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Mitochondrial DNA Haplogroups influence AIDS Progression

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Abstract

Objective—Mitochondrial function plays a role in both AIDS progression and highly active antiretroviral therapy (HAART) toxicity, therefore we sought to determine whether mitochondrial (mt) DNA variation revealed novel AIDS Restriction Genes (ARGs), particularly as mtDNA single nucleotide polymorphisms (SNPs) are known to influence regulation of oxidative phosphorylation, reactive oxygen species (ROS) production, and apoptosis.

Design—Retrospective cohort study.

Methods—We performed an association study of mtDNA haplogroups among 1833 European American HIV-1 patients from five US cohorts, the Multicenter AIDS Cohort Study (MACS), the San Francisco City Clinic Study (SFCC), Hemophilia Growth and Development Study (HGDS), the Multicenter Hemophilia Cohort Study (MHCS), and the AIDS Linked to Intravenous Experiences (ALIVE) cohort to determine whether the mtDNA haplogroup correlated with AIDS progression rate.

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Contribution

All authors contributed to critical revision of the paper. S.L.H. haplogrouped patients, designed statistical tests, created all visuals, and wrote the paper draft. S.L.H. and J.L. organized clinical data and performed analyses. H.B.H. developed genotyping assays. E. S. performed the analysis of geographic structure. D.C.W., E.R.-P. and J.C.P. designed the SNP algorithm to define haplogroups. Contributions to study conception and design, and analysis and interpretation of data were made by D.C.W. and S.J.O.. L.K., J.J.G., D.V., and S.D. were responsible for clinical and epidemiological data.

Results—MtDNA haplogroups J and U5a were elevated among HIV-1 infected people who display accelerated progression to AIDS and death. Haplogroups Uk, H3, and IWX appeared to be highly protective against AIDS progression.

Conclusions—The associations found in our study appear to support a functional explanation by which mtDNA variation among haplogroups influencing ATP production, ROS generation, and apoptosis is correlated to AIDS disease progression, however repeating these results in cohorts with different ethnic backgrounds would be informative. These data suggest that mitochondrial genes are important indicators of AIDS disease progression in HIV-1 infected persons.

Keywords

Mitochondria; AIDS; HIV-1; apoptosis; disease

Introduction

Mitochondria are critical for energy production and control of apoptosis in the cell. Through oxidative phosphorylation, mitochondria convert calories to ATP, release heat to maintain body temperature, and generate reactive oxygen species (ROS). Mitochondrial energetics are accomplished by cooperation of 37 genes encoded by the mitochondrial genome with an estimated 1,500 nuclear genes [1]. While mtDNA encodes only 13 proteins directly involved in ATP production, their roles are central to mitochondrial function. MtDNA variation in these genes from indigenous populations correlates with latitude and climate, suggesting that these differences are adaptive [2–4]. Genotypes differ in coupling efficiency such that there is a trade-off between highly efficient ATP production and increased heat release in colder temperatures. Because mitochondrial gene function is critical, mtDNA variation has also been directly associated with propensity for metabolic disease, neurodegenerative disease, cancer, and microbial infections [1,5–9].

