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ARMS2/HTRA1 Locus Can Confer Differential Susceptibility to the Advanced Subtypes of Age-Related Macular Degeneration

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Abstract

Purpose—To determine if genetic variants that have been associated with age-related macular degeneration (AMD) have a differential effect on the risk of choroidal neovascularization (CNV) and geographic atrophy.

Design—Genetic association study.

Setting: Multicenter study.

Study Population: Seven hundred forty-nine participants with geographic atrophy and 3209 participants with CNV were derived from 4 AMD studies with similar procedures from Tufts Medical Center, the Age-Related Eye Disease Study, University of Utah, and Hopital Intercommunal de Creteil.

Procedures: AMD grade was assigned based on fundus photography and examination using the clinical age-related maculopathy staging system. All samples were genotyped for single nucleotide polymorphisms (SNPs) previously associated with AMD. Allele frequencies were compared between participants with CNV and geographic atrophy using PLINK within each cohort and Mantel-Haenszel meta-analysis was performed to combine odds ratios (OR).

Main Outcome Measures: Differences in allele frequencies between participants with geographic atrophy and CNV.

Results—The frequency of the T allele of *ARMS2/HTRA1* rs10490924 was significantly higher in participants with CNV than in those with geographic atrophy (OR, 1.37; 95% confidence interval, 1.21–1.54; *P* value = 4.2×10^{-7}). This result remained statistically significant when excluding individuals who had geographic atrophy in 1 eye and CNV in the contralateral eye ($P = 2.2 \times 10^{-4}$). None of the other SNPs showed a significant differential effect for CNV vs geographic atrophy, including *CFH, C2/CFB, C3, CFI, LIPC*, and *TIMP3*.

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Supplemental Material available at AJO.com)

Conclusions—Genetic variation at the *ARMS2/HTRA1* locus confers a differential risk for CNV vs geographic atrophy in a well-powered sample.

Age-Related Macular Degeneration (AMD) Is A common, late-onset cause of irreversible vision loss, and it is increasing in prevalence because of aging of the population.[1] Significant visual loss attributable to AMD occurs most commonly when the disease progresses to 1 of 2 advanced stages, geographic atrophy or choroidal neovascularization (CNV). Pathophysiologically and clinically, these 2 advanced forms are distinct.[1] Geographic atrophy involves atrophy of the neurosensory cells in the macula and is typically slowly progressive. CNV involves growth of abnormal choroidal vessels under the macula that bleed and leak fluid, eventually leading to fibrosis if the disease is not treated promptly, and symptoms are usually more sudden in onset than geographic atrophy. Although treatment of the CNV form can lead to atrophy secondarily, the primary form of each subtype is phenotypically distinct and different in appearance upon clinical examination. Both advanced forms can be found in the same patient: geographic atrophy and CNV can occur in the same eye or a patient may have geographic atrophy in 1 eye and CNV in the other. There are also some predisposing pathophysiologic changes in the extracellular matrix of the macula that are seen in both types of AMD.[2] Therefore, some controversy exists as to whether these 2 subtypes are the same disease or have different etiologies.

