

Effect of Host Genetics on Incidence of HIV Neuroretinal Disorder in Patients With AIDS

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Abstract: Approximately 10%–15% of patients with AIDS but without ocular opportunistic infections will have a presumed neuroretinal disorder (HIV-NRD), manifested by reduced contrast sensitivity and abnormal visual fields. The loss of contrast sensitivity often is sufficient to impair reading speed. To evaluate the effect of host genetics on HIV-NRD, we explored validated AIDS restriction gene variants *CCR5Δ32*, *CCR2-64I*, *CCR5 P1*, *SDF-3'A*, *IL-10-5'A*, *RANTES -403A*, *RANTES -28G*, *RANTES-In1.1C*, *CX3CR1-249I*, *CX3CR1-280M*, *IFNG-179T*, *MDR1-3435T*, and *MCP-1364G*, each of which has been implicated previously to influence HIV-1 infection, AIDS progression, therapy response, and antiviral drug metabolism, and an IL-10 receptor gene, *IL-10R1*, in the Longitudinal Study of the Ocular Complications of AIDS cohort. In European Americans (cases = 55, controls = 290), *IL-10-5'A* variant and its promoter haplotype (hazard ratio = 2.09, confidence interval. 1.19 to 3.67, $P = 0.01$), in African Americans (cases = 54, controls = 180), *RANTES-In1.1C* and the associated haplotype (hazard ratio = 2.72, confidence interval.: 1.48 to 5.00, $P = 0.001$), showed increased HIV-NRD susceptibility. Although sample sizes are small and P values do not pass a strict Bonferroni correction, our results suggest that, in European Americans, an IL-10-related pathway, and, in African Americans, chemokine receptor ligand polymorphisms in *RANTES*

are risk factors for HIV-NRD development. Clearly, further studies are warranted.

Key Words: AIDS, HIV-1, host genetics, HIV-neuroretinal disorder
(J Acquir Immune Defic Syndr 2010;54:343–351)

INTRODUCTION

Before the introduction of highly active antiretroviral therapy (HAART), ocular complications, particularly ocular opportunistic infections (OIs), were common among patients with the AIDS.¹ Although the incidence of ocular OIs has been reduced ~80% by HAART,^{2,3} the impact of other noninfectious problems is more evident, particularly an HIV-related presumed neuroretinal disorder (HIV-NRD), manifested by abnormal contrast sensitivity, color vision, and visual fields.^{4–7} The decrease in contrast sensitivity often is sufficiently severe to impair reading speed. The pathogenesis of HIV-NRD is not well understood currently, but hypotheses include direct infection of neural tissue, indirect damage due to immune reaction against HIV infection, and HIV microangiopathy–related cumulative damage to optic nerve and retina.

Host genetics have been shown to affect the acquisition of HIV infection, progression to AIDS and the efficacy of antiretroviral therapy.^{8–12} HIV-NRD may be an outcome of worse AIDS prognosis.^{4,6} Therefore, it is also possible that host genetics that affect progression to AIDS and the efficacy of antiretroviral therapy may also affect the development of HIV-NRD. In this study, we evaluated host genetic factors that may influence HIV-NRD development. We evaluated the effects of variants in the genes *CCR5Δ32*, *CCR2-64I*, *CCR5 P1*, *SDF-3'A*, *IL-10-5'A*, *RANTES -403A*, *RANTES -28G*, *RANTES-In1.1C*, *CX3CR1-249I*, *CX3CR1-280M*, *IFNG-179T*, *MDR1-3435T*, and *MCP-1364G* each of which has been shown to influence HIV-1 infection, AIDS progression, therapy response, and antiviral drug metabolism. Previous studies showed that tumor necrosis factor (TNF) leads to damage in optic nerves.^{13–16} IL-10 is a major regulator/suppressor of TNF and other inflammatory cytokines.^{17,18} Moreover, genetic polymorphisms in *IL-10R1* have been shown to diminish IL-10 signalling through the IL-10 receptor complex.^{19,20} As our initial screen identified *IL-10-5'A* as a genetic risk factor for HIV-NRD, we extended our analyses to polymorphisms in the primary IL-10 receptor gene, *IL-10R1*, that have a crucial role in the IL-10 signaling pathway. Our study participants were HIV-infected European American and African American patients enrolled in

Received for publication November 6, 2009; accepted March 17, 2010.

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Supported in part by contract N01-CO-12400 from the National Cancer Institute to the Laboratory of Genomic Diversity, Frederick, MD, with federal funds from the National Cancer Institute, National Institutes of Health, under contract HHSN26120080001E and cooperative agreements from the National Eye Institute, National Institutes of Health, U10-EY-08052 to the Mount Sinai School of Medicine, New York, NY, U10-EY-08057 to the Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, and U10-EY-08067 to the University of Wisconsin, Madison, Madison, WI.

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the Longitudinal Study of the Ocular Complications of AIDS (LSOCA) cohort.

PATIENTS AND METHODS

Study Population and Clinical Assessment of HIV-NRD

Study patients included 345 European American and 234 African American individuals enrolled in the LSOCA cohort, who did not have ocular OIs. All patients in this study were enrolled beginning in September 1998 and diagnosed with AIDS according to the 1993 Centers for Disease Control and Prevention surveillance case definition for AIDS. Details of the study design and implementation have been published previously.^{2,3} Eighty-seven percent of the European and 86% of African American patients were receiving HAART. The date of HIV-NRD diagnosis was defined as the first date when a patient had log unit contrast sensitivity less than 1.5, in at least 1 eye. Clinical methods for assessing HIV-NRD in LSOCA have been described previously.⁴ The LSOCA program, including a specimen bank for immunologic and genetic testing, was reviewed and approved by the institutional review boards at the participating clinical centers and at the resource centers, and written consent was obtained from each participant.

