Published in final edited form as:

JAMA Ophthalmol. 2013 June ; 131(6): 804–805. doi:10.1001/jamaophthalmol.2013.589.

Coding Variants in *ARMS2* and the Risk of Age-Related Macular Degeneration

Gaofeng Wang, PhD, William K. Scott, PhD, Anita Agarwal, MD, Jonathan L. Haines, PhD, and Margaret A. Pericak-Vance, PhD

John P. Hussman Institute for Human Genomics, Department of Human Genetics, Dr John T. Macdonald Foundation, University of Miami Miller School of Medicine, Miami, Florida

Genetic variation at the chromosome 10q26 locus is strongly associated with the risk of age-related macular degeneration (AMD). Recently, the common coding variant rs2736911 (R38X) in the age-related maculopathy susceptibility 2 gene (*ARMS2*; GenBank NG_011725) was inversely associated with AMD.¹ The R38X variant introduces a premature stop codon that likely leads to a truncated *ARMS2* protein at a lower expression level due to nonsense-mediated decay.² It remains unclear how the missense change A69S increases the risk of AMD, while the truncated R38X is protective. To understand the association of R38X with AMD, we examined 3 *ARMS2* common coding variants, R38X, A69S, and rs10490923 (R3H), as well as the *HTRA1* promoter variant rs11200638 in a large case-control data set.

Methods

The data set contains 1169 AMD cases and 707 controls (eTable 1, <http://www.jamaophth.com>). All participants are unrelated and are non-Hispanic white. Approval for the study was obtained from the institutional review boards at Vanderbilt University Medical Center, Duke University Medical Center, and the University of Miami Miller School of Medicine. The 4 variants were genotyped using Taqman assays (Applied Biosystems). We assessed the association of each variant with AMD using the 2×2 χ^2 test for allelic association and estimated age- and sex-adjusted odds ratios (ORs) using logistic regression. We tested the association of each haplotype containing the 3 coding variants using the rest haplotypes as the reference.

©2013 American Medical Association. All rights reserved.

Correspondence: Dr Wang, John P. Hussman Institute for Human Genomics, Department of Human Genetics, Dr John T. Macdonald Foundation, University of Miami Miller School of Medicine, Miami, FL 33136 (gwang@med.miami.edu).

Conflict of Interest Disclosures: Drs Scott, Agarwal, Haines, and Pericak-Vance, are coinventors on a patent related to use of *ARMS2* genotypes for diagnosis of AMD, licensed to ArcticDx.

Online-Only Material: The eTables are available at <http://www.jamaophth.com>.

Additional Contributions: We thank all the patients, their families, and the control subjects who participated in the study. A subset of the participants was ascertained while Dr Pericak-Vance was a faculty member at Duke University, Durham, North Carolina. William Cade, MPH, provided data analysis, Stephen Schwartz, MD, and Jaclyn Kovach, MD, provided clinical service and sample collection, and Patrice Gay, BA, and Brenda Court, BA, genotyped the sample.

Results

Variants A69S and rs11200638 were associated strongly with the risk of AMD. The variant R3H was inversely associated with the risk of AMD (OR=0.68; $P=.002$), while the variant R38X was not inversely associated with the risk of AMD after adjustment for sex and age in our data set (OR=0.83; $P=.18$) (Table 1). The results did not change much after adjustment for smoking status (data not shown). These 4 variants reside within a region of strong linkage disequilibrium ($D' > 0.92$ for each pair in controls), suggesting that their associations with AMD are not independent. We observed only 4 haplotypes (R-R-A, R-R-S, R-X-A, and H-R-A) containing the 3 *ARMS2* coding variants. Compared with the rest haplotypes, only haplotype R-R-S was significantly associated with the risk of AMD (OR=2.30; $P<.001$) (eTable 2). Haplotypes R-R-A (OR = 0.63; $P<.001$) and H-R-A (OR=0.62; $P=.002$) exhibited protective effects on AMD. The effect of haplotype R-X-A on AMD was not statistically significant (OR = 0.80; $P=.10$). To determine whether the effects of the 3 variants are independent, we performed conditional analysis by stratifying the data set by genotypes at A69S and evaluating the effects of R3H and R38X in the subset of the sample homozygous for the wild-type (nonrisk) allele A at A69S (Table 2). Once the strong effect of A69S was removed, the inverse associations of R3H were no longer statistically significant.

Comment

Yang et al¹ reported that the minor allele of variant R38X in *ARMS2* is less common in individuals with AMD than unaffected controls. This inverse association is insignificant in our case-control data set after adjustment for sex and age. We found that the minor allele of variant R3H exhibits an inverse association with AMD. Additional analyses showed that the inverse association of R3H appears to be due to strong linkage disequilibrium with the nonrisk wild-type allele at A69S. In other words, the association at all 3 loci can be explained by the genotype at A69S. We suggest, owing to the results of this analysis and prior studies, that the A69S variant is the most likely of the 4 tested variants to influence the risk of AMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: This work was supported by grant 2R01EY012118-11 from the National Institutes of Health (Drs Scott, Agarwal, Haines, and Pericak-Vance).

References

1. Yang Z, Tong Z, Chen Y, et al. Genetic and functional dissection of *HTRA1* and *LOC387715* in age-related macular degeneration. *PLoS Genet.* 2010; 6 (2):e1000836. [PubMed: 20140183]
2. Friedrich U, Myers CA, Fritsche LG, et al. Risk- and non-risk-associated variants at the 10q26 AMD locus influence *ARMS2* mRNA expression but exclude pathogenic effects due to protein deficiency. *Hum Mol Genet.* 2011; 20(7):1387–1399. [PubMed: 21252205]

Table 1Association of Variants in *ARMS2* and *HTRA1* With Age-Related Macular Degeneration

Variant	MAF		P Value	Age- and Sex-Adjusted OR (95% CI)
	Cases	Controls		
R3H	0.10	0.13	.002	0.68 (0.53–0.87)
R38X	0.12	0.15	.18	0.83 (0.63–1.08)
A69S	0.41	0.24	<.001	2.27 (1.83–2.81)
rs11200638	0.40	0.24	<.001	2.09 (1.69–2.58)

Abbreviations: MAF, minor allele frequency; OR, odds ratio.

Table 2

Association of Variants R3H and R38X in 485 Individuals Homozygous for the A Allele at A69S

Variant	MAF		P Value	Age- and Sex-Adjusted OR (95% CI)
	Cases	Controls		
R3H	0.16	0.18	.34	0.77 (0.51–1.15)
R38X	0.22	0.20	.44	1.34 (0.95–1.91)

Abbreviations: MAF, minor allele frequency; OR, odds ratio.