Interactions between viral infection and mitochondrial energetics suggest that mtDNA variation could also play a role in viral disease progression. Mitochondria are the key regulators of apoptosis, an important host immune response to viral infection [10]. Many viruses have evolved strategies to prevent viral suppression via apoptosis or even exploit mitochondrial pathways to destroy cells involved in the host immune response. The human immunodeficiency virus (HIV)-1 uses both anti-apoptotic and apoptotic strategies during infection and AIDS progression. Early in infection, HIV-1-encoded Viral protein R (Vpr) impedes apoptosis to prevent eradication of virus [11]. As HIV-1 infection progresses, higher concentrations of Vpr [12,13], and other viral-encoded proteins including Tat [14] and the gp120-gp41 envelope complex [15,16] elicit apoptosis of cells in the immune system. Loss of CD4⁺ T cells in particular correlates well to stage of HIV-1 disease [17]. Compared to HIV-1+ long-term non-progressors, patients with AIDS have a higher frequency of peripheral blood lymphocytes exhibiting mitochondrial membrane permeabilization (MMP), the point of no-return in apoptosis [18]. AIDS progression is also associated with mtDNA depletion [19], disruption of energy production via oxidative phosphorylation, increased ROS production [20], antioxidant enzyme deficiency [21], and increased oxidative damage which accelerates AIDS progression [22]. In addition, mitochondrial toxicity to drugs used in highly active anti-retroviral therapy (HAART) for HIV-1 has been linked to severe side-effects including lipodystrophy, peripheral neuropathy, hepatic steatosis, myopathy, cardiomyopathy, pancreatitis, bone-marrow suppression, and lactic acidosis [23–27]. Nearly all of these side-effects resemble clinical symptoms seen in inherited mitochondrial diseases [28] and mtDNA haplogroup T has been associated with peripheral neuropathy [29].

Because AIDS progression is associated with changes in mitochondrial oxidative phosphorylation, ROS production, and apoptosis, which can be influenced by functional mtDNA variants, herein, we survey the mtDNA haplotypes of 1833 HIV-1 infected European American patients to determine whether host mtDNA haplogroup correlates with AIDS progression rate. We examined mtDNA haplotypes in the context of our recent global mutational phylogeny [30] and describe five associations with AIDS progression that can be interpreted in light of the physiological influences known for the mitochondrial genotypes.

Methods

Cohorts

The study group consisted of 1833 HIV-1 infected European American patients including 633 seroconvertors (infected after study enrollment) and 1200 seropositives (infected prior to enrollment) from five longitudinal cohorts: the Multicenter AIDS Cohort Study (MACS), the San Francisco City Clinic Study (SFCC), Hemophilia Growth and Development Study (HGDS) [31], the Multicenter Hemophilia Cohort Study (MHCS)[32], and the AIDS Linked to Intravenous Experiences (ALIVE) cohort. Informed consent was obtained from all patients. Ninety-seven percent of patients were male. Cohorts can be divided into mode of infection (intravenous versus sexual transmission). There are two cohorts of people with hemophilia who would have likely contacted AIDS through exposure to contaminated blood products: the MHCS is a multi-center longitudinal cohort study enrolling subjects from 17 American or European treatment centers beginning in September 1982 [32] and the HGDS is a US-based multicenter cohort of participants from 14 US treatment centers who became infected between 1982–1983 [31]. Sexual transmission is the most likely mode of infection for the MACS and SFCC. MACS is a US-based ongoing prospective study of HIV-1 infection in adult (ages 18–70) men who have sex with men (MSM) in Baltimore, Chicago, Pittsburgh, and Los Angeles enrolled between 1984 and 1991 [33]. The SFCC is a prospective study of the natural history of HIV and AIDS conducted in adult MSM and bisexual men enrolled in 1978–1980 for studies of hepatitis B (HBV), followed by a HBV vaccine trial in 1980–1983. Recruitment into the SFCC for follow-up studies of HIV and AIDS began in 1983–1992 [34]. SFCC contains more long-term survivors than the other cohorts [35]. ALIVE is a community-based cohort of injecting drug users in Baltimore, Maryland established in 1988 and followed until 2000 [36]. ALIVE patients were included in the analyses of all European Americans, but were not analyzed separately due to limited sample size. Clinical data used here were collected from 1978 to 1996 (or censored), before widespread use of highly active antiretroviral therapy (HAART).

