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THE *ARMS2* A69S VARIANT AND BILATERAL ADVANCED AGE-RELATED MACULAR DEGENERATION

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Abstract

Purpose—To identify genetic associations between specific risk genes and bilateral advanced age-related macular degeneration (AMD) in a retrospective, observational case series of 1,003 patients: 173 patients with geographic atrophy in at least 1 eye and 830 patients with choroidal neovascularization in at least 1 eye.

Methods—Patients underwent clinical examination and fundus photography. The images were subsequently graded using a modified grading system adapted from the Age-Related Eye Disease Study. Genetic analysis was performed to identify genotypes at 4 AMD-associated variants (*ARMS2* A69S, *CFH* Y402H, *C3* R102G, and *CFB* R32Q) in these patients.

Results—There were no statistically significant relationships between clinical findings and genotypes at *CFH*, *C3*, and *CFB*. The genotype at *ARMS2* correlated with bilateral advanced AMD using a variety of comparisons: unilateral geographic atrophy versus bilateral geographic atrophy ($P = 0.08$), unilateral choroidal neovascularization versus bilateral choroidal neovascularization ($P = 9.0 \times 10^{-8}$), and unilateral late AMD versus bilateral late AMD ($P = 5.9 \times 10^{-8}$).

Conclusion—In this series, in patients with geographic atrophy or choroidal neovascularization in at least 1 eye, the *ARMS2* A69S substitution strongly associated with geographic atrophy or

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choroidal neovascularization in the fellow eye. The *ARMS2* A69S substitution may serve as a marker for bilateral advanced AMD.

Keywords

age-related macular degeneration; *ARMS2*; choroidal neovascularization; genotypes; geographic atrophy

Despite continued advances in retinal care, age-related macular degeneration (AMD) remains the leading cause of irreversible visual loss among the elderly in developed countries.¹ Advanced AMD is characterized by geographic atrophy (GA) and/or choroidal neovascularization (CNV), with associated potential severe visual loss.² Bilateral advanced AMD is associated with worse functional outcomes and increased health resource usage and societal costs.³ Recent studies have established AMD susceptibility loci at or near the genes *CFH*,⁴⁻⁷ *ARMS2*,⁸ *C3*,^{9,10} *CFB*,¹¹ and others. However, less is known about the influence of these genes on disease severity or bilaterality. We performed a retrospective study in an observational case series in an attempt to identify genetic associations between genotype in these major AMD risk genes and bilateral advanced AMD.

Methods

This clinic-based data set contained 1,401 unrelated non-Hispanic white patients with AMD, 1,003 of whom had advanced AMD (GA or CNV) in at least 1 eye. Patients were recruited from the Duke University Eye Center, the Vanderbilt Eye Institute, and the Bascom Palmer Eye Institute. Patients were recruited without considering severity or bilaterality of disease. Written informed consent was obtained from all patients. This study was approved by the Institutional Review Boards of all participating institutions, was compliant with the Health Insurance Portability and Accountability Act of 1996, and adhered to the tenets of the Declaration of Helsinki.

All patients were examined by a fellowship-trained retina specialist. Examination techniques included slitlamp biomicroscopy and dilated fundus examination, including indirect ophthalmoscopy. Fundus photography was obtained, and the images were subsequently graded using a modified grading system adapted from the Age-Related Eye Disease Study (Table 1).¹² History of cigarette smoking was obtained from participants via a self-administered questionnaire, and individuals were classified as “ever” smokers if they reported smoking at least 100 cigarettes over their lifetimes.

Whole blood was obtained and processed for DNA extraction using a standard protocol (Puregene; Gentra Systems, Minneapolis, MN). Patient genotypes were determined using previously described assays for *CFH* Y402H (CC, CT, or TT),⁵ *ARMS2* A69S (GG, GT, or TT),¹³ *C3* R102G (GG, GC, or CC),¹⁴ and *CFB* R32Q (GG, GA, or AA).¹⁵ Briefly, regardless of assay, genotypes were obtained by using sample sets randomized regarding clinical status and center of origin, with DNA samples from Foundation Jean Dausset-Centre d’Etude du Polymorphisme Humain families duplicated between and across plates for use as a quality control. All markers included in this analysis had >.95% reproducibility and

efficiency. Genotypes for each marker were in Hardy–Weinberg equilibrium in controls. All laboratory personnel were masked to the affection status of the individuals being genotyped.

