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Serum Lipid Biomarkers and Hepatic Lipase Gene Associations with Age-Related Macular Degeneration

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Abstract

Objective—A genetic variant in the high density lipoprotein (HDL) cholesterol pathway, hepatic lipase (*LIPC*), was discovered to be associated with advanced age-related macular degeneration (AMD) in our genome-wide association study. We evaluated whether *LIPC* is associated with serum lipids and determined if the gene and serum lipids are independently associated with AMD.

Design—Case – control study.

Participants—A total of 458 participants from the Progression Study of Macular Degeneration and the Age Related Eye Disease (AREDS) Ancillary study, including 318 advanced AMD cases with either geographic atrophy (n = 123) or neovascular disease (n = 195) and 140 controls.

Methods—Participants were genotyped for 8 variants associated with AMD: two *CFH* variants, *C2*, *CFB*, *C3*, *CFI*, the *ARMS2/HTRA1* gene region, and *LIPC*. Fasting blood specimens were obtained at study onset, and serum levels of total cholesterol, low density lipoprotein (LDL), HDL, and triglycerides were determined. Logistic regression was used to evaluate associations between serum lipids, *LIPC* genotype and AMD. The relationship between *LIPC* and serum lipids was determined using logistic and linear regression.

Main Outcome Measure—*LIPC* and serum lipid associations with AMD.

Results—The minor T allele of the *LIPC* gene was associated with a reduced risk of AMD (Odds Ratio (OR) = 0.4, 95% Confidence Interval (CI) (0.2 – 0.9) p (trend for number of T alleles) = 0.01, controlling for age and sex. Mean level of HDL was lower (p = 0.05), and mean level of LDL (p = 0.04) was higher in cases of advanced AMD compared with controls. Higher total cholesterol and LDL were associated with increased risk of AMD with a p (trend) of 0.01 for both, in models controlling for environmental and genetic covariates. The T allele of *LIPC* was associated with higher levels of HDL. However, *LIPC* is associated with advanced AMD independent of HDL level.

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Conflict of Interest: JMS: Tufts Medical Center has filed a patent related to materials in this article. No other authors have financial interests to declare.

Conclusions—The HDL raising allele of the *LIPC* gene was associated with reduced risk of AMD. Higher total cholesterol and LDL were associated with increased risk, while higher HDL tended to reduce risk of AMD. The specific mechanisms underlying the association between AMD and *LIPC* require further investigation.

Hepatic lipase (*LIPC*), a gene located on chromosome 15q22, was recently discovered to be associated with age-related macular degeneration (AMD) in our large genome-wide association study (GWAS).¹ This finding was replicated in another GWAS.² This new variant encodes the hepatic lipase enzyme, and affects serum high density lipoprotein cholesterol (HDL-c) levels.³ To date, studies evaluating the association between serum lipids and AMD have been inconsistent.^{4–11} With new evidence of a genetic variant in a lipid pathway related to AMD, we analyzed serum levels of total cholesterol, HDL, low density lipoprotein (LDL), and triglycerides, in cases and controls to further evaluate the lipid-AMD association. We assessed whether the *LIPC* genetic locus is associated with serum lipids and determined if the gene and the serum lipids are associated with AMD. We also assessed whether the effect of *LIPC* on AMD is mediated by HDL.

MATERIALS AND METHODS

Study Population

We selected Caucasian individuals from our Progression Study of Macular Degeneration and Age Related Eye Disease (AREDS) Ancillary cohorts, as previously described.^{12–14} There were 219 participants in the AREDS Ancillary study, and 308 participants in the Progression study with a Clinical Age Related Maculopathy Grading System (CARMS)¹⁵ grade of 1 (no drusen or few small drusen), 2 (more small drusen), 4 (geographic atrophy involving the macula either central or non-central), or 5 (neovascular disease). Individuals with grade 3 (intermediate or large drusen) were excluded from these analyses so we could compare advanced cases (grades 4 and 5) with controls (grades 1 and 2). Cases and controls who had serum lipid measurements, ocular examinations, fundus photography, risk factor, and genetic data were selected which included 265 (86%) of the eligible subjects from the Progression Study and 193 (88%) of the eligible individuals from the Ancillary Study. There were 318 advanced AMD cases: 123 had geographic atrophy (GA) and 195 had neovascular disease (NV) and 140 individuals were classified as controls. The mean ages $\pm$ standard deviation (SD) for the case and control groups were 81 ± 7 years and 76 ± 6.0 years, respectively. There were no significant differences in age and sex between the excluded group and the study cohort included in these analyses. This research complied with the tenets of the Declaration of Helsinki and Institutional Review Board approval was obtained.

