

# Association of *CFH* Y402H and *LOC387715* A69S With Progression of Age-Related Macular Degeneration

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**A**GE-RELATED MACULAR DEGENERATION (AMD) is associated with *CFH* gene polymorphisms, including Y402H on chromosome 1, and the *LOC387715* variant A69S on chromosome 10.<sup>1-9</sup> Both forms of advanced AMD, geographic atrophy and neovascular disease, are related to these polymorphisms.<sup>7,8</sup> Several previous studies have found and confirmed cross-sectional associations between AMD and the *CFH* and *LOC* genes. However, to our knowledge, no study has examined the prospective relationships between these common polymorphisms and progression from early or intermediate stages of maculopathy to advanced forms of AMD associated with visual loss. Factors associated with prevalence may differ from those associated with progression or incidence of disease. We evaluated these associations among 1466 individuals in a large, national multicenter study of age-related eye disease, of whom 281 progressed to late stages of AMD, which are associated with visual impairment and legal blindness.

## METHODS

The Age-Related Eye Disease Study (AREDS) included 2 parts: (1) a randomized clinical trial to assess the effect

**Context** Studies have reported that single-nucleotide polymorphisms in the genes *CFH* and *LOC387715* are associated with age-related macular degeneration (AMD).

**Objective** To assess whether these genetic variants have prognostic importance for progression to advanced AMD and related visual loss.

**Design, Setting, and Participants** Prospective analysis of 1466 white participants in the Age-Related Eye Disease Study (AREDS), a US multicenter clinical trial conducted from 1990 to 2001 with a mean follow-up time of 6.3 years. Age-related macular degeneration status was determined by grading of fundus photographs. Progression (n=281) was defined as newly diagnosed advanced AMD (geographic atrophy, exudative disease, or AMD causing visual loss) in one or both eyes during the course of the study. Genotypic analysis was conducted in 2006.

**Main Outcome Measure** Incidence rates of dry and neovascular advanced AMD.

**Results** The *CFH* Y402H and *LOC387715* A69S polymorphisms were each independently related to progression from early or intermediate stages to advanced stages of AMD, controlling for demographic factors, smoking, body mass index, and AREDS vitamin-mineral treatment assignment, with odds ratios (ORs) of 2.6 (95% confidence interval [CI], 1.7-3.9) for *CFH* and 4.1 (95% CI, 2.7-6.3) for *LOC387715* for the homozygous risk genotypes ( $P < .001$  for trend for each additional risk allele for both genes). The effect of *LOC387715* was stronger for progression to neovascular disease (OR, 6.1; 95% CI, 3.3-11.2) compared with geographic atrophy (OR, 3.0; 95% CI, 1.4-6.5) relative to no progression for the homozygous risk state. The presence of all adverse factors (both risk genotypes, smoking, and body mass index  $\geq 25$ ) increased risk 19-fold. Smoking and high body mass index increased odds of progression within each risk genotype. Genetic plus nongenetic risk scores provided an area under the receiver operating characteristic curve of up to 0.78.

**Conclusions** Common polymorphisms in the genes *CFH* and *LOC387715* are independently related to AMD progression after adjustment for other known AMD risk factors. Presence of these polymorphisms plus AREDS vitamin-mineral treatment, smoking, and body mass index of 25 or higher identify patients who are highly susceptible to developing advanced stages of this visually disabling disease.

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of supplemental antioxidant vitamins (ascorbic acid [vitamin C], vitamin E, and beta carotene) and minerals (zinc and copper) on risk of AMD and cataract, which began in April 1992 and ended in November 2001 and (2) a longitudinal study of progression of AMD. Genotyping was performed in 2006.

Study procedures have been previously reported.<sup>10</sup> The study participants were aged 55 to 80 years and were

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recruited at 11 centers in the United States from the clinic and general populations in those areas. Compared with the general population, participants were relatively well nourished and likely had better medication adherence. The project was approved by the appropriate institutional review boards, and all individuals provided written informed consent to participate in the genetic study.

Grades of AMD were assigned based on ocular examination and reading center photographic grading of fundus photographs. In these analyses, AREDS grade 1 was defined as AMD category 1 in both eyes (essentially free of age-related macular abnormalities), grade 2 was AMD category 2 in the worst eye (mild changes including multiple small drusen, nonextensive intermediate drusen, and/or pigment abnormalities), grade 3 was AMD category 3 in the worst eye (at least 1 large drusen of at least 125  $\mu\text{m}$  in diameter, extensive intermediate drusen, and/or noncentral geographic atrophy), grade 4 was AMD category 4 in one eye (advanced AMD: either neovascular or central geographic atrophy), and grade 5 was AMD category 4 in both eyes.

Race/ethnicity was classified according to participant self-report using the following categories: white (not of Hispanic origin), black (not of Hispanic origin), Hispanic, Asian or Pacific Islander, or other. In these analyses, only white participants were included because genotype frequencies may differ by race.

