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Association of Host Genetic Risk Factors with the Course of Cytomegalovirus Retinitis in Patients Infected with HIV

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Abstract

Purpose—To evaluate the effects of previously reported host genetics factors that influence cytomegalovirus (CMV) retinitis incidence, progression to AIDS, and efficacy of highly active antiretroviral therapy (HAART) for mortality, retinitis progression, and retinal detachment in patients with CMV retinitis and AIDS in the era of HAART.

Design—Prospective, multicenter, observational study.

Methods—Cox proportional hazards model based genetic association tests examined the influence of *IL-10R1_S420L*, *CCR5Δ32*, *CCR2-V64I*, *CCR5 P1*, and *SDF-3'A* polymorphisms among patients with mortality, retinitis progression, and retinal detachment. Participants were 203 European American and 117 African American patients with AIDS and CMV retinitis.

Results—European American patients with the *CCR5 +.P1.* promoter haplotype showed increased risk for mortality (HR=1.83; 95% CI: 1.00–3.40; P=0.05). Although the same haplotype also trended for increased risk for mortality in African American patients, the result was not significant (HR=2.28; 95% CI: 0.93–5.60; P=0.07). However, this haplotype was associated with faster retinitis progression in African Americans (HR=5.22; 95% CI: 1.54–17.71; P=0.007). Increased risk of retinitis progression was also evident for African American patients with the *SDF1-3'A* variant (HR=3.89; 95% CI: 1.42–10.60; P=0.008). In addition, the *SDF1-3'A* variant increased the retinal detachment risk in this patient group (HR=3.05; 95% CI: 1.01–9.16; P=0.05).

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None of the authors have conflict of interest with any aspect of this study.

Conclusion—Besides overall immune health, host genetic factors influence mortality, retinitis progression, and retinal detachment in patients with AIDS and CMV retinitis that are receiving HAART.

Introduction

Cytomegalovirus (CMV), a common opportunistic pathogen in patients with acquired immune deficiency syndrome (AIDS), leads to the end stage organ disease CMV retinitis that causes substantial ocular morbidity.^{1–7} The incidence of CMV retinitis has declined to 10–20% of its incidence before the availability of highly active antiretroviral therapy (HAART). However, the decline in CMV retinitis incidence and related mortality has leveled off and CMV retinitis continues to be the major cause of visual impairment and blindness in the era of HAART.^{8–13} Immune recovery does not control retinitis in all patients.^{14–18} A recent five-year follow-up of patients with AIDS and CMV retinitis showed that these patients also remain at risk for mortality, retinitis progression, visual impairment, and blindness even after immune recovery.¹⁹ Therefore the need to assess additional risk factors remains, such as host genetics, for CMV retinitis related outcomes in patients with AIDS.

Host genetics have been shown to influence significantly HIV infection and progression to AIDS outcomes, and to contribute to the heterogeneity of response to antiretroviral therapy.^{20–21} Of the examined host genes, polymorphisms in the chemokine receptors (HIV co-receptors) and their ligands have been shown to extend their pre-treatment protective or susceptible roles to a post-HAART influence. The chemokine receptor 5 (CCR5) plays a key role in HIV cell entry. A 32 base-pair deletion in the coding sequence of CCR5 (*CCR5-Δ32*) results in a truncated, functionless protein that is protective against HIV infection,²² progression to AIDS outcomes,²² and has a positive effect on HAART outcome.^{21–23–25} Similarly, a valine to isoleucine amino acid change in a neighboring chemokine receptor, the chemokine receptor 2, (*CCR2-V64I*) slows down progression to AIDS,²⁶ though without strong influence in post-HAART studies.^{23–25–27–29} On the other hand, genetic acceleration to AIDS and delayed HIV viral suppression on HAART have been associated with a promoter haplotype (+.PI.+) of *CCR5*.³⁰ Stromal cell-derived factor (SDF-1, also known as CXCL12) is the principal ligand for the chemokine receptor CXCR4, another co-receptor for HIV-1 strains. An untranslated region (UTR) polymorphism *SDF-1 3'G>A* (*SDF-1 3'A*) that may be involved in SDF-1 mRNA stability³¹ also influences the course of AIDS progression and HAART response.^{23–32–33}

Host genetics in the AIDS epidemic not only modulates HIV dynamics, but also modulates susceptibility to other opportunistic infections, such as CMV. The CMV genome contains a human interleukin-10 homolog³⁴ that CMV uses to evade the human immune system.³⁵ Recently, an amino acid changing mutation (S420L) in the cytoplasmic domain of interleukin-10 receptor (IL-10R1) has been shown to be protective against CMV retinitis incidence in patients with AIDS.³⁶ However, the role of this IL-10R1 mutation has not been investigated on CMV retinitis-related ocular outcomes.