Genotyping

DNAs were extracted from immortal lymphoblastoid B cell lines for each patient. An initial six haplotype-tagging SNPs were used to put individuals into major mitochondrial N, M and L groups. Individuals within the Western European (N) subset were further parsed into haplogroups using the Mitochondrial Haplogrouping using Candidate Functional Variants (MHCFV), a multi-step haplotyping strategy that interrogates key European mtDNA polymorphisms located at internal branch points of the global human mitochondrial phylogenetic tree. Based on the hierarchical nature of the tree we devised a strategy for identifying haplotypes by subdividing the samples using highly conserved polymorphic sites located at key haplogroup branch points. In this way, samples were defined to a high degree using the minimal number of SNPs. In total the study used 32 sequential SNPs (Supplemental Online Material (SOM): http://home.ncifcrf.gov/ccr/lgd/publications/index_n.asp) to define haplogroups. Genotyping was performed using TaqMan Assays-by-Design(SM). Thermocycling conditions were an initial 95°C hold for 3 minutes, followed by 30 cycles of 92°C for 15s, and 56°–62°C annealing for 1 minute depending on primer specificity.

Analyses

Because mtDNA is inherited maternally as a single haplotype a “dominant” genetic model was tested. Analyses were performed in each successive level of the phylogenetic tree of N haplogroups. All analyses were performed with SAS version 8.1 (SAS Institute, Inc, Cary NC). SAS analyses were visualized with the ARG ARRAY and ARG Highway software created at National Cancer Institute and ABCC, Frederick MD [37]. Statistical significance in these figures was declared at $p \leq 0.05$.

AIDS Progression

Four separate end points reflecting advancing AIDS morbidity were considered: (i) $CD4 < 200$ cells/mm³, (ii) AIDS-1993, the Centers for Disease Control and Prevention 1993 definition [38] (HIV-1 infected plus AIDS-defining illness, decline of CD4 T lymphocytes to < 200 or death), (iii) the more stringent AIDS-1987 definition [39] (HIV-1 infection plus AIDS defining illness) or death, and (iv) death during follow-up from AIDS of an HIV-1-infected patient.

Tests for association were performed using both categorical case-control and Cox Proportional Hazards models [40]. For survivorship models, only known seroconvertors ($n=633$) were used for analysis. Therefore, we also performed categorical analyses using time categories (< 8 years and ≥ 8 years for dichotomous, and < 3.5 , 3.5 to ≥ 7 , 7 to ≥ 10 , 10 to ≥ 13 , 13 to ≥ 16 and ≥ 16 for multipoint models [41] in order to capture the information available from the additional 1200 seropositives with estimated seroconversion dates in our study. A Fisher’s Exact test was used for dichotomous categorical analyses and a Mantel-Hanzel chi-square test was used for multipoint models. Cox proportional hazard models were stratified by age at seroconversion (0–20, 20–40 and > 40 years). Survival analyses were performed on all European American seroconvertors in the study, on subgroups separated by mode of transmission, and on individual cohorts in the case of the MACS and SFCC, which had larger samples of seroconvertors than the other cohorts. Significance was based on the log-likelihood chi-square test ($p < 0.05$).

Population Structure

For seroconvertors, we used data for 304 SNPs from previous studies [35,42–44] (for which the missing genotype information was less than five percent) and applied the EIGENSOFT [45] program to examine and adjust for potential population stratification. ANOVA F-statistic was performed on the recovered eigenvectors given the mitochondrial haplogroups.

Despite that we found no significant geographic substructure amongst the mitochondrial haplogroups based on the nuclear markers, we did adjust for known European AIDS restriction genes including *CCR5-Δ32*, *CCR2-64I*, *CCR5 P1* haplotype, *HLA* class I *B27*, *B57*, *B35-Px* alleles and *HLA* class I homozygosity [46,47], some of which are known to have geographic substructure.