Participants were determined to be progressors or nonprogressors without knowledge of the participants' genetic loci. Progressors or those with incident advanced stages of AMD were defined based on the AMD grade at the end of the clinical trial in 2001, with a mean follow-up time of 6.3 years, as individuals with early or intermediate AMD (grades 2 or 3) at baseline who progressed to advanced AMD (grades 4 or 5) during follow-up, as well as individuals with advanced AMD in one eye (grade 4) at baseline who progressed to advanced AMD in both eyes (grade 5). Progressors to unilateral and bilateral disease were also analyzed in

separate models. The Clinical Age-Related Maculopathy Grading System (CARMS) was also assessed in a secondary analysis, which assessed grade 4 (both central and noncentral geographic atrophy) and grade 5 (neovascular disease) AMD.<sup>11</sup>

Risk factor data were obtained at the baseline visit from questionnaires and height and weight measurements. Samples of DNA were obtained from the AREDS Genetic Repository in 2005-2006. Acquisition of DNA samples began during the course of AREDS, and 2231 (49%) of the 4566 participants had a DNA specimen available at the time of the study. Participants with AREDS grade 1 at baseline ( $n=574$ ) were excluded from these prospective analyses since grade 1 rarely progresses in this age group. In addition, we excluded 128 patients who were missing the *CFH* and *LOC387715* genotypes (see below), 58 nonwhite patients, and 5 patients who were missing covariate data, yielding a study population of 1466 patients.

Individuals were genotyped in 2006 for the common coding single-nucleotide polymorphism in the *CFH* gene (1q31, exon 9, rs1061170, 1277T>C, Y402H) and for *LOC387715* (10q26, exon 1, rs10490924, A69S). Genotyping for *CFH* Y402H was performed using primer mass extension and matrix-assisted laser desorption ionization-time-of-flight mass spectrometry analysis by the MassEXTEND method of Sequenom (San Diego, Calif) at the Broad Institute Center for Genotyping and Analysis, Cambridge, Mass. Genotyping for *LOC387715* A69S was performed using Sanger sequencing at Prevention Genetics, Marshfield, Wis.

Individuals whose disease status progressed to advanced AMD were compared with nonprogressors with regard to genotype and other risk factor data. Rates of progression were calculated for each of the 9 combinations of *CFH* and *LOC387715* genotypes. Logistic regression analyses were performed to evaluate the relationships between progression of AMD and genetic risk factors, controlling for age ( $\geq 70$  vs  $< 70$  years), sex, education (high school or less vs more than

high school), and baseline AMD grade (grades 2-4). A multivariate logistic regression model was used to further adjust for the effects of other risk factors for AMD, including cigarette smoking (never vs ever), body mass index (BMI) ( $< 25$  vs  $\geq 25$ ; calculated as weight in kilograms divided by height in meters squared), and study group assignment in the AREDS randomized clinical trial (supplementation with antioxidants alone, zinc [with a small amount of copper], both antioxidants and zinc, or placebo). An additional model included both genotypes together. Tests for multiplicative interactions between the 2 genetic polymorphisms were calculated using cross-product terms according to genotypes. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each risk factor and within the 3 genotype groups for each polymorphism. Tests for trend for the number of risk (C) alleles for *CFH* or number of risk (T) alleles for *LOC387715* (0, 1, or 2 for each) were calculated.

Attributable risks (ARs) were calculated to estimate the risk of progression attributed to genetic and other factors. Since ARs for specific genotypes are not additive, we present an overall AR for the 2 genotypes combined and an additional AR for the 2 genotypes combined plus environmental factors. To assess AR for the 2 genotypes combined, we subdivided the data into 9 strata according to the cross-classified *CFH* Y402H and *LOC387715* A69S genotypes. We then obtained the relative risk for each of the strata relative to the first stratum defined by the non-risk genotype for both the Y402H genotype (TT) and the *LOC* genotype (GG). We then computed the overall AR.

Attributable risk represents the proportion of AMD progression that would be prevented if each participant in non-referent strata were in the referent stratum. A similar approach was used to assess AR for genetic and environmental (ie, smoking and BMI) factors in which the number of strata from cross-classified *CFH* Y402H  $\times$  *LOC387715* A69S  $\times$  ever smoking  $\times$  BMI of 25 or higher was 36 and the referent strata consisted of participants with the 2 non-

risk genotypes who were nonsmokers and had a BMI of less than 25.

An age-adjusted C statistic (ie, the area under the receiver operating characteristic curve) was calculated for each model to assess the probability that the risk score based on the group of risk factors in that model from a random progressor was higher than the corresponding risk score from a random nonprogressor within the same 10-year age group.<sup>12</sup> Similar analyses were conducted using an alternative AMD classification system.<sup>8,13-15</sup> SAS software, version 9.0 (SAS Institute Inc, Cary, NC) was used in the analysis, and  $P < .05$  was considered statistically significant.

**RESULTS**

Among the 1466 eligible participants in the study, AMD progressed in 281 according to the AREDS scale. The distributions of the genetic and selected other variables according to progression to advanced AMD and the incidence rates and relative risks for progression to incident late AMD associated with these factors are shown in TABLE 1. Compared with nonprogressors, progressors were older, had fewer years of education, were more likely to smoke, and had higher BMI. Individuals with AMD grade 3 (intermediate AMD) or grade 4 (advanced AMD in one eye) at baseline were far more likely to be progressors than those with grade 2 (early AMD).

