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Association of Complement Factor H Y402H Genotype with Posterior Involvement in Sarcoid-related Uveitis

Ian A. Thompson[1], **Baoying Liu**[1], **H. Nida Sen**[1], **Xiadong Jiao**[2], **Robert Katamay**[1], **Zhiyu Li**[1], **Mengjun Hu**[1], **Fielding Hejtmancik**[2], and **Robert B. Nussenblatt**[1]

[1]Laboratory of Immunology National Eye Institute National Institutes of Health Bethesda, MD 20892

[2]Ophthalmic Genetics and Visual Function Branch National Eye Institute National Institutes of Health Bethesda, MD 20892

Abstract

Purpose—To determine whether the complement factor H (CFH) Y402H variant, recently shown to be associated with age-related macular degeneration (AMD) and multifocal choroiditis, is associated with specific ocular sarcoidosis clinical phenotypes in Blacks and Whites.

Design—Case-control Study

Methods—The *CFH* Y402H polymorphism (rs1061170) was genotyped in 41 subjects with ocular sarcoidosis and 393 control subjects. Allele frequencies in the ocular sarcoidosis cases were compared with controls using χ^2 score tests. Genotypic model-based (dominant, recessive, and additive) associations of the rs1061170 allele were tested using multivariate logistic regression. Bayesian Information Criteria was used to formalize model selection. Genotypes were correlated with disease characteristics and severity of ocular inflammation.

Results—The C allele (rs1061170) was found in 35% of controls, but occurred with a significantly higher frequency (48.7%) in ocular sarcoidosis cases (OR = 1.72, 95% confidence interval [CI], 1.09 to 2.78, p =0.018). Logistic regression demonstrated an association between

[1]Correspondence and requests for reprint should be addressed to Laboratory of Immunology, Building 10, Room 10N112, 10 Center Drive, Bethesda, MD 20892 (Tel: 301-496-3123, Fax: 301-480-1122, (drbob@nei.nih.gov). .
Ian A. Thompson iat7med@gmail.com
Baoying Liu liuba@nei.nih.gov
H. Nida Sen senh@mail.nih.gov
Xiadong Jiao jiaox@nei.nih.gov
Robert Katamay robert@katamay.ch
Zhiyu Li lizhi@mail.nih.gov
Mengjun Hu jean.hu@gmail.com
J. Fielding Hejtmancik f3h@helix.nih.gov
Ian A. Thompson, is a fellow in the Clinical Research Training Program at the National Institute of Health. He received his Bachelors degree in Economics from Harvard University. He will receive his medical degree and masters of public health in epidemiology from Case Western Reserve School of medicine in 2013.

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rs1061170 and ocular sarcoidosis under two out of three genetic models (additive: p = 0.0078; recessive: p = 0.0018). Posterior and pan-uveitis were significantly over-represented in cases with the homozygous variant genotype (CC, 91%, p = 0.047). The population attributable risk related to this CFH risk variant was 20%.

Conclusion—The Tyr402His polymorphism of CFH appears to be associated with ocular sarcoidosis in Blacks and Whites. Carriage of the CFH Y402H polymorphism in both alleles is associated with an increased risk for posterior and pan-uveitis presentation. The prognostic importance of this genotype will require prolonged follow-up studies.

INTRODUCTION

Sarcoidosis is a systemic inflammatory disease characterized by the presence of noncaseating granulomas in multiple organ tissues. Ocular manifestations have been described in 25-60% of sarcoidosis patients,[1] are the initial presenting sign in 10-20% of patients,[2,3] and are responsible for 3- 8% of all uveitis cases.[4] The pathogenesis of sarcoidosis is not fully known, but familial clustering,[5] racial variation, clinical heterogeneity, and genetic studies support the likelihood that the disorder is triggered by unidentified antigenic exposures in genetically susceptible hosts.

