

# The *LOC387715* Gene, Smoking, Body Mass Index, Environmental Associations with Advanced Age-Related Macular Degeneration

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## Key Words

AMD · Environmental risk factor · Epidemiologic approaches · Gene-environment interaction · Genotype · Macular degeneration

## Abstract

**Background and Aims:** Age-related macular degeneration (AMD) is the leading cause of blindness in the Western World. It is now evident that both genetic and environmental factors contribute to disease susceptibility. We tested the hypotheses that (a) a common coding SNP in the *LOC387715* gene is associated with advanced AMD (geographic atrophy or choroidal neovascularization), and (b) that modifiable environmental exposures alter AMD susceptibility associated with this SNP. **Methods:** A case-control association analysis was performed on participants (530 advanced AMD cases and 280 controls) ascertained as part of the multi-center Age-Related Eye Disease Study. AMD status was determined by the reading center from fundus photographs using the AREDS AMD grading categorization. Environmental risk factor exposure data was collected from participants whose DNA was

also genotyped for the *LOC387715* gene SNP rs10490924. Multivariate logistic regression analyses were performed. **Results and Conclusions:** The number of risk alleles at the *LOC387715* SNP was associated with advanced AMD, with odds ratios (OR) = 3.0 (95% confidence interval (CI) 2.1–4.3) for the GT heterozygous genotype and OR = 12.1 (5.6–26.5) for the homozygous TT risk genotype, after controlling for demographic and behavioral risk factors. The *LOC387715* SNP was associated with both forms of advanced AMD. Current cigarette smoking and body mass index were independently related to AMD, controlling for genotype. However, there was no statistical interaction between *LOC387715* genotype and smoking with regard to advanced AMD development.

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## Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world [1, 2]. It is now undisputed that both genetic [3–5] and environmental factors [2] contribute to its development. Keys to establishing the pathogenesis of the condition will be to understand the epigenetic and epistatic interactions between the many genes and environmental factors involved.

Considerable progress has been made in the last two years in identifying susceptibility genes for AMD. The

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association of coding single nucleotide polymorphisms (cSNPs) in the *CFH* [6–10] and *LOC387715* [11, 12] genes with advanced AMD susceptibility have now been replicated in a number of independent studies [13–15], and non-coding SNPs have also been identified [15]. However, as yet, there is very limited functional data to implicate ‘causality’ of these sequence variants in disease development. From an epidemiologic standpoint, a number of factors have been identified that appear to confer increased risk of developing AMD including cigarette smoking [16, 17], higher body mass index (BMI) [18, 19], and nutritional factors [20–23].

We have previously examined the role of the common *CFH* polymorphism (exon 9, 1277T>C, Y402H, rs1061170) in the development of advanced AMD in the Age-Related Eye Disease (AREDS) cohort of patients [14]. The AREDS study was a randomized clinical trial to assess the effect of antioxidant and mineral supplements on risk of AMD (and cataract) and a longitudinal study of progression of AMD which ended in December, 2005. We found a strong association between the *CFH* cSNP and advanced AMD development, controlling for environmental factors, and independent associations with smoking and increased body mass index when controlling for genotype. The association between advanced AMD and BMI varied dependent on genotype, but no interaction was seen between *CFH* Y402H and smoking.

In this article, we examine the role of the *LOC387715* cSNP (exon 1, G>T, A69S, rs10490924) in determining advanced AMD development in the AREDS cohort and assess possible interactions with environmental factors.

## Materials and Methods

The AREDS study procedures have been previously reported [19, 20]. DNA was extracted from venous blood from approximately half the AREDS participants and was obtained from the AREDS Genetic Repository.

As in our previous study, Caucasian participants (who had provided a DNA sample) were divided into two groups representing the most discordant phenotypes: no AMD with either no drusen or non-extensive small drusen ( $n = 280$ , AREDS grade 1), or advanced AMD with visual loss ( $n = 530$ , AREDS grade 4) [20]. The advanced form of AMD was then reclassified into the three subtypes: geographic atrophy (GA,  $n = 147$ , choroidal neovascular (CNV) disease ( $n = 241$ ) and those who have both forms of advanced AMD in the same eye or bilaterally ( $n = 142$ ) as in the Clinical Age-Related Maculopathy Grading System [24]. These case groups are mutually exclusive categories and each was compared with the control group (AREDS grade 1). To further investigate the possible selective effects of genotype on advanced AMD phenotype, cases were divided into three categories:

CNV, GA, or those with CNV and GA in the same or fellow eye.