Both genetic polymorphisms, *CFH* Y402H and *LOC387715* A69S, were associated with progression to more advanced AMD. The absolute incidence rates of progression to advanced AMD over a 6-year period for the *CFH* Y402H genotype were 10% for the TT genotype, 18% for the CT genotype, and 30% for the CC genotype. For the *LOC387715* A69S gene, these rates were 9.5% for the GG genotype, 24% for the GT genotype, and 40% for the TT genotype.

Rates of AMD progression according to the *CFH* and *LOC387715* genotypes are shown in the FIGURE. The probability of progression was 48% for the highest-risk genotype (presence of homozygous risk alleles for both genes) vs 5% for the low-risk genotypes (homo-

**Table 1.** Baseline Characteristics and Progression to Advanced AMD\*

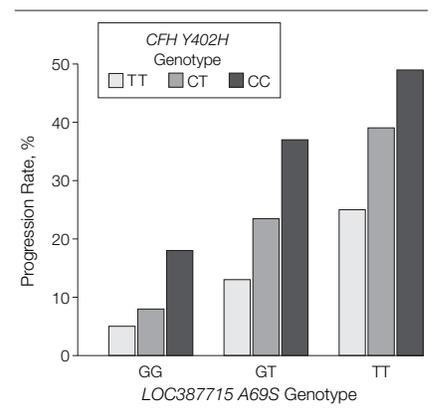
Characteristics	No. (%)		Incidence Rate of Progression, %	RR (95% Confidence Interval)	P Value
	Progression (n = 281)	Nonprogression (n = 1185)			
Age, y					
50-59	8 (3)	46 (4)	14.8	1 [Reference]	<.001†
60-69	132 (47)	707 (60)	15.7	1.1 (0.5-2.1)	
≥70	141 (50)	432 (36)	24.6	1.7 (0.9-3.2)	
Sex					.60‡
Female	164 (58)	713 (60)	18.7	1 [Reference]	
Male	117 (42)	472 (40)	19.9	1.1 (0.9-1.3)	
Education					.003‡
High school or less	119 (42)	390 (33)	23.4	1 [Reference]	
More than high school	162 (58)	795 (67)	16.9	0.7 (0.6-0.9)	
Baseline AMD grade					<.001†
2	7 (2)	463 (39)	1.5	1 [Reference]	
3	166 (59)	570 (48)	22.6	15.1 (7.2-32.0)	
4	108 (38)	152 (13)	41.5	27.9 (13.2-59.0)	
Smoking					.009‡
Never	110 (39)	567 (48)	16.2	1 [Reference]	
Ever	171 (61)	618 (52)	21.7	1.3 (1.1-1.7)	
BMI§					.002‡
<25	72 (26)	423 (36)	14.5	1 [Reference]	
≥25	209 (74)	762 (64)	21.5	1.5 (1.2-1.9)	
<i>CFH</i> Y402H					<.001†
TT	41 (15)	380 (32)	9.7	1 [Reference]	
CT	119 (42)	527 (44)	18.4	1.9 (1.4-2.6)	
CC	121 (43)	278 (23)	30.3	3.1 (2.2-4.3)	
<i>LOC387715</i> A69S					<.001†
GG	65 (23)	622 (52)	9.5	1 [Reference]	
GT	147 (52)	458 (39)	24.3	2.6 (2.0-3.4)	
TT	69 (25)	105 (9)	39.7	4.2 (3.1-5.6)	

Abbreviations: AMD, age-related macular degeneration; RR, relative risk.  
 \*Age-Related Eye Disease Study grade 2 was AMD category 2 in one or both eyes (worst eye), grade 3 was AMD category 3 in one or both eyes (worst eye), grade 4 was AMD category 4 in one eye (worst eye), and grade 5 was AMD category 4 in both eyes.  
 †P value is for test for linear trend.  
 §Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.  
 ‡P values are pairwise comparisons with the reference category.

zygous nonrisk alleles for both genes). The 2 genotypes were each independently related to AMD progression.

Cross-classifications of the *CFH* Y402H and the *LOC387715* A69S genotypes are shown in TABLE 2. The frequency of the homozygous *LOC387715* risk genotype (TT) according to the 3 *CFH* genotypes suggested a mild positive association ( $\chi^2 = 20.2$ ;  $P < .001$ ) between these 2 genes. The homozygous *LOC387715* risk genotype (TT) was present among 13% of individuals with the homozygous *CFH* risk genotype (CC) and was present in only 7% of those with the homozygous nonrisk *CFH* genotype (TT). When we excluded individuals with the heterozygous genotype for either gene, the odds of having the *LOC387715* A69S TT genotype for individuals with the *CFH* Y402H CC genotype was 2.4 times

**Figure.** Progression Rates of Age-Related Macular Degeneration According to *CFH* and *LOC387715* Genotypes



higher than the odds of having the *LOC387715*A69S TT genotype for individuals with the *CFH* Y402H TT geno-

type, indicating a mild positive association in our AMD population.