For this manuscript we examined the roles of *CCR5-Δ32*, *CCR2-V64I*, *CCR5 P1*, *SDF1-3'A*, and *IL-10R1_S420L* variants on mortality, retinitis progression, and retinal detachment during a five year follow-up among European American and African American patients with CMV retinitis and AIDS enrolled in Longitudinal Study of the Ocular Complications of AIDS (LSOCA) cohort.

Patients and Methods

Study population and clinical assessment of CMV retinitis outcomes

Study patients included CMV retinitis diagnosed European American (n=203) and African American (n=117) individuals (race self reported) enrolled in the LSOCA prospective observational cohort between September 1998 and December 2008. All patients were diagnosed with AIDS according to the 1993 Centers for Disease Control and Prevention surveillance case definition for AIDS. Further details of the LSOCA cohort and enrollment design have been published previously.¹¹⁻³⁷ 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.

Detailed medical history, nadir CD4+T-cell count (lowest count prior to enrollment), plasma HIV RNA, and antiretroviral therapy were recorded for each patient at enrollment. Participants were seen every three months for follow-up. A complete ophthalmologic examination was performed at each visit. Cytomegalovirus retinitis was diagnosed by study-certified ophthalmologists with expertise in AIDS.¹⁴ Retinitis progression was graded at the Reading Center, as described previously, and defined as a) the movement of a border of a CMV lesion at least ½ standard disc diameter along a front ½ disc diameter in size or b) the occurrence of a new lesion $\geq$ ¼ disc area in size.^{5, 11} Retinal detachments were diagnosed clinically.

Genotyping of Single Nucleotide Polymorphisms (SNPs)

Previously identified functional polymorphisms rs2229114, rs333, rs1799864, rs1799988, and rs1801157 were genotyped for *IL-10R1_S420L*, *CCR5Δ32*, *CCR2-V64I*, *CCR5 P1* (*CCR5_59353C*), and *SDF1-3'A* mutations, respectively. All SNPs were genotyped with the ABI-TaqMan method (Applied Biosystems, Foster City, CA, USA). Although overall genotyping success rate was over 95%, a few samples (n=9) failed genotyping and they were omitted from SNP-based association analyses. The presence of *CCR5_59353C* (rs1799988) in the absence of *CCR2-V64I* and *CCR5Δ32* defines the *CCR5 P1* promoter haplotype +.P1.+³⁰ All haplotypes are inferred by the expectation maximization algorithm with SAS Genetics (SAS Institute, Cary, NC, USA).

Statistical Analyses

Each SNP and haplotype found at $\geq$ 1% frequency in the study population was evaluated for mortality, retinitis progression, and retinal detachment. The dominant model analyzed genotypes as absence or presence of the rare alleles. The recessive model analyzed the homozygous rare allele genotypes against the others. The outcome of retinitis progression was determined by the occurrence in either eye and analyzed as patient-related event. All hazard ratios and associated P-values were calculated with Cox proportional hazards regression models, accounting for the correlation between eyes when necessary.³⁸ For comparisons between groups of eye-related events (i.e., retinal detachment), P-values were adjusted for the correlation between eyes. All Cox proportional hazard models were adjusted for log₁₀HIV-1 viral load, CD4+ T-cell count, HAART, age, gender, and patient group. Patient groups were defined and coded as: 1-Previously-diagnosed and immune-recovered (CD4+ T-cell count $\geq$ 100 cells/ μ L), 2-Previously-diagnosed and immune-compromised (CD4+ T-cell count < 100 cells/ μ L), or 3- Newly-diagnosed (CMV retinitis diagnosed $\leq$ 45 days prior to study enrollment or diagnosed during follow-up). HAART use refers to those on HAART at enrollment. All analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC, USA). Nominal P-values were reported throughout the manuscript.

