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Association of *LIPC* and advanced age-related macular degeneration

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Learning objectives

Upon completion of this activity, participants will be able to:

1. Assess the clinical stages and clinical consequences of AMD
2. Describe the relationship between *LIPC* and hepatic triglyceride lipase
3. Analyze the relationship between *LIPC* and advanced AMD

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LABORATORY STUDY

Association of *LIPC* and advanced age-related macular degeneration

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Abstract

Purpose **To determine whether there is an association between hepatic lipase (*LIPC*) and age-related macular degeneration (AMD) in two independent Caucasian cohorts.**
Methods **A discovery cohort of 1626 patients with advanced AMD and 859 normal controls and a replication cohort of 2159 cases and 1150 controls were genotyped for two single-nucleotide polymorphisms (SNPs) in the promoter region of *LIPC*. The associations between the SNPs and AMD were examined by χ^2 tests.**
Results **In the discovery cohort, rs493258 and rs10468017 were both associated with advanced AMD ($P = 9.63E-3$ and $P = 0.048$, respectively). The association was corroborated in the replication cohort ($P = 4.48E-03$ for rs493258 and $P = 0.015$ for rs10468017). Combined analysis resulted in even more significant associations ($P = 1.21E-04$ for rs493258 and $P = 1.67E-03$ for rs10468017).**
Conclusion **The *LIPC* promoter variants rs493258 and rs10468017 were associated with advanced AMD in two independent Caucasian populations, confirming that *LIPC* polymorphisms may be a genetic risk factor for AMD in the Caucasian population.**
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Keywords: LIPC; hepatic lipase; advanced age-related macular degeneration; genetics

Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness for elderly individuals in the developed world. It is estimated that >9 million people in the United States suffer from intermediate or advanced AMD.[1,2] Depending on the severity, AMD can be classified into two separate stages. Early AMD is characterized by soft drusen and pigmentary changes in the retinal pigment epithelium (RPE). Advanced AMD leads to vision loss and can be further subdivided into geographic atrophy (GA, dry AMD) and choroidal neovascularization (wet AMD). Despite the high prevalence and significant public health burden of AMD, its etiology and pathophysiology remain poorly understood.

AMD is a multi-factorial progressive disease that involves complex interactions between genetic and environmental factors.[3,4] Candidate gene association studies have identified multiple genes related to AMD, including *CFH*,[5,6] *ARMS2/HTRA1*,[7–9] *C2I*,[10] and *CFB*.[11] Identification of these genes has led to extensive studies on the alternative complement pathway and mitochondria-related oxidation pathways in relation to AMD.[12–14] Despite significant progress in identifying AMD-associated genes, genetic susceptibility loci discovered thus far only account for approximately half the heritability of AMD.[15] Recent studies demonstrated that antioxidant micronutrients and lipids may also have an important role in AMD;[16–19] a genome-wide association study found a significant association between advanced AMD and hepatic lipase (*LIPC*), the gene encoding hepatic triglyceride lipase.[20] In this study, we confirmed the association of *LIPC* with advanced AMD in two independent Caucasian cohorts.

Materials and methods

Subjects and clinical diagnosis

This study was approved by the Institutional Review Board of the University of California, San Diego, CA, USA. The research adhered to

the tenets of the Declaration of Helsinki. Informed consent was signed by all subjects before participation in the study. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

In total, 1626 nonfamilial advanced AMD patients and 859 normal age-matched controls (age 50 years or older without drusen or RPE changes) were recruited at the University of California, San Diego, CA, USA. Demographics, medical history, and a blood sample were collected at the baseline visit. All participants underwent standard ophthalmic examinations, including slit lamp exams and indirect ophthalmoscopy. A pair of stereoscopic color fundus photographs (50°) was taken, centered on the fovea using a Topcon fundus camera (Topcon TRV-50VT, Topcon Optical Company, Tokyo, Japan). Grading was carried out using a standard grid classification suggested by the International Age-related Maculopathy Epidemiological Study Group.[21] In total, 2159 cases and 1150 controls from the Michigan, Mayo, AREDS, and Pennsylvania data set were included in this study as a replication cohort.