Genotyping and Haplotype Construction

Previously identified functional polymorphisms, rs333, rs1799864, rs1799988, rs1801157, rs1800872, rs2107538, rs2280788, rs2280789, rs3732379, rs3732378, rs2069709, rs1045642, and rs2857657, were genotyped for *CCR5Δ32*, *CCR2-64I*, *CCR5 P1*, *SDF-3'A*, *IL-10-5'A*, *RANTES -403A*, *RANTES -28G*, *RANTES-In1.1C*, *CX3CR1-249I*, *CX3CR1-280M*, *IFNG-179T*, *MDR1-3435T*, and *MCP-1364G* (intronic 767G, representative of haplotype 7) mutations, respectively. Additionally, 11 haplotype tagging single-nucleotide polymorphisms (SNPs) (promoter region: rs17351243, rs4072227, rs6667202, rs1800890, rs1800896, and rs1800894; intronic: rs3021094, rs3024508; 3' UTR: rs3024496, rs3024498, and rs3024500) covering the *IL-10* region were also selected. rs1800896 (-1082) and rs1800872 (-592) were used to construct the proximal promoter *IL-10* haplotypes of ATA, ACC, and GCC that were reported to be associated with differential *IL-10* production.²¹⁻²⁴ rs1800871 (-819) was not genotyped due to complete linkage with rs1800872. Functional and haplotype tagging SNPs for *IL-10R1* region were rs3135932 (replacement), rs2228055 (replacement), rs4252279 (Intron), rs4252314 (Intron), rs4252286 (Intron), rs2229113 (replacement), and rs2229114 (replacement). All SNPs were genotyped with the ABI-TaqMan method (Applied Biosystems, Foster City, CA). We could not get clear genotyping results for a few individuals for the *IL-10* and *IL-10R1* SNPs, and they were omitted from SNP-based association analyses.

All haplotypes are inferred by the expectation maximization algorithm using SAS Genetics (SAS Institute, Cary, NC) and the HaploView software.²⁵ The presence of *CCR5_59353C* (rs1799988) in the absence of *CCR2-64I* and *CCR5Δ32* defines the *CCR5 P1* promoter haplotype +.P1.+.²⁶ The *RANTES -403A*, *RANTES -28G*, and *RANTES-In1.1C* genotypes define the

RANTES haplotypes. *RANTES -H1*=G-C-T, *RANTES -H2*=A-C-T, and *RANTES -H3*=A-C-C (low producer haplotype).^{8,27}

Statistical Analyses

Each SNP and haplotype found at $\geq 1\%$ frequency in the study population were evaluated for NRD development with 3 different models of inheritance: allelic, dominant, and codominant. Allelic analyses were used to examine individual allele effects. Genotypes were coded as 0, 1, and 2 copies of the rare allele for the codominant model. The dominant model analyzed genotypes as absence or presence of the rare alleles. Odds ratios (ORs) for the codominant model were calculated by logistic regression and for the allelic and dominant models by 2×2 tables. Nominal *P* values are reported. As the patients were diagnosed with AIDS before study entry, a staggered entry²⁸ approach was adapted, and time to HIV-NRD was analyzed using the Cox proportional hazards model. The method of staggered entry allows inclusion of prevalent cases into a survival analysis of time from diagnosis to event. The main assumption is that prevalent cases without the event of interest at baseline have the same risk over time as incident cases without the event of interest at the same time as entry into the study of the prevalent cases. The method of staggered entry creates risk sets (ie, number at risk) to compare incident and prevalent AIDS patients at similar times since AIDS diagnosis. Unlike standard survival methods in which the number at risk can only decrease over time, the number at risk can increase or decrease over time. We checked the main assumption using only incident cases and did not see a significant loss in statistical power. As the main assumption was not violated, this method can control for varying lengths of follow-up. Cox models were adjusted for square root of nadir CD4⁺ T-cell count, highest log₁₀ HIV-1 load, age, and gender. To increase sample size and statistical power, analyses were extended to include each eye separately by a sandwich estimate of covariates in the Wald tests for the global null hypothesis and null hypotheses of individual parameters (by PROC PHREG covsandwich procedure in SAS). Only patients with visual acuity 20/20 Snellen equivalents (Standard ETDRS letters = 85) or better were included in the Cox analyses to avoid cases of decreased contrast sensitivity attributable to other major ocular complications, cataracts, or glaucoma. All analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC). Throughout the article, cases represent study patients who developed HIV-NRD, and controls represent study patients who did not develop HIV-NRD.

RESULTS

There were significant differences in terms of male gender percentage ($P = 0.001$), age ($P = 0.01$), CD4⁺ T-cell counts ($P = 0.01$), and time since AIDS diagnosis ($P = 0.01$) at study enrollment between European American ($n = 345$) and African American study patients ($n = 234$; Table 1). However, the HIV-NRD cases and controls did not differ significantly from each other for the clinical variables considered within European American patients, except more of the control patients were on HAART compared with HIV-NRD cases (89% vs. 78%; $P = 0.01$). African American patients with HIV-NRD were slightly older compared with the patients who did not develop HIV-NRD (44.7 ± 7.5 vs. 40.5 ± 7.9 ; $P = 0.003$).