Recent investigations suggest age-related macular degeneration [AMD], a degenerative disorder of diseased retinal pigment epithelium [RPE], may result from dysregulation of the local inflammatory response in which complement may play an inciting role.[6] Factor H is a serum glycoprotein that down-regulates complement activation. The Tyr402His (Y402H) single nucleotide polymorphism [SNP], a coding variant of the Complement Factor H [CFH] gene (the C allele of rs1061170), is the most significant known contributor to AMD disease risk.[7-10]

CFH polymorphisms occur in a variety of immune mediated diseases including glomerulonephritis,[11] atypical hemolytic uremic syndrome (aHUS),[12] Alzheimer (in ApoE4 risk allele carriers)[13], artherosclerosis[14], and lupus.[15] Recently, it has been shown that multifocal choroiditis, an ocular inflammatory disease of unknown origin, and AMD share the same Y402H high-risk polymorphism.[16] Ocular sarcoidosis, like multifocal choroiditis and AMD, can affect the RPE and the choroid. Additionally, ocular sarcoidosis and AMD share alterations in monocyte and macrophage function.[17-20] We aimed to evaluate whether these shared clinical features suggest a common genetic basis for disease. We employed a candidate gene approach to investigate the association between the complement factor h SNP Y402H and ocular sarcoidosis.

MATERIALS AND METHODS

Subjects

This case-control study was approved by the Neuroscience Institutional Review Board of the National Institute of Health and conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients. The ocular sarcoidosis cohort consisted of 41 consecutive patients recruited in the National Eye Institute Clinic (mean age, 50.4 years; male-to-female ratio, 42%:58%) during a 26 month period (from July 2009 to

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September 2011). The control cohort included 393 sarcoidosis-free subjects. Ninety-one control samples were from persons seen in the National Eye Institute Clinic with non sarcoidosis-related diagnoses of uveitis. Three hundred and two control samples were collected from volunteers with no self-reported personal history of sarcoidosis or uveitis at the NIH Blood Bank and American Red Cross Blood Services.

All cases had undergone an extensive systemic evaluation, followed by complete ophthalmic examination prior to their enrollment in the study. Uveitis was categorized according to the anatomic location of the inflammatory process as defined by the Standardization of Uveitis Nomenclature (SUN) criteria.[21] Ocular sarcoidosis was defined as *definitive* in patients with positive histopathological examination of biopsy tissue in the presence of "compatible" uveitis. Ocular sarcoidosis cases were considered *presumed* in patients presenting with any of the following 7 ocular signs (Mutton-fat keratic precipitates, trabecular meshwork and/or peripheral anterior synechiae, snowball vitreous opacities, chorioretinal peripheral lesions, nodular periphlebitis, retinal macroaneurism, optic disc nodules/granulomas, bilaterality of ocular inflammation) in the presence of radiographic bilateral hilar lymphadenopathy (supported by X-ray or CT scan) and one positive laboratory finding (elevated angiotensin-converting enzyme or elevated serum lysozyme level).[2]

Genomic DNA extraction from whole blood

Genomic DNA was extracted from the peripheral blood of each individual using a DNA extraction and purification kit (Qiagen Blood DNA Mini Kit, Valencia, CA, USA), according to the manufacturer's instructions. DNA was stored at minus 80°C until PCR analyses.

Single Nucleotide Polymorphism Genotyping

The *CFH* gene was amplified by polymerase chain reaction. Genotyping was carried out by directional sequencing using Big Dye Terminator Ready reaction mix according to manufacturer instructions (Applied Biosystems, Foster City, CA). Sequencing was performed on an ABI PRISM 3130xl Genetic Analyzer (Applied Biosystems). Sequence traces were analyzed using Mutation Surveyor (Soft Genetics Inc., State College, PA, USA) and the Seqman program of DNASTAR Software (DNASTAR Inc., Madison, WI, USA).

Statistical analyses

All data were analyzed using Golden Helix SVS software suite 7 (Golden Helix, Bozeman, MT, U.S.A.), Excel 2011 (Microsoft, Redmond, WA, U.S.A.), and Graphpad Prism (Graphpad Software, San Diego, CA, U.S.A.). Demographic characteristics of the study population were compared using χ^2 tests. Deviations of the genotype distribution from Hardy-Weinberg equilibrium [HWE] were assessed with the HWE exact test. Allele frequencies were compared between patients and controls using Pearson's χ^2 test for independence. The CFH variant adjusted odds ratio (OR) and corresponding 95% confidence interval (CI) was determined in multivariate logistic regression models that included *Sex*, *Race*, and a *CFH**Race* interaction term. We examined 3 potential genetic models: dominant, recessive, and additive. Correction for multiple comparisons was carried out using a Bonferroni adjustment. We computed the log likelihood (LL, probability of the