Results

Our study included 1833 European Americans within the N haplogroup, which is ancestral to almost all European and many Eurasian haplogroups [48]. The N subgroup frequencies (‘f’ in Figure 1) in our study were consistent with an independent population dataset (D.C.W. unpublished). Genetic association tests were performed on major haplogroups, and then on haplotypes from successively more definitive phylogenetic nodes (Figure 1a). Minor haplogroups with frequencies less than 0.01 were collapsed into more inclusive haplogroups to minimize type I errors. Statistical tests were non-independent for two reasons: 1) the phylogenetic overlap of haplogroups and subgroup haplotypes; and, 2) the non-independence of varying AIDS endpoint association tests. Since non-independence precludes Bonferroni corrections for multiple tests, we focused on signals that were a) repeated within successive

nested haplogroups, b) replicated in cohorts tested separately in survivorship analyses, and/or c) had strong p-values in related hypotheses. We are also aware that the European American combined and MSM combined analyses had more power due to a larger sample size. This is important given the relative rarity of some of the haplogroups [49]. Figure 1 presents a visual heat plot display of p-values for genetic association for each of the 34 mtDNA genotypes. Based on ARGARRAY visualization routine [37], more intense color intensity represents increasing levels of statistical significance. MtDNA haplotypes related by a phylogenetic tree can be inspected individually or as a group for each AIDS progression test. Figure 1b presents the same ARGARRAY display for candidate SNP variants included within the mtDNA haplotypes that showed association signals in Figure 1a. The significant tests, p-values, RH, and CI values are tabulated in Tables 1 and 2. (Unabridged test results are provided in SOM: http://home.ncifcrf.gov/ccr/lgd/publications/index_n.asp). The association tests revealed five mtDNA haplogroups that showed consistent, significant associations: IWX, U5a, Uk, J and H3 (Figure 1; Tables 1 and 2). Each haplogroup will be described separately.

The J haplogroup was associated with accelerated progression to AIDS'87 (RH=1.55, 95% CI=1.08–2.23, p=0.024) and AIDS-related death (RH=1.53, 95% CI=1.03–2.26, p=0.043) in all European Americans. This association appears to be primarily driven by the cohorts who were infected via sexual transmission (RH=1.84, 95% CI=1.22–2.76, p=0.006) (Figure 1a; Figure 2a, Table 1), however the signal is observed in AIDS'87 and not in AIDS'93. Perhaps the J haplogroup specifically increases the risk of Kaposi's sarcoma, an AIDS-defining condition seldom that occurred at high rates in MSM cohorts but that was seldom seen in injection drug use and hemophilia cohorts. Additional research will be needed to examine this hypothesis. When we consider the MSM cohorts individually, there is a significant acceleration of AIDS'87 with J haplotypes in the MACS cohort (RH=1.69, 95% CI=1.08–2.66, p=0.03), and a non-significant trend for acceleration in the SFCC (RH= 2.74, 95% CI=0.97–7.70, p=0.08). Within haplogroup J, both sub-haplogroups J1 and J2 are associated with accelerated disease progression. J1 is associated with accelerated AIDS'87 in European Americans (RH=1.57, 95% CI=1.03–2.38, p=0.046), and in MSM cohorts (RH=1.80, 95% CI=1.12–2.87, p=0.023). The J1 association signal for accelerated AIDS progression is driven largely by the J1c-14798* haplotype (f=0.057) which is consistently highly significant in Caucasian, MSM, and individual MSM cohorts (MACS and SFCC; Figure 1a; Table 1). J1c was significant for AIDS'87 (All RH=1.67, CI=1.07–2.61, p=0.034, MSM RH=1.94, 95% CI=1.18–3.17, p=0.016, MACS RH 2.25, 95% CI=1.27–3.98, p=0.012), AIDS'93 (MSM RH=1.64, 95% CI=1.05–2.55, p=0.041, MACS RH=1.82, 95% CI=1.08–3.09, p=0.038), and death (all RH=1.72, 95% CI=1.07–2.78, p=0.038). J2 shows an association with accelerated AIDS progress in the SFCC (CD4<200: RH=23.13, 95% CI=2.33–229.65, p=0.044; AIDS'87: RH=63.69, 95% CI=3.61–1124.28, p=0.019; AIDS'93: RH=44.26, 95% CI= 3.71–528.15, p=0.024). As this cohort is biased towards long-term survivors [35], this signal may represent a moderate, late-term effect.

