Published in final edited form as:

Ophthalmology. 2010 August ; 117(8): 1560–1566. doi:10.1016/j.ophtha.2009.11.020.

C-Reactive Protein and *CFH*, *ARMS2/HTRA1* Gene Variants Are Independently Associated with Risk of Macular Degeneration

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Abstract

Purpose—Genetic variants *CFH* and *ARMS2/HTRA1* gene regions as well as high-sensitivity C-reactive protein (CRP) levels are related to age-related macular degeneration (AMD). We evaluated their independent and combined effects on risk of AMD, as well as their interactions.

Design—Case-control study.

Participants—Subjects with AMD (n = 244) or no or minimal maculopathy (n = 209) in the Age Related Eye Disease Ancillary Study.

Methods—Risk factors, genotypes, and biomarkers were assessed by questionnaire, direct measurement, and analyses of blood specimens. The independent and joint effects of serum CRP and *CFH* (*rs1061170*) and *ARMS2/HTRA1* (*rs10490924*) genotypes were assessed using logistic regression analyses, adjusting for age, gender, education, smoking, body mass index, and vitamin/mineral supplementation.

Main Outcome Measures—We defined AMD as large drusen, geographic atrophy, or neovascular disease.

Results—Higher CRP levels were associated with a higher risk of AMD, controlling for genotype and demographic and behavioral risk factors, with odds ratio 2.6 for levels of 3.0 mg/L and above versus below 1.0 mg/L (95% confidence interval, 1.01–6.7). Single nucleotide polymorphisms (SNPs) in both genes were also independently associated with risk of AMD, controlling for the level of CRP and other factors. Presence of both highest level of CRP together with risk genotypes for both SNPs, conferred the highest risk of AMD (OR 5.4, 95% CI 1.4–21.1).

Conclusions—High-sensitivity CRP and polymorphisms in the *CFH* and *ARMS2/HTRA1* genes are independently associated with risk of AMD. Higher CRP level tends to confer a higher risk of AMD within most genotype groups.

Studies have documented the importance of genetic, biologic, and environmental factors in the development of age-related macular degeneration (AMD).^{1–4} Genetic variants in the complement pathway, as well as the *ARMS2/HTRA1* gene region, have been confirmed to

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Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.

Financial Disclosure(s)

The authors have made the following disclosures:

Johanna Seddon - Tufts Medical Center - patent; Genentech – financial support.

be strongly associated with prevalence and incidence of AMD.^{5–14} Given the hypotheses that inflammation plays a role in the pathogenesis of AMD¹⁵ and that cardiovascular risk factors are also related to AMD, including high-sensitivity C-reactive protein (CRP), a biomarker for systemic inflammation,¹⁶ we have evaluated the relationship between CRP and AMD. C-Reactive protein has been found to be associated with onset, as well as progression of AMD.^{17–19} In this study, we have evaluated the joint and independent effects of serum CRP and 2 common single nucleotide polymorphisms, as well as their interactions on risk of intermediate and advanced stages of AMD.

Methods

Age-Related Eye Disease Study-Ancillary Study Population

Participants were part of a study that was ancillary to the Age-Related Eye Disease Study (AREDS). Details of the AREDS design and the selection of cases and controls for the ancillary study have been described elsewhere.^{17,20} The AREDS was a prospective cohort study designed to assess the incidence, clinical course, prognosis, and risk factors for AMD and cataract. The AREDS also included a double-masked randomized clinical trial to assess the effects of high-dose antioxidants (vitamins C, E, and β -carotene) on AMD and cataract and the effect of high-dose zinc on AMD.²¹ In 1995, the AREDS Executive Committee, the AREDS Data and Safety Monitoring Committee, and the National Eye Institute approved this ancillary study under the direction of JMS. Subjects were enrolled from the 2 highest-recruiting AREDS clinical centers: The Massachusetts Eye and Ear Infirmary (Boston, MA) and the Devers Eye Institute (Portland, OR). Individuals were classified based on clinical examination and fundus photography as having no AMD, mild maculopathy (small drusen), large drusen (≥ 125 microns), geographic atrophy (GA), or neovascular (NV) disease in 1 eye. Between January 1996 and April 1997, 465 participants at each center had fasting serum and plasma specimens drawn for this ancillary study. Blood samples were processed immediately and then were sent to Boston and frozen in liquid nitrogen freezers at -140°C . The study was approved by the human subjects committees of the 2 clinical centers, and all participants signed an informed consent statement. Blood was drawn for DNA extraction in the AREDS centers beginning in May 1998.