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observed results given the parameter estimates) for an initial constrained model in which only the constant was included. This was used as the baseline against which our full models were assessed. The difference between the −2LL of our full and constrained model (the Likelihood ratio) has a chi-square distribution with degrees of freedom equal to the difference in the number of parameters between the two competing models. To determine the best-fitting genetic model, we used Bayesian Information Criterion (BIC).[22] The BIC for any model is equal to −2LL + Ln(sample size)*(number of estimated parameters). We used the BIC to compare all models, and to select the best-fitting genetic model. Patients were grouped by genotype according to the genetic model with the lowest value of the BIC (the most parsimonious of the best-fitting models) and compared for disease characteristics and severity using one way ANOVA and Freeman-Halton extensions of Fisher exact tests. Population attributable risk, which is the reduction in prevalence that would be observed if the risk allele were completely removed from the current population, was calculated using the formula (P(OR-1)/[P(OR-1)+1]) × 100, where P is the prevalence of ocular sarcoidosis in the study population exposed to the risk variant, and OR is the odds ratio.

RESULTS

Baseline Characteristics of Study Participants

A total of 434 subjects were enrolled in this study, including 41 patients with ocular sarcoidosis and 393 sarcoidosis-free control individuals. Sixty-three percent (26/41) of the ocular sarcoidosis cases were biopsy proven and therefore considered “definitive”. There was no statistically significant difference in mean age or gender between the ocular sarcoidosis cases and the control cohort. The percentage of Black cases was significantly different from the percentage of Black controls (p = 0.001).

Complement Factor H Allele Distribution

The frequency of the C allele of rs1061170 (Y402H) in each race is summarized in Table 1. The difference between the C allele frequency (rs1061170 or Y402H) in Black and White Controls did not show statistical significance (p = 0.5). These allele frequencies were consistent with prior published studies.[7-10,23]

Case-Control Analysis: Main Effect

The genotyping data of rs1061170 on chromosome 1q31 did not show any significant deviations from Hardy-Weinberg equilibrium tests in each group (HWE p-value for cases = 0.492, HWE p-value for controls = 0.439). Rs1061170 was found to be significantly associated with ocular sarcoidosis (OR=1.72, 95% CI, 1.09 - 2.78, p = 0.018) (Table 2). This corresponded to a population attributable risk fraction of 20% (formula provided in Materials and Methods Section).

Models of Inheritance: Genotype-based Association Tests

The genotype-specific associations of the CFH-variant with ocular sarcoidosis are summarized in Table 3. Rs1061170 remained significantly associated with ocular sarcoidosis in an additive model and a recessive model [p (genotypic) = 0.008 and 0.002 respectively] but not in a dominant model [p (genotypic) = 0.217]. The data were best fit by

an additive model (Additive: BIC = 269.619, $\chi^2 = 20.04$, df = 3 p = 0.004) with significant main effects of race, genotype, and race*genotype (Table 4).

Clinical Features and Genotype

Using an additive model, (based on the BIC from the genotype analysis) the clinical characteristics and severity of illness associated with genotype CC, CT, and TT were compared using the following categories: 1) history of cystoid macular edema, 2) biopsy positive disease (definitive ocular sarcoidosis), 3) bilateral involvement, 4) number of extraocular organ involvement, 5) anatomical site of ocular inflammation according to SUN criteria. Analysis of clinical data revealed no significant differences between genotypes in categories 1- 4 (See Table 5). Significant differences between genotypes were found when comparing the sites of ocular inflammation. Ninety-one percent of patients (10 of the 11 patients) with a homozygous variant genotype presented with pan-uveitis, suggesting that rs1071160 may be associated with greater severity of disease in a genotype-dependent fashion.

DISCUSSION

Y402H has been previously implicated as a genetic risk factor for AMD[7-9,24] and multifocal choroiditis.[16] In this study, we provide evidence that CFH Y402H may also influence ocular sarcoidosis incidence and severity. We found a significant increase in the frequency of the Y402H allele (49%) in ocular sarcoidosis patients compared with control subjects (35%). The Y402H allele frequency in the White sarcoidosis cohort (67%) was even higher than that reported for AMD (55.3%-58.7%) and multifocal choroiditis (55.3%) in White populations.[7,8,16] Carriage of the Y402H allele was associated with a 1.72-fold higher risk for ocular sarcoidosis. Subjects with two copies of the Y402H variant had an increased odds ratio of 2.87 for ocular sarcoidosis. We also report that the homozygous variant genotype is correlated with enhanced pathogenicity as represented by the significantly high rate of pan-uveitis presentation.