We calculated Hardy-Weinberg equilibrium for the study population based on results shown in Table 2. We found that the *LOC387715 A69S* single-nucleotide polymorphism (SNP) was barely in Hardy-Weinberg equilibrium ( $P=.08$ ) and that the *CFH Y402H* SNP was not ( $P<.001$ ). These results are consistent with the fact that the study population is composed of individuals with various degrees of maculopathy and does not represent a random sample of the general population. Therefore, we would not expect Hardy-Weinberg equilibrium to be maintained for either variant, each of which is associated with AMD.

Adjusted and multivariate ORs for progression to advanced AMD according to genotype are shown in TABLE 3. For the *Y402H* polymorphism in the *CFH* gene, the ORs were similar for all 3 models. For the multivariate model controlling for smoking, BMI, and AREDS treatment assignment (multivariate model 1), compared with the nonrisk TT genotype, the ORs were 1.6 (95% CI, 1.1-2.4) for the heterozygous CT genotype and 2.6 (95% CI, 1.7-3.9) for the homozygous CC risk allele genotype. The trend toward increased risk of progression for each additional C allele was statistically significant ( $P<.001$ ). For the *A69S* polymorphism in the *LOC387715* gene, the ORs for AMD progression

were also similar for all 3 models. In multivariate model 1, compared with the nonrisk GG genotype, the heterozygous GT genotype had an OR of 2.7 (95% CI, 1.9-3.7) and the TT genotype was associated with a 4.1-fold increased risk (95% CI, 2.7-6.3). There was a statistically significant trend toward increased risk of AMD progression for each additional T allele ( $P<.001$ ). When either genetic polymorphism was adjusted for the other (multivariate model 2), the estimates were virtually unchanged, suggesting that the effects of these 2 genes on risk of progression were independent. Smoking tended to increase risk of progression (OR, 1.2; 95% CI, 0.9-1.7) and higher BMI increased risk of progression (OR, 1.5; 95% CI, 1.1-2.1). These results were essentially the same with and without controlling for the genetic variants.

Genotype and treatment had no significant interaction with regard to progression of AMD for either the *CFH Y402H* or *LOC387715 A69S* genotypes. Furthermore, the ORs for gene

**Table 2.** Cross-Classification of *CFH Y402H* and *LOC387715 A69S* Genotypes\*

<i>LOC387715 A69S</i>	<i>CFH Y402H</i>			Total
	TT	CT	CC	
GG	214 (51)	305 (47)	168 (42)	687 (47)
GT	179 (43)	247 (38)	179 (45)	605 (41)
TT	28 (7)	94 (15)	52 (13)	174 (12)
Total	421 (29)	646 (44)	399 (27)	1466

\*All data are shown as No. (%).

**Table 3.** Adjusted and Multivariate Odds Ratios for Progression to Advanced AMD and Subtypes of Advanced AMD According to Genotype and Behavioral Factors

Variables	Adjusted OR (95% CI)*	P Value for Trend, No. of C Alleles ( <i>CFH</i> ) or No. of T Alleles ( <i>LOC387715</i> )	Model 1 OR (95% CI)†	P Value for Trend, No. of C Alleles ( <i>CFH</i> ) or No. of T Alleles ( <i>LOC387715</i> )	Model 2 OR (95% CI)‡				
					Overall	Unilateral Advanced Progressors (n = 131)	Bilateral Advanced Progressors (n = 150)	Geographic Atrophy Progressors (n = 69)	Neovascular AMD Progressors (n = 122)
<i>CFH Y402H</i>									
TT	1 [Reference]	<.001	1 [Reference]	<.001	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	
CT	1.6 (1.1-2.4)		1.6 (1.1-2.4)		1.6 (1.0-2.4)	1.7 (0.97-2.9)	1.5 (0.8-2.7)	1.2 (0.6-2.4)	2.1 (1.1-3.9)
CC	2.6 (1.7-3.9)		2.6 (1.7-3.9)		2.6 (1.7-3.9)	3.0 (1.7-5.3)	2.3 (1.3-4.2)	2.6 (1.3-5.3)	2.9 (1.5-5.6)
<i>LOC387715 A69S</i>									
GG	1 [Reference]	<.001	1 [Reference]	<.001	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	
GT	2.7 (1.9-3.7)		2.7 (1.9-3.7)		2.7 (1.9-3.8)	3.1 (2.0-4.8)	2.5 (1.5-4.1)	2.1 (1.2-3.7)	3.5 (2.1-5.7)
TT	4.1 (2.7-6.3)		4.1 (2.7-6.3)		4.1 (2.7-6.3)	3.1 (1.7-5.8)	5.4 (3.0-9.7)	3.0 (1.4-6.5)	6.1 (3.3-11.2)
Smoking									
Never					1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	
Ever					1.2 (0.9-1.7)	1.4 (0.9-2.1)	1.0 (0.7-1.6)	1.1 (0.7-2.0)	
BMI§									
<25					1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	
≥25					1.5 (1.1-2.1)	1.6 (1.05-2.5)	1.5 (0.9-2.4)	2.2 (1.2-4.0)	

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index; CI, confidence interval; OR, odds ratio.