TABLE 1. Clinical Aspects of European American and African American LSOCA Patients Used in This Study

| Variable | European Americans | | | | African Americans | | | |
|---|--------------------|----------------------------|--------------------|----------------------------|-------------------|----------------------------|--------------------|----------------------------|
| | Cases (n = 55) | | Controls (n = 290) | | Cases (n = 54) | | Controls (n = 180) | |
| | Mean ± SD | Median (25th%, 75th% tile) | Mean ± SD | Median (25th%, 75th% tile) | Mean ± SD | Median (25th%, 75th% tile) | Mean ± SD | Median (25th%, 75th% tile) |
| Male gender (%)* | 92 | | 88 | | 73 | | 61 | |
| Age at study entry (yrs)* | 44.6 ± 9.6 | 44.0 (38, 50) | 43.0 ± 7.7 | 42.0 (38, 47) | 44.7 ± 7.5 | 46.0 (41, 49) | 40.5 ± 7.9 | 43.0 (35, 46) |
| Nadir CD4 ⁺ T-cell count (cells/mL) | 74.5 ± 63.5 | 55.0 (17, 127) | 77.7 ± 99.4 | 48.0 (17, 99) | 60.4 ± 63.7 | 36.0 (8, 98) | 59.9 ± 73.6 | 30.0 (10, 93) |
| CD4 ⁺ T-cell count (cells/mL) | 301.7 ± 201.7 | 284.0 (147, 387) | 255.0 ± 205.6 | 220.0 (93, 347) | 209.4 ± 186.7 | 162.0 (68, 284) | 207.2 ± 202.9 | 146.0 (76, 283) |
| Peak HIV viral load (log ₁₀ copies/mL) | 5.5 ± 2.4 | 5.4 (4.9, 5.7) | 5.6 ± 2.4 | 5.3 (4.5, 5.7) | 5.5 ± 2.4 | 5.2 (4.4, 5.7) | 5.5 ± 2.3 | 5.3 (4.7, 5.7) |
| Baseline HIV viral load (log ₁₀ copies/mL) | 4.8 ± 2.3 | 2.9 (2.2, 4.4) | 4.8 ± 2.2 | 2.7 (2.2, 4.6) | 5.1 ± 2.3 | 3.7 (2.6, 4.9) | 4.9 ± 2.3 | 3.2 (2.3, 4.7) |
| Time since AIDS diagnosis (yrs)† | 5.1 ± 3.7 | 4.9 (2.0, 7.0) | 5.0 ± 3.6 | 4.7 (2.1, 7.2) | 4.6 ± 4.0 | 3.6 (1.0, 7.5) | 4.2 ± 3.6 | 3.5 (1.0, 6.5) |
| HAART use (%)‡ | 78 | — | 89 | — | 84 | — | 87 | — |

*Significantly different between NRD cases and controls in African Americans (*P* = 0.003).

†Years before study entry (see Methods for staggered entry study design).

‡Significantly different between NRD cases and controls in European Americans (*P* = 0.01).

European American Analyses

In SNP-based analyses, we observed an increased frequency of *IL-10-5A'* (rs1800872) variant in the European American patients with HIV-NRD. Persons carrying this allele were more likely to develop HIV-NRD in all 3 models (allelic, codominant, and dominant) of association tests (Table 2). Further analysis of *IL-10* region haplotype tagging SNPs identified 2 other variants with reduced risk of HIV-NRD development (see **Table, Supplemental Digital Content 1**, <http://links.lww.com/QAI/A54>). We also observed a trend toward HIV-NRD susceptibility associated with an intronic variant in *IL-10R1* (see **Table, Supplemental Digital Content 1**, <http://links.lww.com/QAI/A54>).

After individual SNP analyses, haplotypes were constructed and analyzed. There were 19 and 8 haplotypes with ≥1% frequency inferred for *IL-10* and *IL-10R1*, respectively (Fig. 1; see **Figure, Supplemental Digital Content 2**, <http://links.lww.com/QAI/A55>). A strong linkage disequilibrium pattern around *IL-10* driving the nonindependent nominally significant SNP-based HIV-NRD associations was evident (ie, high *D'* values observed between several SNPs, Fig. 1).

Three well-studied *IL-10* proximal promoter haplotypes ATA, ACC, and GCC, including rs1800896 (A/G), rs1800871 (C/T), and rs1800872 (C/A), were easily discerned using rs1800896 (A/G) and rs1800872 (C/A) as AA, AC, and GC by red, yellow, and green highlights, respectively, in Figure 1. Three *IL-10* haplotypes showed increased HIV-NRD susceptibility, each of which had AA (rs1800896-A and rs1800872-A) haplotype (highlighted red in Fig. 1; see **Table, Supplemental Digital Content 3**, <http://links.lww.com/QAI/A56>). The effect of the fifth haplotype (Hap5) was more evident compared with the other haplotypes (see **Table, Supplemental Digital Content 3**, <http://links.lww.com/QAI/A56>), which, in part,

may be due to its larger sample size. Individual *IL-10* proximal promoter AA, AC, and GC haplotypes were pooled to form combined haplotype groups HG1, HG2, and HG3 (Fig. 1). Similar to individual AA haplotypes, the combined HG1 haplotypes showed increased HIV-NRD susceptibility in all models of association (Table 3). The combined HG3 haplotypes showed decreased susceptibility, although the results were not always significant (Table 3). Moreover, *IL-10R1*-Hap5 was enriched in the HIV-NRD cases (see **Table, Supplemental Digital Content 4**, <http://links.lww.com/QAI/A57>). Finally, patients with HIV-NRD had more *CCR5 P1* promoter allele defining haplotype +.P1.+ than expected by chance (Table 3).

The effects of individual SNPs and haplotypes on HIV-NRD development were also evaluated by the Cox proportional hazards models adjusted for age, gender, CD4⁺ T-cell count and HIV-1 viral load of patients. The increased HIV-NRD risk associated with *IL-10-5A'* (rs1800872) and HG1 (Table 4), and *IL-10R1* rs4252314 (see **Table, Supplemental Digital Content 5**, <http://links.lww.com/QAI/A58>), were still evident. When each eye was assessed individually, all the aforementioned susceptible and protective variant effects were stronger [hazard ratio (HR): 2.02–2.46, *P* = 0.02–0.0002; Table 4 and **Table footnotes, Supplemental Digital Content 5**, <http://links.lww.com/QAI/A60>].