Results

Clinical Characteristics of the Study Groups

The male gender fraction, age, CD4+ T-cell count, HIV viral load, and HAART use were significantly different ($P=0.01-0.001$) between European Americans ($n=203$) and African Americans ($n=117$; Table 1). The fraction of immune-recovered patients was higher in European Americans (50%) compared to African Americans (32%). A higher fraction of African Americans were diagnosed at study entry (39% vs. 27%). Patients from each group with previously diagnosed CMV retinitis had long-standing disease with median times of 1198 days (interquartile range 1437 to 919; European Americans) and 925 days (interquartile range 1334 to 539; African Americans) for those with immune-recovery. The median time from diagnosis of CMV retinitis to study enrollment for European American and African American patients with persistent immune compromise was 497 days (interquartile range 1476 to 177) and 630 days (interquartile range 1242 to 198), respectively.

In European American patients with immune recovery, the median CD4+ T-cell count was 299 (interquartile range 447 to 191), whereas for the immune-compromised group it was 21 (interquartile range 53 to 10). The median $\log_{10}$ HIV viral loads were 2.60 (interquartile range 3.41 to 1.70) and 5.05 (interquartile range 5.63 to 4.19) for the immune-recovered and immune-compromised group, respectively. African American patients with immune recovery had a median CD4+ T-cell count of 273 (interquartile range 396 to 170), whereas the immune-compromised group had a count of 26 (interquartile range 77 to 7). The median $\log_{10}$ HIV viral loads were 3.22 (interquartile range 4.69 to 1.70) and 4.95 (interquartile range 5.60 to 3.34) for the immune-recovered and immune-compromised group, respectively among the African American patients.

Due to significant clinical variable differences between European American and African American patients, and between patient groups with persistent immune compromise and immune recovery, genetic association models were adjusted for HIV-1 viral load, CD4+ T-cell count, HAART, age, gender, and patient group.

Genetic Association Analyses in European American Patients

Patients with the *CCR5* +*PI*.+ promoter haplotype progressed to death faster than patients without this haplotype, suggesting increased susceptibility for mortality (HR=1.83; 95% CI: 1.00–3.40; $P=0.05$; Table 2). However, this haplotype did not have a significant effect on retinitis progression or retinal detachment (Table 2). None of the other examined gene variants had a significant influence on mortality, retinitis progression, or retinal detachment.

Being immune-compromised (HR=4.0; 95% CI: 1.23–12.74; $P=0.02$) and having a high HIV viral load (HR=1.49; 95% CI: 1.15–1.93; $P=0.003$) were the biggest risk factors for mortality. We checked whether the +*PI*.+ haplotype was overrepresented in the immune-compromised group thereby biasing the genetic association results. The frequency of +*PI*.+ haplotype was not significantly different compared to other promoter haplotypes between the patient groups with immune recovery and with immune-compromise (22% vs. 25%; $P=0.57$; Supplemental Table 1) but was 19% higher in the newly diagnosed CMV retinitis group (Supplemental Table 1). However, the HIV viral load of patients with the +*PI*.+ haplotype was slightly higher than patients that did not have this haplotype (3.89 vs. 3.23; $P=0.004$; Supplemental Table 1).

The distribution of other examined gene variants between the immune-recovered, immune-compromised, and newly diagnosed groups was not significantly different (all P -values >

0.4). Moreover, carrying either one of these variants did not have a significant effect on the HIV viral load (Supplemental Table 1).

Genetic Association Analyses in African American Patients

African American patients with the *+.P1.+ CCR5* promoter haplotype showed a trend towards faster progression to death than African American patients without this haplotype (HR=2.28; 95% CI: 0.93–5.60; P=0.07; Table 2). Moreover, patients with this haplotype showed increased risk for retinitis progression (HR=5.22; 95% CI: 1.54–17.71; P=0.007; Table 2; Figure 1). Increased risk of retinitis progression was also evident for patients with the *SDF1-3'A* variant (HR=3.89; 95% CI: 1.42–10.60; P=0.008; Table 2; Figure 1). Also, the *SDF1-3'A* variant increased the retinal detachment risk (HR=3.05; 95% CI: 1.01–9.16; P=0.05; Table 2).