Genotyping

Genomic DNA samples were extracted from peripheral blood leukocytes with the Qiagen kit (Qiagen Inc., Chatsworth, CA, USA), according to the manufacturer's instructions. The discovery cohort of 1626 advanced AMD patients were genotyped for the *LIPC* variants rs10468017 and rs493258. Variance and position of the two single-nucleotide polymorphisms (SNPs) are shown in Supplementary Table 1. Allele frequencies were compared with 859 age and ethnicity-matched normal controls by laboratory personnel blinded to case/control status. The findings were tested for replication in an independent cohort of 2159 advanced AMD patients and 1150 controls.

Genotyping of both SNPs was achieved by primer extension of multiplex PCR products followed by SNaPshot on an ABI 3100 genetic analyzer (Applied Biosystems, Foster City, CA, USA). All genotyping results were of high quality, with an average call rate of 98.5%.

Statistical analysis

Deviation from Hardy–Weinberg equilibrium was assessed with a statistical significance level of 0.01. χ^2 tests under the additive model were performed to assess evidence for association between the *LIPC* genotype and advanced AMD between cases and controls. The statistical significance level was adjusted by Bonferroni correction. Odds ratios and 95% confidence intervals were also calculated to estimate risk size of the risk alleles by using SPSS 11.5 software (Chicago, IL, USA). Linkage disequilibrium (LD) patterns were defined by Haploview 4.1 software (Cambridge, MA, USA).

Results

The demographics of the discovery cohort are presented in Table 1. The promoter variant rs493258 was found to be significantly associated with advanced AMD in the discovery cohort ($P = 9.63E-03$), replication cohort ($P = 4.48E-03$), and combined cohort ($1.21E-04$; Table 2a). For rs10468017, a significant association with advanced AMD was also found in the discovery cohort ($P = 0.048$), replication cohort ($P = 0.015$), as well as the combined cohort ($P = 1.67E-03$; Table 2b).

Overall, the frequency of the minor (A) allele of rs493258 was 43.4% in cases *vs* 47.1% in controls, whereas the frequency of the minor (T) allele of rs10468017 was 26.7% in cases *vs* 29.5% in controls. Haplotype analysis did not show strong LD between the two SNPs ($r^2 = 0.369$). Genotype counts are shown in Supplementary Tables 2a and b.

Discussion

Here, we confirmed the genetic association between AMD and *LIPC* and expand upon previous reports by analyzing two independent Caucasian populations. Our findings were consistent with previous studies in which both SNPs were reported to be significantly associated with AMD.[20,22]

The *LIPC* gene encodes hepatic triglyceride lipase, which is expressed in the liver. *LIPC* catalyzes the

Table 1 Discovery cohort demographics

	AMD cases	*Controls*
Age		
Mean ± SD	79.31 ± 8.96	72.57 ± 8.71
Sex, n *(%)*		
Female	924 (56.8)	539 (61.5)
Male	704 (43.2)	338 (38.5)
BMI		
Mean ± SD	26.87 ± 5.71	26.28 ± 5.65
Smoking status, n *(%)*		
Current smokers	125 (8.9)	33 (6.0)
Past smokers	627 (44.4)	188 (34.4)
Nonsmokers	660 (46.7)	325 (59.5)

Table 2 (a) Association between *LIPC*-rs493258 and advanced AMD; (b) association between *LIPC*-rs10468017 and advanced AMD

Cohort	*Phenotype*	N	*Minor allele (A) frequency*	*Trend* P-*value*	*Allelic* P-*value*	OR_{het} *(95%CI)*	OR_{hom} *(95%CI)*
(a)							
Discovery cohort	Advanced AMD	1626	0.430	8.76×10^{-3}	9.63×10^{-3}	0.79 (0.65, 0.97)	0.73 (0.57, 0.95)
	Control	858	0.468				
Replication cohort	Advanced AMD	2159	0.437	4.48×10^{-3}	4.48×10^{-3}	0.88 (0.74, 1.04)	0.74 (0.60, 0.92)
	Control	1150	0.473				
Combined cohort	Advanced AMD	3785	0.434	1.11×10^{-4}	1.21×10^{-4}	0.84 (0.74, 0.96)	0.74 (0.63, 0.87)
	Control	2008	0.471				
(b)							
Discovery cohort	Advanced AMD	1617	0.261	0.047	0.048	0.90 (0.75, 1.08)	0.72 (0.53, 1.02)
	Control	859	0.288				
Replication cohort	Advanced AMD	2159	0.272	0.015	0.015	0.88 (0.75, 1.02)	0.74 (0.57, 0.99)
	Control	1150	0.300				
Combined cohort	Advanced AMD	3776	0.267	1.69×10^{-3}	1.67×10^{-3}	0.89 (0.79, 1.00)	0.74 (0.60, 0.92)
	Control	2009	0.291				