\*Adjusted model was adjusted for age (50-69 vs 70-95 years), sex, education (high school or less vs more than high school), 1 genotype, and baseline AMD grade.

†Multivariate model 1 was adjusted for age (50-69 vs 70-95 years), sex, education (high school or less vs more than high school), 1 genotype, baseline AMD grade, smoking (never vs ever), BMI (<25 vs ≥25), and treatment assignment (antioxidants, zinc, antioxidants and zinc, or placebo).

‡Multivariate model 2 was adjusted for all variables listed for multivariate model 1 plus both genotypes.

§Body mass index was calculated as weight in kilograms divided by height in meters squared.

effects on AMD progression changed minimally when the treatment variable was added to the models as a covariate for both genes and there was no evidence for an interaction between treatment and genotype.

We also evaluated whether progression to unilateral advanced AMD (AREDS grade 4; n=131 progressors) differed from progression to bilateral advanced AMD (AREDS grade 5; n=150 progressors). As shown in Table 3, among those who were homozygous for the *LOC387715 A69S* risk genotype (TT) compared with those with the GG genotype, the OR for progression to bilateral advanced disease was slightly higher (OR, 5.4; 95% CI, 3.0-9.7) than the OR for progression to unilateral advanced disease (OR, 3.1; 95% CI, 1.7-5.8), controlling for the other risk factors. The effect of the *CFH* variant was similar for both unilateral and bilateral advanced AMD (ORs for risk vs nonrisk homozygous genotypes of 3.0 [95% CI, 1.7-5.3] and 2.3 [95% CI, 1.3-4.2], respectively).

An alternative classification system of phenotype was also evaluated.<sup>11</sup> In this system, progression rates from stages 2 or 3 to stage 4 (any geographic atrophy; n=69 progressors) or from stages 2, 3, or 4 to stage 5 (neovascular disease with or without geographic atrophy; n=122 progressors), were evaluated, as shown in Table 3. Using this system, the total number of progres-

sors (191) is less than the total number of progressors (281) on the AREDS scale. Relative to the homozygous nonrisk genotype, the effect of the homozygous risk *LOC387715 A69S* genotype on rate of progression to neovascular disease was somewhat higher (multivariate OR, 6.1; 95% CI, 3.3-11.2) compared with progression to geographic atrophy (OR, 3.0; 95% CI, 1.4-6.5). The effect of the *CFH Y402H* homozygous risk genotype was similar for the 2 end points (ORs, 2.9 [95% CI, 1.5-5.6] for neovascular disease and 2.6 [95% CI, 1.3-5.3] for atrophy). For the heterozygous genotypes, smaller differences were seen, with slightly higher ORs for neovascular disease for both genes.

To evaluate the potential impact of these polymorphisms on risk of AMD progression after controlling for the effect of the other risk factors, we calculated the AR (TABLE 4). Risks of progression attributable to these genotypes in this study population were 71.8% for both the *CFH Y402H* and *LOC387715 A69S* genotypes and 81.2%

for both genotypes combined with smoking and BMI.

Probabilities that a random progressor had a higher risk score than a random nonprogressor within each 10-year age group for various statistical models are also shown in Table 4. This C statistic, based on the receiver operating characteristic analysis, was 0.758 for the model with both genes, 0.768 for the model with these genes plus smoking and BMI, and 0.775 with the addition of the AREDS treatment variable.

The effects of interactions between the *CFH* and *LOC387715* genotypes on risk of AMD progression were assessed based on the number of risk alleles (TABLE 5). There were no gene-gene interactions associated with risk of AMD progression, and the test for interaction between these 2 genotypes was not significant (*P* = .50). For *CFH Y402H*, the risk of progression controlling for the other genotype increased from 2- to 2.5-fold from the low-risk genotype (TT) to the high-risk genotype (CC) (1.0 to 2.4 for *LOC387715*

**Table 4.** Attributable Risk and C Statistic Models\*

Variables	Attributable Risk, %	C Statistic (SE)
<i>CFH Y402H</i> and <i>LOC387715 A69S</i>	71.8	0.758 (0.019)
<i>CFH Y402H</i> , <i>LOC387715 A69S</i> , smoking, body mass index	81.2	0.768 (0.019)
<i>CFH Y402H</i> , <i>LOC387715 A69S</i> , smoking, body mass index, and treatment assignment		0.775 (0.019)

\*Attributable risk and C statistic models control for age (within 10 years for C statistic), sex, education, baseline age-related macular degeneration grade, and variables listed.