Association of AMD grade with sex was assessed by chi-square test of association, and association with age was assessed by one-way analysis of variance. Univariate association of AMD severity with genotype at each polymorphism was assessed with Fisher exact test. Association of genotype at each polymorphism (coded in additive fashion—0, 1, 2—as the number of minor alleles) with highest AMD grade and occurrence of late AMD in the fellow eye was examined using unconditional logistic regression, adjusting for age at examination and sex. Modification of associations by cigarette smoking was examined by incorporating the main effect of smoking (coded 1 if ever smoked 100 cigarettes and 0 otherwise) and an interaction term between genotype and smoking and testing the significance of these terms in the model. All analyses were conducted using the SAS system Version 9.1 (SAS Institute, Cary, NC).

Results

The mean age at examination and sex distribution of the case series is described by grade in the more severely affected eye in Table 2. We enrolled 1,401 unrelated patients with AMD (Grade 3 or above). Of these, 1,003 patients had advanced AMD (Grade 4 or above): 173 had GA (Grade 4) in at least 1 eye and 830 had CNV (Grade 5) in at least 1 eye. All patient groups were ~60% women. Patients with Grade 3 disease (i.e., no GA or CNV) were significantly younger than patients with GA or CNV ($P < 0.0001$).

The distribution of genotypes at *CFH*, *C3*, *CFB*, and *ARMS2* by grade is described in Table 3. There were no significant differences among the patients with Grade 3, 4, or 5 disease regarding genotypes at *CFH*, *C3*, and *CFB*, adjusting for age and sex. There was a statistically significant relationship between the *ARMS2* genotype and the grade of AMD. With advancing grades of disease, there was an increasing allele frequency of the *ARMS2* A69S TT genotype (Fisher exact $P = 8.20 \times 10^{-11}$).

Of the 173 patients with GA, 167 patients had clinical data recorded for both eyes. Of these 167 patients, 121 (72%) had GA in the fellow eye and 46 (28%) had milder disease (Grades 1–3) in the fellow eye. Of the 830 patients with CNV, 808 patients had clinical data recorded for both eyes. Of these 808 patients, 496 (61%) had GA or CNV in the fellow eye and 312 (39%) had milder disease (Grades 1–3) in the fellow eye.

The associations of the risk alleles at *CFH*, *C3*, *CFB*, and *ARMS2* with the presence of bilateral advanced AMD, adjusted for age and sex, are described in Table 4. Three comparisons were performed: unilateral GA versus bilateral GA, unilateral CNV versus bilateral CNV, and unilateral late AMD (GA and CNV combined) versus bilateral late AMD (GA and CNV combined). There were no significant differences in genotypes at *CFH*, *C3*, and *CFB* in any of these 3 comparisons. There was a statistically significant relationship between the *ARMS2* genotype and bilateral advanced AMD. In patients with GA in at least 1 eye, the presence of GA in the fellow eye was weakly associated with increasing numbers of T alleles (test for trend odds ratio = 1.57; $P = 0.08$). In patients with CNV in at least 1 eye,

the presence of CNV in the fellow eye was more strongly associated with the T allele (odds ratio = 1.82; $P = 9.0 \times 10^{-8}$). Similarly, in individuals with either GA or CNV in 1 eye, the T allele was strongly associated with bilateral AMD (odds ratio = 1.73, $P = 5.9 \times 10^{-8}$). No effect modification or confounding by cigarette smoking was detected for any genotype or comparison tested (data not shown).

The age of onset of symptoms or age at first diagnosis of AMD was not available for the majority of these participants; only the age of enrollment in the study was available. Therefore, the duration of disease could not be considered in the analysis. Age at enrollment, however, was available and considered as a covariate, and mean ages for each group are described in Table 4.

Discussion

There is a complex relationship between various genetic markers and the risk of AMD.^{16,17} A growing body of literature suggests that certain features of bilateral AMD may be associated with specific genetic variants. The Blue Mountains Eye Study reported that the *CFH* Y402H CC genotype associates with bilateral involvement of any soft drusen, distinct soft drusen, and pigmentary abnormalities, but not with bilateral late AMD (GA or CNV).¹⁸ Conversely, a study in U.S. Hispanic/Latino cases found that the *CFH* Y402H CT and TT genotypes associated with bilateral intermediate-to-large soft drusen.¹⁹ Finally, a study by Chen et al²⁰ reported that the A allele for *HTRA1* polymorphism rs11200638, which is in strong linkage disequilibrium ($r^2 > 0.9$) with *ARMS2* A69S, associates with bilateral CNV and GA.

