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Association of Single-Nucleotide Polymorphisms in Age-Related Macular Degeneration With Pseudodrusen
Secondary Analysis of Data From the Comparison of AMD Treatments Trials

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IMPORTANCE Previous studies investigating the association of single-nucleotide polymorphisms (SNPs) that confer increased risk of age-related macular degeneration (AMD) with pseudodrusen have yielded conflicting results and have not evaluated other AMD SNPs or pseudodrusen subtypes.

OBJECTIVE To determine the association of SNPs in the complement factor H (*CFH*), age-related maculopathy susceptibility 2 (*ARMS2*), HtrA serine peptidase 1 (*HTRA1*), complement C2 (*C2*), complement C3 (*C3*), lipase C (*LIPC*), and complement factor B (*CFB*) genes with the presence of pseudodrusen and pseudodrusen subtypes (ie, dot, reticular, and confluent).

DESIGN, SETTING, AND PARTICIPANTS In this post hoc analysis of cross-sectional data from US participants in the Comparison of AMD Treatments Trials, genotyping was performed in 835 participants with TaqMan assays for the SNPs rs1061170 (Y402H variant in *CFH*), rs800292 (I62V variant in *CFH*), rs10490924 (A69S variant in *ARMS2*), rs11200638 (*HTRA1*), rs547154 (*C2*), rs2230199 (R102G variant in *C3*), rs10468017 (*LIPC*), and rs4151667 (L9H variant in *CFB*).

MAIN OUTCOMES AND MEASURES Presence and subtype of baseline pseudodrusen in either eye determined using color fundus photography, red-free images, and fluorescein angiograms.

RESULTS Among 835 participants enrolled for genotyping, 755 (90.4%) were evaluated for pseudodrusen. Of these, 471 (62.4%) were female and 750 (99.3%) were white, and the mean (SD) age was 78.3 (7.5) years. A total of 213 of 755 participants (28.2%) had pseudodrusen (107 [14.2%] had dot pseudodrusen, 180 [23.8%] had reticular pseudodrusen, and 102 [13.5%] had confluent pseudodrusen). After adjusting for age, sex, and smoking status, the *ARMS2* risk allele T was associated with higher risk of pseudodrusen (odds ratio [OR], 1.93; 95% CI, 1.19-3.12) for TT vs GG (P = .04). A similar association was found for *HTRA1* (OR, 2.04; 95% CI, 1.26-3.31) for AA vs GG (P = .03). The *CFH* Y402H risk allele C was associated with lower risk of pseudodrusen (OR, 0.61; 95% CI, 0.38-0.97) for CC vs TT but was not statistically significant after correcting for multiple comparison (P = .20). *CFH* Y402H, *ARMS2*, *HTRA1*, and *C3* were significantly associated with reticular pseudodrusen.

CONCLUSIONS AND RELEVANCE Among patients with neovascular AMD, the AMD risk alleles *ARMS2* and *HTRA1* were associated with an increased risk of pseudodrusen and the risk allele *CFH* Y402H was associated with lower risk of pseudodrusen, supporting findings from previous studies. Understanding the role of these SNPs in the development of pseudodrusen might improve our understanding of the pathogenesis of AMD and help develop future therapies.

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Supplemental content

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Drusen, or focal deposits of extracellular material external to the retinal pigment epithelium, are the hallmark of age-related macular degeneration (AMD). Pseudodrusen are subretinal deposits but are located internal to the retinal pigment epithelium. They are a distinct feature of AMD. Although pseudodrusen are a risk factor for advanced AMD, the pathophysiologic mechanism is unclear.[1,2] Studies of the influence of genes on pseudodrusen have conflicting results.[3-11]

The Comparison of AMD Treatments Trials (CATT)[12] compared the efficacy of treatment with ranibizumab or bevacizumab for neovascular AMD. In CATT, fellow eyes with baseline pseudodrusen had a 2-fold increased risk of developing neovascular AMD or geographic atrophy within 2 years after accounting for large drusen, pigmentary changes, and other risk factors.[2] Also, dot pseudodrusen were associated only with neovascular AMD, whereas confluent pseudodrusen were associated only with geographic atrophy.[2] A subgroup of CATT participants provided blood samples for genetic testing, allowing evaluation of the association between AMD-associated SNPs and pseudodrusen.[13]

Key Points

Question Are single-nucleotide polymorphisms that confer increased risk of age-related macular degeneration (AMD) associated with higher risk of pseudodrusen and subtypes of pseudodrusen?