AMD has a 3- to 6-fold higher recurrence ratio in siblings than in the general population.[1,3,4] Several genetic studies have revealed that common variations at 2 loci, complement factor H (*CFH*) and the age-related maculopathy susceptibility 2/HtrA serine peptidase 1 (*ARMS2/HTRA1*) region, have a significant effect on the likelihood of developing the disease.[5–13] The critical role of the alternative complement pathway in disease pathogenesis has been further emphasized by discovery of additional loci in the *CFH* gene as well as 3 additional risk loci in this pathway: complement factor B/complement component 2 (*CFB/C2*), 2 independent reports of complement component 3 (*C3*), and complement factor I (*CFI*).[13–17] These aforementioned case-control association studies have most commonly included patients with geographic atrophy and patients with CNV together as advanced cases. Subanalyses performed as part of some of these investigations have not found significant differences in the risk allele frequencies for geographic atrophy vs CNV.[9,12,13,15,17,18] Some of these negative results may be attributable to limited power to detect differences between the 2 subtypes of advanced AMD given the relatively small number of patients with geographic atrophy in these investigations. In a previous study of progression to advanced AMD in 2007, our group found that the effect of the homozygous risk locus for *ARMS2/HTRA1* rs10490924 was higher for progression to CNV (odds ratio [OR] 6.1, 95% confidence interval [CI] 3.3–11.2) compared to progression to geographic atrophy (OR 3.0, 95% CI 1.4–6.5).[19] We also found that progression to bilateral advanced AMD was more strongly associated with this same locus than unilateral advanced AMD.[19] A similar trend was seen for risk of progression to CNV vs geographic atrophy for the same single nucleotide polymorphism (SNP) in a multivariate model that included 6 SNPs and pertinent demographic, ocular, and environmental risk factors associated with AMD; homozygosity for the risk allele for rs10490924 conferred higher odds of progression for CNV (OR 5.2, 95% CI 2.9–9.4) than geographic atrophy (OR 1.8, 95% CI 0.8–4.2).[20] A similar stronger association with bilateral advanced AMD vs unilateral advanced AMD was seen in that analysis as well. Another study that evaluated subphenotypes of AMD found that as the number of *ARMS2/HTRA1* risk alleles increased, the proportion of the CNV cases increased.[21] A more recent study demonstrated an association between the high risk allele of the *ARMS2* locus and fibrovascular lesions secondary to CNV.[22] We sought to further explore the potential differential effect of the SNP rs10490924 and to determine if other known and newly identified genetic variants may show a differential effect on the risk

of developing CNV vs geographic atrophy in a larger, well-powered sample of participants with these 2 advanced phenotypes.

Methods

Study Sample Description

Some methods have been described in detail previously.[13,17] Subjects were derived from ongoing AMD study protocols with similar procedures including the Progression of AMD Study, AMD Registry Study, Family Study of AMD, The US Twin Study of AMD, and the Age-Related Eye Disease Study (AREDS). Additional samples were provided from ongoing AMD studies at the University of Utah and the Hopital Intercommunal de Creteil. Only individuals of European ancestry were included for this analysis. AMD grade was assigned based on fundus photography and ocular examination using the clinical age-related maculopathy staging system,[23] in which geographic atrophy (central or noncentral macular involvement) and CNV correspond to grades 4 and 5, respectively.

Genotyping

DNA was extracted from blood samples obtained from the participants. All genotyping was performed using Sequenom technology at the Broad Institute Center for Genotyping and Analysis, Cambridge, Massachusetts, USA. More information on this technology can be found on their website (http://www.sequenom.com/applications/hme_assay.php).

Single Nucleotide Polymorphism Selection

We genotyped 115 SNPs within selected candidate genes on all of the samples. There were various rationales for choosing these SNPs. Some SNPs were chosen to attempt replication of positive findings from genome-wide association studies (GWAS).[24,25] Other SNPs were chosen to look with more detail at regions where these GWAS revealed a SNP that met genome-wide significance. Our GWAS discovered that a SNP in the hepatic lipase (*LIPC*) gene was associated with advanced AMD,[24] and this was corroborated in a separate GWAS.[25] *LIPC* is a critical enzyme in high-density lipoprotein (HDL) cholesterol metabolism and has been shown to be expressed in the retina.[24] We therefore evaluated this locus using the most highly associated SNP in our scan, rs10468017,[24] and also examined other SNPs that, like *LIPC*, are involved in the HDL lipid metabolism pathway and have been associated with serum lipid levels.[26] These GWAS also suggested an association between these other HDL pathway SNPs and AMD, namely rs12678919 (lipoprotein lipase, *LPL*), rs1883025 (ATP-binding cassette, subfamily A, member 1, *ABCA1*), and rs173539 (cholesterol ester transfer protein, *CETP*), as well as a SNP in the tissue inhibitor of metalloproteinase 3 (*TIMP3*) region–rs9621532.[24,25] A few SNPs were chosen based on their association with other phenotypes that may share pathophysiologic or etiologic features with AMD. Finally, SNPs that have been consistently established as being associated with advanced AMD were included as positive controls.