**Table 5.** Assessment of Combined Effects of *CFH* and *LOC387715* Variants on Risk of Progression to Advanced AMD

Genotype		No. (%)	Adjusted OR (95% CI)*	Multivariate Model 1 OR (95% CI)†
<i>CFH Y402H</i>	<i>LOC387715 A69S</i>			
TT	GG	214 (15)	1 [Reference]	1 [Reference]
CT	GG	305 (21)	1.1 (0.5-2.3)	1.0 (0.5-2.2)
CC	GG	168 (11)	2.5 (1.2-5.2)	2.4 (1.1-5.1)
TT	GT	179 (12)	1.9 (0.9-4.2)	1.9 (0.9-4.2)
CT	GT	247 (17)	3.8 (1.9-7.6)	3.8 (1.9-7.7)
CC	GT	179 (12)	5.5 (2.7-11.1)	5.4 (2.7-11.1)
TT	TT	28 (2)	3.6 (1.2-11.2)	3.7 (1.2-11.6)
CT	TT	94 (6)	6.0 (2.8-13.0)	5.7 (2.6-12.4)
CC	TT	52 (4)	7.1 (3.0-16.5)	7.0 (3.0-16.5)

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio.

\*Adjusted model was adjusted for age (50-69 vs 70-95 years), sex, education (high school or less vs more than high school), both genotypes, baseline and AMD grade.

†Multivariate model 1 was adjusted for age (50-69 vs 70-95 years), sex, education (high school or less vs more than high school), both genotypes, baseline AMD grade, smoking (never vs ever), body mass index (<25 vs ≥25, calculated as weight in kilograms divided by height in meters squared), and treatment assignment (antioxidants, zinc, antioxidants and zinc, or placebo).

genotype GG, 1.9 to 5.4 for *LOC387715* GT genotype, and 3.7 to 7.0 for the *LOC387715* TT genotype). For *LOC387715* A69S, risk of AMD progression controlling for the other genotype increased 3- to 6-fold from the low-risk (GG) to the high-risk (TT) genotypes (1.0 to 3.7 for the *CFH* TT genotype, 1.0 to 5.7 for the *CFH* CT genotype, and 2.4 to 7.0 for the *CFH* CC genotype). Compared with the low-risk genotypes for both genes, the risk increased 7-fold in the presence of the homozygous risk allele states for both polymorphisms (OR, 7.0; 95% CI, 3.0-16.5 in the multivariate model controlling for other risk factors).

Interactions between smoking and BMI and these 2 gene variants with regard to AMD progression were assessed (TABLE 6). Relative to leaner individuals, higher BMI tended to increase risk of progression for the heterozygous and homozygous *CFH* risk genotypes but not for the homozygous non-risk genotype. However, unlike our previous case-control analyses,<sup>8</sup> there was no significant interaction noted between BMI and genotype (*P* = .15). Heavier weight increased risk of AMD within each of 3 *LOC387715* genotypes relative to lean weight (from an OR of 2.8 to an OR of 4.2 for the heterozygous state and from an OR of 5.2 to an OR of 6.2 for the homozygous state). This relationship was similar

across all genotypes, and no statistical interaction was observed. Smoking increased risk relative to nonsmoking in both the homozygous nonrisk and risk *CFH* genotypes (ORs increased from 1.0 to 1.6 and from 2.8 to 3.8, respectively). Risk of AMD progression among smokers was slightly increased among all of the *LOC387715* genotypes. No statistical gene-environment interaction was observed for smokers.

Compared with being a nonsmoker with low BMI and having the homozygous nonrisk genotypes, the presence of all 4 risk factors, including high BMI, smoking, and having the homozygous risk allele state for both genes, was associated with an OR of 19 for risk of AMD progression. With the presence of both heterozygous genotypes, smoking, and high BMI, the OR was 7.8.

**COMMENT**

To our knowledge, this is the first report to prospectively evaluate the association between 2 reported common genetic polymorphisms and progression from early stages of AMD (drusen and pigment alterations) to advanced AMD (geographic atrophy or neovascular AMD), with its associated visual loss and reduced quality of life. In this large series of patients who all underwent careful phenotyping for presence or absence of AMD using standardized examinations and photogra-

phy, we were able to evaluate both *CFH* Y402H and *LOC387715* A69S genotypes and multiple environmental factors simultaneously, including BMI and smoking. These 2 common variants were both associated with AMD progression, controlling for demographic and environmental risk factors, which underscores the need to discourage smoking and control body weight, regardless of genotype.<sup>13,16,17</sup> In the presence of both homozygous risk genotypes, the risk of progression increased approximately 7-fold compared with the homozygous nonrisk genotypes. For the more common heterozygote state for both variants, the risk of AMD progression increased almost 4-fold.

Risk associated with the *LOC387715* genotype was more strongly related to neovascular disease compared with geographic atrophy and was somewhat greater for progression to bilateral advanced disease compared with unilateral advanced AMD, although the 95% CIs for these ORs overlapped. The effects of the *CFH* gene on AMD progression did not differ substantially for these subtypes of advanced disease.