Findings In this post hoc analysis of the Comparison of AMD Treatment Trials, among 755 patients with neovascular AMD, the AMD risk alleles of age-related maculopathy susceptibility 2 (*ARMS2*; rs10490924) and HtrA serine peptidase 1 (*HTRA1*; rs11200638) were significantly associated with an increased risk of pseudodrusen.

Meaning These findings suggest AMD single-nucleotide polymorphisms have a role in the development of pseudodrusen.

Methods

This is a post hoc analysis of CATT data. Details of the CATT methodology and CATT genetics study have been published previously.[2,12,13] Written informed consent was obtained from all study participants. Institutional review board approval was obtained by all participating centers.

Genotype Determination

DNA was extracted and purified from leukocytes, as previously described.[13] The following 8 AMD-associated SNPs were evaluated using TaqMan genotyping: rs1061170 (Y402H variant of complement factor H [*CFH*]), rs800292 (I62V variant of *CFH*), rs10490924 (A69S variant of age-related maculopathy susceptibility 2 [*ARMS2*]), rs11200638 (HtrA serine peptidase 1 [*HTRA1*]), rs547154 (complement C2 [*C2*]), rs2230199 (R102G variant of complement C3 [*C3*]), rs10468017 (lipase C [*LIPC*]), and rs4151667 (L9H variant of complement factor B [*CFB*]).

Pseudodrusen Evaluation

Pseudodrusen in each eye at baseline were graded using color fundus photography, red-free images, and fluorescein angiography.[2] Digital color fundus photographs were reviewed with the green channel only and the blue channel only in Adobe Photoshop because pseudodrusen are usually more visible under these conditions. Fluorescein angiography images were used to distinguish pseudodrusen from other drusen. Dot pseudodrusen were identified as discrete, round to oval dots, with areas between dot pseudodrusen exhibiting no marked changes. Reticular pseudodrusen formed a complex network of curvilinear lesions or interlocking ribbons, with areas between reticular pseudodrusen exhibiting no marked changes. Confluent pseudodrusen were lesions that merged or coalesced.[2]

Statistical Analysis

Associations between SNPs and baseline pseudodrusen in either eye were assessed using logistic regression models with adjustment for age, sex, and smoking status. We calculated the odds ratios and its 95% confidence intervals for genotypes and tested for linear trends in number of risk alleles. For SNPs with a significant association with presence of pseudodrusen, we performed similar analyses for each subtype of pseudodrusen. The Hochberg procedure was used to correct for the multiple comparisons from 8 SNPs. Statistical analyses were performed using SAS version 9.4 (SAS Institute). Statistical significance was set at $P < .05$, and all P values were 2-tailed.

Results

Among 835 patients in the genetics study, 755 (90.4%) had sufficient image quality to evaluate baseline pseudodrusen in both eyes. The mean (SD) age was 78 (7.5) years, and 471 (62.4%) were female and 73 (9.7%) were current smokers. Among these 755 participants, 213 (28.2%) had pseudodrusen in either eye and 115 (15.2%) had pseudodrusen in both eyes; 107 (14.2%) had dot pseudodrusen, 180 (23.8%) had reticular pseudodrusen, and 102 (13.5%) had confluent pseudodrusen (subtypes are not mutually exclusive).

In logistic regression models, risk of pseudodrusen increased with the number of risk alleles of *ARMS2* (odds ratio, 1.93; 95% CI, 1.19-3.12) for TT vs GG and of *HTRA1* (odds ratio, 2.04; 95% CI, 1.26-3.31) for AA vs GG. For both *CFH* Y402H and *C3*, risk of pseudodrusen decreased with the number of risk alleles, but the associations were not significant after correcting for multiple comparisons (**Table 1**). We did not find any significant associations with pseudodrusen for *LIPC*, *CFB*, *C2*, and *CFH* I62V. *CFH* Y402H, *ARMS2*, *HTRA1*, and *C3* were associated with reticular pseudodrusen but were not associated with dot pseudodrusen (**Table 2**). *HTRA1* was also associated with confluent pseudodrusen.