Increased HIV viral load (HR=1.56; 95% CI: 1.18–2.06; P=0.002) and decreased CD4+T-cell count (HR=1.14; 95% CI: 1.02–1.25; P=0.02) adversely influenced mortality rate. Faster retinitis progression was seen in patients with increased HIV viral load (HR=1.37; 95% CI: 1.05–1.79; P=0.02). Although the patients with *+.P1.+* promoter haplotype and *SDF1-3'A* variant had lower CD4+T-cell counts and higher HIV viral loads compared to other patients, the differences were not statistically significant (all P-values > 0.1; Supplemental Table 2). The distributions of examined gene variants among the immune-recovered, immune-compromised, and newly diagnosed groups were not significantly different (all P-values > 0.2). Also, none of the examined variants had a significant effect on HIV viral loads or on CD4+ T-cell counts (all P-values > 0.5; Supplemental Table 2).

Discussion

We investigated the effects of gene variants, which have previously been shown to influence progression to AIDS outcomes, therapy efficacy, and CMV retinitis development, on the course of ocular complications in AIDS patients with CMV retinitis. Our results suggest that the *CCR5 +.P.+* promoter haplotype increases risk for mortality in European American patients. Moreover, this haplotype influences retinitis progression in African Americans. We also observed that African American patients with the *SDF1-3'A* variant were at increased risk for both retinitis progression and retinal detachment.

Our study has both strengths and weaknesses. First, we acknowledge that our sample size is not large. However, this is the largest cohort unbiased by race, gender, or HIV exposure available that can investigate the CMV retinitis outcomes. Second, we examined five genes and conducted multiple tests, which requires a correction for multiple tests. A strict Bonferroni filtering accepts only the P-value less than 0.01 to be statistically significant. Therefore, some of our results should be interpreted cautiously. However, the increased risk associated with *CCR5* and *SDF1* variants and multiple outcomes is highly suggestive of a biological role for these variants that deserves further attention.

The *CCR5 +.P.+* promoter haplotype is associated with rapid progression to AIDS, particularly in the early years after infection, in treatment-naïve European and African descent patients.^{30, 39} However, a negative effect of the *CCR5* promoter haplotype on viral suppression and CD4+ T-cell response to HAART also has been reported.^{23, 25} We also observed increased HIV viral load and decreased CD4+ T-cell trends associated with this promoter haplotype in both ethnic groups, though the trends were not always statistically significant. These observations may suggest that patients with the *CCR5* promoter haplotype are more susceptible to worse AIDS prognosis and cannot benefit as effectively from HAART compared to patients that do not have this promoter haplotype.

The role of *SDF1-3'A* in AIDS progression is complex. Both slower and faster progressions to AIDS have been reported with *SDF1-3'A* in pre-HAART cohorts.^{33, 40, 41} The influence of *SDF1-3'A* is increasingly pronounced in later stages of HIV-1 infection, a stage where SDF-1 is proposed to be involved in the transition from HIV-1 R5 to the more pathogenic HIV-1 X4 strains, leading to fast CD4 lymphocyte depletion.⁴² In most patients, this period coincides with initiation of HAART. Studies of patients on HAART suggested delayed HIV viral suppression and CD4+ T-cell response associated with *SDF1-3'A*.^{23, 32} however not without contradicting reports.^{27, 28} We observed a negative effect of this variant on retinitis progression and retinal detachment in African Americans. In this patient group, lower CD4+ T-cell count and increased HIV viral load were risk factors for faster retinitis progression, but *SDF1-3'A* did not have a significant effect on these clinical variables. Either we did not have enough statistical power to detect significant effect of SDF-1 on CD4+ T-cell and HIV viral load levels due to small sample size in this cohort, or SDF-1 has an alternative negative influence on the retina during CMV infection.

