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Progression of Geographic Atrophy and Genotype in Age-Related Macular Degeneration

Michael L. Klein, MD[1], **Frederick L. Ferris III, MD**[2], **Peter J. Francis, MD, PhD**[1], **Anne S. Lindblad, PhD**[3], **Emily Y. Chew, MD**[2], **Sara C. Hamon, PhD**[4], and **Jurg Ott, PhD**[4,5]

[1] Macular Degeneration Center, Casey Eye Institute, Oregon Health & Science University, and Devers Eye Institute, Portland, Oregon [2] National Eye Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland [3] The EMMES Corporation, Rockville, Maryland [4] Laboratory of Statistical Genetics, Rockefeller University, New York, New York [5] Beijing Institute of Genomics, Chinese Academy of Sciences, Beijing., China

Abstract

Purpose—To determine if genotype is associated with rate of growth of geographic atrophy (GA) in eyes with age-related macular degeneration (AMD).

Design—Prospective analysis of participants in a randomized controlled clinical trial.

Participants—114 eyes of 114 participants in the Age-Related Eye Disease Study (AREDS).

Methods—Fundus photographs from AREDS participants with GA from whom a DNA specimen had been obtained and serial photographs had been taken over a minimum of 2 years were evaluated for progression as determined by change in cumulative area of GA. All fundus photographs were scanned, digitized, and centrally graded longitudinally for area of GA. The relationship of GA progression with previously identified genetic variants associated with AMD was assessed.

Main Outcome Measures—Genotype frequencies and change in cumulative area of GA.

Results—The mean growth rate of geographic atrophy for the 114 eyes was 1.79 mm^2/year (range= 0.17–4.76 mm^2/year). No association between growth rate and genotype was present for variants in the *CFH*, *C2*, *C3*, *APOE*, and *TLR3*genes. For the single nucleotide polymorphism (SNP) rs10490924 in *LOC387715/ARMS2*, there was a significant association of GA growth rate, both adjusted and unadjusted for initial lesion size, with the homozygous risk genotype as compared to the homozygous non-risk genotype (unadjusted p-value = 0.002; Bonferroni corrected p-value = 0.014) and for allelic association(Bonferroni corrected p-value = 0.011). Analyses of other measures of geographic atrophy progression (progression to central GA from extrafoveal GA and development of bilateral GA in those initially with unilateral GA) showed no statistically significant association between progression and the *LOC387715/ARMS2/HTRA1* genotype.

Correspondence: Michael L. Klein, MD, Casey Eye Institute, 3375 SW Terwilliger Blvd., Portland, OR 97239. Phone 503 494-3055, FAX 503 494-7233, kleinm@ohsu.edu.

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Conclusion—GA growth rates calculated from digitized serial fundus photographs showed no association with variants in the *CFH*, *C2*, *C3*, *APOE*, and *TLR3* genes. There was a nominally statistically significant association with the *LOC387715/ARMS2/HTRA1* genotype, although this finding was not supported by analyses of secondary measures of GA progression. Replication in other populations would be needed to establish the existence of an association.

Age-related macular degeneration (AMD) is the leading cause of visual impairment in the western world, accounting in some countries for as much as one-half the cases of legal blindness.[1–3] Visual loss from AMD is typically caused by one or both forms of advanced disease: (1) "wet" or neovascular AMD, or (2) the advanced "dry" form of AMD, geographic atrophy (GA). Treatment with anti-angiogenic drugs is beneficial in most cases of neovascular AMD.[4, 5] However, there is currently no effective treatment for GA, which, in population-based studies has been reported to occur in approximately 45% of all advanced AMD cases.[6] Several studies have assessed the ocular, systemic, and environmental risk factors associated with prevalence, incidence, and progression of AMD.[6–16] In these studies, age, cigarette smoking, body mass index (BMI), family history, and retinal features comprised of drusen and pigment changes were among the strongest associations with both the neovascular and the geographic atrophy forms of advanced AMD. Most recently, genetic variants have also been shown to be strong risk factors for both advanced forms of AMD[17–31] and for progression of intermediate to advanced AMD.[32]

There is, however, little information about the relationship of genetic risk factors with progression in eyes with already established advanced AMD, and specifically GA. The primary purpose of this study was to determine if genotype is associated with progression of established GA as determined by rate of growth of GA area.

Methods

Written consent was obtained from all participants in the Age-Related Eye Disease Study (AREDS), including those involved in the genetics ancillary study. Institutional Review Board approval had been obtained by each of the participating clinics.