Discussion

Others have examined the association of the major AMD SNPs with pseudodrusen with conflicting results (eTable in the

Table 1. Association of Age-Related Macular Degeneration Single-Nucleotide Polymorphisms (SNPs) With Pseudodrusen in the Study Eye or Fellow Eye in 755 Participants

Genotype	No.	Pseudodrusen, No. (%)	Adjusted Odds Ratio (95% CI)[a]	*P* Value[b] (Corrected *P* Value[c])
CFH Y402H				
TT	156	57 (36.5)	1 [Reference]	.04 (.20)
TC	354	104 (29.4)	0.79 (0.51-1.20)	
CC	245	52 (21.2)	0.61 (0.38-0.97)	
ARMS2				
GG	246	57 (23.2)	1 [Reference]	.006 (.04)
GT	353	107 (30.3)	1.52 (1.02-2.26)	
TT	156	49 (31.4)	1.93 (1.19-3.12)	
HTRA1				
GG	252	60 (23.8)	1 [Reference]	.004 (.03)
AG	354	104 (29.4)	1.36 (0.92-2.01)	
AA	149	49 (32.9)	2.04 (1.26-3.31)	
C3				
CC	411	132 (32.1)	1 [Reference]	.04 (.20)
CG	292	71 (24.3)	0.73 (0.51-1.05)	
GG	52	10 (19.2)	0.56 (0.26-1.19)	
LIPC				
TT	41	8 (19.5)	1 [Reference]	.37 (.95)
CT	312	90 (28.9)	1.52 (0.66-3.53)	
CC	401	115 (28.7)	1.61 (0.70-3.71)	
CFB				
TT	710	198 (27.9)	1 [Reference]	.95 (.95)
AT	43	15 (34.9)	1.26 (0.63-2.51)	
TT	2	0	NA	
C2				
TT	4	1 (25.0)	1 [Reference]	.78 (.95)
GT	135	37 (27.4)	0.83 (0.07-9.84)	
GG	615	174 (28.3)	0.90 (0.08-10.30)	
CFH I62V				
GG	477	128 (26.8)	1 [Reference]	.76 (.95)
AG	178	50 (28.1)	0.87 (0.58-1.31)	
AA	14	5 (35.7)	1.32 (0.41-4.25)	

Abbreviation: NA, not applicable.

[a] Risk allele is C for *CFH* Y402H and *LIPC*, T for *ARMS2* and *CFB*, A for *HTRA1* and *CFH* I62V, and G for *C3* and *C2*.

[b] Adjusted linear trend *P* value adjusted by age (continuous), sex, and smoking status (never, quit, and current).

[c] Multiple comparison–corrected *P* value corrected using Hochberg procedure.

Supplement), likely because of small numbers of individuals with pseudodrusen and differences in the study population. In our study of 755 CATT participants, risk alleles in *ARMS2* and *HTRA1* were associated with higher risk of pseudodrusen.

Most studies have shown that the risk allele T in *ARMS2* is associated with higher risk of pseudodrusen[4-9,11] (eTable in the Supplement). Because there is high linkage disequilibrium between *ARMS2* and *HTRA1*, *HTRA1* has also been associated with pseudodrusen as well.[5,6] While the *CFH* Y402H risk allele is associated with increased risk of AMD, the association of *CFH* Y402H with pseudodrusen has been controversial thus far.[3-11] Several studies of patients with AMD found no association between the *CFH* Y402H risk allele and pseudodrusen,[7,8,10] while other studies among participants with and without AMD reported an increased risk of pseudodrusen.[3-6] Smith et al[11] found a decreased risk of pseudodrusen in patients with AMD, which is consistent with our finding that risk of pseudodrusen among patients with neovascular AMD decreased with the number of *CFH* Y402H risk alleles, although our association was not significant after correcting for multiple comparisons (eTable in the Supplement). These studies varied in their study population, with some studies evaluating the presence of SNPs in the population (with and without AMD) and other studies only evaluating those who had AMD. Population-based studies[3-5] have compared the presence of *CFH* Y402H in individuals with and without pseudodrusen, without consideration of AMD status. Thus, perhaps there was no true association between *CFH* Y402H and pseudodrusen within the AMD population or even an inverse association within patients with AMD, as we have found. Our results support the hypothesis by Smith et al[11] that *CFH* Y402H confers an alternative complement response that may be protective against the development of pseudodrusen.