African American Analyses

African Americans patients with the *CCR2-64I* (rs1799864) and *RANTES-In1.1C* (rs2280789) variants showed increased risk of HIV-NRD development in allelic, dominant, and codominant models of association (Table 2). Haplotype analyses confirmed the *RANTES* association where the H3 (A-C-C) haplotype carrying the *In1.1C* variation showed higher odds of developing HIV-NRD (Table 3).

TABLE 2. Allelic Distribution and Association Tests of Genetic Polymorphisms in HIV-NRD Cases and Controls

| Gene-Variant | SNP | European Americans | | | | | | | |
|-----------------------|-----------|----------------------|--------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| | | Allele Frequency (%) | | Allelic | | Codominant | | Dominant | |
| | | Cases (n = 55) | Controls (n = 290) | OR | P | OR | P | OR | P |
| <i>CCR5-Δ32</i> | rs333 | 7 | 9 | 0.72 | 0.32 | 0.70 | 0.38 | 0.71 | 0.40 |
| <i>CCR2-64I</i> | rs1799864 | 8 | 10 | 0.72 | 0.43 | 0.71 | 0.42 | 0.73 | 0.47 |
| <i>CCR5-59353C</i> | rs1799988 | 56 | 51 | 1.23 | 0.32 | 1.25 | 0.30 | 1.69 | 0.20 |
| <i>SDF-3A</i> | rs1801157 | 19 | 21 | 0.89 | 0.67 | 0.89 | 0.67 | 0.87 | 0.66 |
| <i>IL-10-5A</i> | rs1800872 | 31 | 21 | 1.70 | 0.02 | 1.74 | 0.02 | 2.06 | 0.01 |
| <i>RANTES-403A</i> | rs2107538 | 19 | 22 | 0.86 | 0.56 | 0.85 | 0.55 | 0.74 | 0.34 |
| <i>RANTES-28G</i> | rs2280788 | 0 | 3 | —* | — | —* | — | —* | — |
| <i>RANTES-In1.1C</i> | rs2280789 | 9 | 14 | 0.59 | 0.13 | 0.59 | 0.13 | 0.60 | 0.17 |
| <i>CX3CR1-249I</i> | rs3732379 | 28 | 27 | 1.04 | 0.87 | 1.04 | 0.88 | 1.03 | 0.93 |
| <i>CX3CR1-280M</i> | rs3732378 | 16 | 15 | 1.00 | 0.91 | 1.03 | 0.92 | 1.14 | 0.74 |
| <i>IFNG-179T</i> | rs2069709 | 0 | 0 | —* | — | —* | — | —* | — |
| <i>MDR1-3435T</i> | rs1045642 | 56 | 46 | 1.48 | 0.11 | 1.41 | 0.14 | 1.26 | 0.55 |
| <i>MCPI-767G (H7)</i> | rs2857657 | 17 | 19 | 0.85 | 0.60 | 0.85 | 0.61 | 0.66 | 0.28 |

| Gene-Variant | African Americans | | | | | | | |
|-----------------------|----------------------|--------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| | Allele Frequency (%) | | Allelic | | Codominant | | Dominant | |
| | Cases (n = 54) | Controls (n = 180) | OR | P | OR | P | OR | P |
| <i>CCR5-Δ32</i> | 2 | 2 | 1.11 | 0.90 | 1.12 | 0.90 | 1.11 | 0.90 |
| <i>CCR2-64I</i> | 20 | 13 | 1.79 | 0.04 | 1.75 | 0.05 | 2.24 | 0.01 |
| <i>CCR5-59353C</i> | 46 | 41 | 1.24 | 0.49 | 1.21 | 0.51 | 1.26 | 0.62 |
| <i>SDF-3A</i> | 7 | 4 | 1.72 | 0.22 | 1.78 | 0.21 | 1.78 | 0.21 |
| <i>IL-10-5A</i> | 38 | 40 | 1.15 | 0.55 | 1.07 | 0.75 | 1.06 | 0.84 |
| <i>RANTES-403A</i> | 57 | 56 | 1.02 | 0.90 | 1.03 | 0.90 | 1.15 | 0.74 |
| <i>RANTES-28G</i> | 0.9 | 0.6 | 1.64 | 0.68 | 1.65 | 0.69 | 1.65 | 0.68 |
| <i>RANTES-In1.1C</i> | 27 | 17 | 1.76 | 0.03 | 1.72 | 0.03 | 2.17 | 0.01 |
| <i>CX3CR1-249I</i> | 10 | 12 | 0.80 | 0.55 | 0.79 | 0.55 | 0.79 | 0.55 |
| <i>CX3CR1-280M</i> | 3 | 3 | 1.04 | 0.96 | 0.97 | 0.96 | 1.08 | 0.91 |
| <i>IFNG-179T</i> | 0.9 | 2 | 0.40 | 0.37 | 0.39 | 0.38 | 0.39 | 0.36 |
| <i>MDR1-3435T</i> | 18 | 22 | 1.33 | 0.30 | 1.33 | 0.31 | 0.71 | 0.30 |
| <i>MCPI-767G (H7)</i> | 5 | 5 | 1.08 | 0.86 | 0.92 | 0.87 | 0.92 | 0.97 |

Adjusting the models for square root of nadir CD4⁺ T-cell cell count, highest log₁₀ HIV-1 load, age, and gender does not significantly change the results.

*OR not calculated in European Americans due to small sample size and lack of HIV-NRD cases.

Values in bold are significant at $\alpha = 0.05$.