hydrolysis of phospholipids, mono-, di-, and triglycerides, and acyl-CoA thioesters, and it has an important role in the metabolism of lipoproteins, including high-density lipoprotein (HDL)[23–25] and low-density lipoprotein.[26] Previous studies have demonstrated that *LIPC* is associated with metabolic syndrome,[27,28] atherosclerosis,[29,30] and other cardiovascular disorders.[31,32]

The mechanism(s) underlying the relationship between *LIPC* and AMD is unknown. Despite the association of *LIPC* and serum HDL levels, the correlation between AMD and serum HDL levels is inconsistent.[21,33] These findings suggest that *LIPC* may modulate AMD risk through a mechanism independent from its effect on HDL levels. Central to AMD progression is the buildup of cellular debris, proteins, and lipids within Bruch's membrane, which results in the formation of drusen.[34] These changes in Bruch's membrane result in tissue hypoxia and the production of angiogenic signaling molecules (eg, VEGF) that promote aberrant blood vessel growth.[35] In addition, oxidative stress in the eye can cause the oxidation of phospholipids. These oxidation products are pro-inflammatory and can also lead to RPE apoptosis, VEGF production, and angiogenesis.[36,37] As *LIPC* is an important enzyme in lipid metabolism and has been shown to be related to both the accumulation of drusen and progression from large drusen to advanced AMD,[38] it may modulate AMD risk by affecting lipid homeostasis and the accumulation of damaging biomolecules in the eye. Further studies evaluating the role of lipoproteins in the pathogenesis and progression of AMD will elucidate the role of *LIPC* in AMD and may lead to novel strategies for AMD prevention and treatment.

Summary

What was known before

- A recent genome-wide association study found a significant association between advanced AMD and the *LIPC* gene.

What this study adds

- Our article confirms the genetic association between AMD and LIPC and expands upon previous reports by analyzing two independent Caucasian populations.

Conflict of interest

The authors declare no conflict of interest.

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1. You are seeing a 76-year-old woman with a history of AMD along with hyperlipidemia, obesity, and impaired fasting glucose. Which of the following statements regarding AMD and its clinical stages is most accurate?

A It is the leading cause of blindness among older adults in developed countries
B Early AMD is characterized by geographic atrophy
C Choroidal neovascularization is required to meet criteria for advanced AMD
D Environmental factors do not affect the risk of AMD

2. What should you consider regarding the relationship between hepatic triglyceride lipase and AMD as you evaluate this patient?

A Hepatic triglyceride lipase is encoded by the *LIPC* gene
B The most important function of hepatic triglyceride lipase is the creation of albumin
C Hepatic triglyceride lipase activity is associated with a higher risk of pancreatitis
D There is a strong correlation between AMD and serum HDL levels

3. In the current study by Lee and colleagues, what was the role of *LIPC* in the prevalence of advanced AMD?

A *LIPC* was associated with a reduced prevalence of advanced AMD
B *LIPC* was associated with an increased prevalence of advanced AMD
C Only one SNP in the promoter region of *LIPC* was associated with advanced AMD
D *LIPC* was not found to be associated with the prevalence of advanced AMD

Activity evaluation

1. The activity supported the learning objectives.

Strongly disagree				Strongly agree
1	2	3	4	5

2. The material was organized clearly for learning to occur.

Strongly disagree				Strongly agree
1	2	3	4	5

3. The content learned from this activity will impact my practice.

Strongly disagree				Strongly agree
1	2	3	4	5

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Strongly disagree				Strongly agree
1	2	3	4	5