We also evaluated the association of *LIPC*, *CFH* I62V, *CFB*, *C2*, and *C3* with pseudodrusen. In contrast, Puche et al[6] showed that the risk allele of *C3* was associated with higher risk of pseudodrusen when considering individuals without AMD, but there was no association among those with AMD.

Table 2. Association of Age-Related Macular Degeneration Single-Nucleotide Polymorphisms (SNPs) With Each Type of Pseudodrusen in the Study Eye or Fellow Eye in 755 Participants

Genotype	No.	Pseudodrusen, No. (%)		
		Dot	Reticular	Confluent
CFH Y402H				
TT	156	26 (16.7)	52 (33.3)	28 (18.0)
TC	354	57 (16.1)	83 (23.5)	54 (15.3)
CC	245	24 (9.8)	45 (18.4)	20 (8.2)
P value[a,b] (corrected *P* value[c])	NA	.20 (.40)	.04 (.04)	.04 (.08)
ARMS2				
GG	246	27 (11.0)	48 (19.5)	26 (10.6)
GT	353	58 (16.4)	88 (24.9)	50 (14.2)
TT	156	22 (14.1)	44 (28.2)	26 (16.7)
P value[a,b] (corrected *P* value[c])	NA	.11 (.40)	.006 (.01)	.03 (.08)
HTRA1				
GG	252	30 (11.9)	51 (20.2)	26 (10.3)
AG	354	55 (15.4)	85 (24.0)	50 (14.1)
AA	149	22 (14.8)	44 (29.5)	26 (17.5)
P value[a,b] (corrected *P* value[c])	NA	.15 (.40)	.005 (.01)	.01 (.04)
C3				
CC	411	60 (14.6)	117 (28.5)	63 (15.3)
CG	292	42 (13.4)	55 (18.8)	37 (12.7)
GG	52	5 (9.6)	8 (15.4)	2 (3.85)
P value[a,b] (corrected *P* value[c])	NA	.82 (.82)	.007 (.01)	.12 (.12)

Abbreviation: NA, not applicable.

[a] Risk allele is C for *CFH* Y402H, T for *ARMS2*, A for *HTRA1*, and G for *C3*.

[b] Adjusted linear trend *P* value adjusted by age (continuous), sex, and smoking status (never, quit, and current).

[c] Multiple comparison–corrected *P* value corrected using Hochberg procedure.

Pseudodrusen have different appearances in imaging and have been classified into subtypes (ie, dot, reticular, and confluent).[2] We found that dot pseudodrusen were associated with neovascular AMD, whereas confluent pseudodrusen were associated with geographic atrophy.[2] Elfandi et al[14] found no association for both *ARMS2* and *CFH* Y402H with dot-dominant pseudodrusen vs dot-reticular pseudodrusen but found *CFH* I62V was more common in patients with dot-dominant pseudodrusen. Shijo et al[15] did not find any association between subtypes of pseudodrusen with *CFH* I62V or *ARMS2*. Despite the fact that our study is limited to individuals with neovascular AMD and possible misclassification of pseudodrusen, we found that the risk alleles of *ARMS2* and *HTRA1* were associated with higher risk of reticular pseudodrusen and confluent pseudodrusen, while the risk allele of *C3* was associated with a lower risk of reticular pseudodrusen. We also found the risk allele of *CFH* Y402H was associated with a significantly lower risk of reticular pseudodrusen.

Conclusions

In conclusion, our results suggest that there are associations of AMD SNPs with pseudodrusen and their subtypes. Understanding the role of these AMD SNPs in the development of pseudodrusen might contribute to the understanding of the pathogenesis of pseudodrusen and ultimately to development of future therapies.

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