C-Reactive Protein Analysis

Serum samples were obtained as part of the Ancillary Study. They were assayed for high-sensitivity CRP. C-Reactive protein was measured with a high-sensitivity assay as previously described.¹⁷ The concentration of CRP was determined using an immunoturbidimetric assay on the Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN), using reagents and calibrators from Denka Seiken (Niigata, Japan). In this assay, an antigen–antibody reaction occurs between CRP in the sample and an anti-CRP antibody that has been sensitized to latex particles, and agglutination results. This antigen–antibody complex causes an increase in light scattering, which is detected spectrophotometrically, with the magnitude of the change being proportional to the concentration of CRP in the sample. The coefficients of variation of the assay at concentrations of 0.65 and 13.38 mg/L are 9.4% and 1.1%, respectively.

Genotyping

The DNA samples used for the analyses described in this manuscript were obtained from the National Eye Institute AREDS Genetic Repository. For the genetic variant on chromosome 10, *ARMS2*, it remains a subject of debate whether the gene *HTRA1* adjacent to it may in fact be the AMD-susceptibility gene on 10q26^{22–24}; however, the relevant single nucleotide polymorphisms in these 2 genes have been reported to be nearly perfectly correlated. Thus, although the other single nucleotide polymorphism is a promising candidate variant,

rs10490924 used in this study can be considered a surrogate for the causal variant, which resides in this region. Genotyping for *CFH* Y402H (1q31, exon 9, rs1061170, 1277T>C) and *ARMS2/HTRA1* (10q26, exon 1, rs10490924), was performed in 2006 using primer mass extension and MALDI-TOF MS analysis by the MassEXTEND methodology of Sequenom (San Diego, CA) at the Broad Institute Center for Genotyping and Analysis (Cambridge, MA).

Risk Factors and Statistical Analysis

Ancillary study subjects included in this manuscript had a CRP measurement and genotypes for both genes (n = 453). From the original cohort of 930 subjects with a CRP measurement, 417 did not have genetic data available and 60 others were missing 1 of the 2 genotypes. Subjects did not have genetic data available for several reasons, including refusal to participate in the genetics study (which was implemented after blood specimens were collected for this ancillary study), a second specimen did not validate the original specimen, lack of participation in a third phase of AREDS (during which time the validation specimen was drawn), and participant death before collection of the validation specimen. A comparison between the 2 groups (417 individuals without genetic data available and 453 with both genotypes) revealed significant differences with regard to race (3.6% non-white vs 0%; $P < 0.0001$) and age (mean of 72 vs 70 years; $P < 0.0001$). For these analyses only Caucasian individuals were included and age was adjusted as a continuous variable.

Individuals with NV AMD or any GA in 1 eye (n = 69) and individuals with large drusen in 1 eye (but no NV AMD or GA in either eye; n = 175) were compared with the control group of individuals with mild or no AMD (n = 209), with regard to genotype, CRP, and risk factor data. A multivariate logistic regression analysis was performed to evaluate the relationship between CRP and the 2 AMD case groups, additionally controlling for factors known to be associated with this disease including age at the time of blood drawing (continuous), gender, education (high school or less, more than high school), smoking status (never vs ever), body mass index (BMI) (<25, 25–29.9, 30), and supplementation with the AREDS antioxidant formulation. Likelihood ratio tests for multiplicative interactions were calculated using cross-product terms according to genotype and the 3 clinically established CRP levels: low (<1 mg/L), medium (1.0 mg/L, <3.0 mg/L), or high (≥3.0 mg/L).²⁵ Odds ratios (ORs) and 95% confidence intervals (CI) were calculated for CRP categories within the genotype groups. Tests for trend for the number of risk (*CFH*: C; *ARMS2/HTRA1* T) alleles (0, 1, 2) were calculated for analyses looking at each genotype individually. Risk of AMD for low-, medium-, and high-risk genotypes based on both genes jointly were also calculated within CRP categories. Interactions for the CRP-combined gene models were also determined. All analyses were performed using SAS software, version 9.2 (SAS Inc., Cary, NC).