The U5a haplogroup is associated with accelerated AIDS progression to CD4<200 in European Americans (RH=1.78, 95% CI=1.11–2.85, p=0.028) and in MSM pooled cohorts (RH=2.06, 95% CI=1.17–3.63, p=0.024). The signal is largely driven by the U5a1-15218 haplotype, which comprises 79% of the U5a haplotype (Figure 1a; Table 1).

The Uk haplotype was associated with a decrease in the rate of AIDS progression to CD4 <200 cells/ μ L in both dichotomous and multipoint categorical models (OR=0.47, 95% CI=0.24–0.85, p=0.008; Common OR=0.60, 95% CI=0.37–0.97, p=0.038 respectively) as shown in Table 2 and Figure 3. Uk was also protective against AIDS'93 (Figure 3c–d) (OR=0.50, 95% CI=0.27–0.87, p=0.012; Common OR=0.61, 95% CI=0.40–0.95, p=0.022, dichotomous and multipoint models respectively). In survivorship analyses (Figure 1a, Table 1), only one signal

was observed indicating Uk is protective against AIDS^{'87} in the MSM cohorts (RH=0.53, 95% CI=0.29–1.00, p=0.031).

A strong association signal suggests H3 was protective for hemophiliacs against progression to AIDS^{'93} (RH= 0.21, 95% CI=0.06–0.72, p=0.003), AIDS^{'87} (RH=0.12, CI=0.02–0.94, p=0.006); and death (RH=undefined p=0.0004) (Figure 1a, Table 1). However, this result is based on few individuals as only seven of the hemophiliacs analyzed in the survival model are in haplogroup H3, and of those, one patient developed AIDS and no patients died. Protection, albeit relatively weak and inconsistent, was also observed in H4, H5 and H6 (Figure 1a; Table 1).

IWX haplogroup was associated with delayed progression to CD4<200 cells/μL in MSM cohorts, driven largely by the MACS cohort (RH=0.56, 95% CI=0.33–0.96, p=0.022, RH=0.52, 95% CI=0.29–0.94, p=0.017), however we do not see an association when we look at all European Americans combined. Within the IWX group, The W (W8994) haplotype showed the strongest protective association among MSM cohorts pooled or individually (Figure 1a; Table 1).

Haplogroups U and J contain a number of functional variants that we analyzed separately (Figure 1b). Strong disease accelerating associations consistent with parent haplotypes were observed for SNP 3010 G>A (included in J1 and H1 haplotypes) and SNP 13708G>A found at the root of the J haplogroup. The 13708G>A SNP is a amino acid altering variant in the *ND5* protein coding gene. Since both associated SNP variants, 3010G>A and 13708G>A are carried together on the J1 haplogroups, it was not possible to resolve their independent contributions to the J1 association with rapid AIDS progression among MSM. However, the 3010G>A association may explain the accelerating association seen in H1, which is counter to the protective associations observed for H3 and other H sub-haplogroups. The Uk haplotype protecting against AIDS progression was recapitulated by non-synonymous CYTB-14798T>C SNP. SNP 14798T>C is present on J1 and Uk haplotypes, but the protective influence was only apparent in Uk.

Discussion

We determined the mitochondrial haplogroups of 1833 HIV-infected patients from five AIDS cohort studies in the United States and found certain haplogroups associated with progression to AIDS and death. For these analyses, we used a nested phylogenetic approach that allowed us to look for consistent signals between related clades at different levels of the mitochondrial tree, and to pinpoint associations within specific haplogroups. The strongest signals for AIDS survival indicate haplogroups U5a and J are associated with accelerated AIDS progression, whereas haplogroups IWX and H3 are associated with a delay in AIDS onset (Fig 1, 2; Table 1). In categorical analyses, Uk was found to be lower AIDS risk (Fig 3).