Genotyping

DNA samples were obtained and genotyped for 8 single nucleotide polymorphisms (SNPs) in genes demonstrated to be related to AMD: 1) Complement Factor H (*CFH*) Y402H (*rs1061170*) in exon 9 of the *CFH* gene on chromosome 1q32, a change 1277T>C, resulting in a substitution of histidine for tyrosine at codon 402 of the CFH protein, 2) *CFH* rs1410996 an independently associated SNP variant within intron 14 of *CFH*, 16–21 3) *ARMS2/HTRA1* rs10490924, a non-synonymous coding SNP variant in exon 1 of *LOC387715* on chromosome 10 resulting in a substitution of the amino acid serine for alanine at codon 69, 22–25 4) Complement Component 2 or *C2* E318D (*rs9332739*), the non-synonymous coding SNP variant in exon 7 of *C2* resulting in a substitution of aspartic acid for glutamic acid at codon 318, 5) Complement Factor B or *CFB* R32Q (*rs641153*), the non-synonymous coding SNP variant in exon 2 of *CFB* resulting in the substitution of the amino acid glutamine for arginine at codon 32, 26 6) Complement Component 3 or *C3* R102G (*rs2230199*), the non-synonymous coding SNP variant in exon 3 of *C3* resulting in

the substitution of the amino acid glycine for arginine at codon 102, 27·28 7) Complement Factor I or *CFI* (*rs10033900*), an independently associated SNP located in the linkage peak region of chromosome 4, 2781 base pairs upstream of the 3' untranslated region of *CFI*· 29 and 8) Hepatic Lipase C or *LIPC* (*rs10468017*), a promoter variant on chromosome 15q22.1

For the genetic variant on chromosome 10, *ARMS2*, it remains a subject of debate whether the gene *HTRA1* adjacent to it may in fact be the AMD-susceptibility gene on 10q26; however, the relevant SNPs in these 2 genes have been reported to be nearly perfectly correlated. Thus, while the other SNP is a promising candidate variant, rs10490924 used in this study can be considered a surrogate for the causal variant which resides in this region. 22–25 For the *C2/CFB* genes, there are two independent associations to the *C2/CFB* locus, but because of linkage disequilibrium we do not know which of the two genes or both are functionally affected. 26 Genotyping was performed using primer mass extension and MALDI-TOF MS analysis (MassEXTEND methodology of Sequenom, San Diego, CA) at the Broad Institute Center for Genotyping and Analysis (Cambridge, MA).

Serum Samples and Lipids

Participants had fasting blood samples drawn at baseline for the Progression Study and at the onset of the AREDS Ancillary study and stored at -80°C to -140°C . Fasting serum samples were analyzed for total cholesterol, HDL, triglycerides, and LDL. Lipids were measured on a Hitachi 917 analyzer with reagents and calibrators from Roche Diagnostics as previously described.³⁰

Covariates

Smoking history was collected at onset of the study procedures from a standardized risk factor questionnaire. Smokers were defined as having smoked at least one cigarette per day for six months or longer. Height and weight were measured at baseline to calculate body mass index (BMI) (weight in pounds multiplied by 703 divided by height in inches squared). Blood pressure was measured at the onset of the studies, and categorized according to the American Heart Association (<http://www.americanheart.org/presenter.jhtml?identifier=4450> Accessed: October 13, 2009) as follows: 1) Normal: systolic less than 120 mm/Hg and diastolic less than 80 mm/Hg, 2) Prehypertension: systolic 120–139 mm/Hg or diastolic 80–89 mm/Hg, 3) Hypertension Stage 1: systolic 140–159 mm/Hg or diastolic 90–99 mm/Hg, 4) Hypertension Stage 2: systolic 160 mm/Hg or higher or diastolic 100 mm/Hg or higher.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for genetic and behavioral variables using logistic regression controlling for age (≤ 79 , 80+) and sex to assess their relationship with advanced AMD. P values ≤ 0.05 were considered statistically significant for all analyses.