Similar to European American analyses, there were 18 and 7 haplotypes with $\geq 1\%$ frequency constructed for *IL-10* (see **Figure, Supplemental Digital Content 6**, <http://links.lww.com/QAI/A59> and see **Table, Supplemental Digital Content 7**, <http://links.lww.com/QAI/A60>) and *IL-10R1*, respectively (see **Figure, Supplemental Digital Content 2**, <http://links.lww.com/QAI/A55> and see **Table, Supplemental Digital Content 4**, <http://links.lww.com/QAI/A57>). Whereas only 6 *IL-10* haplotypes were common between European American and African American individuals, the *IL-10R1* haplotypes were nearly identical in both groups. The *IL-10R1* Hap5, with increased frequency in European American HIV-NRD cases, also suggested an increased risk of HIV-NRD for African American patients (see **Table, Supplemental Digital Content 4**, <http://links.lww.com/QAI/A57>).

The Cox analyses strengthened the observation of increased HIV-NRD risk associated with *RANTES-In1.1C* and H3 (A-C-C) and also indicated a protective role for H2 (A-C-T) (Table 4). Although *CCR2-64I* still trended

for HIV-NRD susceptibility (see **Table, Supplemental Digital Content 5**, <http://links.lww.com/QAI/A58>) and *IL-10R1* Hap3 for protection (HR = 0.49; $P = 0.06$; see **Table, Supplemental Digital Content 4**, <http://links.lww.com/QAI/A57>), the results were less significant after clinical covariates were adjusted. When each eye was analyzed independently, similar HIV-NRD association trends were observed, with a possible increased HIV-NRD risk for patients with *SDF-3A'* variant (HR = 2.24, confidence interval: 1.24 to 4.03, $P = 0.007$; see **Table footnotes, Supplemental Digital Content 5**, <http://links.lww.com/QAI/A58>).

DISCUSSION

We investigated the role of host genetics in HIV-NRD development and explored the influence of variants of several genes known to influence other aspects of HIV infection. Our analyses suggest that European American patients with the *IL-10-5A'* variant and with the associated haplotype (proximal promoter HG1) are more likely to progress to HIV-NRD.