There are at least two potential explanations consistent with the results. First, because of the strong phylo-geographic structure of mitochondrial haplogroups, it is possible that the associations observed in our study are correlated with background nuclear genetic effects that are distinctive between geographically separated populations. However, population stratification analysis using 304 autosomal markers did not find significant difference between the major haplogroups, and we adjusted for known ARGs as an additional control against population substructure. However, replicating these haplotype associations in additional cohorts from different ethnic backgrounds would be informative. Second, an interesting trend was observed that uncoupled haplogroups with lower ATP and ROS production (U5 and J) are associated with accelerated disease, whereas more tightly coupled groups (H3 and H4, H5, and H6) are associated with protection, suggesting mitochondrial functional variation plays a role

in AIDS progression. Combined data on longevity [50–52], neurodegenerative disease susceptibility [5,6,52,53], sperm motility [54,55], sprint performance [56], and climate adaptation [1,2] suggests functional mtDNA variation in different haplogroups influences ATP production efficiency, and correlated ROS and heat generation. Less efficient ATP production in partially uncoupled mitochondria (haplogroups J and U5) would accelerate AIDS because it would exacerbate the energetic effects of the mtDNA depletion [19], disruption of oxidative phosphorylation, antioxidant enzyme deficiency [21], apoptosis [12,13,15], and increased oxidative damage observed during AIDS progression [22,57]. Whereas in tightly coupled haplogroups (H3, H4, H5, H6), increased ATP production would allow HIV-infected patients to remain healthy for longer, and increased ROS production may enhance innate immunity and thus retard AIDS progression. Perhaps relevant is the report that haplogroup H has also been found to increase the survival rate of individuals with sepsis [7]. It may also be important that the H signal was observed only in the transfusion patients, and not in MSM groups, even though the MSM sample is much larger, and mitochondria genetic studies with small samples size and rare haplogroups have been found to be less reliable [49]. Haplogroup Uk lowers AIDS risk in categorical analyses (Fig 1a). The most common subhaplogroup of UK, Uk1, harbors functional variants ND3 A10398G (T114A) and cytb T14798C (F18L), which it share with J1c, and variants tRNA^{Leu(CUN)} A12308G and 16S rRNA A1811G which it share with U4. HIV-1 relies on mitochondrial ATP production for replication and productive infection, yet inhibits mitochondrial ATP production [58]. One possibility is that, the large number of uncoupling SNPs in Uk causes ATP production to fall below the threshold level needed for productive viral replication. Further, since AIDS viral transcription is driven by NFκB [59] and NFκB is activated by ROS [60], the low ROS production of Uk would be protective. The IWX association with slow progression is intriguing, but cannot be interpreted in the context of uncoupling/AIDS acceleration since coupling status of IWX is unknown.

Further functional studies and replication in other cohorts are needed for a better understanding of whether and how functional differences between haplogroups influence AIDS progression. Nonetheless, the associations here observed, interpreted in the limited functional inferences about mtDNA phylogeography and function, offer important genetic insight in the complex interaction of HIV and host physiology in AIDS pathogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
A) An ARGARRAY display [37] of categorical and survival analyses for AIDS progression in 34 Caucasian mitochondrial haplogroups. A phylogenetic tree showing the relationship between haplogroups is shown on the left [29]. Each major haplogroup was analyzed, and then successively more definitive subgroups within the haplogroups were analyzed separately. The haplogroups known to contain uncoupling SNPs are in red type in the phylogenetic tree. B) Individual SNP genotypes within the U and J Mitochondrial haplogroups. Locations of SNP in coding genes of the mitochondria are given. *=non-synonymous substitution. Significant values are shown in color (non-grey). Hazardous hazard and odds ratios are indicated by orange

and red squares, while significant protection is shown in green and blue. In AIDS progression Categorical analyses, 2= dichotomous categorical analysis, M=multi-point categorical analysis. The AIDS association tests illustrated on the horizontal are non-independent. However, the hypothesis study groups: AIDS progression in MSM patients and AIDS progression in patients with hemophilia can be considered independent although tests within each hypothesis study group are related. The five associations IWX, U5a, Uk, J, and H3 did not replicate between MSM cohorts and hemophilia cohorts perhaps as a result of fewer study participants among the hemophiliacs (N=158 versus MSM N=615).