A number of studies suggest that the complement pathways are important mediators of ocular inflammation. CFH is synthesized and expressed in human retinal pigment epithelium cells.[25] Elevated concentrations of numerous complement activation products and regulatory proteins, such as C3a, C3d, C5a, Ba, Bb, factor D and the complex C5b-9 in drusen, have been found in the peripheral blood of patients with AMD.[26] The presence of complement can modify the development of experimental autoimmune anterior uveitis.[27] Additionally treatment responses to AREDs-recommended supplements appear to be influenced by CFH genotype.[24, 28] Thus, we have multiple lines of evidence supporting a functional role for complement in ocular inflammation.

The specific Tyr402His SNP is thought to decrease the ability of CFH to locally regulate the complement alternative pathway, resulting in inappropriate systemic and local complement activation.[29] If dysregulation of the complement cascade and an increase in local complement components are key factors in the pathogenesis of age-related macular degeneration, then they may also be critical factors in the development of sarcoid uveitis.

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The damage from immunological insult in both diseases may result in autoreactivity to sequestered antigen.

The notion that sequestered antigen may contribute to ongoing ocular inflammation is based on the observation that the presence of specific risk alleles in complement genes is associated with elevation of complement activation products.[30] Presumably, the loss of appropriate CFH regulatory function leaves host cells with lower thresholds for injury and inflammation. This phenomenon may result in increased availability and presentation of antigen from cells not normally subject to complement related degradation. It is conceivable that diminished efficiency of complement pathway regulation, in the setting of increased intracellular protein turnover and an overly active complement cascade, may expose antigen presenting cells to peptides not normally subject to immune surveillance. An expansion in the pool of available antigen mayincrease the potential source of "sarcoid antigen" driving granuloma formation.

The concept of sequestered antigen has clinical relevance in human disease. S-antigen, a component of rod outer segments thought to be immunopathogenic for certain forms of human uveitis,[31] has multiple pathogen sites that can elicit experimental autoimmune uveitis.[32] The pineal gland stains for S-antigen, even though it has no known photoreceptor function. Its relative involvement in autoimmune inflammation is unknown, but the possibility of peptide sequence similarity means it could serve as the initial antigenic trigger for autoimmune uveitis.[29] Relapsing polychondritis—a condition affecting cartilage of the ear nose and respiratory tract—can often cause a severe episcleritis or scleritis. This uveitis is postulated to be an autoimmune reaction to the evolutionary carryover of vestigial cartilage components in the sclera.[33] These examples reinforce the plausibility of a pathologic role for atypically exposed antigen in triggering sarcoidosis.

To better understand the underlying genetic model for the CFH association with ocular sarcoidosis, logistic regression was applied to the entire case/control group. A significant association between rs1061170 and ocular sarcoidosis was observed under the additive model and recessive model ($p = 0.008$ and 0.002 respectively). The results indicate that in the best-fitting model (additive) the CFH-variant can increase susceptibility to ocular sarcoidosis independent of the interaction term *race*genotype*, and the covariates *race* and *sex*, (OR = 3.08, CI = 1.31 – 7.24, $p = 0.002$).

We also found that under the suggested additive and recessive models, our multivariate logistic regressions provided considerable statistical support for the association of race (Black) and increased ocular sarcoidosis risk ($p = 0.001$ and 0.0001 respectively). This independent race effect is consistent with the published epidemiological data. In the United States, the association of African ancestry with sarcoidosis is well established.[34,35] Additionally, ocular involvement is more prevalent in Blacks than in Whites.[36] Our study suggests that there is a separate genetic basis for the ocular disease phenotype, and our findings point to the influence of these other genetic and environmental factors in the pathways that influence immunogenicity in Blacks.

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The role of CFH in ocular sarcoidosis needs to be functionally defined because it is possible that Y402H is in linkage disequilibrium with an unidentified “true” disease modifying locus. To provide evidence of clinical import and biological relevance, we used an additive model to compare the 3 possible Y402H genotypes (CC, CT, and TT) within our sarcoidosis patients for differences in clinical severity. The only clinical feature that correlated with number of C alleles was the presence of posterior or pan-uveitis. Pan-uveitis, a generalized inflammation of the whole uveal tract, vitreous humor, and retina, occurs in 6-33% of patients with sarcoidosis.[1] It is a poor prognostic factor and is associated with less favorable visual outcome when compared to other anatomical sites of inflammation.[37] Consistent with previously published studies, pan-uveitis occurred in 25% of our sarcoidosis cohort. In contrast to the reported prevalence estimates, pan-uveitis was present in 91% of our patients with a homozygous variant genotype. This finding supports the notion of a biological relationship between the CFH variant and ocular sarcoidosis. It may also explain how CFH may contribute to the pathogenesis of multiple ocular inflammatory diseases in that the genetic defect may be targeted specifically to the RPE in the posterior eye. Both AMD and multifocal choroiditis are associated with local inflammatory responses in the RPE.[38,39] We demonstrated that individuals with Y402H homozygosity, who go on to develop sarcoidosis, overwhelmingly present with posterior segment inflammation. CFH polymorphisms and altered complement regulation may alter RPE homeostasis, and this common immunopathogenic pathway may be involved in several ocular inflammatory phenotypes. Hence, the multiple reports describing the association of CFH Y402H polymorphisms with retinal diseases. The present findings suggest that genotype may serve as a useful predictor of the expected course and presentation of uveitis in sarcoidosis.

