	0.001
African subhaplogroup L1c (vs. all others)	3.0 (1.0-8.6)	0.04	3.7 (1.1-12.0)	0.03
Baseline $CD4^+$ T lymphocytes (per 100 cell/mm^3 increase)	0.87 (0.74-1.0)	0.10	0.88 (0.71-1.1)	0.24
Baseline HIV RNA (per $\log_{10}$ copy/mL increase)	1.3 (0.9-1.8)	0.21	0.9 (0.6-1.5)	0.72
Male sex (vs. female)	1.6 (0.7-3.3)	0.26	1.0 (0.4-2.6)	0.94

OR= Odds ratio; CI= Confidence interval

[a] Adjusted for all other covariates listed in the Table.