Environmental risk factor data was obtained by a trained interviewer at the baseline visit from participants using standardized validated questionnaires and height and weight measurements [20].

### Genotyping

The non-synonymous coding single nucleotide polymorphism (SNP) in the *LOC387715* gene (rs10490924) was evaluated. Genotyping was performed using Sanger sequencing at Prevention Genetics (Marshfield, Wisc., USA). Genotyping of the *CFH* Y402H variant was performed at the Broad Institute (Cambridge, Mass., USA).

### Statistical Analyses

Adjusted unconditional logistic regression analysis was performed to determine the relationship between the *LOC* genotype and AMD status using a model that adjusted for age (50–69, 70–95), gender, education (high school, >high school) smoking (never, past, current), BMI (<25, 25–29,  $\geq 30$ ), antioxidants (taking a supplement containing antioxidants or taking study supplements containing no antioxidants) and *CFH* genotype (TT, TC, CC) [14]. Additionally, a test for trend related to the number of risk alleles (0, 1, 2) was calculated. The cross product terms according to genotype and the individual risk factors were used to test for multiplicative interactions. Odds ratios and the corresponding 95% confidence intervals were calculated for each of the risk factors.

## Results

The distribution of the variables according to *LOC387715* genotype, for controls and cases with geographic atrophy (GA), choroidal neovascularization (CNV), or both GA and CNV are shown in table 1. Compared to controls, cases were older, had fewer years of education, were more likely to smoke, and had higher body mass index.

The odds ratios for the adjusted and multivariate models, comparing advanced AMD cases with controls, for genetic, demographic, and behavioral risk factors are shown in table 2. The data show that the number of risk alleles at the *LOC387715* SNP was associated with advanced AMD, OR = 3.0 (95% confidence interval, CI, 2.1–4.3) for the GT heterozygous genotype and OR = 12.2 (5.6–26.6) for the homozygous TT risk genotype, after controlling for demographic and behavioral risk factors. For the homozygous TT genotype, OR's for the sub-phenotypes of advanced AMD were 7.9 (CI 2.9–21.0) for geographic atrophy, 10.0 (4.4–23.3) for neovascular AMD, and 29.3 (11.4–75.6) for both GA and neovascular AMD, compared with controls.

For each additional ‘T’ allele, there was an increased risk of advanced AMD, and this ‘dose effect’ for the ‘T’

**Table 1.** Distribution of demographic and behavioral risk factors for advanced AMD in the AREDS cohort

	Controls		Geographic atrophy		Neovascular AMD		Neovascular AMD and geographic atrophy (n = 142)	
	(n = 280)		(n = 147)		(n = 241)		(n = 142)	
	n	%	n	%	n	%	n	%
Age, years								
50–69	204	73	82	56	126	52	65	46
70–95	76	27	65	44	115	48	77	54
Gender								
Male	127	45	68	46	99	41	55	39
Female	153	55	79	54	142	59	87	61
Education								
High school or less	79	28	58	39	104	43	65	46
Some college or more	201	72	89	61	137	57	77	54
Smoking								
Never	143	51	57	39	89	37	56	39
Past	122	44	74	50	121	50	74	52
Current	15	5	16	11	31	13	12	8
Body Mass Index								
<25	103	37	48	33	67	28	35	25
25–29.9	114	41	54	37	105	44	60	42
≥30	63	23	45	31	69	29	47	33
AREDS RX								
No antioxidants	151	54	82	56	124	51	74	52
Antioxidants	129	46	65	44	117	49	68	48

Data are numbers (percentages rounded to the nearest whole number).

allele was highly significant (all  $p$  values  $<0.001$ ). Controlling for genotype and other factors, age 70 years or older was associated with a significant 2- to 4-fold greater risk of advanced AMD. Controlling for age, genotype, and other factors, gender had no effect on risk of developing advanced AMD. Higher educational status (more than high school) was associated with a lower risk of AMD for both GA and CNV (OR's 0.5 and 0.6 respectively) compared with high school or less education.

To determine what the mode of gene action was we also performed a test to determine if the influence of the gene was additive or dominant. We found that there was significant evidence that *LOC387715* ( $p < 0.0001$ ) acted in an additive manner. Under logistic regression because of the logit transform the additive model is multiplicative. There was no evidence ( $p = 0.48$ ) that *LOC387715* had any dominant gene action, i.e. there was no evidence that the heterozygote deviated from what is expected under an additive gene model.