We implemented quality control filters for the SNPs for each dataset. We removed SNPs for a low call rate (>5% genotypes missing), for failing the Hardy-Weinberg equilibrium test at $P < 10^{-3}$, and for failing a differential missing test between cases and controls at $P < 10^{-5}$. All quality control steps were performed using PLINK.[27]

Choroidal Neovascularization vs Geographic Atrophy Analysis

For the primary analysis, we compared individuals who had CNV in at least 1 eye to those with geographic atrophy in at least 1 eye. CNV was defined as exudative AMD including nondrusenoid pigment epithelial detachments, serous or hemorrhagic retinal detachments, choroidal neovascular membrane with subretinal or subretinal pigment epithelial

hemorrhages or fibrosis, or scars consistent with treatment of AMD.[23] Geographic atrophy was defined as the presence of atrophy involving the macular center or non-central atrophy at least 350 μm in size.[23] If a patient had geographic atrophy in 1 eye and CNV in the contralateral eye, he or she was classified as a CNV case for the primary analyses, and in a subanalysis these individuals were excluded. For the Utah cohort, we included only the subset of participants for whom we had bilateral eye grading in the secondary analysis.

To reduce population stratification, association testing was performed separately using PLINK for each of 4 sample collections: 1) the samples derived from ongoing studies at the Tufts Medical Center, Department of Ophthalmology, 2) the AREDS samples, 3) samples from the University of Creteil, and 4) samples from the University of Utah. To examine the association of each particular SNP with CNV as compared with geographic atrophy, we used χ^2 analysis in the case-control samples. Results were combined by Mantel-Haenszel meta-analysis of the odds ratios. We also repeated the above analysis excluding any participant with geographic atrophy in 1 eye and CNV in the contralateral eye. To correct for multiple hypothesis testing for the 115 SNPs examined, we implemented a Bonferroni correction to determine the threshold for statistical significance of the meta-analysis *P* values. Using an a priori *P* value threshold of .05, after correction for the 115 SNPs tested, the corrected *P* value threshold was 4.3×10^{-4}.

Results

The overall study population consisted of 3209 participants with CNV and 749 participants with geographic atrophy. The number of participants included in each individual SNP analysis varies because of genotype missingness which differed depending on the SNP. All participants were white. The age and gender distributions of participants in the various cohorts are listed in Table 1.

Among the 115 SNPs analyzed, the only variant that was significantly associated with CNV vs geographic atrophy was rs10490924. Table 2 shows the results of the association testing for rs10490924. The T allele of rs10490924 was more frequent in participants with CNV than in participants with geographic atrophy in all 4 sample groups. With meta-analysis of the 4 cohorts, the increased relative risk of CNV vs geographic atrophy was statistically significant, with a *P* value of 4.2×10^{-7} (OR 1.37, 95% CI 1.21–1.54). Excluding the participants who had geographic atrophy in 1 eye and CNV in the contralateral eye did not significantly alter these findings (Table 3). The T allele of rs10490924 was still more frequent in participants with CNV than in participants with geographic atrophy in all 4 samples. The meta-analysis *P* value was 2.2×10^{-4} (OR 1.28, 95% CI 1.12–1.46). The Creteil cohort did not include any samples from participants with CNV in 1 eye and geographic atrophy in the contralateral eye. For the Utah samples, we excluded cases that did not have information for both eyes for this subanalysis. The rs10490924 genotype frequencies for all CNV cases, geographic atrophy cases, and the CNV cases excluding samples from participants with CNV in 1 eye and geographic atrophy in the contralateral eye are shown in the Supplemental Table (Supplemental Material at AJO.com).