Higher BMI and smoking increased risk within categories of the risk genotypes for both variants. The combination of being overweight and a smoker and having the homozygous risk genotypes for both *CFH* Y402H CC and *LOC387715* A69S TT conferred a 19-

**Table 6.** Risk of Progression to Advanced AMD According to BMI, Smoking, and Genotype and Assessment of Interactions

	<i>CFH</i> Y402H*				<i>LOC387715</i> A69S*			
	TT	CT	CC	<i>P</i> Value for Trend	GG	GT	TT	<i>P</i> Value for Trend
No. of progressors	41	119	121		65	147	69	
No. of nonprogressors	380	527	278		622	458	105	
OR (95% CI)								
BMI†								
<25	1 [Reference]	1.3 (0.6-2.6)	1.6 (0.8-3.4)		1 [Reference]	2.8 (1.4-5.4)	5.2 (2.3-11.7)	
≥25	1.0 (0.5-2.2)	1.8 (0.9-3.4)	3.2 (1.7-6.2)		1.6 (0.9-3.1)	4.2 (2.4-8.1)	6.2 (3.2-12.2)	
<i>P</i> value for interaction		.50 (CT vs TT)	.16 (CC vs TT)	.15		.94 (GT vs GG)	.52 (TT vs GG)	.60
Smoking								
Never	1 [Reference]	2.1 (1.1-4.2)	2.8 (1.4-5.6)		1 [Reference]	3.1 (1.8-5.3)	4.7 (2.5-9.2)	
Ever	1.6 (0.8-3.3)	2.1 (1.1-4.0)	3.8 (2.0-7.6)		1.4 (0.8-2.5)	3.5 (2.1-5.9)	5.3 (2.8-9.9)	
<i>P</i> value for interaction		.28 (CT vs TT)	.79 (CC vs TT)	.93		.58 (GT vs GG)	.59 (TT vs GG)	.63

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index; CI, confidence interval; OR, odds ratio.

\*Multivariate model 1 was adjusted for age (50-69 vs 70-95 years), sex, education (high school or less vs more than high school), 1 genotype, baseline AMD grade, smoking (never vs ever), BMI (<25 vs ≥25), and treatment assignment (antioxidants, zinc, antioxidants and zinc, or placebo).

†Body mass index was calculated as weight in kilograms divided by height in meters squared.

fold higher risk of AMD progression compared with leaner non-smokers who had the homozygous nonrisk genotypes. The discriminatory ability of the AMD progression risk score (C statistic), calculated based on age, sex, education, genotype, smoking history, and BMI, as well as treatment assignment, was relatively high (up to 0.78 for all factors combined among individuals of the same age). This is a multivariable-based risk estimate of AMD progression that could be used as a prognostic model to identify individuals for increased clinical surveillance and earlier treatment. This AMD score was only slightly lower than the Framingham risk score for coronary heart disease (0.79 for men and 0.83 for women),<sup>18</sup> although the latter values were not a comparison among same-sex persons with the same age, which would tend to inflate the C statistic.

The attributable risks for AMD progression in this study population were about 72% for the *CFH* Y402H and *LOC387715* A69S genotypes combined, and this increased somewhat to about 81% when smoking and BMI were added to the models. It is noteworthy that both genes were independently associated with progression to both subtypes of advanced AMD, geographic atrophy (dry) and neovascular (wet) disease, despite their very different phenotypic appearances. These prospective analyses expand on our previous cross-sectional case-control analyses, in which these variants were also associated with both dry and wet types of advanced AMD.<sup>7,8,19</sup>

The *CFH* gene is known to be involved in inflammatory and immune pathways,<sup>1-4</sup> and other haplotypes of this gene are associated with AMD,<sup>7,20</sup> although *CFH* Y402H has been the most replicated to date. The function of *LOC387715* A69S, however, remains unknown. Our recent report suggests that association in this region persists after conditioning on the SNP rs10490924 and that the gene region *HTRA1* contains SNPs that are genetically identical to the *LOC387715* SNP.<sup>7</sup> Two studies have shown that a variant

of the *HTRA1* gene may also increase susceptibility to AMD in white and Chinese populations.<sup>21,22</sup> Whether the *LOC387715* gene is related more strongly to neovascular mechanisms and conversion to the wet form of disease deserves further exploration. These disparate forms of advanced AMD are often seen in members of the same family.<sup>23</sup> Perhaps modifying genes, environmental factors, or both could influence the pathways that lead to either the dry or wet advanced forms of AMD. Researchers in AMD are increasingly emphasizing the contributions of both genetic and environmental factors and their associations with AMD,<sup>8,19,24-26</sup> which will help to shed light on these mechanisms.

Unique features of this study include the prospective design and the large, well-characterized population of white patients with early and intermediate disease in one or both eyes or advanced disease in one eye, some of whom progressed and some did not, from various geographic regions in the United States. Further strengths include 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 since grades were assigned without knowledge of risk factors or genotype, and outcomes (progression) were determined after collection of the baseline data and without knowledge of the genetic data. We controlled for known AMD risk factors, including age, education, BMI, smoking, and treatment assignment in the assessment of the effect of the 2 genetic variants on incidence of advanced AMD. Both the environmental and genetic risk factors were independently associated with progression of AMD, when considered simultaneously. 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, smoking, and BMI and a strong risk factor for AMD progres-

sion to explain these results. Although this is a selected population, participants who progressed likely represent typical patients with early or intermediate stages of AMD at risk of progression, and 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. This large sample size and well-characterized population provided a unique opportunity to evaluate gene-environment associations and interactions. Furthermore, the biological effects of *CFH* and *LOC387715* together with the modifiable factors do not appear to differ in major ways among various white populations with AMD.