Results

The distributions of CRP and genotypes according to AMD case and control groups are shown in Table 1. Compared with controls, individuals in the case groups were more likely to have high levels of CRP, especially for the advanced AMD group. For example, for the GA and NV group, 59% had CRP levels in the high range compared with 38% of controls, and 43% of large drusen. Table 2 shows the main effects for CRP and genotypes for both case groups, adjusting for age, gender, education, smoking, BMI, and AREDS supplementation, as well as CRP and genotype. For CRP ≥3.0 mg/L, an increased risk of advanced AMD was seen when compared with CRP <1.0 mg/L (OR, 2.6; 95% CI, 1.01–6.7). The *CFHY402H* genotypes CT and CC, and *ARMS2/HTRA1* genotypes GT and TT, were strongly associated with risk of advanced AMD, and more weakly associated with large drusen, compared with their respective nonrisk reference groups. To assess whether

there was a difference in the relationship between CRP and AMD when only 1 genetic locus was controlled for rather than both, 2 additional models were analyzed as in Table 2, including 1 gene at a time. Results were essentially the same as those shown in Table 2, and there was no significant difference in the effect of the 2 genes on the association between CRP and AMD. Table 3 displays the effect of CRP within *CFH* genotypes for each case group, as well as the *P*-values for interaction between CRP and *CFH*, based on a model controlling for genotype, CRP, and demographic and behavioral factors.

Large Drusen

Compared with the TT nonrisk genotype among those with low CRP levels, there was a nonsignificant increased risk of large drusen for the CC homozygote among persons with the highest CRP levels (OR, 2.5; 95% CI, 0.8–7.5). There were no significant interactions between CRP and genotype.

Geographic Atrophy or Neovascular Age-related Macular Degeneration

Relative to the TT nonrisk genotype and the lowest CRP levels, high CRP levels were associated with an increased risk of GA or NV AMD for both the CT heterozygote (OR, 5.4; 95% CI, 1.1–28.2) and the CC homozygote (OR, 9.0; 95% CI, 1.6–50.4). Medium CRP levels (1.0 mg/L, < 3.0 mg/L) and the CC homozygote were also associated with increased risk of GA or NV AMD (OR, 10.7; 95% CI, 1.8 – 63.2). Having 1 or 2 risk alleles was associated with a greater risk of GA or NV AMD for high CRP levels (OR, 6.3; 95% CI, 1.3–31.4). These effects of the inflammatory marker and the genotype seemed to be additive and there were no significant interactions between CRP and genotype.

Table 4 displays the effect of CRP within each *ARMS2/HTRA1* genotype for each case group, as well as the *P*-values for interaction between CRP and genotypes, after controlling for genotypes, CRP, and demographic and behavioral factors.

Large Drusen

Compared with the GG nonrisk genotype among those with lowest CRP levels, there was an increased risk of large drusen for the TT homozygote among persons with the highest CRP levels (OR, 6.4; 95% CI, 1.2–34.9). There were no significant interactions between CRP and genotype.

Geographic Atrophy or Neovascular Age-related Macular Degeneration

High CRP level was associated with increased risk of GA or NV AMD for both the GT (OR, 4.7; 95% CI, 1.2–18.8) and the TT (OR 21.5, 95% CI 2.7–173.9) genotypes, compared with the referent category (GG genotype, low CRP). Having 1 or 2 risk alleles along with high CRP was associated with increased risk of GA or NV AMD (OR, 6.0; 95% CI, 1.6–23.2).