In this series, an allele at *ARMS2*, but not at *CFH*, *C3*, or *CFB*, is strongly associated with the presence of bilateral advanced AMD. The relationship appears to exist with both CNV and GA, although the subset of GA patients is smaller than the subset of CNV patients. This is an observational, nonconsecutive series of non-Hispanic white patients that represents only a small fraction of the patients seen at three clinical sites in the southeastern United States. These patients may not be representative of all AMD patients or of the elderly population as a whole. There is no documented longitudinal follow-up, which may be important because at least some of the patients with unilateral advanced AMD will develop bilateral disease with time. However, this result is consistent with and extends previous studies that have demonstrated a strong relationship between *ARMS2* A69S and advanced AMD. For example, *ARMS2* A69S has been reported to be an independent risk factor for CNV.²¹ There is a reported association between various features of advanced AMD and *ARMS2*, but not *CFH*.²²

This study confirms and extends the results reported by Chen et al, who demonstrated that the A allele in *HTRA1* promoter polymorphism rs11200638 was more frequent in bilateral late AMD.²⁰ The *ARMS2* A69S substitution and *HTRA1* polymorphisms are in very strong linkage disequilibrium, and their effects are indistinguishable statistically. Although studies have suggested a functional effect of each single nucleotide polymorphism underlying the association with AMD, evidence that the *HTRA1* polymorphism is functional and influences gene expression is inconsistent.²³⁻³¹ This inconsistency, coupled with the observation that

the *ARMS2* A69S variant changes the amino acid sequence of this protein, has suggested that *ARMS2* is the more likely AMD gene in this region. Although this continues to be debated in the literature, the lack of certainty on which gene is the AMD locus does not change the interpretation of the present findings: Our results are consistent with those reported by Chen et al, and both studies demonstrate that the AMD susceptibility locus in this region is associated with bilateral late AMD. These findings build on those from Chen et al, demonstrating that A69S is associated with several combinations of bilateral late AMD (including mixed GA and CNV), rather than simply bilateral GA (relative to unilateral GA) or bilateral CNV (relative to unilateral CNV).

The relationship between *ARMS2* and CNV appears stronger than the relationship between *ARMS2* and GA. A recent study reported that *ARMS2* is associated with classic CNV, fibrovascular lesions, and poor visual acuity.³² One series reported that *ARMS2*, but not *CFH*, *C2*, *C3*, *APOE*, or *TLR3*, was associated with progression of GA calculated from serial fundus photographs, but not with secondary measures of GA progression.³³ Another series reported that *ARMS2*, *CFH*, and *C3* are associated with the presence, but not the progression, of GA.³⁴

The function of the *ARMS2* gene product is unknown, as is its role in the pathogenesis of AMD.^{35,36} These data suggest that the *ARMS2* gene product may act at a different step in the pathogenesis of AMD—perhaps a more advanced stage—than do the complement factors and other studied genes.

This report offers confirmation that the T allele at the *ARMS2* A69S substitution associates with bilateral advanced AMD and that most of this association is because of a very strong association between this allele and bilateral CNV. If these data can be validated, there may be prognostic and therapeutic implications.

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Table 1**Fundus Photograph Grading System**

Grade	Description
1	No drusen or small nonextensive drusen, without pigment abnormalities
2	Extensive small drusen or nonextensive intermediate drusen or pigment abnormalities associated with AMD
3	Extensive intermediate drusen or any large drusen
4	GA, with or without involvement of the center of the macula
5	Exudative AMD, including nondrusenoid pigment epithelial detachments, serous or hemorrhagic retinal detachments, subretinal or sub-retinal pigment epithelium hemorrhage or fibrosis, or photocoagulation scars consistent with treatment of AMD

Table 2

Description of 1,401 AMD Cases by AMD Grade, Sex, and Age

Grade	N	Women (%)	<i>P</i>	Mean Age (SD), years	<i>P</i>
3	398	61.8	0.91	73.8 (8.2)	<0.0001
4	173	60.1		79.2 (7.3)	
5	830	61.7		77.8 (7.5)	