The major limitations of this study are the relatively small sample size and lack of replication group. The significance of these findings on the at-large population of Blacks and Whites is not yet clear. Heterogeneity in demographic traits such as race and gender can be important confounders in smaller association studies (e.g. if a higher proportion of cases than controls is sampled from a particular subpopulation with a higher prevalence of disease, the results may suffer from ascertainment bias and the proposed association could be spurious). In the current study, the genetic association observed was likely not due to race or gender. The ratio of males-to-females in the cases did not differ from the controls, thus the reported susceptibility could not be due to a bias caused by gender differences in the study population. Additionally, while the racial distribution of cases was statistically different from the racial distribution of controls, there was no statistically significant difference between Blacks and Whites with respect to the risk-allele frequency of CFH (see Table 2). Our measured risk allele frequencies in the control population were similar to those reported in the literature,[23] and Race (as defined by Black and White) is not correlated with rs1061170. It is unlikely that race biased our results. Additionally, we have strong statistical support from our logistic regression analysis that the association between CFH Y402H genotype and sarcoid uveitis persists despite adjustments for Race and Gender. To avoid the contribution of potentially unmeasured peculiarities of our cohort population, additional studies replicating the CFH risk allele association in larger racial groups will be necessary to confirm our association results. Effect size will need to be compared across studies, as there may be differential disease susceptibilities across study populations.

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An advantage of our study was the creation of a heterogeneous control group through the recruitment of Black and White blood donors. The creation of a heterogeneous control group allowed us to control for differences in the racial distribution of cases and controls. Nonetheless there were some limitations inherent in our study design. (a) Failure to include non-ocular sarcoidosis patients prevented us from determining if the association was specific to the eye or present in both ocular and non-ocular forms of sarcoidosis. Many of the patients had at some point in time evidence of systemic sarcoidosis. However, at the time of blood draw, none of the cases were symptomatic for systemic disease. The correlation between genotype and severity of ocular presentation is suggestive of an association that is specific to ocular sarcoidosis, but the present data did not permit us to determine if non-ocular sarcoidosis is also associated with the Y402H risk allele. (b) Seventy-seven percent (302/393) of the control group participants did not receive eye exams. These participants were self-reported to be healthy (without clinical disease including sarcoidosis and uveitis), but without ophthalmic examination we cannot exclude the possibility of residual confounding from undiagnosed or subclinical uveitis. (c) Although, our ocular sarcoidosis cases were compared to a control group that was sarcoidosis free, twenty-three percent (91/393) of our control group had a non-sarcoidosis related uveitis. This comparison was intentionally undertaken to ensure that our findings would be specific to ocular sarcoidosis. Because we included non-sarcoidosis uveitis patients in our control group, we were able to perform a sensitivity analysis in which we used an allelic chi-square test to compare frequencies of the risk allele in uveitis cases (41 sarcoidosis and 91 non-sarcoidosis) and the non-uveitis controls. The CFH Y402H allele frequency in the uveitis cases (0.39) did not significantly differ from the frequency in controls (0.36) ($p = 0.31$). Therefore, the observed association is likely not generalizeable to non-sarcoidosis related uveitis.

Our results suggest CFH genotype as a surrogate marker for human disease and present CFH as a reasonable candidate for analysis in a larger population. CFH Y402H may be associated with a sarcoidosis ocular phenotype. In our study it was also associated with a more severe posterior disease. If confirmed, these findings may inform genotype-based clinical prediction models for the course and treatment of sarcoidosis and sarcoidosis-related uveitis. Elucidation of the genetic background of sarcoidosis has great potential to expand our understanding of granulomatous diseases. Further studies examining the functional implication and biological relevance of the CFH SNP should be undertaken and may provide insight into immune mechanisms involved in ocular sarcoidosis and non-infectious uveitis.