We adjusted serum lipid measurements for sex and age and calculated mean values for controls, all cases, and the NV and GA advanced subtypes separately. Logistic regression was used to calculate P values to compare differences between the case groups and controls. We determined the mean levels of serum lipids according to *LIPC* genotype (CC, CT, TT), and used linear regression to calculate p-values for each continuous lipid variable to evaluate whether lipids were related to *LIPC* genotype, controlling for age and sex.

Logistic regression was used to calculate ORs and 95% CIs to assess the relationship between quartile of lipid and AMD. Model A was adjusted for age, sex, smoking (never, past, current), BMI (<25 , 25–29.9, 30+), and blood pressure (normal, pre-hypertension, hypertension stage 1, hypertension stage 2). Model B was adjusted for the same covariates

as in model A plus genotypes *CFH* Y402H (TT, CT, CC), *CFH:rs1410966* (TT, CT, CC), *C2* (GG, CG/CC), *CFB* (CC, CT/TT), *ARMS2/HTRA1* (GG, GT, TT), *C3* (CC, CG, GG), *CFI* (CC, CT, TT), and *LIPC* (CC, CT, TT).

We sought to determine the relative effects of HDL and *LIPC* on risk of advanced AMD. ORs and 95% CIs were calculated to assess associations between *LIPC* genotype and advanced AMD using logistic regression in four models adjusting for various combinations of the following covariates: age, sex, smoking, BMI, blood pressure, HDL, *CFH* Y402H (TT, CT, CC), *CFH:rs1410966* (TT, CT, CC), *C2* (GG, CG/CC), *CFB* (CC, CT/TT), *ARMS2/HTRA1* (GG, GT, TT), *C3* (CC, CG, GG), *CFI* (CC, CT, TT), and *LIPC* (CC, CT, TT).

RESULTS

In Table 1 (available at <http://aaajournal.org>) the distributions of baseline demographic, behavioral, blood pressure, and genotype data for the different study groups are displayed. Advanced AMD was associated with older age. AMD cases were more likely to be current smokers or past smokers, with a significant P value of 0.01 for past smokers in the NV group. Cases tended to have higher BMI than controls, although the association was not significant. There was a higher risk of advanced AMD for hypertension stage 2 compared with normal blood pressure (OR = 2.5, 95% CI 1.1 – 6.0 for all cases combined), with similar risk in the GA and NV groups. The *CFHY402H*, *CFH:rs1410966*, and *ARMS2/HTRA1* risk genotypes were significantly related to advanced AMD with a p (trend) of <0.01 for the total AMD group and both subtypes separately. For *C2*, the C allele was in the direction of a protective effect as previously documented.²⁶ *CFB* had inconsistent associations with advanced AMD. For both *C2* and *CFB* the low frequency of the C and T alleles, respectively, may influence these results.

The GG genotype of *C3* increased risk two-fold (OR = 2.1 for all case groups), although this did not reach statistical significance. For *CFI*, the TT genotype increased risk (OR = 1.8, 95% CI 0.9 – 3.2) for the total case group, and there was a trend for increasing risk with increasing number of T alleles for the NV group (P trend = 0.02). The T allele of the *LIPC* gene was associated with reduced risk of advanced AMD for all case groups (P trend for number of T alleles = 0.01–0.02).

Table 2 displays sex adjusted serum lipid means and ranges for controls, all cases, and the GA and NV groups separately. LDL was significantly higher for all cases and the NV subtype compared with controls (P = 0.03, 0.04, respectively). HDL was significantly lower for all cases and the NV subtype (P = 0.05, 0.03, respectively). Mean levels of total cholesterol and triglycerides were somewhat higher among cases compared with controls, but differences did not reach statistical significance.

Table 3 shows associations between serum lipids and advanced AMD in multivariate models. There were significant trends for increasing risk of AMD with higher quartile of LDL in Model A and Model B, with P (trend) = 0.03, 0.01, respectively. The OR's for the highest vs. the lowest quartile for LDL were 2.0 (P=0.03) and 2.5 (P=0.01) for models A and B, respectively. There was also a significant trend for increasing risk of AMD with higher total cholesterol in Model B controlling for all genotypes (OR =2.2 for the 4th vs the 1st quartile, P=0.02, and P trend = 0.01). Higher levels of HDL tended to be associated with reduced risk of AMD when controlling for all covariates, with OR=0.6 for the highest vs the lowest quartile (P=0.08) in model A and OR= 0.5 (P=0.09) in model B, although these associations were not statistically significant. Triglyceride level did not appear to be related to AMD in these analyses controlling for other variables.