None of the other variants tested showed a statistically significant difference in allele frequencies between the 2 forms of advanced AMD. In particular, none of the polymorphisms in the complement cascade showed a difference between the 2 groups. Table 4 shows the results for the *CFH* variant rs1061170. None of the individual studies showed a significant difference in the frequency of the C allele between the 2 groups. The *P* value for the meta-analysis was .92 (OR 1.09, 95% CI .97–1.23). The same is also true for the other *CFH* variant, rs1410996, which we have previously reported to be associated with AMD independently from rs1061170 (Table 5).[13] For this SNP, rs1410996, the *P* value for the

meta-analysis was .77 (OR 1.06, 95% CI .91–1.22). Table 6 shows the results for the *C3* variant rs2230199. The *P* value for the meta-analysis was .50 (OR 1.04, 95% CI .92–1.18).

In recent GWAS for advanced AMD, rs10468017 in the *LIPC* region and rs9621532 in the *TIMP3* region were found to be significantly associated with overall advanced AMD, including both geographic atrophy and CNV cases.[24,25] In the current analysis, the *P* values for these *LIPC* and *TIMP3* SNPs when comparing CNV cases to geographic atrophy cases were .84 (OR 1.07, 95% CI .94–1.23) and .10 (OR .78, 95% CI .58–1.05), respectively (Tables 7 and 8). Although not significant, the direction of effect for reduced risk of CNV compared with geographic atrophy for the C allele of *TIMP3* was consistent in 3 of the 4 studies with larger numbers of GA cases.

Discussion

Genetic variation at the *ARMS2/HTRA1* locus, SNP rs10490924, can confer increased risk of neovascular AMD compared with risk of geographic atrophy in this analysis of 4 cohorts with a total of 3937 advanced cases. None of the other variants that have been associated with advanced AMD overall show this effect in our study, including rs1061170 (*CFH*), rs1410996 (*CFH*), rs2230199 (*C3*), rs9621532 (*TIMP3*), and rs10468017 (*LIPC*). Given that the minor allele frequency of rs9621532 is less than 5%, even the current analysis may not have enough statistical power to assess the effect of *TIMP3* or other SNPs with low minor allele frequency on the risk of developing CNV or geographic atrophy.

The magnitude of the effect for rs10490924 was similar among 3 of the cohorts (Tufts, AREDS, and Creteil), with the odds ratios for CNV ranging from 1.34 to 1.56. Although the magnitude of the effect in the Utah cohort was smaller and not significant, the odds ratio was in the same direction of effect (higher risk of CNV AMD with the T allele) as the other cohorts and is thus consistent with the effect in the other cohorts. The inability to detect a statistically significant difference in the Utah cohort is most likely attributable to the sample being individually underpowered.

The differential effect of genetic variation at the 10q26 locus for CNV compared with geographic atrophy may offer some insight into why some patients progress to CNV instead of geographic atrophy. The causal variant at this locus has not been definitively identified and the function of this gene still remains unknown.

The ARMS2 protein was localized to the mitochondrial outer membrane according to 1 report.[28] The authors postulate that mitochondrial dysfunction could lead to the degeneration of photoreceptors via impairment of energy metabolism, generation of reactive oxygen species, and activation of the apoptotic pathway.[28] To date, there has been no evidence that this protein is involved in the angiogenesis related to CNV in AMD. The HTRA1 protein has been localized to vascular endothelium and may favor neovascularization by enhancing degradation of extracellular matrix components through increased expression of matrix metalloproteinases or by binding to transforming growth factor beta, an angiogenic factor.[29] Further understanding of the gene's function could reveal novel pathways in the pathophysiology of advanced AMD. Interestingly, none of the confirmed variants in complement pathway genes showed a significant differential effect between the 2 forms of advanced AMD.

Some previous studies with smaller numbers of participants with geographic atrophy and CNV have not found a differential effect for this same variant.[9,12,18] A study that included some of the same Utah samples included in this paper evaluated the *HTRA1* variant, rs11200638, and reported similar risk for CNV and geographic atrophy.[30] This *HTRA1* variant is in high linkage disequilibrium with rs10490924. However, that study only

included 408 and 138 participants with CNV and geographic atrophy, respectively. The finding of a differential effect for rs10490924 in the current study was possibly attributable to the larger, well-powered sample of participants with geographic atrophy and participants with CNV. Other studies have also suggested a difference similar to what we have found in this study.[19–21]

The main strength of the present study is the larger number of participants with advanced AMD, including a large number of participants with geographic atrophy. In addition, phenotyping of all participants was based on ocular examination and AMD grades were assigned by ophthalmologists. Genotyping was performed at the same institution at the same time, thereby minimizing bias from differential genotyping conditions. There are some limitations to our study. Participants were drawn from different cohorts and slightly different European-derived populations. However, we analyzed each cohort separately and used meta-analysis techniques to minimize bias from population stratification.