Figure 2.

Representative Kaplan-Meier plots for significant results. a) J haplogroup and AIDS'87 progression in sexual transmission cohorts, b) SNP 13708 from the J haplogroups and AIDS'87 progression in sexual transmission cohorts, c) Haplogroup U5a and drop to CD4 < 200 cells/ μ L, and d) SNP 3010, which is in haplogroups J1 and H1 and time to death in sexual transmission cohorts. RH, p-values and numbers shown in the lower left of each graph are from Cox Proportional Models controlling for confounding variables (nuclear ARG genotype, age).

Figure 3.

Frequencies of Uk in categorical analyses for Uk using dichotomous (a, c) and multipoint (b, d) models to CD4<200 cells/μL (a,b) and AIDS'93 (c,d). *Odds ratios shown for multipoint models are Common Odds Ratios.

Table 1
Significant results in AIDS association tests for Cox Proportional Model

Haplogroup	pop	Endpoint	N events	N	RH	95% CI	P
IWX	MSM	AIDS'93	285	452	0.65	0.42–1.01	0.0426
IWX	MACS	AIDS'93	240	384	0.64	0.4–1.03	0.0490
IWX	MSM	CD4<200	234	452	0.56	0.33–0.96	0.0215
IWX	MACS	CD4<200	194	384	0.52	0.29–0.94	0.0170
X	MACS	CD4<200	193	383	0.00	0-∞	0.0329
W	MSM	AIDS'87	206	455	0.35	0.11–1.1	0.0316
W	MACS	AIDS'87	179	387	0.36	0.11–1.12	0.0366
W	MSM	AIDS'93	285	452	0.41	0.17–1	0.0225
W	MACS	AIDS'93	240	384	0.44	0.18–1.08	0.0420
W	SFCC	AIDS'93	45	68	0.00	0-∞	0.0369
W	MSM	CD4<200	234	452	0.32	0.1–1.01	0.0191
W	MACS	CD4<200	194	384	0.36	0.11–1.14	0.0402
U5a	EA	CD4<200	339	615	1.78	1.11–2.85	0.0277
U5a	MSM	CD4<200	236	453	2.06	1.17–3.63	0.0237
U5a1-15218	EA	AIDS'93	395	620	1.77	1.05–2.98	0.0493
U5a1-15218	EA	CD4<200	338	614	1.99	1.18–3.38	0.0197
U5a1-15218	MSM	CD4<200	235	452	2.04	1.13–3.67	0.0317
U5b	SFCC	Death	21	69	0.00	0-∞	0.0182
U1811*	SFCC	Death	21	69	10.07	1.51–67.39	0.0372
U4-U1811*	SFCC	Death	21	69	10.07	1.51–67.39	0.0372
U4	EA	AIDS'93	396	620	2.40	1.12–5.15	0.0464
Uk	MSM	AIDS'87	206	456	0.53	0.29–1	0.0309
J	EA	AIDS'87	277	628	1.55	1.08–2.23	0.0236
J	MSM	AIDS'87	206	457	1.84	1.22–2.76	0.0061
J	MACS	AIDS'87	179	388	1.69	1.08–2.66	0.0302
J	EA	Death	239	627	1.53	1.03–2.26	0.0428
J1	EA	AIDS'87	277	627	1.57	1.03–2.38	0.0463
J1	MSM	AIDS'87	206	456	1.80	1.12–2.87	0.0228
J1	MACS	AIDS'87	179	388	1.91	1.13–3.25	0.0263
J1c	EA	AIDS'87	277	626	1.67	1.07–2.61	0.0338