The relationship between *LIPC* genotype and serum lipids was explored. As seen in Table 4, mean level of HDL increased with each T allele of the *LIPC* gene (p trend = 0.05). Mean level of HDL was 49 mg/dL ($\pm$ 14) for the CC genotype and 54 mg/dL ($\pm$ 17) for the TT genotype. Total cholesterol, LDL, and triglycerides were not significantly associated with *LIPC*.

In Table 5, ORs and 95% CIs for AMD according to *LIPC* genotype, controlling for covariates are shown in 4 models. Models A and B show a protective effect of *LIPC* on AMD controlling for age and other covariates not including HDL. In Models C and D, HDL is included with and without genotype. For all four models, the ORs remain at 0.6 for the CT genotype. In Models A, B, and C for the TT genotype the ORs are 0.4, and in Model D the OR is 0.5.

DISCUSSION

To our knowledge, this is the first report to assess the *LIPC* gene together with lipid biomarkers and their associations with AMD. Based on this recent gene discovery and the various hypotheses regarding the role of cholesterol on AMD pathogenesis, we assessed the relationship between circulating lipids, *LIPC*, and AMD. Results show the TT genotype of the *LIPC* gene is significantly associated with reduced risk of advanced AMD for both NV and GA subtypes. Analysis of serum lipids suggested that elevated HDL may be associated with reduced risk of advanced AMD and the NV subtype, and that higher LDL is significantly associated with increased risk of advanced AMD and the NV subtype. Elevated total cholesterol also tended to be associated with AMD. There was a significant trend for increasing HDL with increasing number of *LIPC* T alleles. HDL level did not appear to mediate the association between *LIPC* and AMD based on the independent associations of both *LIPC* and HDL when considered simultaneously.

Cardiovascular disease (CVD) and AMD have been shown to share some of the same risk factors including high BMI, C-reactive protein, other cytokines, and history of smoking.^{14, 31–32} It is possible that CVD could provide a comparison model for the role of cholesterol in AMD pathogenesis,³³ and several studies have evaluated the AMD – cholesterol relationship, with inconsistent results.^{4–11}

The significant association between elevated level of total cholesterol and AMD reported here is consistent with three studies that found a similar relationship.^{8–10–11} Like our study, these reports used a case-control design, and included participants with well-defined GA and/or NV disease, although they had varying population sizes and did not include genotypes. In our study, we found total cholesterol to be significantly related to an increased risk of AMD in multivariate models, both with and without genetic variables included.

Our study found an inverse association between HDL levels and AMD, which supports the finding by Nowak et al.¹⁰ In contrast, a few studies found HDL to be a risk factor^{4,6}. When the results of the Blue Mountains, Rotterdam and Beaver Dam Studies were pooled, there was no significant association, positive or negative, between HDL and incident AMD.⁷ These study cohorts combined however, had a total of only 38 GA cases and 67 NV cases in a population of ~9400.⁷ In another small ($n = 84$) case-control study there was no significant association with any of the serum lipids.⁹ Our study population had a larger number of GA and NV cases, and our multivariate analyses controlled for genotypes which could partially account for some of the differences in results.

As well as having a systemic implication in the etiology of AMD, cholesterol also functions locally in the retina. Cholesterol has been found in drusen and in Bruch's membrane.^{33–34} LDL and HDL transport cholesterol, vitamin E, and lutein/zeaxanthin within the retinal

pigment epithelium (RPE) and Bruch's membrane for use by photoreceptors. However, in older eyes these lipoproteins cannot move across the Bruch's membrane as readily from degeneration due to aging, which could lead to deposits, drusen, and stress on the RPE, which may lead to AMD.³³ Although the origin of cholesterol found within the retina is uncertain, it has been hypothesized that it may be generated systemically.³⁴

In our study we found significant associations between hypertension stage 2 (systolic blood pressure ≥ 160 mm/Hg and diastolic blood pressure ≥ 100 mm/Hg) and the total case group as well as the NV group, adding to the evidence of shared risk factors between CVD and AMD. Different definitions of hypertension have also been considered as potential risk factors for AMD in other studies. Among the population based studies, Rotterdam and Beaver Dam also found a significant association between higher systolic blood pressure and late and early cases of AMD, ^{5,35} but the Blue Mountains group found no association between blood pressure and late AMD (NV or GA).³⁶ When these population based results were pooled, based on 102 cases of AMD, there was no significant association with AMD and blood pressure.⁷ However, the results of case-control studies, with larger numbers of advanced AMD cases, showed significant associations between high blood pressure and risk of AMD. ^{6,8,11}