Cigarette smoking was associated with a statistically significant increased risk of advanced AMD for all subtypes, controlling for genotype and other factors, with

multivariate OR's for current smoking ranging from 2.2 to 3.7, and OR's 1.6 to 2.0 for past smoking. Body mass index of  $\geq 30$  kg/m<sup>2</sup> conferred increased risk for advanced AMD (OR from 1.6 to 2.4), and these associations were significant for the overall case group as well as the combination of GA and NV case group, compared with controls.

Potential interactions between *LOC387715* genotype and modifiable risk factors (BMI and smoking) are shown in table 3. No interaction was seen between increased body mass index and either the 'TT' risk genotype or the number of 'T' alleles. Borderline evidence favoring an interaction between lower BMI ( $<25$ ) and GA was seen but this became non-significant when corrected for multiple testing. Any of the non-significant interaction values could have been the result of limitations in sample size.

Increased risk of AMD was seen for smoking within each genotype, and for all types of advanced AMD. For example, in the overall advanced AMD case group, comparing smokers to those who never smoked, for heterozygotes the risk increased from 3- to 6-fold, and for the homozygote risk genotype, risk increased from about 10- to 27-fold. Increased risk associated with the presence of

**Table 2.** Association between advanced AMD and genetic, behavioral, and demographic risk factors

	Advanced AMD		Geographic atrophy		Neovascular AMD		Neovascular AMD and Geographic atrophy	
	OR (CI)	p value	OR (CI)	p value	OR (CI)	p value	OR (CI)	p value
No. of cases/controls	530		147		241		142	
Genotype	1.0		1.0		1.0		1.0	
GG	1.0		1.0		1.0		1.0	
GT	3.0 (2.1–4.3)	<0.001	2.9 (1.8–4.7)	<0.001	2.9 (1.9–4.5)	<0.001	4.7 (2.6–8.5)	<0.001
TT	12.2 (5.6–26.6)	<0.001	7.9 (2.9–21.0)	<0.001	10.0 (4.3–23.3)	<0.001	29.3 (11.4–75.6)	<0.001
No. of T alleles (p trend)	<0.001		<0.001		<0.001		<0.001	
Age	1.0		1.0		1.0		1.0	
<70	1.0		1.0		1.0		1.0	
≥70	2.8 (2.0–4.1)	<0.001	2.3 (1.4–3.8)	<0.001	3.0 (1.9–4.6)	<0.001	4.4 (2.5–7.7)	<0.001
Gender	1.0		1.0		1.0		1.0	
Female	1.0		1.0		1.0		1.0	
Male	1.1 (0.8–1.6)	0.542	0.9 (0.6–1.5)	0.677	1.1 (0.7–1.8)	0.590	1.8 (1.0–3.2)	0.052
Education	1.0		1.0		1.0		1.0	
≤HS	1.0		1.0		1.0		1.0	
>HS	0.5 (0.4–0.8)	0.001	0.6 (0.4–1.0)	0.039	0.6 (0.4–0.9)	0.007	0.6 (0.3–1.0)	0.065
Smoking	1.0		1.0		1.0		1.0	
Never	1.0		1.0		1.0		1.0	
Past	1.8 (1.2–2.6)	0.002	1.6 (1.0–2.7)	0.061	2.0 (1.3–3.2)	0.003	2.0 (1.1–3.7)	0.017
Current	3.3 (1.7–6.7)	0.001	3.7 (1.5–9.0)	0.005	3.5 (1.6–7.7)	0.001	2.2 (0.8–6.4)	0.146
BMI	1.0		1.0		1.0		1.0	
<25	1.0		1.0		1.0		1.0	
25–29.9	1.1 (0.7–1.7)	0.639	0.9 (0.5–1.6)	0.711	1.2 (0.7–2.0)	0.455	1.4 (0.7–2.8)	0.299
≥30	1.8 (1.2–2.9)	0.009	1.6 (0.9–2.9)	0.138	1.7 (1.0–3.0)	0.066	2.4 (1.2–4.9)	0.018
AREDS RX	1.0		1.0		1.0		1.0	
No antioxidants	1.0		1.0		1.0		1.0	
Antioxidants	1.2 (0.8–1.6)	0.438	1.1 (0.7–1.7)	0.790	1.3 (0.9–2.0)	0.206	1.2 (0.7–2.1)	0.496

OR = Odds Ratio; CI = 95% confidence interval.

a T allele was seen for both smokers and non-smokers, although the risks for AMD were higher for smokers. The tests for interaction between genotype and cigarette smoking were not statistically significant.