Definitions

For this study, GA is defined as 1 or more sharply circumscribed areas of retinal pigment epithelial depigmentation occurring in the macular area (defined as a 3000 micron diameter circle centered at the fovea), generally circular in shape, within which visualization of underlying choroidal blood vessels are usually visible as defined on stereoscopic color fundus photography. Central GA refers to GA involving the center of the fovea, which was determined by retinal vascular configuration and pigment alteration on stereoscopic fundus photographs.

Patient population

All subjects for this study were participants in the AREDS, a prospective, multicenter clinical trial evaluating the effects of antioxidants and zinc on the progression of AMD.[33, 34] Each individual was between 55 and 80 years of age at the baseline study visit, and had signed an informed consent to participate in the study which had been approved by institutional review boards of the participating centers. All participants had stereoscopic fundus photographs of both eyes taken at entrance into the AREDS, 2 years later, and at yearly intervals thereafter for up to 14 years.

Participants in this study represent a subset of those selected for a study of growth characteristics of GA.[35] In that study, photographs from AREDS participants with geographic atrophy who met 1 of the following 2 criteria were selected for digitization and

grading by the AREDS Reading Center: (a) GA=>0.5 DA within 1500 microns of the center of the fovea at entrance into the AREDS in 1 or both eyes, and (b) no GA at entrance into AREDS, but GA=>0.5 DA within 1500 microns of the center of the fovea in both eyes developing during follow-up. After meeting either criterion, and excluding those eyes with neovascular AMD present at the time of GA diagnosis, a total of 251 eyes of 181 participants were available for study. All subsequent study visit photographs were digitized, graded, and assessed.

Of these 181 participants, 114 comprise the subset of individuals who met the following criteria and were enrolled into this study: (1) availability of a DNA specimen; (2) minimum initial cumulative lesion size =>2 mm^2 (0.75 disc areas), chosen because lesions this size and larger exhibited linear growth rates over time; and (3) minimum follow-up period of 2 years, to allow for an adequate observation period. One eye per individual was selected for evaluation. If GA were present in 1 eye only, it was identified as the study eye. If GA were present in both eyes, 1 eye was chosen by randomization to be the study eye.

In addition, AREDS participants with no AMD (N=448) had been selected as a control group for an association analysis of the genetic variants assessed in this study. This control group was defined as having no drusen or less than 5 small drusen (<63 microns in smallest diameter) in both eyes.

Digitalization and grading of photographs

The process is described in full elsewhere.[35] Briefly, photographs were digitized and evaluated at the University of Wisconsin Fundus Reading Center (Madison, Wisconsin). All study photographs at all AREDS centers had been taken using the same camera system (Zeiss 30 degree FF2, FF3, or FF4). The images were scanned using a Nikon Coolscan 4000 film scanner at a resolution of 500 pixels/inch, imported into an image viewer-and-grading software package (Topcon IMAGEnet) and the area of GA determined and quantified using computerized planimetry. Growth of GA was expressed as the increase in the cumulative GA area (mm^2 per year). The images were evaluated by 4 graders, and a 10% subset was regraded by at least 2 graders. In addition, a sample of 87 photographs of 19 eyes were graded independently at the Doheny Image Reading Center (Los Angeles, California) with similar results obtained by both reading centers.[35]

Genotyping

Genotyping was performed at deCODE Genetics (Reykjavik, Iceland) using the Taqman genotyping platform (Applied Biosystems, Inc., Foster City, California) and at PreventionGenetics (Marshfield, WI). The analysis comprised 7 single nucleotide polymorphisms (SNPs) in 6 genes previously reported to be associated with AMD: rs1061170 in complement factor H (*CFH*), rs10490924 in *LOC387715/ARMS2/HTRA1,* rs9332739 in complement component 2 (*C2*), rs2230199 in complement component 3 (*C3*), rs7412 and rs429358 in apolipoprotein E (*APOE)*, and rs3775291 in toll-like receptor 3 (*TLR3*). Because of evidence for high linkage disequilibrium, we considered that the *LOC387715* SNP (rs10490924) served as a surrogate for the rs11200638 SNP in *HTRA1* as well as the *LOC 387715* indel variant.[22, 25, 36]

Statistical Analysis

Growth rate per year (mm^2) was calculated for all study eyes over the follow-up period. This growth rate was treated as a continuous variable, and analyses were performed to determine relationship of GA growth and genotype for the 6 genes studied.