Overall immune health, characterized by CD4+ T-cell levels and HIV viral load, have been suggested as the primary risk factors for increased mortality, retinitis progression, visual impairment, and blindness in patients with CMV retinitis and AIDS who are on HAART (Jabs et al. accepted). *CCR5* and *SDF1* variants have been shown previously shown, and have trended in this study to influence CD4+ T-cell recovery and viral suppression in AIDS patients receiving HAART. Possibly these variants are genetic risk factors for worse prognosis in patients with CMV retinitis by modulating overall immune health. However, the effects of *CCR5* and *SDF1* variants were still evident even after accounting for CD4+ T-cell levels, HIV viral load, and immune status in the genetic association models. This suggests that the interaction between genetic factors and CMV retinitis outcomes may be more complex than a simple indicator of more severe HIV infection.

CMV produces a human immunosuppressive cytokine (interleukin-10) homolog^{34, 43} and interferes with the recruitment of inflammatory and natural killer cells.⁴⁴ Therefore it is an immunosuppressive infectious agent. Moreover, CMV can activate HIV latent provirus,⁴⁵ alter the tropism of HIV,⁴⁶ encode an alternative receptor for HIV,⁴⁷ and act as a cofactor enhancing progression of AIDS even in the era of HAART.^{10, 48} Yet, a recent observation showed that CMV- infected cells can secrete soluble factors that are able to increase CCR5 surface expression on uninfected bystander cells.⁴⁹ One can speculate that the *CCR5 +.p1.* + promoter haplotype associated with increased CCR5 expression may be upregulated further due to CMV activation, making immune cells more susceptible to HIV-1 infection. Clearly, further studies are warranted to understand the interactions between host genetics and HIV and CMV co-infections in the pathogenesis of AIDS.

In addition to its role in HIV infection and AIDS progression, stromal cell-derived factor-1 (SDF-1) is expressed constitutively in a broad range of tissues and is a chemoattractant for monocytes, naïve and memory T lymphocytes, and B lymphocytes.^{50–52} It also plays a crucial role in angiogenesis.⁵³ A damaging role of SDF-1 in recruitment of leucocytes into the eye in sympathetic ophthalmia,⁵⁴ pathogenic angiogenesis in ischemic retinal tissue,⁵⁵ and in other models of (auto)inflammatory⁵⁶ and neovascularization complications have been suggested.^{57–59} Based on these reports, the *SDF1-3'A* variant may worsen the course of pathological lesions in the retina that are initiated by CMV activation.

In conclusion, host genetic variation in chemokines and their receptors may continue to influence HIV infection progression even in patients who are on HAART and may affect retinitis progression, retinal detachment, and mortality in patients with CMV retinitis and AIDS. The statistical power of association tests in this study were limited by the small sample size (particularly, the events) in each ethnic group. Further studies with more

patients may uncover other gene variants that affect the examined ocular outcomes and may elucidate the contribution of these variants on the overall immune health and local (retinal) pathophysiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Kaplan-Meier plots comparing retinitis progression among Cytomegalovirus Retinitis diagnosed African American LSOCA patients with *CCR5* +.p1.+ promoter haplotype (Left) and *SDF1*-3'A variant against other genotypes (Right).

Table 1

Clinical aspects of European American and African American LSOCA patients followed for the course of Cytomegalovirus Retinitis used in this study

Variable	European Americans (n=203)		African Americans (n=117)	
	Mean±SD	Median (25 th %, 75 th %-tile)	Mean±SD	Median (25 th %, 75 th %-tile)
Male gender (%) ^a	92.1		64.1	
Age (yrs) ^a	42.2±7.2	41.0 (37,47)	38.9±8.1	38.0 (34,44)
CD4+ T-cell count (cells/μL) ^a	192±202	114 (307,20)	131±154	66 (187,17)
Baseline HIV viral load (log ₁₀ copies/mL) ^a	3.7±1.5	3.7 (5.1,2.3)	4.1±1.5	4.7 (5.3,5.9)
HAART use (%) ^a	80.4		68.4	
Time since CMV retinitis diagnosis(days) ^b	1113±718	1104 (610, 1456)	912±672	833 (338, 1244)
<u>Outcomes (%)</u>				
Mortality	47.7		55.6	
Retinitis progression	27.3		28.2	
Retinal detachment	13.0		11.2	
<u>Patient group (%)^c</u>				
1	49.5		31.6	
2	23.5		29.1	
3	27.0		39.3	
<u>Genetic variants (%)^d</u>				
<i>IL-10R1_S420L</i>	4.1		3.7	
<i>CCR5-delta32</i>	15.2		2.8	
<i>CCR2-V64I</i>	14.1		19.1	
<i>CCR5 +.PI.+</i>	63.4		47.2	
<i>SDF1-3'A</i>	36.3		10.2	