LIPC is associated with decreased hepatic lipase activity and elevated HDL cholesterol for those with the T allele.^{3, 37} This was confirmed in our study population where we found an association between increased HDL level with increasing number of *LIPC* T alleles. Based on our GWAS studies, a few other new genes in the lipid pathway may also be related to AMD, including *ABCA1* and *CETP*, although the results for these other genes did not reach genome-wide significance.^{1,2} The effects of these genes on AMD are not consistent relative to raising or lowering HDL levels. The HDL raising allele of *LIPC* reduces risk, whereas the HDL raising allele of *ABCA1* and *CETP* increases risk of AMD. Our evaluation of HDL, *LIPC* genotype, and AMD suggests that HDL and *LIPC* are independently associated with AMD. Therefore, the *LIPC* association may not be due to an effect on raising HDL levels, but could represent a pleiotropic effect of the same functional unit¹ and may involve other mechanisms.

Some of the advantages of our study population include the well characterized study population for whom AMD status was based on ocular examinations and fundus photography. Behavioral and blood pressure data were collected using standardized questionnaires and measurements, and fasting serum specimens were used to measure levels of lipids. Although the number of advanced cases is relatively large, even larger sample sizes as well as prospective studies will be needed to confirm and expand upon these findings.

The discovery of a genetic variant in the HDL pathway, *LIPC*, provides new insight into the pathogenesis of AMD. *LIPC* is associated with reduced risk of GA and NV AMD. HDL may be associated with reduced risk of advanced AMD, and LDL and total cholesterol increased risk of AMD. Further investigation into the relationships among *LIPC*, serum lipids, and AMD as well as elucidation of other mechanisms involved in this new pathway is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 2

Mean Levels of Serum Lipids According to Maculopathy Group

Serum Lipid [§]	Controls* (n = 140) mean (min, max)	All Cases [†] (n = 318) mean (min, max)	p value [‡]	Geographic Atrophy (n = 123) mean (min, max)	p value [‡]	Neovascular (n = 195) mean (min, max)
High Density Lipoprotein (HDL) (mg/dL)	53 (20 – 103)	49 (24 – 94)	0.05	50 (24 – 94)	0.28	48 (25 – 94)
Low Density Lipoprotein (LDL) (mg/dL)	135 (52 – 310)	144 (59 – 296)	0.03	143 (64 – 296)	0.15	145 (59 – 232)
Total Cholesterol (mg/dL)	216 (136 – 420)	223 (120 – 373)	0.18	224 (127 – 373)	0.22	222 (120 – 306)
Triglycerides (mg/dL)	140 (41 – 387)	143 (38 – 490)	0.94	144 (43 – 490)	0.93	144 (38 – 485)

* Clinical Age-Related Maculopathy Staging System (CARMS) grades 1 and 2

[†] CARMS grades 4 geographic atrophy (GA), 5 neovascular (NV)[‡] P values adjusted for age, and reflect a comparison between GA, NV, or all cases vs. controls.[§] Adjusted for sex

Table 3
Association Between Serum Lipids and Advanced Age-Related Macular Degeneration in Multivariate Models