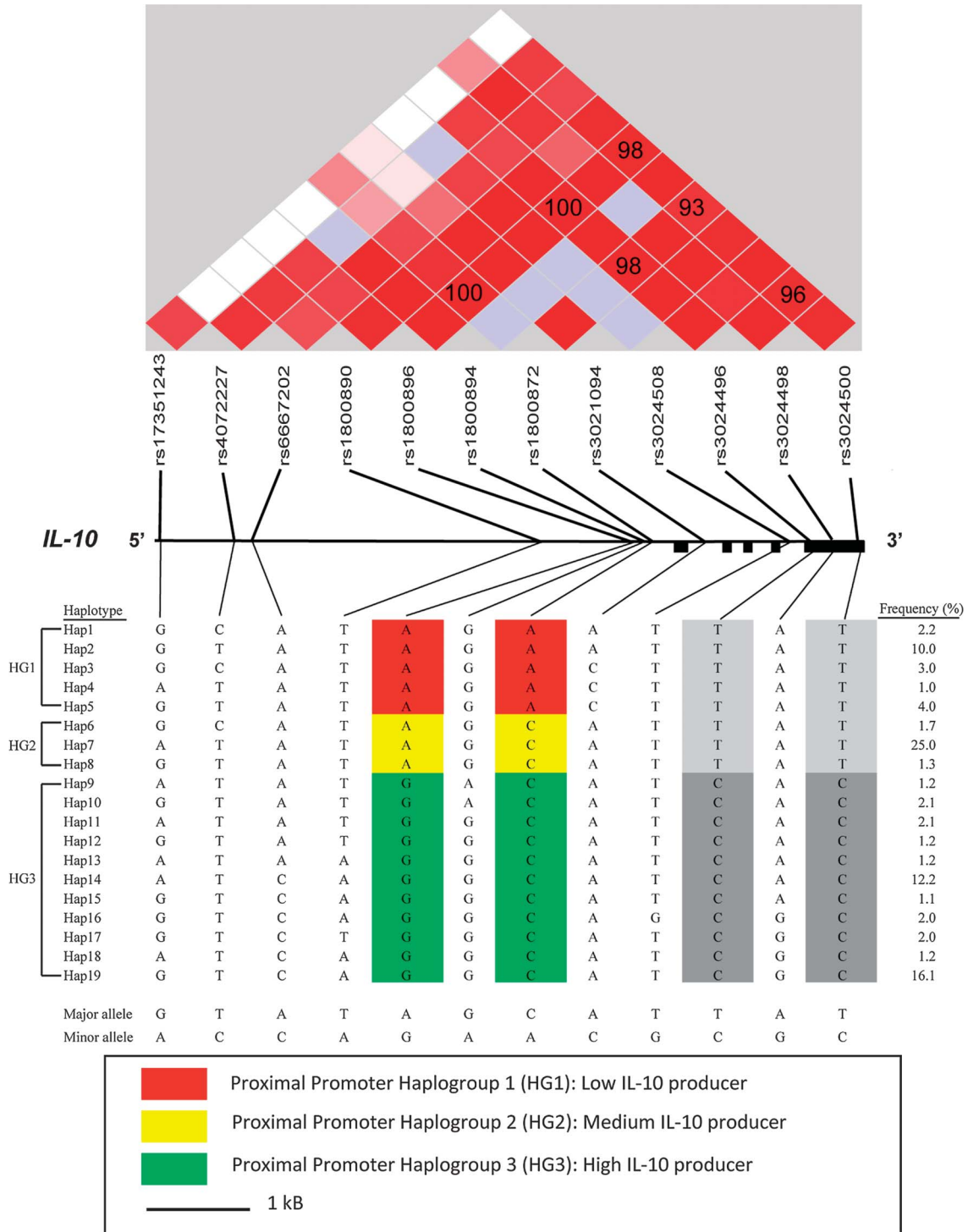


FIGURE 1. Inferred haplotypes, their frequencies, and LD structure across the *IL-10* region in European American samples. Black filled rectangles show *IL-10* exons. Lines indicate the actual physical position of SNPs with respect to each other. Brightness of red color represents the pair-wise D' (%) values. High D' values ($D' > 80$) are shown with bright red, low D' values are shown in light red and blue squares. The P values associated with D' estimates ranged from 10^{-22} for the rs1800872 and rs1800896 pair to 10^{-73} for the rs3024500 and rs3024496 pair. Pair-wise D' values (%) for these SNPs are shown in the squares. Previously described proximal promoter haplogroups associated with low, medium, and high IL-10 production²¹⁻²⁴ are combined to form HG1 (low IL-10 producer), HG2 (medium IL-10 producer), and HG3 (high IL-10 producer), respectively. The minor alleles of rs3024496 and rs3024500, highlighted in dark grey color, show high LD with HG3 ($P = 10^{-20}$) (see Table, Supplemental Digital Content 1, <http://links.lww.com/QAI/A54>, for association of these 2 SNPs with HIV-NRD development).

TABLE 3. Haplotype Analyses for HIV-NRD Development in European American and African American Patients

| Gene Haplotypes | European Americans | | | | | | | | |
|------------------|-------------------------|--------------------|-------------|-------------|-------------|-------------|-------------|-------------|--|
| | Haplotype Frequency (%) | | Allelic | | Codominant | | Dominant | | |
| | Cases (n = 55) | Controls (n = 290) | OR | P | OR | P | OR | P | |
| <i>CCR5</i> | | | | | | | | | |
| + <i>PI</i> .+ | 43 | 34 | 1.45 | 0.07 | 1.90 | 0.04 | 1.89 | 0.04 | |
| <i>RANTES</i> | | | | | | | | | |
| <i>H1(G-C-T)</i> | 81 | 79 | 1.13 | 0.65 | 1.13 | 0.65 | 1.01 | 0.67 | |
| <i>H2(A-C-T)</i> | 10 | 7 | 1.49 | 0.26 | 1.35 | 0.33 | 1.27 | 0.57 | |
| <i>H3(A-C-C)</i> | 9 | 14 | 0.61 | 0.16 | 0.61 | 0.16 | 0.63 | 0.22 | |
| <i>IL-10*</i> | (n = 55) | (n = 290) | | | | | | | |
| <i>HG1</i> | 32 | 21 | 1.74 | 0.01 | 1.70 | 0.02 | 2.05 | 0.01 | |
| <i>HG2</i> | 30 | 30 | 0.99 | 0.97 | 0.99 | 0.97 | 0.95 | 0.86 | |
| <i>HG3</i> | 38 | 49 | 0.66 | 0.05 | 0.67 | 0.06 | 0.71 | 0.26 | |
| Gene Haplotypes | African Americans | | | | | | | | |
| | Haplotype Frequency (%) | | Allelic | | Codominant | | Dominant | | |
| | Cases (n = 54) | Controls (n = 180) | OR | P | OR | P | OR | P | |
| <i>CCR5</i> | | | | | | | | | |
| + <i>PI</i> .+ | 22 | 25 | 0.88 | 0.63 | 0.87 | 0.57 | 0.79 | 0.46 | |
| <i>RANTES</i> | | | | | | | | | |
| <i>H1(G-C-T)</i> | 36 | 40 | 0.86 | 0.50 | 0.83 | 0.46 | 1.00 | 1.00 | |
| <i>H2(A-C-T)</i> | 39 | 44 | 0.82 | 0.38 | 0.87 | 0.46 | 0.70 | 0.25 | |
| <i>H3(A-C-C)</i> | 25 | 17 | 1.67 | 0.05 | 1.63 | 0.06 | 2.12 | 0.02 | |
| <i>IL-10*</i> | (n = 50) | (n = 172) | | | | | | | |
| <i>HG1</i> | 38 | 39 | 0.96 | 0.86 | 0.96 | 0.87 | 0.95 | 0.65 | |
| <i>HG2</i> | 28 | 28 | 0.99 | 0.97 | 0.99 | 0.97 | 1.01 | 0.97 | |
| <i>HG3</i> | 33 | 32 | 1.10 | 0.72 | 1.09 | 0.72 | 1.32 | 0.39 | |

Adjusting the models for square root of nadir CD4⁺ T-cell cell count, highest log₁₀ HIV-1 load, age, and gender does not significantly change the results.

Values in bold are significant at $\alpha = 0.05$.

*HG1, HG2 and HG3 correspond to the combined proximal promoter *IL-10* haplotypes (Fig. 1).

Moreover, IL-10R1 receptor variants may also influence this complication in European Americans. On the other hand, *RANTES* polymorphisms (*RANTES-In1.1C*) and associated haplotypes (H2 and H3) are the main effectors on HIV-NRD development in African American patients.

In this study, we focused on 11 different genes. Using a strict Bonferroni correction, each gene necessitates a P value $\leq 4.5 \times 10^{-3}$ to be considered statistically significant. Moreover, some genes were analyzed for more than 1 SNP (variant) and inferred haplotypes. When all these individual