^aSignificantly different between European Americans and African Americans ($P < 0.01$)

^bTime from diagnosis of CMV retinitis to study enrollment

^cPatient groups: 1-Previously-diagnosed and immune-recovered (CD4+ T-cell count ≥ 100 cells/μL), 2- Previously-diagnosed and immune-compromised (CD4+ T-cell count < 100 cells/μL), 3- Newly-diagnosed (CMV retinitis diagnosed ≤ 45 days prior to study enrollment or diagnosed during follow-up)

^dMinor allele frequencies of examined genes. *CCR5 +.PI.+* represents the *CCR5* promoter haplotype (presence of *CCR5_59353C* promoter polymorphism in the absence of *CCR5-delta32* and *CCR2-V64I*)

Table 2

Association tests of examined host genetic factors with Mortality, Retinitis Progression, and Retinal Detachment outcomes among European American and African American patients with Cytomegalovirus Retinitis

Outcome	European Americans						African Americans					
	<i>IL-10R1</i> <i>S420L</i>	<i>CCR5</i> <i>Delta-32</i>	<i>CCR2</i> <i>V64I</i>	<i>CCR5</i> <i>promoter</i>	<i>SDF1</i> <i>3'A</i>		<i>IL-10R1</i> <i>S420L</i>	<i>CCR5</i> <i>Delta-32</i>	<i>CCR2</i> <i>V64I</i>	<i>CCR5</i> <i>promoter</i>	<i>SDF1</i> <i>3'A</i>	
Mortality												
n/events ^a	145/68	145/68	135/55	145/68	142/61		72/38	72/38	72/38	73/38	73/38	
HR	0.32	1.21	1.06	1.83	0.91		0.22	1.01	1.17	2.28	1.54	
95% CI	0.04–2.35	0.61–2.40	0.52–2.17	1.00–3.40	0.52–1.59		0.02–2.03	0.13–7.61	0.52–2.64	0.93–5.60	0.70–4.43	
P-value	0.26	0.59	0.87	0.05	0.73		0.18	0.99	0.70	0.07^b	0.29	
Retinitis Progression												
n/events ^a	168/48	159/42	159/42	168/48	166/46		83/24	84/25	84/25	84/25	84/25	
HR	0.74	0.73	1.21	1.31	1.01		^c	6.68	0.47	5.22	3.89	
95% CI	0.18–3.05	0.34–1.58	0.50–2.93	0.6–2.60	0.54–1.89		-	0.73–60.1	0.11–2.12	1.54–17.71	1.42–10.60	
P-value	0.67	0.42	0.67	0.44	0.97		-	0.10	0.33	0.007^b	0.008	
Retinal Detachment												
n/events ^a	218/25	218/25	205/23	218/25	217/25		117/14	117/14	117/14	117/14	117/14	
HR	1.83	0.51	1.49	0.78	1.17		6.06	^c	0.69	1.11	3.05	
95% CI	0.38–8.89	0.14–1.87	0.53–4.19	0.36–1.69	0.56–2.45		0.81–45.15	-	0.12–3.99	0.14–8.50	1.01–9.16	
P-value	0.45	0.31	0.55	0.53	0.67		0.08	-	0.68	0.92	0.05	

All Cox proportional hazard models are adjusted for log10HIV-1 viral load, CD4+ T-cell count, HAART, age, gender and patient group. Dominant model association results are presented unless otherwise stated. *CCR5* promoter represents the +.PI.+ haplotype.

^aFor mortality and retinitis progression, “n” represents the number of individuals analyzed and “events” represent occurrences counted once per individual; for retinal detachment “n” represents the number of eyes analyzed and “events” represent occurrences counted per eye.

^bRecessive model results reported. Dominant model HR=1.28 (0.68–2.45), P=0.45 for mortality; HR=1.29 (0.57–2.92), P=0.54 for retinitis progression.

^cAssociation tests could not be conducted because patients with the variant allele and necessary clinical data did not have any events.