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Table 1

Risk Allele Frequencies of Complement Factor H polymorphism Y402H in different Black and White populations

	All Cases	Whites		Blacks	
		Cases	**Controls**	**Cases**	**Controls**
This Study	0.487	0.625	0.346	0.431	0.369
Edwards 7		0.34		--	
Klein 10		0.35		--	
Haines 9		0.33		--	
Hageman 8		0.34		--	
Grassi 23		--			0.35

Abbreviations: Y402H, Tyrosine402Histidine; Shown are reported allelic frequencies of the Complement factor H Y402H variant from this current study and five recently published studies.[7-10, 23]

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Table 2

Association of Complement Factor H Y402H allele with Ocular Sarcoidosis

SNP	CFH Y402H	
Phenotype	Case ($n = 41$)	Control ($n = 393$)
Risk Allele Freq	48.7% (C)	35.6% (C)
Allelic p value [a]	p = 0.018 *	
Odds Ratio	1.72 (1.09, 2.78)	

Abbreviations: Y402H, Tyrosine402Histidine

[a] Allelic p-value is derived from Pearson chi-squared test.

* = $p < 0.05$

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Table 3

Multivariate Model-fitting: Complement Factor H Y402H association with Ocular Sarcoidosis

Genotype	Cases (%)	Controls (%)	Additive Model [a,b]		Recessive Model [a,b]		Dominant Model [a,b]	
			OR (95% CI)	p - value	OR (95% CI) [a]	p - value	OR (95% CI) [a]	p - value
CC	11 (27)	53 (13)						
CT	18 (44)	174 (44)						
			3.08 (1.31, 7.24)	0.008 *	7.18 (2.24, 24.97)	0.002 *	2.22 (0.58, 8.44)	0.217
TT	12 (29)	166 (42)						

Abbreviations: OR, Odds Ratio; CI, Confidence Interval

[a] Analyses for model-based Odds Ratios were adjusted by the following covariates: Sex, Race, and CFH*Race interaction.

[b] Model-based P-values are derived from the Likelihood Ratio test which compares the Full model to a model which only includes the adjusting factors and thereby tests if the CFH Genotype is a predictor for susceptibility in a given model.

* = $p < 0.0167$ (Bonferroni- corrected significance level = 0.05/3 for 3 model specific tests)

C = Risk allele.

CC = Homozygous variant (2 risk alleles).

CT = Heterozygous variant (1 risk allele).

TT = Homozygous wildtype (No risk alleles).

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Table 4

Multivariate Model-fitting: Covariate association with ocular sarcoidosis

	MODEL		
Parameters	**Additive OR [a]**	**Dominant OR [a]**	**Recessive OR [a]**
Rs1061170	3.08	--	7.18
Race	7.13	3.79	5.32
Sex	--	--	--
Rs1061170*Race	0.42	--	0.16
LogLikelihood	125.715	130.222	126.497
P value (Rs1061170) [b]	0.008	0.217	0.002
BIC	269.619	272.590	271.213

Abbreviations: OR, Odds Ratio; BIC, Bayesian Inference Criteria

[a]Odds Ratios were determined using multivariate logistic regression. Odds ratios for covariates that changed the adjusted RS1061170-OR by more than 10% were reported.

[b]P-values are derived from the Likelihood Ratio test and are adjusted for the following covariates (Race; Sex; Race*Genotype)

Rs1061170 = The identification number for the Complement factor H Y402H polymorphism

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Table 5

Clinical Characteristics of Ocular Sarcoidosis patients - Additive Model

	CC n = 11 (%)	CT n = 18 (%)	TT n = 12 (%)	p Value
Biopsy Positive	8 (73)	13 (72)	5 (42)	p = 0.19[a]
Bilaterality	9 (82)	15 (83)	9 (75)	p = 0.88[a]
History of Macular Edema	6 (55)	7 (39)	5 (42)	p = 0.71[a]
No. Involved Organ Systems	2.27	1.94	2.16	p = 0.51[b]
Posterior/Pan Uveitis	10 (91)	8 (44)	7 (58)	p = 0.047[a]

[a] = Freeman-Halton Fisher Exact Probability Test.

[b] = One-way ANOVA test.

C= Risk allele.

CC = Homozygous variant (2 risk alleles).

CT = Heterozygous variant (1 risk allele).

TT = Homozygous wildtype (No risk alleles).