## Discussion

The results of this study show that the number of risk alleles at the *LOC387715* SNP was associated with advanced AMD, OR = 3.0 (2.1–4.3) for the GT heterozygous genotype and OR = 12.2 (5.6–26.6) for the homozygous TT risk genotype, after controlling for demographic and behavioral risk factors. The *LOC387715* SNP was associated with both forms of advanced AMD. Current cigarette smoking and higher BMI were independently related to AMD, controlling for genotype. However, we did not observe an interaction between the *LOC387715* genotype and BMI or smoking with regard to diagnosis of advanced AMD.

Advanced AMD is characterized by poor central vision following the development of: (1) neovascularization (CNV) which leads to hemorrhage and scarring in the retina or (2) patches of retinal pigment epithelial atrophy, 'geographic atrophy' (GA). These two forms may coexist either in the same eye or in both eyes [1].

The Age-Related Eye Disease Study was an eleven-center double-masked clinical trial. Participants were enrolled in the AMD trial arm which investigated the effects of oral antioxidant and vitamin supplements on disease progression if they had extensive small drusen, intermediate drusen, large drusen, non-central geographic atrophy, or pigment abnormalities in one or both eyes, or advanced AMD or vision loss due to AMD in one eye. At least one eye had best-corrected visual acuity of 20/32 or better [20]. About half of the enrolled subjects provided a blood sample for genotyping analysis. For this study, we chose the most discordant participants regarding AMD phenotype: cases with advanced AMD and controls with no significant drusen. To further investigate the possible selective effects of genotype on advanced

**Table 3.** Risk of age-related macular degeneration according to BMI, smoking and genotype and assessment of interactions

	Genotype			p (trend) for no. of T alleles
	GG	GT	TT	
<b>Number of cases</b>				
Advanced AMD	167	261	102	
Geographic atrophy	54	75	18	
Neovascular AMD	82	118	41	
Neovascular AMD and geographic atrophy	31	68	43	
<b>Number of controls</b>				
	181	91	8	
<b>BMI</b>				
<b>Advanced AMD</b>				
<25	1.0	3.8 (2.0–7.1)	17.9 (3.96–83.1)	
25+	1.61 (0.96–2.67)	4.4 (2.6–7.55)	15.85 (6.1–40.9)	
P (interaction)		0.36 (GG vs. GT)	0.53 (GG vs. TT)	0.31
<b>Geographic atrophy</b>				
<25	1.00	4.95 (2.1–11.68)	24.83 (4.22–146.02)	
25+	1.81 (0.86–3.78)	4.18 (1.96–8.88)	7.11 (1.96–25.79)	
P (interaction)		0.1323 (GG vs. GT)	0.0943 (GG vs. TT)	0.04
<b>Neovascular AMD</b>				
<25	1.00	2.74 (1.28–5.87)	12.44 (2.36–65.53)	
25+	1.38 (0.74–2.57)	4.03 (2.15–7.56)	13.2 (4.68–37.25)	
P (interaction)		0.9465 (GG vs. GT)	0.7718 (GG vs. TT)	0.89
<b>Neovascular AMD and Geographic atrophy</b>				
<25	1.00	5.17 (1.75–15.22)	30.4 (4.88–189.4)	
25+	1.82 (0.69–4.81)	8.91 (3.46–22.9)	49.87 (14.03–177.27)	
P (interaction)		0.8531 (GG vs. GT)	0.9628 (GG vs. TT)	0.90
<b>Smoking</b>				
<b>Advanced AMD</b>				
Never	1.00	3.15 (1.84–5.39)	10.61 (3.44–32.72)	
Ever	2.01 (1.24–3.26)	5.9 (3.57–9.76)	27.52 (9.22–82.14)	
P (interaction)		0.8088 (GG vs. GT)	0.7736 (GG vs. TT)	0.9961
<b>Geographic atrophy</b>				
Never	1.00	2.81 (1.36–5.82)	6.84 (1.65–28.38)	
Ever	1.78 (0.91–3.49)	5.1 (2.59–10.03)	16.04 (4.12–62.49)	
P (interaction)		0.9200 (GG vs. GT)	0.8387 (GG vs. TT)	0.8475
<b>Neovascular AMD</b>				
Never	1.00	2.99 (1.54–5.79)	8.02 (2.37–27.1)	
Ever	2.19 (1.2–3.97)	6.06 (3.28–11.19)	27.66 (8.31–92.05)	
P (interaction)		0.8275 (GG vs. GT)	0.6238 (GG vs. TT)	0.8597
<b>Neovascular AMD and Geographic atrophy</b>				
Never	1.00	4.6 (1.92–10.99)	18.29 (4.7–71.15)	
Ever	1.82 (0.76–4.33)	8.96 (3.91–20.53)	77.82 (20.21–299.6)	
P (interaction)		0.9086 (GG vs. GT)	0.3859 (GG vs. TT)	0.4937