As previously shown in these participants, no adjustments were necessary for the following variables, each of which was non-significant: age, gender, BMI, treatment assignment, and cigarette smoking.[35] To determine if education status and family history affected GA growth rate in this study population, we performed a linear regression. Neither of these variables were significant predictors of growth. Therefore, only baseline GA area was a significant predictor of subsequent growth and prior to assessing the influence of genotype on GA growth, we adjusted for initial GA area by fitting a regression model. The residuals from the regression model were added back to the grand mean to produce an adjusted phenotype value for each individual. Differences in GA growth rate means among genotypes were evaluated by a 1-way ANOVA. The unadjusted mean values for each of the 7 genetic variants are presented for genotype frequencies in Table 1 and allele frequencies in Table 2. The results for the adjusted and unadjusted GA growth were similar, and significance levels of the adjusted analysis are presented.

Power calculations were performed using the following assumptions: sample size of 114 individuals, three genotypes per SNP, a between-group variance of 0.20 $mm^{2/}$year, a within-group variance of 0.95 mm^2/year.

An association analysis was performed comparing the frequencies of the chosen genetic variants in the geographic atrophy cohort (N=114) and the control group (N=448). Genotype and allele frequencies, odds ratios, and significance levels were calculated for each of the 7 variants of the 6 genes assessed in our study.

Progression from non-central to central GA and unilateral to bilateral GA

These indirect measures of GA progression rate and their relationship to genotype were also analyzed from participants drawn from the entire AREDS population using the Cox proportional hazards model and adjusting for age, BMI, smoking status, gender, and initial lesion size. For the analysis of progression from non-central to central GA, eyes of AREDS participants who had non-central GA at baseline or developed non-central GA during subsequent study visits were included and assessed for later progression to central GA. For bilateral cases, only 1 eye was included (the initially affected eye). Similarly, for the analysis of progression from unilateral to bilateral GA, all AREDS participants with any unilateral GA at baseline or who developed GA in 1 eye at a subsequent study visit were included and assessed for development of GA in the fellow eye.

Results

A total of 114 individuals met study criteria and were analyzed. Mean age was 69.4 at enrollment (range=56–80). There were 45 males and 69 females. Twenty-nine individuals had GA in one eye and drusen in the fellow eye, 10 individuals had GA in one eye and choroidal neovascularization (CNV) in the fellow eye, and 75 individuals had GA in both eyes with no CNV in either eye..

In comparing the GA cohort (N=114) with the “no AMD” control group (N=448), there was a significant association between genotype and presence of GA for *CFH* (rs1061170), *LOC387715* (rs1040924), *C3* (rs2230199), and *C2* (rs9332739). There was no significant association for *APOE* (rs7412 and rs429358) and for *TLR3* (rs3775291) genotypes. More information is available in Table 3 (available at http://aaojournal.org).

Growth determinations were available for the 114 eyes of 114 individuals with GA. Their median follow-up was 6 years. The mean follow-up time was 6.4 years, with a standard deviation of 2.7 years and a range of 2 to 11 years. The mean growth rate of geographic atrophy was 1.79 mm^2/year (range = 0.17 – 4.76), and the growth rate was normally

distributed. There were no significant differences in baseline lesion size for each of the 3 *LOC387715/ARMS2/HTRA1* SNP genotypes.

Our power calculations showed that there was an 80% likelihood of detecting a clinically relevant association of genotype with growth rate at a significance level of p=0.05 after adjusting for multiple testing. Associations between growth rate adjusted for baseline lesion size and genotype were non-significant for all genes except for *LOC387715/ARMS2/HTRA1*. For this gene, there was a significant association of GA growth rate with the homozygous risk genotype (2.34 mm^2/year) compared with the homozygous non-risk genotype (1.51 mm^2/year). The unadjusted p-value= 0.002. With Bonferroni correction, the genotypic p-value was 0.014. For allelic association, the Bonferroni corrected p-value for this gene was 0.011

In 243 eyes of 243 individuals with non-central GA on at least 1 study examination, there was no significant association between the *LOC387715/ARMS2/HTRA1* genotype and progression to central GA at subsequent examinations (RR=1.13 [0.68–1.88] p=0.63). In 178 individuals with unilateral GA on at least 1 study examination, there was also no significant association between *LOC387715/ARMS2/HTRA1* and progression to bilateral GA at subsequent examinations (RR=0.61 [0.32–1.15] p=0.13).