Table 5 displays the effect of CRP within the combinations of the 2 genotypes for the combined case group. For the high-risk genotype group (1 risk allele for each gene) compared with the low-risk genotype group (no risk alleles) with low CRP, the ORs for the low, medium, and high CRP groups were 3.6 (95% CI, 0.8–16.0), 3.5 (95% CI 0.9–14.3), and 5.4 (95% CI 1.4–21.1), respectively, for the outcome of either large drusen, GA, or advanced AMD.

For the analyses overall, there was a trend for a higher risk of AMD for higher CRP level within genotypes for both genes, although not all of these associations achieved significance. This suggests possible independent effects for these 2 genetic factors and CRP on risk of AMD.

Discussion

Our study's major findings are the apparent independent associations between CRP and AMD while controlling for genotype, and the higher risk of AMD within genetically susceptible individuals when CRP was in the higher range. These results imply that both a biologic serum marker of inflammation as well as genetic factors in the inflammatory pathway (CFH) and another pathway (*ARMS2/HTRA1*) are related to AMD.

Another study found an increased risk of late AMD with higher CRP among individuals who were homozygotes for the *CFHY402H* risk allele adjusting for age and gender,²⁶ and a study in another population reported an increased risk of early and late AMD with increased levels of CRP for the *LOC387715* polymorphism, adjusting for age, gender, and smoking.²⁷ In our analyses, we found a combined effect of higher risk of AMD for higher CRP and risk genotypes for both genes, which was more pronounced for advanced AMD, controlling for several covariates: age, gender, education, smoking, BMI, and AREDS supplementation.

It is becoming increasingly apparent that inflammatory factors are associated with AMD, as shown by the relationship between AMD and genes in the complement pathways, as well as with inflammatory serum or plasma biomarkers.^{5–19,26–32} The other known risk factors for AMD—namely, smoking and higher overall and abdominal obesity—are also directly related to higher levels of these inflammatory cytokines.^{32–33} These factors also increase oxidative stress, and antioxidant mechanisms are known to be related to AMD as shown by the lower risk of development of AMD and progression to advanced disease and visual loss with foods and supplements containing antioxidant vitamins and minerals^{21,34} and greater intake of omega-3 fatty acids.^{35,36} Our results expand on these findings and suggest that a genetic locus involved in the immune, inflammatory pathway, as well as a genetic locus with as of yet unclear function, together with a systemic marker of inflammation, CRP, act independently to increase risk of AMD, adjusting for smoking, BMI, and antioxidants. The combined effects of genetic susceptibility and higher levels of the inflammatory marker increase risk above the individual risks attributed to each factor alone.

One study demonstrated a 2.5-fold higher level of CRP, a CFH-binding protein and acute-phase reactant, in the retinal pigment epithelium–choroid of eyes with the *CFH* homozygous risk genotype,³⁷ which the authors speculated could reflect a state of chronic inflammation in those with the at-risk allele. They further commented that binding interactions between CRP and *CFH* could be affected by the polymorphism.³⁷ Another group demonstrated reduced binding of serum factor H to CRP in samples with the *CFH* risk genotype compared with the nonrisk genotype.³⁸ Both local inflammatory as well systemic reactions could be involved in the mechanisms relating CRP and genes to AMD. Serum complement proteins could also play a role.^{32,39} The mechanisms and associations related to the *ARMS2/HTRA1* locus and CRP remain to be elucidated.

Strengths of this study include the well-characterized population of Caucasian patients from 2 different geographic regions in the United States, the standardized collection of risk factor information, direct measurements of height and weight, and classification of maculopathy by standardized ophthalmologic examinations and grading of fundus photographs. Misclassification was unlikely because grades were assigned without knowledge of risk factors, genotype, or CRP status. We controlled for known AMD risk factors, including age, education, BMI, smoking, and antioxidants in the assessment of the effect of CRP and the 2 genetic variants on risk of AMD. There may be some other unmeasured and therefore uncontrolled factors that might still be confounding these relationships, but they would have to be highly related to genotype and CRP, and a strong risk factor for AMD to explain these results. Although this is a selected population, the overall population is similar to others in

this age range in terms of smoking and prevalence of obesity, as well as the distribution of the genotypes. Furthermore, the biological effects of the genes together with the modifiable factors do not seem to differ in major ways among various Caucasian populations with AMD.