These results and other similar reports on genes yet to be discovered may in the future affect the management of this disease. People with the high-risk genotype are more likely to progress from intermediate dry forms of AMD to advanced dry or wet forms of the disease. They are not necessarily destined to develop the disease, since some people with AMD who progress have the nonrisk genotype and some people without AMD progression carry the risk genotype. However, individuals with the risk genotype, if identified and appropriately advised, may be more motivated to adhere to healthy lifestyle habits, which are known to be related to a reduced risk of AMD. These include not smoking, maintaining a normal or lean weight, getting exercise, and eating an antioxidant-rich diet with fruits and vegetables as well as fish.

We believe it is premature at this time to consider genotyping individuals with various stages of AMD. Screening should consider (1) that genotyping of about 30 individuals with drusen/pigment changes would be required to identify 1 individual who is homozygous for the risk allele for both genes and (2) the observation that many but not all individuals with those genotypes will develop the disease. However, in the future, a risk profile that includes genetic and environmental factors, such as the one calculated herein, may ultimately lead to targeted screening and closer monitoring of

individuals who are at higher risk of visual loss due to AMD progression.

In summary, these 2 common genetic variants are independently associated with progression to advanced forms of AMD, which cause visual impairment and blindness. The combination of genetic variants and risk factors reported herein predicts which individuals are at greatest risk of progressing to loss of vision because of AMD.

**Author Contributions:** Drs Seddon and Rosner had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Seddon, Rosner, Klein.

**Acquisition of data:** Seddon, Schultz, Klein.

**Analysis and interpretation of data:** Seddon, Rosner, Francis, George, Klein.

**Drafting of the manuscript:** Seddon, George, Rosner.

**Critical revision of the manuscript for important intellectual content:** Seddon, Francis, George, Schultz, Rosner, Klein.

**Statistical analysis:** Rosner, Seddon.

**Obtained funding:** Seddon, Klein.

**Administrative, technical, or material support:** Seddon, Francis, George, Klein.

**Study supervision:** Seddon, Rosner, Klein.

**Financial Disclosures:** Dr Seddon reports that she is named as an inventor on a patent application (US Patent Application No. 11/066,641, filed by Massachusetts Eye and Ear Infirmary on February 25, 2005, and published as US-2005-0250745-A1 on November 10, 2005) regarding biomarkers for age-related macular degeneration.

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## Confidentiality of Medical Information After Death

**To the Editor:** In their Commentary, Drs Robinson and O'Neill<sup>1</sup> state that "to prevent erosion of the right to confidentiality after death, it is important that physicians and other health care workers strive to ensure that this confidentiality is preserved to the maximum degree possible." This is actually a familiar concept in the US medical ethics tradition.

The policy of the American Medical Association (AMA) provides clear guidelines for physicians who are faced with requests to disclose medical information after a patient's death. The AMA Code of Medical Ethics<sup>2</sup> states that medically related confidences and information contained within a deceased patient's medical record "should be kept confidential to the greatest possible degree." This ethical standard is almost identical to that suggested by Robinson and O'Neill.

In addition, the AMA ethical opinion<sup>2</sup> suggests that confidentiality of medical information postmortem receive the same protection as information would receive in life. Medical information during life is granted a great amount of protection, subject only to legal requirements to disclose and situations that justify disclosure due to overriding considerations (and even then, only minimal information may be disclosed).<sup>3</sup> The ethical opinion also provides factors that should be considered when a physician is deciding whether to disclose information, such as imminence of harm to identifiable individuals or the public health, potential benefits to at-risk persons or the public health, and the impact the disclosure would have on the deceased patient.

When discussing ethical issues, professional guidelines provide advice and guidance to resolve common problems faced by physicians. Although laws may not resolve the question of whether disclosure of medical information postmortem is permissible, ethical obligations do provide one answer.

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**Editor's Note:** Dr Sade is chair of the Council on Ethical and Judicial Affairs for the American Medical Association.

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**In Reply:** Dr Sade's comments are a useful reminder of the often divergent agendas of law and clinical ethics. However, it is clear that the AMA guidelines,<sup>1</sup> with which we are in agreement, may not be shared by all North American writers on medical ethics.<sup>2</sup> Given the still underdeveloped nature of ethics teaching in many medical schools worldwide,<sup>3,4</sup> his letter points to 2 professional development imperatives: (1) staffing, funding, and curricular status of medical ethics teaching must be strengthened, and (2) professional organizations must continue to lobby intensively for legislation that is sensitive to ethical clinical practice. As our Commentary indicates, this is particularly relevant to freedom of information legislation.

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## CORRECTIONS

**Error in Wording:** In the Original Contribution entitled "Association of CFH Y402H and LOC387715 A69S With Progression of Age-Related Macular Degeneration" published in the April 25, 2007, issue of *JAMA* (2007;297:1793-1800), there was an error in the "Conclusions" section of the abstract. The second sentence of that section should have read, "Presence of these polymorphisms plus smoking and body mass index of 25 or higher, controlling for AREDS vitamin-mineral treatment, identifies patients who are highly susceptible to developing advanced states of this visually disabling disease."