There might be small differences in the other genetic loci with low minor allele frequency that will require even larger sample sizes than in the current study. Understanding of the functional effects of the *ARMS2/HTRA1* locus (represented by SNP rs10490924) on CNV and geographic atrophy could be leveraged to find these other variants. Such insights into the genetic architecture of different forms of AMD may allow more accurate counseling of patients regarding their risk of progressing to specific forms of AMD. Knowledge of these mechanisms may also lead to new targets for prevention and treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Gender and Age Distribution of Participants With Age-Related Macular Degeneration According to Study Cohort

	Percent Male	Mean Age (Years)
Tufts	45.0	80.8
CNV	44.6	80.7
GA	46.7	81.3
AREDS	44.0	80.2
CNV	43.4	80.3
GA	46.0	80.0
Creteil	31.2	79.1
CNV	30.1	79.1
GA	34.1	78.9
Utah	47.2	81.5
CNV	50.1	81.3
GA	38.9	82.3

AREDS = Age-Related Eye Disease Study; CNV = choroidal neovascularization; GA = geographic atrophy.

Table 2

Association Results for *ARMS2/HTRA1* rs10490924 in All Age-Related Macular Degeneration Participants With Choroidal Neovascularization vs Geographic Atrophy

	CNV		GA				
Sample	**T Allele Frequency**	**n**	**T Allele Frequency**	**n**	**OR**	**95% CI**	**χ^2 *P* Value**
Tufts	0.469	1140	0.371	284	1.50	1.23–1.82	4.85×10^{-5}
AREDS	0.464	598	0.393	247	1.34	1.08–1.66	.007
Creteil	0.450	888	0.344	45	1.56	1.00–2.42	.0496
Utah	0.405	513	0.373	155	1.14	0.88–1.49	.31
Total		3139		731			
Meta-analysis					1.37	1.21–1.54	4.2×10^{-7}

AREDS = Age-Related Eye Disease Study; CI = confidence interval; CNV = choroidal neovascularization; GA = geographic atrophy; OR = odds ratio.

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Table 3

Association Results for *ARMS2/HTRA1* rs10490924 in Age-Related Macular Degeneration Participants With Neovascularization vs Geographic Atrophy, Excluding Those With Geographic Atrophy in 1 Eye and Neovascularization in the Contralateral Eye

	CNV		GA				
Sample	**T Allele Frequency**	**n**	**T Allele Frequency**	**n**	**OR**	**95% CI**	**χ^2 *P* Value**
Tufts	0.442	882	0.371	264	1.34	1.10–1.64	.0038
AREDS	0.439	449	0.393	247	1.21	0.96–1.51	.0961
Creteil	0.450	888	0.344	45	1.56	1.00–2.42	.0496
Utah	0.400	130	0.373	154	1.57	0.80–1.57	.52
Total		2349		710			
Meta-analysis					1.28	1.12–1.46	2.2×10^{-4}

AREDS = Age-Related Eye Disease Study; CI = confidence interval; CNV = choroidal neovascularization; GA = geographic atrophy; OR = odds ratio.

Table 4

Association Results Comparing Choroidal Neovascularization vs Geographic Atrophy Phenotypes of Age-Related Macular Degeneration for *CFH* rs1061170 Gene Variant

	CNV		GA				
Sample	**C Allele Frequency**	**n**	**C Allele Frequency**	**n**	**OR**	**95% CI**	**χ^2 *P* Value**
Tufts	0.613	1127	0.570	270	1.19	0.99–1.44	.07
AREDS	0.626	600	0.611	248	1.07	0.86–1.32	.56
Creteil	0.538	888	0.567	45	0.89	0.58–1.36	.59
Utah	0.561	513	0.555	154	1.03	0.79–1.33	.85
Total		3128		717			
Meta-analysis					1.09	0.97–1.23	.92

AREDS = Age-Related Eye Disease Study; CI = confidence interval; CNV = choroidal neovascularization; GA = geographic atrophy; OR = odds ratio.