TABLE 4. Cox Proportional Hazards Analyses for HIV-NRD Development in European American and African American Patients

| Gene/Haplotype | SNP | European Americans | | | | African Americans | | | |
|----------------------|-----------|--------------------|-------------|-----------------------|--------------|-------------------|-------------|-----------------------|--------------|
| | | Events/n | HR | (95% CI) | P | Events/n | HR | (95% CI) | P |
| <i>RANTES-403A</i> | rs2107538 | 48/299 | 0.67 | (0.37 to 1.24) | 0.21 | 49/198 | 1.09 | (0.48 to 2.46) | 0.84 |
| <i>RANTES-28G</i> | rs2280788 | 0/239 | — | — | — | 52/219 | 1.78 | (0.24 to 13.19) | 0.57 |
| <i>RANTES-In1.1C</i> | rs2280789 | 50/329 | 0.53 | (0.26 to 1.10) | 0.09 | 52/218 | 2.56 | (1.40 to 4.68) | 0.002 |
| <i>H1(G-C-T)</i> | | 50/328 | 0.69 | (0.21 to 2.30) | 0.55 | 52/218 | 1.08 | (0.59 to 1.96) | 0.81 |
| <i>H2(A-C-T)</i> | | 50/328 | 1.28 | (0.57 to 2.91) | 0.55 | 52/218 | 0.55 | (0.31 to 0.99) | 0.04 |
| <i>H3(A-C-C)</i> | | 50/328 | 0.56 | (0.27 to 1.16) | 0.11 | 52/218 | 2.72 | (1.48 to 5.00) | 0.001 |
| <i>IL-10-5A'</i> | rs1800872 | 49/330 | 2.07 | (1.18 to 3.63) | 0.01* | 52/219 | 1.28 | (0.72 to 2.27) | 0.40 |
| <i>HG1</i> | | 49/329 | 2.09 | (1.19 to 3.67) | 0.01* | 48/207 | 1.31 | (0.72 to 2.37) | 0.38 |
| <i>HG2</i> | | 49/329 | 0.71 | (0.51 to 1.58) | 0.90 | 48/207 | 0.99 | (0.55 to 1.77) | 0.97 |
| <i>HG3</i> | | 49/329 | 0.76 | (0.42 to 1.36) | 0.35 | 48/207 | 1.33 | (0.73 to 2.40) | 0.35 |

*When each eye is considered separately, *IL-10-5A'* HR = 2.46, $P = 0.0002$; *IL-10* HG1 haplotype HR = 2.44, $P = 0.0002$ in European Americans.

Values in bold are significant at $\alpha = 0.05$.

CI, confidence interval.

tests considered (>100), the expected Bonferroni significance cut-off goes down to roughly $P < 10^{-5}$. None of the P values observed in this study will meet this conservative cut-off value. However, given the linkage disequilibrium pattern around these genes, it is clear that neither the individual SNPs nor the inferred haplotype association tests are independent comparisons. In other words, if we assume all individual SNP and haplotype comparisons as independent and we correct for multiple tests, type 1 error will inflate. Using a gene-based P value cut-off of 4.5×10^{-3} , only the RANTES associations in African Americans would be considered statistically significant. Given the size of the available sample (especially the number of HIV-NRD cases), our limited statistical power is not surprising. When each eye was considered independently, our sample size (nearly) doubled and the observed association list expanded to include variants $+PI.+$ (*CCR5* promoter) haplotype and *SDF-3A'* in European and African Americans, respectively. Overall, IL-10 (and possibly its receptor), RANTES, and SDF associations suggest a potential biological basis for our results.

IL-10 is a key regulatory cytokine involved in a wide spectrum of immune responses, particularly the suppression of T helper type-1 (Th1) immune responses involved in cellular immunity.¹⁸ Variations in the promoter region of *IL-10* affect IL-10 production.^{21,22,24,29,30} Moreover, one of these variants, the low producer *IL-10-5A'* and its associated ATA haplotype (represented by HG1 in this study), has been shown to influence HIV-1 infection and accelerate progression to AIDS^{23,31,32} in European Americans. RANTES, a CC chemokine receptor 5 (*CCR5*) ligand, is a potent inhibitor of HIV-1 cell entry and replication.³³ RANTES variants and haplotypes influence RANTES production and have been shown to affect HIV-1 infection, progression to AIDS, and HAART outcome.^{8,10,34-37} SDF-1 is a natural ligand for CXCR4 receptor and a potent inhibitor of HIV-1 cell entry and replication.³³ The *SDF-3A'* variant is associated with increased SDF production^{38,39} and has also been shown to affect AIDS progression and response to HAART.^{10,40-42} Finally, the significant effects of *CCR5* promoter haplotype variant ($+PI.+$) on AIDS progression and response to HAART are well documented.^{10,12,26} Most of the genetic risk factors for HIV-NRD observed in this study are ones that make a patient more susceptible to AIDS. In other words, the patients who are more susceptible to HIV-NRD development in this study are genetically similar to patients from earlier studies who have increased susceptibility to both faster AIDS progression and HAART failure. However, the *CCR2-64I* and *SDF-3A'* variants have been previously reported to have protective effects against AIDS progression,^{11,39,42} although their effect on AIDS patients' prognosis who received HAART were inconclusive^{12,41,43-45} if not suggesting a negative effect on some reports.^{10,46}

Clearly, interpretations of gene-disease interactions are difficult because of the complexity of these relationships. HIV-NRD is a rare disease with no known etiology; it occurs only in patients with advanced AIDS. Therefore, it is impossible to completely untangle AIDS effects from NRD-specific effects. In addition, there is an inherent survival bias in any study of HIV-NRD; all affected individuals have survived to advanced stages of AIDS and have probably experienced other AIDS-

related illnesses. A possible and simple explanation for the similar genetic associations of HIV-NRD and AIDS progression is that HIV-NRD is present in patients with a worse HIV prognosis. The host genetics may be affecting the severity of the AIDS progression rather than exerting a direct effect on neuroretinal tissue and the development of HIV-NRD.