In conclusion, these results suggest that high sensitivity CRP and the *CFHY402H* and *ARMS2/HTRA1* genetic variants are independently related to risk of AMD. Although genetic factors confer a strong predisposition, environmental and biologic factors such as smoking and BMI,^{11–12} and factors leading to higher levels of the systemic inflammatory marker, CRP,³³ can modify genetic susceptibility to AMD.

Acknowledgments

The authors thank Richard F. Dreyer, MD, Director of the Devers AREDS clinic 1991–1999, AREDS staff of the Devers Eye clinic, and the Good Samaritan Fund of Devers Eye Institute, Oregon Health & Science University, Portland for assistance with collection of serum samples in 1996–1997.

Supported by grants from the National Institutes of Health (NIH) National Eye Institute R01-EY11309; Massachusetts Lions Eye Research Fund, Inc, Northboro, MA; Individual Research Grant from Genentech, Inc.; and the Macular Degeneration Research Fund, New England Eye Center, Tufts Medical Center, Tufts University School of Medicine.

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Table 1

Distribution of Age-related Macular Degeneration (AMD) Group According to C-reactive Protein Levels, Genotype, and Demographic Factors

	AMD Group*					
	Controls (n = 209)		Large Drusen (N = 175)		Any GA or NV AMD (N = 69)	
	n	%	n	%	n	%
Number per group	209	100	175	100	69	100
C-reactive protein						
Low (<1 mg/L)	42	20	39	22	8	12
Medium (1.0 mg/L, <3.0 mg/L)	87	42	61	35	20	29
High (3.0 mg/L)	80	38	75	43	41	59
<i>CFH</i>						
TT	90	43	48	27	7	10
CT	89	43	85	49	30	44
CC	30	14	42	24	32	46
<i>ARMS2/HTRA1</i>						
GG	125	60	87	50	25	36
TG	68	32	72	41	34	49
TT	16	8	16	9	10	15
Median age (yrs)	69		71		73	
Gender - female	133	64	102	58	41	59

GA = any geographic atrophy in 1 eye; Letters T, C, G = nucleotides for the respective single nucleotide polymorphisms; NV AMD = neovascular AMD in 1 eye.

* Includes subjects with a measurable genotype for both genes.

Table 2

Main Effects Model for Risk of Large Drusen and Advanced Age-related Macular Degeneration (AMD)

Effect	Large Drusen		Any GA or NV AMD	
	Odds Ratio*	95% CI	Odds Ratio*	95% CI
C-Reactive protein, mg/L				
Low (<1 mg/L)	1.0		1.0	
Medium (1.0 mg/L, <3.0 mg/L)	0.9	0.5–1.6	1.4	0.5–3.7
High (≥3.0 mg/L)	1.2	0.7–2.2	2.6	1.01–6.7
<i>P</i> for trend	0.22		0.02	
<i>CFH</i>				
TT	1.0		1.0	
CT	1.8	1.1–2.9	4.6	1.8–11.4
CC	2.6	1.4–4.8	13.9	5.3–36.7
<i>ARMS2/HTRA1</i>				
GG	1.0		1.0	
GT	1.5	0.97–2.4	2.4	1.3–4.7
TT	1.5	0.7–3.2	4.0	1.5–10.9

CI = confidence interval; GA = any geographic atrophy in 1 eye; Letters T, C, G = nucleotides for the respective single nucleotide polymorphisms; NV AMD = neovascular AMD in 1 eye.

* Main effects model adjusted for age at the time of blood draw (continuous), gender, education (high school diploma or less vs some college or more), smoking (never vs ever), body mass index (<25, 25–30, ≥30), supplementing with antioxidant formulations, and genotype. Odds ratios >1 imply that group was associated with increased risk of large drusen, geographic atrophy, or advanced AMD when compared with the first (reference) group.