Haplogroup	pop	Endpoint	N events	N	RH	95% CI	p
J1c	MSM	AIDS*87	206	456	1.94	1.18–3.17	0.0159
J1c	MACS	AIDS*87	179	388	2.25	1.27–3.98	0.0116
J1c	MSM	AIDS*93	287	453	1.64	1.05–2.55	0.0408
J1c	MACS	AIDS*93	241	385	1.82	1.08–3.09	0.0383
J1c	EA	Death	239	625	1.72	1.07–2.78	0.0381
J1c-14798*	EA	AIDS*87	277	626	1.80	1.12–2.91	0.0247
J1c-14798*	MSM	AIDS*87	206	456	2.24	1.3–3.84	0.0082
J1c-14798*	MACS	AIDS*87	179	388	2.01	1.09–3.7	0.0403
J1c-14798*	SFCC	AIDS*87	27	68	6.23	1.33–29.23	0.0351
J1c-14798*	EA	Death	239	625	2.03	1.24–3.33	0.0101
J1c-14798*	MSM	Death	175	455	2.27	1.27–4.05	0.0123
J1c-14798*	SFCC	Death	21	68	9.13	1.68–49.67	0.0177
J2	SFCC	AIDS*87	27	68	63.69	3.61–1124.28	0.0194
J2	SFCC	AIDS*93	46	68	44.26	3.71–528.15	0.0236
J2	SFCC	CD4<200	41	68	23.13	2.33–229.65	0.0441
T	HE	AIDS*87	68	159	0.30	0.11–0.86	0.0125
H1	HE	AIDS*87	68	159	2.38	1.11–5.09	0.0386
H1	MHCS	AIDS*87	68	159	2.38	1.11–5.09	0.0386
H1	SFCC	AIDS*93	46	68	0.00		0.0317
H1	EA	Death	240	629	1.50	1.04–2.16	0.0403
H3	HE	AIDS*87	68	159	0.12	0.02–0.94	0.0060
H3	HE	AIDS*93	104	156	0.21	0.06–0.72	0.0025
H3	HE	Death	63	159	0.00	0–∞	0.0004
H5	EA	Death	239	626	0.39	0.15–1.07	0.0326
H5	MSM	Death	175	456	0.30	0.07–1.21	0.0381
H6	HE	AIDS*93	104	155	0.07	0.01–0.66	0.0040
V	HE	Death	62	157	7.76	1.61–37.44	0.0381
HV*	SFCC	AIDS*87	27	68	28.37	2.1–383.55	0.0418

Table 2
Significant results in AIDS association tests for Progression categorical analysis

Haplogroup	disease	comparison	n risk haplo	n alt haplo	N	OR	95% CI	p-value
U4-U1811*	CD<200	D2	34	795	829	2.02	0.95–4.27	0.0423
Uk	CD<200	D2	81	748	829	0.47	0.24–0.85	0.0081
Uk	CD<200	DM	60	604	664	0.60	0.37–0.97	0.0381
Uk	AIDS'93	D2	93	928	1021	0.50	0.27–0.87	0.0121
Uk	AIDS'93	DM	72	764	836	0.61	0.4–0.95	0.0224
J1c-14798-3394	ALL	3	12	826	838	0.29	0.1–0.84	0.0175
H	CD<200	D2	333	506	839	1.39	1.02–1.89	0.0328
H	AIDS'93	D2	418	615	1033	1.34	1.01–1.77	0.0374
H4	CD<200	DM	6	658	664	0.13	0.03–0.57	0.0287

Note. - D2= dichotomous model with events occurring before 8 years and greater than 8 years. DM-multipoint models with the following intervals: ≤3.5, 3.5–7, 7–10, 10–13, 13–16, and >16 years. p-values from these categorical models are from the Fisher's Exact test and Mantel-Hanzel test respectively.