Quartile of Serum Lipid	N (%)		Model A		Model B	
	Controls (n = 140)	All Cases* (n = 318)	Odds Ratio [†]	(95% Confidence Interval)	Odds Ratio [‡]	(95% Confidence Interval)
High Density Lipoprotein (HDL)						
1	27 (19)	90 (28)	1.0		1.0	
2	39 (28)	78 (25)	0.7 (0.4 – 1.3)	0.23	0.7 (0.4 – 1.4)	
3	32 (23)	80 (25)	0.8 (0.4 – 1.5)	0.47	0.8 (0.4 – 1.6)	
4	42 (30)	70 (22)	0.6 (0.3 – 1.1)	0.08 0.13	0.5 (0.3 – 1.1)	
Low Density Lipoprotein (LDL) [§]						
1	45 (32)	68 (22)	1.0		1.0	
2	35 (25)	75 (24)	1.5 (0.8 – 2.6)	0.19	1.6 (0.8 – 3.1)	
3	34 (24)	86 (27)	1.6 (0.9 – 2.9)	0.11	1.9 (1.0 – 3.6)	
4	26 (19)	86 (27)	2.0 (1.1 – 3.6)	0.03 0.03	2.5 (1.2 – 4.9)	
Cholesterol						
1	40 (29)	80 (25)	1.0		1.0	
2	41 (29)	70 (22)	0.8 (0.4 – 1.4)	0.37	1.1 (0.6 – 2.0)	
3	34 (34)	77 (24)	1.0 (0.6 – 1.9)	0.90	1.6 (0.8 – 3.0)	
4	25 (18)	91 (29)	1.6 (0.9 – 3.0)	0.13 0.10	2.2 (1.1 – 4.5)	
Triglycerides						
1	30 (21)	76 (24)	1.0		1.0	
2	39 (28)	84 (68)	0.8 (0.4 – 1.4)	0.38	0.6 (0.3 – 1.2)	
3	37 (26)	76 (24)	0.7 (0.4 – 1.3)	0.30	0.6 (0.3 – 1.3)	
4	34 (24)	82 (26)	0.8 (0.4 – 1.5)	0.43 0.45	0.9 (0.4 – 1.8)	

* Clinical Age Related Maculopathy Staging System (CARMS) grades 4 (geographic atrophy), 5 (neovascular)

[†] Adjusted for age, sex, smoking, body mass index (BMI), blood pressure.

[‡] Adjusted for age, sex, smoking, BMI, blood pressure, *CFH* Y402H (TT, CT, CC), *CFHrs* 1410966 (TT, CT, CC), *C2* (GG, CG/CC), *CFB* (CC, CT/TT) *ARMS2/HTRA1* (GG, GT, TT), *C3* (CC, CG, GG), *CFI* (CC, CT, TT), *LIPC* (CC, CT, TT)

[§] Some individuals have missing values

|| p (trend)

Table 4Association Between Hepatic Lipase C (*LIPC*), Genotypes and Serum Lipids

	<i>LIPC</i> :rs10468017 genotype			p trend [†]
	C C	C T	TT	
	N = 244 Mean ± SD [§]	N = 176 Mean ± SD [§]	N = 38 Mean ± SD [§]	
Serum Lipid*				
High Density Lipoprotein (HDL) (mg/dL)	49 ± 14	51 ± 16	54 ± 17	0.05
Low Density Lipoprotein (LDL) (mg/dL)	142 ± 36	139 ± 37	149 ± 32	0.77
Total Cholesterol (mg/dL)	219 ± 40	221 ± 40	232 ± 37	0.13
Triglycerides (mg/dL) [‡]	5 ± 1	5 ± 1	5 ± 0.4	0.14
Cholesterol/HDL (mg/dL)	5 ± 2	5 ± 2	5 ± 2	0.47

* Adjusted for sex, age

[†] P (trend) for number of *LIPC* T alleles, adjusted for age and sex[‡] Log value[§] Standard deviation

Association Between Hepatic Lipase C (*LIPC*), High Density Lipoprotein (HDL), and Advanced Age-Related Macular Degeneration in Multivariate Models

Table 5

	Model A [‡]		Model B [‡]		Model C [§]	
	Controls (N = 140)	All Cases* (N = 318)	Odds Ratio (95% Confidence Interval)	p value	Odds Ratio (95% Confidence Interval)	p value
<i>LIPC</i> :rs10468107	N (%)	N (%)				
CC	61 (44)	183 (58)	1.0		1.0	
CT	61 (44)	115 (36)	0.6 (0.4 – 0.9)	0.02	0.6 (0.4 – 0.9)	0.03
TT	18 (13)	20 (6)	0.4 (0.2 – 0.9)	0.02	0.4 (0.2 – 0.9)	0.03

* Clinical Age Related Maculopathy Staging System (CARMS) grades 4 (geographic atrophy), 5 (neovascular)

[‡] Adjusted for age, sex, smoking, body mass index (BMI), blood pressure

[§] Adjusted for same variables in Model A plus: *CFH* Y402H (TT, CT, CC), *CFHRs1410966* (TT, CT, CC), *C2* (GG, CG/CC), *CFB* (CC, CT/TT), *ARMS2/HTRA1* (GG, GT, TT), *C3* (CC, CG, GG), *CFI* (CC, CT, TT), *LIPC* (CC, CT, TT)

[§] Adjusted for same variables in Model A plus HDL

|| Adjusted for same variables in Model B plus HDL