There are, however, several reasons to suspect that the presence of HIV-NRD may be more complex than a simple indicator of more severe HIV infection. The first comes from comparisons of AIDS-related clinical parameters. CD4⁺ T-cell counts, HIV viral load, and age are the major clinical parameters that influence HIV infection, progression, and response to therapy. Patients with lower CD4⁺ T-cell counts and higher HIV viral loads (or rebounds after therapy) are expected to be more prone to faster HIV progression to AIDS and associated complications. If the sole explanation was that HIV-NRD was a marker for more severe HIV infection, one might expect significant differences between HIV-NRD cases and controls in these clinical parameters even though CD4⁺ T-cell count and HIV viral load comparisons may not be a comprehensive representation of disease severity in a seroprevalent cohort. We did not see significant difference in either of these parameters between HIV-NRD cases and AIDS controls in either European Americans or in African Americans. Moreover, the statistical models were adjusted for these 4 major HIV-related clinical variables, and the genetic associations with HIV-NRD were still evident. However, we do acknowledge that CD4⁺ T-cell count and HIV viral load comparisons may not be a true representation of disease severity in a seroprevalent cohort. Still, the presence of HIV-NRD may be more complex than a simple indicator of more severe HIV infection.

Second, not all of the variants associated with susceptibility and rapid progression to AIDS influenced HIV-NRD significantly, and 2 protective variants (*CCR2-64I* and *SDF-3A'*) that are associated with slower AIDS progression actually "increased" the risk of HIV-NRD. One can speculate that increased proinflammatory signaling could be beneficial from a standpoint of AIDS progression, but that long-term activation of these pathways resulting from a longer chronic stage of HIV-infection could have other detrimental effects including damage to neuronal tissues in the eyes. However, for the moment, this must remain speculative as genetic associations are complicated and need replication and functional follow-up not possible in this particular rare incidence effect cohort.

Finally, neurotoxic effects of HIV infection itself in neural tissues are well documented.⁴⁷ For example, neuropathologies affect up to 40% of adult patients with AIDS,⁴⁸ and autopsy studies have shown a substantial (up to 50%) loss of optic nerve fibers in patients with AIDS.⁴⁹ In the cohort in this genetic study, 18% of the European American patients with HIV-NRD also had an HIV-related neurological disorder, whereas only 8% of the patients without HIV-NRD developed a similar neurological disorder. The fractions of HIV-related neurological complications in African Americans were 12% and 8% for patients with and without HIV-NRD, respectively. Given that only a small fraction of patients with neurological damage from HIV can be diagnosed reliably in patients with AIDS, these fractions could represent an underestimate of ongoing neuronal damage in patients with AIDS in this cohort.

Neuroimmunological studies of patients with AIDS provide information suggesting potential mechanisms of neurodegeneration associated with HIV-1 infection.⁵⁰ Previously, both in vivo and in vitro examinations showed that cytokine expression, especially the TNF leads to myelin and/or membrane damage in optic nerves.^{13–16} IL-10 is a major regulator/suppressor of TNF and other inflammatory cytokines.^{17,18} The association of low IL-10 producer variant in European Americans and increased HIV-NRD risk may be explained in part by an increased immune activity (ie, higher TNF production) leading to an increased damage to the optic neurons. In addition to the damaging cytokines, prostaglandins, proteases, arachidonic acid, and other metabolites, viral gp120, gp41, tat, vpr, and nef proteins can be directly neurotoxic.⁵¹ These neurotoxic viral proteins are produced irrespective of productive HIV infection and can be transported along the neural pathways causing damage at remote sites.⁵² In other words, the cascade of reactions leading to neurotoxicity may be started by relatively small amounts of viral proteins and need not depend on high viral loads or viral reproduction in a cell.⁵³ HIV-1 infection of nervous system, and therefore the potential start of destructive lesions in neural tissues, occurs at an early stage, well before HAART typically is begun. Hence, the presence of these neuronal complications in the HAART era, despite substantially more effective therapies, improved CD4⁺ T-cell counts, and decreased HIV loads, may not be surprising.

Another crucial observation is the presence of HIV coreceptors CCR5 and CXCR4 in neurons.^{54,55} Studies suggest an important role for gp120-activated CXCR4 and CCR5 in HIV-associated neuronal damage.^{56,57} It has been shown that the CCR5 ligand, RANTES, can protect neurons against gp 120-induced toxicity,^{51,56,57} whereas SDF-1 can induce toxicity and trigger neuronal death in a CXCR4-dependent manner.^{51,56,57} These reports suggest a biological basis for the increased HIV-NRD risk in African Americans associated with low RANTES and high SDF producing variants and may also explain the opposite effect of SDF-3A' on AIDS (protective) vs. HIV-NRD (susceptible). We observed different gene variants to be associated with HIV-NRD in African Americans and European Americans. This may be due to allele frequency differences between the 2 ethnic groups, genetic heterogeneity in African Americans or other clinical and/or social factors that we cannot account for in this study.

In conclusion, some host genetic risk factors that influence AIDS progression, response to HAART, and overall immune health, seem to affect ocular health in HIV-infected patients. Our results suggest a role for the IL-10 pathway in European Americans and for the chemokine ligands, RANTES and SDF-1, in African Americans leading to damage to retina and/or optic nerve. It will be interesting to study a cohort of patients who develop HIV-NRD independent of AIDS to test if the observed associations are specific for HIV-NRD.

ACKNOWLEDGMENTS

We thank the patients and staff of all the participating centers in the study. We are also grateful to Michael Malasky, Mary Thompson, Bailey Kessing, Christiana Martin, Nick

Edler, Nicole Shifflett, Katy Limpert, Natalie Baggett, Kelly Subramanian and Alyssa Drosdak for their assistance. Finally, we acknowledge the constructive criticism from 2 reviewers who helped in the final version of the article. The content of this publication neither does necessarily reflect the views or policies of the Department of Health and Human Services, nor does any mention of trade names, commercial products, or organizations imply endorsement by the U.S. government (see acknowledgements for LSOCA Clinical Centers Credit Roster; **Supplemental Digital Content 8**, <http://links.lww.com/QAI/A61>).

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