Table 3

Association of Clinical Severity in 1,401 AMD Cases with Genotypes at *CFH*, *ARMS2*, *C3*, and *CFB* Polymorphisms

	<u>Grade 3, N = 398</u>	<u>Grade 4, N = 173</u>	<u>Grade 5, N = 830</u>	<i>P</i>
	Frequency	Frequency	Frequency	
<i>CFH</i> Y402H				0.91
CC	0.34	0.36	0.35	
CT	0.47	0.48	0.48	
TT	0.19	0.16	0.17	
<i>ARMS2</i> A69S				8.2×10^{-11}
GG	0.50	0.41	0.30	
GT	0.40	0.39	0.45	
TT	0.10	0.20	0.25	
<i>C3</i> R102G				0.61
GG	0.55	0.51	0.53	
GC	0.37	0.37	0.39	
CC	0.08	0.12	0.09	
<i>CFB</i> R32Q				0.48
GG	0.91	0.90	0.91	
GA	0.09	0.10	0.08	
AA	0	0	0.01	

Table 4Association of Genotype Frequencies in *CFH*, *ARMS2*, *C3*, and *CFB* With Bilateral AMD

	Comparison 1		Comparison 2		Comparison 3	
	Unilateral GA N =46, Mean Age = 76.3 years	Bilateral GA N = 121, Mean Age = 80.4 years	Unilateral CNV N = 312, Mean Age = 75.9 years	Bilateral CNV N = 496, Mean Age = 79.0 years	Unilateral Late N = 358, Mean Age = 75.9 years	Bilateral Late N =617, Mean Age = 79.3 years
CFH Y402H						
CC	0.32	0.38	0.35	0.35	0.34	0.36
CT	0.57	0.46	0.47	0.48	0.48	0.48
TT	0.11	0.16	0.18	0.16	0.17	0.16
Test for trend	OR = 0.94; 95% CI, 0.56–1.59; <i>P</i> = 0.83		OR = 0.89; 95% CI, 0.71–1.10; <i>P</i> = 0.28		OR = 0.89; 95% CI, 0.73–1.09; <i>P</i> = 0.26	
ARMS2 A69S						
GG	0.47	0.40	0.40	0.25	0.41	0.28
GT	0.47	0.38	0.40	0.48	0.41	0.46
TT	0.07	0.22	0.20	0.27	0.18	0.26
Test for trend	OR = 1.57; 95% CI, 0.94–2.61; <i>P</i> = 0.08		OR = 1.82; 95% CI, 1.46–2.27; <i>P</i> = 9.0 × 10 ^{−8}		OR = 1.73; 95% CI, 1.42–2.12; <i>P</i> = 5.9 × 10 ^{−8}	
C3 R102G						
GG	0.58	0.49	0.50	0.54	0.51	0.53
GC	0.28	0.40	0.40	0.38	0.38	0.39
CC	0.14	0.11	0.10	0.08	0.11	0.08
Test for trend	OR = 1.14; 95% CI, 0.66–1.96; <i>P</i> = 0.64		OR = 0.87; 95% CI, 0.69–1.10; <i>P</i> = 0.23		OR = 0.91; 95% CI, 0.74–1.13; <i>P</i> = 0.39	
CFB R32Q						
GG	0.91	0.88	0.91	0.93	0.91	0.92
GA	0.09	0.12	0.08	0.07	0.08	0.08
AA	0	0	0.01	0	0.01	0
Test for trend	OR = 1.10; 95% CI, 0.33–3.71; <i>P</i> = 0.87		OR = 0.81; 95% CI, 0.49–1.33; <i>P</i> = 0.41		OR = 0.86; 95% CI, 0.54–1.36; <i>P</i> = 0.52	

Unilateral late, Grade 1, 2, or 3 Grade 4 or 5 in 1 eye and in the fellow eye; bilateral Grade 1, 2, or 3 in the fellow eye; unilateral GA, Grade 1 GA, Grade 4/4; bilateral late, Grade 4/4, 4/5, 5/5; bilateral 4 in 1 eye and Grade 1, 2, leral CNV, Grade 5/5; OR, or 3 in the fellow eye; unilaterate odds ratio; CI, confidence intf