BMI = body mass index; P (interaction) = probability of interaction occurring between environmental factor and LOC387715 genotype.

AMD phenotype, cases were divided into three categories: CNV, GA, or those with CNV and GA in the same or fellow eye. The number of cases with advanced AMD is slightly less than the number included in our previous analysis of CFH in the AREDS group [14] due to reduced genotyping efficiency.

After adjustment for demographic and behavioral factors, the reported variant [5, 11–13, 15] of the *LOC387715* gene on chromosome 10q26 was strongly associated with advanced AMD, and similar effects were seen for both geographic atrophy and neovascular disease (odds ratios between 7.9 and 12.2). For those cases with both neovas-

cular disease and GA, the odds ratio rose to 29.3 (95% confidence intervals 11.4–75.6) for those with the ‘TT’ genotype. This high odds ratio is probably due to the fact that the GA/CNV individuals are the most extreme genetic cases. This is further illustrated by the fact that 80% of the GA/CNV individuals have both eyes affected, whereas only 44% of the CNV individuals and 60% of the GA individuals have both eyes affected. When we compare the influence of the *LOC387715* TT genotype on individuals who have only one eye affected with advanced AMD we observe an odds ratio of 5.0–5.5 whereas the odds ratio jumps to 25.4–27.6 when we consider individuals with both eyes affected. This suggests that it may not necessarily be the presence of both GA and CNV that is as important as how many eyes are affected. No comparisons with previous studies are possible, since these did not include a combined advanced AMD category [11–15]. Currently, the function of the *LOC387715* gene product is unknown. Our recent report suggests association in this region persists after conditioning on the SNP, rs10490924, and that the gene region HTRA1 contains snp’s that are genetically identical to the *LOC387715* SNP [15].

Prior to the identification of *LOC387715* as the susceptibility gene at the much described 10q26 AMD susceptibility locus [25–28], Weeks and colleagues [29] suggested an interaction between smoking and this chromosomal interval. This was also reported by Schmidt et al. [13]. However, studies by Jacobsdottir et al. [11] and Rivera et al. [12], and now the AREDS cohort described in this study found no interaction between the *LOC387715* SNP rs10490924 and smoking.

In this AREDS cohort, data collection was prospective and smoking prevalence (48.9% controls, 61.8% cases) and ages of patients and controls were comparable to Schmidt’s cohort. In contrast to Schmidt’s cohort [13], these AREDS analyses did not include intermediate degrees of AMD in the case group, smokers were divided into ‘past’ and ‘current’ which were both associated with advanced AMD, and we found that smoking increased risk of AMD within all genotypes, not only the GT and TT genotypes. We found no interaction between *LOC387715* rs10490924 and cigarette smoking.

## Conclusions

This study supports evidence that the *LOC387715* gene is an important susceptibility gene for age-related macular degeneration, independent of demographic and behavioral factors. Although both cigarette smoking and

higher BMI were related to advanced AMD, no interactions were observed between the *LOC* gene and these modifiable risk factors.

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### *Role of Sponsor*

The funding organizations did not influence the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation or approval of the manuscript.

### *Author Contributions*

Each author had full access to the data and take responsibility for the integrity and accuracy of the data analyses.

*Study concept and design:* Klein, Francis, Seddon

*Acquisition of data:* Klein, Seddon

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

*Drafting of manuscript:* Francis

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*Statistical expertise:* Hamon, Ott, Rosner

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*Study supervision:* Seddon, Klein.

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