Discussion

Previous studies have demonstrated that mean growth rate of GA in eyes of patients with AMD is between 1.3 and 2.8 mm^2 per year with considerable variation between individuals [12, 35, 37–40] None of these studies found systemic or environmental risk factors, including age, gender, BMI, smoking, and systemic hypertension, that might account for these intra-individual differences. However, ocular features have been reported that might help predict features of future GA growth. Factors that favored increased GA growth rate included larger initial lesion size[35] (lesions less than 2.0 mm^2 in diameter exhibited a slower growth rate), and multifocal GA compared with unifocal GA.[40] Furthermore, due to the high concordance of GA growth rates in both eyes of bilateral cases,[12, 35, 40] knowledge of GA growth characteristics in 1 eye could be informative of growth in the fellow eye. Finally, it has been reported that patterns of fundus autofluorescence are related to disease progression in eyes with GA.[12]

With regard to genetic risk factors, minimal information exists regarding the potential association of genotype and growth of GA area in eyes with established GA. A recent report described a study of 99 individuals with bilateral GA followed over a mean period of 3.0 years. The investigators found an association of variants in *CFH* (Y402H), *ARMS2* (A69S), and *C3* (R102G) with the presence of GA, but no correlation with the progression of GA.[41]

In planning this study, we hypothesized that since certain AMD susceptibility genes had been previously demonstrated to predict progression from intermediate to advanced AMD,[32] it was plausible that these or other genes might be associated with progression of already established advanced AMD, specifically GA. Our objective therefore was to determine if known AMD-associated genetic variants might also be related to GA growth rate.

Not all the chosen susceptibility variants were significantly associated with the presence of GA in our cohort. We found a significant association between presence of GA and CFH, C2, C3 and LOC387715/ARMS2/HTRA1 genotypes, while there was no association with APOE and TLR3. The lack of association with the TLR3 variant with presence of GA is not entirely unexpected due to previously reported conflicting results.[30, 31, 42]

With regard to GA growth, we found no relationship between GA progression and variants in the *CFH*, *C2*, *C3*, *APOE*, and *TLR3* genes. Only the rs10490924 (A69S) variant in the *LOC387715/ARMS2/HTRA1* locus showed evidence of association with GA progression (Tables 1 and 2). Since eyes with the *LOC387715/ARMS2/HTRA1* non-risk genotype (GG) demonstrated mean GA growth of 1.51mm^2/year, while those with the homozygous risk genotype (TT) had mean GA growth of 2.34mm^2/year, the rate of GA growth for individuals with the homozygous risk genotype was 54% greater than that for the non-risk genotype.

The *LOC387715/ARMS2/HTRA1* locus on 10q26 is strongly associated with risk for advanced AMD as well as progression to both forms of advanced AMD.[20, 21, 23, 32, 43–45] At present, the identity of the specific gene at that site remains uncertain. Recently, evidence has been presented for 2 genes in high linkage disequilibrium, L*OC387715/ARMS2* and *HTRA1*, as the most likely candidates.[25–27, 36, 45]

In the case of both genes, biological plausibility exists for association with AMD as well as progression of GA. *LOC387715/ARMS2* mRNA has been detected in the human retina and encodes a protein which appears to localize to the mitochondrial outer membrane when expressed in mammalian cells.[25] Altered mitochondrial function associated with the rs10490924 (A69S) variant could conceivably result in increased susceptibility to AMD and GA progression through a variety of mechanisms, including alteration of energy metabolism and activation of the apoptotic pathway. *HTRA1* encodes a serine protease expressed in retina and may be a key modulator of extracellular matrix degradation. Altered expression of this protein associated with the rs11200638 variant in the promoter region may influence remodeling of Bruch's membrane and retinal pigment epithelium in AMD eyes,[43] and progression of GA.

While our study found an association between *LOC387715/ARMS2/HTRA1* genotype and GA progression as determined by serial measurements of cumulative GA area, we were unable to find support from additional analyses that assessed 2 indirect measures of GA progression: advancement from non-central to central GA and progression from unilateral to bilateral GA. For these analyses, we found no statistically significant associations with *LOC387715/ARMS2/HTRA1* genotype. This may have been due to less sensitivity of these indirect measures of GA progression to demonstrate an effect compared with the direct assessment of change in the continuous variable (GA area).

Our findings indicating a lack of an association between GA progression and variants in genes involved in complement regulation might be taken as evidence against the potential efficacy of drugs targeting the complement system in the treatment of established GA. However, little is known about any causal relationship between known gene variants and AMD, and the lack of an association at the genomic level does not rule out the potential efficacy of therapeutic approaches targeting the complement system through their effect on biochemical cellular processes.

In conclusion, we found no association between progression of GA and variants in the *CFH*, *C2*, *C3*, *APOE*, and *TLR3* genes. We found nominally statistically significant evidence for an association with the rs10490924 (A69S) variant in the *LOC387715/ARMS2* gene that was not supported by analyses of secondary measures of GA progression. Replication of this finding is needed to establish an association.