Table 3

Risk of Age-related Macular Degeneration (AMD) according to Low, Medium, or High C-reactive Protein (CRP) and *CFH Y402H* Genotype

	Genotype-<i>CFH Y402H</i>			P value
	TT	CT	CC	
No of cases				
Large drusen	48	85	42	
Any GA or NV AMD	7	30	32	
Total	55	115	74	
No of controls	90	89	30	
Outcome *: OR (95% CI)				(Overall interaction)
Large drusen				
Low CRP (<1 mg/L)	1.0	1.3 (0.5–3.6)	2.2 (0.6–8.0)	
Medium CRP (1.0 mg/L, <3.0 mg/L)	0.5 (0.2–1.3)	1.7 (0.7–4.4)	1.9 (0.6–6.0)	
High CRP (≥3.0 mg/L)	1.4 (0.5–3.7)	1.6 (0.6–4.0)	2.5 (0.8–7.5)	
<i>P</i> (interaction)		0.11 (CT vs TT)	0.68 (CC vs TT)	0.33
Any GA or NV AMD				
Low CRP (<1 mg/L)	1.0	0.9 (0.1–7.6)	5.5 (0.7–41.9)	
Medium CRP (1.0 mg/L, <3.0 mg/L)	0.4 (0.04–3.2)	1.8 (0.3–10.6)	10.7 (1.8–63.2)	
High CRP (≥3.0 mg/L)	0.9 (0.1–6.4)	5.4 (1.1–28.2)	9.0 (1.6–50.4)	
<i>P</i> (interaction)		0.43 (CT vs TT)	0.35 (CC vs TT)	0.22
	TT	CT or CC		
Large drusen				
Low CRP (<1 mg/L)	1.0	1.5 (0.6–3.9)		
Medium CRP (1.0 mg/L, <3.0 mg/L)	0.5 (0.2–1.3)	1.8 (0.7–4.4)		
High CRP (≥3.0 mg/L)	1.4 (0.5–3.7)	1.8 (0.7–4.5)		
<i>P</i> (interaction)		0.13		
Any GA or NV AMD				
Low CRP (<1 mg/L)	1.0	2.0 (0.3–12.0)		
Medium CRP (1.0 mg/L, <3.0 mg/L)	0.4 (0.05–3.1)	3.8 (0.7–19.7)		
High CRP (≥3.0 mg/L)	0.9 (0.1–6.2)	6.3 (1.3–31.4)		
<i>P</i> (interaction)		0.52		

CI = confidence interval; GA = any geographic atrophy in 1 eye; Letters T, C = nucleotides for single nucleotide polymorphism; NV AMD = neovascular AMD in 1 eye; OR = odds ratio.

* All models adjusted for age (continuous), gender, education (high school, >high school), smoking status (never, ever), body mass index (<25, 25–29.9, ≥30), supplementing with antioxidant formulation. Odds ratios >1 imply that group was associated with increased risk of large drusen, geographic atrophy, or advanced AMD when compared with the low CRP/TT (reference) group.

Table 4

Risk of Age-related Macular Degeneration (AMD) according to Low, Medium, or High C-reactive Protein (CRP) and *ARMS2/HTRA1* Genetic Variant