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Table 5

Association Results Comparing Choroidal Neovascularization vs Geographic Atrophy Phenotypes of Age-Related Macular Degeneration for *CFH* rs1410996 Gene Variant

	CNV		GA				
Sample	**C Allele Frequency**	**N**	**C Allele Frequency**	**n**	**OR**	**95% CI**	**χ^2 *P* Value**
Tufts	0.801	1151	0.781	279	1.12	0.90–1.41	.31
AREDS	0.818	595	0.806	247	1.08	0.83–1.41	.57
Creteil	0.763	875	0.761	44	1.01	0.61–1.67	.97
Utah	0.766	509	0.779	154	0.93	0.68–1.26	.63
Total		3130		724			
Meta-analysis					1.06	0.91–1.22	.77

AREDS = Age-Related Eye Disease Study; CI = confidence interval; CNV = choroidal neovascularization; GA = geographic atrophy; OR = odds ratio.

Table 6

Association Results Comparing Choroidal Neovascularization vs Geographic Atrophy Phenotypes of Age-Related Macular Degeneration for *C3* rs2230199 Gene Variant

	CNV		GA				
Sample	**G Allele Frequency**	**n**	**G Allele Frequency**	**n**	**OR**	**95% CI**	**χ^2 *P* Value**
Tufts	0.573	1149	0.598	275	0.90	0.74–1.09	.28
AREDS	0.434	595	0.416	245	1.07	0.87–1.33	.28
Creteil	0.725	829	0.700	40	1.13	0.69–1.84	.63
Utah	0.722	489	0.660	150	1.34	1.01–1.76	.04
Total		3062		710			
Meta-analysis					1.04	0.92–1.18	.50

AREDS = Age-Related Eye Disease Study; CI = confidence interval; CNV = choroidal neovascularization; GA = geographic atrophy; OR = odds ratio.

Table 7

Association Results Comparing Choroidal Neovascularization vs Geographic Atrophy Phenotypes of Age-Related Macular Degeneration for Gene Variant *LIPC* rs10468017

	CNV		GA				
Sample	**T Allele Frequency**	**n**	**T Allele Frequency**	**n**	**OR**	**95% CI**	**χ^2 *P* Value**
Tufts	0.249	1154	0.237	276	1.06	0.86–1.32	.58
AREDS	0.264	601	0.233	247	1.18	0.92–1.51	.18
Creteil	0.254	877	0.256	45	0.99	0.61–1.61	.97
Utah	0.292	506	0.296	152	0.98	0.74–1.30	.88
Total		3138		720			
Meta-analysis					1.07	0.94–1.23	.84

AREDS = Age-Related Eye Disease Study; CI = confidence interval; CNV = choroidal neovascularization; GA = geographic atrophy; OR = odds ratio.

Table 8

Association Results Comparing Choroidal Neovascularization vs Geographic Atrophy Phenotypes of Age-Related Macular Degeneration for Gene Variant *TIMP3* rs9621532

	CNV		GA				
Sample	**C Allele Frequency**	**n**	**C Allele Frequency**	**n**	**OR**	**95% CI**	**χ^2 *P* Value**
Tufts	0.041	1080	0.047	236	0.87	0.54–1.40	.56
AREDS	0.038	596	0.06	242	0.66	0.41–1.08	.10
Creteil	0.023	867	0.011	45	2.10	0.30–14.78	.46
Utah	0.026	498	0.037	148	0.69	0.34–1.42	.32
Total		3041		671			
Meta-Analysis					0.78	0.58–1.05	.10

AREDS = Age-Related Eye Disease Study; CI = confidence interval; CNV = choroidal neovascularization; GA = geographic atrophy; OR = odds ratio.