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Table 1

Relationship Between Genotype Frequencies for Single Nucleotide Polymorphisms in Age-Related Macular Degeneration-Associated Genes (*CFH*, *LOC387715*, *C2*, *C3*, *APOE*, and *TLR3*) and the Progression of Geographic Atrophy (Mean Growth Rate, mm,^{2} per Year)[a]

	Genotype	N=114 eyes of 114 patients	Mean	Standard error	p-value	Bonferroni adjusted p-value
CFH	TT	16	1.74	0.256		
rs1061170	CT	47	1.84	0.146	0.70	1
	CC	41	1.99	0.151	0.38	1
LOC387715	GG	33	1.51	0.159		
rs10490924	GT	49	1.84	0.140	0.13	1
	TT	24	2.34	0.202	**0.002**	**0.014**
C2	GG	111	1.91	0.095		
rs9332739	CG	2	1.38	0.900	0.46	1
C3	CC	48	1.87	0.128		
rs2230199	CG	54	1.83	0.149	0.87	1
	GG	12	2.26	0.283	0.22	1
APOE	CC	87	1.85	0.101		
rs7412	CT	26	2.09	0.228	0.27	1
APOE	CC	94	1.95	0.106		
rs429358	CT	19	1.66	0.183	0.24	1
TLR3	GG	54	1.85	0.144		
rs3775291	AG	46	1.92	0.141	0.72	1
	AA	9	2.14	0.306	0.43	1

[a]There were no adjustments necessary for the following variables: age, body mass index (BMI), education, treatment, gender, smoking, and family history, each of which was non-significant.

Table 2

Relationship Between Allele Frequencies for Single Nucleotide Polymorphisms in Age-Related Macular Degeneration-Associated Genes (*CFH, LOC387715, C2, C3, APOE,* and *TLR3*) and the Progression of Geographic Atrophy (Mean Growth Rate, mm^2, per Year)[a]

	Allele	N=114 eyes of 114 patients	Mean	Standard error	p-value	Bonferroni adjusted p-value
CFH	T	79	1.78	0.103		
rs1061170	C	129	1.96	0.083	0.17	1
LOC387715	G	115	1.65	0.088		
rs10490924	T	97	2.09	0.102	**0.001**	**0.011**
C2	G	224	1.91	0.063		
rs9332739	C	2	1.58	0.989	0.62	1
C3	G	150	1.84	0.074		
rs2230199	C	78	1.99	0.116	0.27	1
APOE	C	200	1.88	0.065		
rs7412	T	26	2.10	0.218	0.26	1
APOE	C	207	1.92	0.066		
rs429358	T	19	1.66	0.187	0.24	1
TLR3	G	154	1.89	0.079		
rs3775291	A	64	1.96	0.111	0.64	1

[a]There were no adjustments necessary for the following variables: Age, body mass index (BMI), education, treatment, gender, smoking, and family history, each of which was non-significant.

Table 3

Odds Ratios, Confidence Intervals, and P-values for Single Nucleotide Polymorphisms in Age-Related Macular Degeneration-Associated Genes (CFH, LOC387715, C2, C3, APOE, and TLR3) in Age-Related Eye Disease Study Participants with Geographic Atrophy (N=114) and Age-Related Eye Disease Study Controls with no Age-Related Macular Degeneration[a] (N=448)

Gene SNP	type	N[b]	Genotypic OR (CI)[c]	Genotypic P-value	Allelic OR (CI)[d]	Allelic P-Value
CFH **rs1061170**	GA	107	7.36 (3.87 –13.97)	<0.0001	2.77 (2.042–3.77)	<0.0001
	No AMD	437				
LOC387715 **rs10490924**	GA	106	6.01 (3.48–10.38)	<0.0001	3.67 (2.67–5.05)	<0.0001
	No AMD	436				
C2 **rs2230199**	GA	113	-	-	0.23 (0.07–0.75)	0.0134
	No AMD	447				
C3 **rs9332739**	GA	114	6.22 (2.79–13.85)	<0.0001	2.5 (1.81–3.45)	<0.0001
	No AMD	448				
APOE **rs7412**	GA	112	-	-	1.37 (0.84–2.22)	0.256
	No AMD	447				
APOE **rs429358**	GA	113	-	-	0.61 (0.37–0.99)	0.062
	No AMD	443				
TLR3 **rs3775291**	GA	114	1.55 (0.77–1.67)	0.149	1.22 (0.896–1.67)	0.233
	No AMD	448				

[a] Less than 5 small drusen (<63 micron diameter) in both eyes

[b] Number of participants genotyped

[c] Risk homozygote vs. non-risk homozygote. For C2 and APOE, there was an insufficient frequency of the minor-allele homozygotes for calculation of genotypic odds ratios.

[d] allelic odds ratio (confidence interval)