	Genotype- <i>ARMS2/HTRA1</i>			P value
	GG	GT	TT	
No of cases				
Large drusen	87	72	16	
Any GA or NV AMD	25	34	10	
Total	112	106	26	
No of controls	125	68	16	
Outcome *: OR (95% CI)				(Overall interaction)
Large drusen				
Low CRP (<1 mg/L)	1.0	2.5 (0.9–7.0)	0.8 (0.2–3.4)	
Medium CRP (1.0 mg/L, <3.0 mg/L)	1.0 (0.5–2.2)	1.3 (0.6–3.1)	1.0 (0.2–4.1)	
High CRP (3.0 mg/L)	1.3 (0.6–2.9)	1.6 (0.7–3.8)	6.4 (1.2–34.9)	
P(interaction)		0.54 (GT vs GG)	0.28 (TT vs GG)	0.29
Any GA or NV AMD				
Low CRP (<1 mg/L)	1.0	3.7 (0.7–19.7)	†	
Medium CRP (1.0 mg/L, <3.0 mg/L)	1.3 (0.3–5.4)	1.7 (0.4–7.5)	4.1 (0.7–25.4)	
High CRP (3.0 mg/L)	1.7 (0.4–7.0)	4.7 (1.2–18.8)	21.5 (2.7–173.9)	
P(interaction)		0.34 (GT vs GG)	(TT vs GG) †	0.55
	GG	GT or TT		
Large drusen				
Low CRP (<1 mg/L)	1.0	1.8 (0.7–4.5)		
Medium CRP (1.0 mg/L, <3.0 mg/L)	1.0 (0.5–2.2)	1.3 (0.6–2.9)		
High CRP (3.0 mg/L)	1.3 (0.6–3.0)	2.0 (0.9–4.5)		
P(interaction)		0.84		
Any GA or NV AMD				
Low CRP (<1 mg/L)	1.0	1.9 (0.4–9.6)		
Medium CRP (1.0 mg/L, <3.0 mg/L)	1.3 (0.3–5.5)	2.2 (0.5–9.0)		
High CRP (3.0 mg/L)	1.8 (0.4–7.4)	6.0 (1.6–23.2)		
P(interaction)		0.61		

CI = confidence interval; GA = any geographic atrophy in 1 eye; Letters G, T = nucleotides for single nucleotide polymorphism; NV AMD = neovascular AMD in 1 eye; OR = odds ratio.

* All models adjusted for age (continuous), gender, education (high school, >high school), smoking status (never, ever), body mass index (<25, 25–29.9, 30), supplementing with antioxidant formulation. Odds ratios >1 imply that group was associated with increased risk of large drusen, geographic atrophy, or advanced AMD when compared with the low CRP/GG (reference) group.

† No outcome events in this category, or calculation could not be performed.

Table 5

Risk of Age-related Macular Degeneration (AMD) according to Low, Medium, or High C-reactive Protein (CRP) and a Combination of *CFH* *Y402H* and *ARMS2/HTRA1* Genetic Variants

	Genotype Combination (<i>CFH</i> <i>Y402H</i> & <i>ARMS2/HTRA1</i>)							
	Low Risk		Intermediate Risk 1		Intermediate Risk 2		High Risk	
	<i>CFH</i> <i>TT</i>	<i>ARMS2/HTRA1</i> <i>GG</i>	<i>CFH</i> <i>TT</i>	<i>ARMS2/HTRA1</i> <i>TG or TT</i>	<i>CFH</i> <i>CT or CC</i>	<i>ARMS2/HTRA1</i> <i>GG</i>	<i>CFH</i> <i>CT or CC</i>	<i>ARMS2/HTRA1</i> <i>TG or TT</i>
No of cases								
Large drusen		20		28		67		60
Any GA or NV AMD		2		5		26		39
Total		22		33		93		99
No of controls		54		36		71		48
Outcome [*] ; OR (95% CI)								
Large Drusen, any GA or NV AMD								
Low CRP (<1 mg/L)		1.0		2.2 (0.4–10.8)		1.9 (0.5–8.0)		3.6 (0.8–16.0)
Medium CRP (1.0 mg/L, <3.0 mg/L)	0.5 (0.1–2.2)			1.1 (0.2–4.9)		3.0 (0.8–11.8)		3.5 (0.9–14.3)
High CRP (≥3.0 mg/L)	1.6 (0.4–6.9)			2.7 (0.6–12.3)		2.8 (0.7–11.1)		5.4 (1.4–21.1)

CI = confidence interval; GA = any geographic atrophy in 1 eye; Letters C, G, T = nucleotides for single nucleotide polymorphisms; NV AMD = neovascular AMD in 1 eye; OR = odds ratio.

^{*} All models adjusted for age (continuous), gender, education (high school, >high school), smoking status (never, ever), body mass index (<25, 25–29.9, ≥30), supplementing with antioxidant formulation. Odds ratios >1 imply that group was associated with increased risk of large drusen, geographic atrophy, or advanced AMD when compared with the Low CRP/*CFH*: *TT*/*ARMS2/HTRA1*: *GG* (reference) group.