Association between well-characterized lipoprotein-related genetic variants and carotid intimal medial thickness and stenosis: The Framingham Heart Study

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Received 29 August 2005; received in revised form 15 November 2005; accepted 12 December 2005
Available online 23 January 2006

Abstract

Objective: To determine the association of well-characterized lipoprotein-related genetic variants with carotid intimal medial thickness (IMT) and stenosis.

Methods: 3380 men and women from the Framingham Offspring Study underwent carotid ultrasound to determine carotid IMT and stenosis ≥ 25%. We genotyped 12 variants in 10 lipoprotein-related genes known to be associated with significant differences in lipoprotein levels.

Results: For most of the variants, there was no association with carotid IMT. In multivariable, sex-specific analyses, the rare allele of the cholesterol ester transfer protein (CETP) TaqIB variant was associated with lower ICA IMT in men. Hypertension was associated with higher ICA IMT only in male carriers of the rare allele of the APOCIII Sst-1 variant (p for the interaction = 0.041). In analyses of carotid stenosis in male, carriers of the lipoprotein lipase (LPL) N291S rare variant showed a higher risk of carotid stenosis (OR = 2.59, 95% confidence interval: 1.11–6.02, p = 0.028) compared to NN genotype.

Conclusions: While there is no evidence for a significant association of several common lipoprotein-related genetic variants with carotid IMT, our results are consistent with the previously reported role of CETP and LPL genetic variants in cardiovascular risk and the possible modulation of the association between hypertension and carotid IMT by APOCIII Sst-1 variant.

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Keywords: Carotid; Epidemiology; Genetics; Lipids

1. Introduction

Dyslipidemia resulting from environmental and genetic factors is implicated in the etiology of atherosclerosis. Lowering of LDL cholesterol reduces the risk of atherosclerosis events [1]. Given the link between dyslipidemia and atherosclerosis, one focused strategy to understanding the genetic determinants underlying atherosclerosis has been to identify genetic variants within genes in key lipoprotein pathways and then to examine associations with lipoprotein levels and atherosclerosis phenotypes. Several well-characterized
lipoprotein-related genetic variants have been previously studied [2–11] and most have been shown to be associated with significant differences in measured levels of some or all lipid traits across genotypes [2–4,6–9,11] in the Framingham Heart Study: APOA1 75G>A [2], APOA4 G360H, APOC3 Sst-1 polymorphism [3], plasma cholesterol ester transfer protein (CETP) TaqIB polymorphism [4], cholesterol 7-α-hydroxilase (CYP7B1) 204A>C [5], intestinal fatty acid binding protein (FABP2) A54T [6], hepatic lipase (LIPC) S14C>T [7], lipoprotein lipase (LPL) D9N, N291S [8] and S447X variants [9], microsomal triglyceride transfer protein (MTP) 493G>T [10], and PPARA L162V [11].

Carotid intimal medial thickness (IMT) is associated with incident stroke and myocardial infarction [12], and it is used as a surrogate measure of global atherosclerosis burden. Other carotid phenotypes such as carotid plaque, stenosis, echogenicity, lumen diameter, distensibility, and stiffness are also used as a measure of atherosclerosis and can represent different stages in this complex process [13]. Data from different studies demonstrate that there is a substantial heritable component to these carotid atherosclerosis phenotypes [14,15].

Common genotypes of these well-characterized lipoprotein-related genetic variants may be associated with differences in quantitative measures of atherosclerosis. The aim of the research reported here was to determine the association of these well-characterized lipoprotein-related genetic variants with carotid IMT and stenosis in a community-based sample.

2. Methods

2.1. Study population

The Framingham original cohort began enrollment in 1948, with the recruitment of 5209 men and women. Subjects included in this analysis were participants in the offspring cohort of the Framingham Heart Study, which began in 1971 with the recruitment of 5124 men and women who were offspring and spouses of offspring of the original cohort and ranged in age from 5 to 70 years [16]. There were 3532 participants in Offspring Study examination cycle 6 (1996–1998). A total of 3380 of these participants underwent B-mode carotid ultrasonography. Of these, data on the determined lipoprotein-related genetic variants ranged from 1621 to 2632 participants. The research protocol was approved by the Institutional Review Board of Boston University. All participants provided informed consent.

2.2. Carotid ultrasonography

A standard, reproducible protocol was used for carotid ultrasound acquisition and image analysis [12]. A single trained sonographer made all the measurements and was over-read by one of the investigators (J.F.P.). Briefly, the common carotid artery (CCA) and internal carotid artery (ICA) maximal IMT measurements in the near and far walls were averaged. CCA and ICA IMT were defined as the mean of the maximal IMT measurements for the right and left sides. Based upon 25 readings by two separate readers, intraclass correlation coefficients for the mean and maximum ICA and CCA IMT were 0.74, 0.74, 0.86, and 0.90, respectively.

A subjective estimate of ICA narrowing, graded as 0, 1–24, 25–49%, was made by the sonographer when Doppler-derived peak-systolic velocities in the ICA were <150 cm/s. ICA narrowing of hemodynamic significance (≥50%) was defined as present when peak-systolic velocities in the ICA were ≥150 cm/s. We defined the degree of stenosis based upon the maximum stenosis in either ICA, and the stenosis was defined as present if it was ≥25%. The intra-reader reproducibility of carotid stenosis (≥25%) from 158 paired readings on 79 studies was comparable with that reported in other studies (Kappa value = 0.69).

2.3. Genotyping

Genotyping was performed for 12 variants in 10 lipoprotein-related genes in a sample of participants with DNA available and the following variants were determined [2–11]: APOA1 75G>A (rs670), APOA4 G360H (rs5110), APOC3 Sst-1 polymorphism (rs5128), CETP TaqIB polymorphism (rs708272), CYP7B1 204A>C (rs3808607), FABP2 A54T (rs1799883), LIPC S14C>T (rs1800588), LPL D9N (rs1801177), N291S (rs268) and S447X (rs238) variants, MTP 493G>T (rs1800591), and PPARA L162V (rs1800206). There were no differences between genotyped and non-genotyped subjects in the main demographic and clinical characteristics.

2.4. Other clinical variables

Data regarding the medical history, physical examination (age, systolic blood pressure, hypertension drug treatment, diabetes mellitus, cigarette smoking, and body mass index, as well as menopause status and use of hormone replacement therapy in women) and lipid variables (triglycerides, total, LDL and HDL cholesterol) were derived from the 6th examination cycle and were determined as previously reported [11].

2.5. Statistical methods

Analysis of covariance was used to determine the carotid IMT means across different genotypes, adjusted for potential confounders, separately for men and women. Covariates in the multivariate analyses included age, systolic blood pressure, hypertension treatment, diabetes mellitus, cigarette smoking, and body mass index, as well as menopause status and use of hormone replacement therapy in women. Lipid variables were not initially included as covariates because they have been implicated in the pathway of the association. These adjusted analyses also accounted for correlations due...
to familial relationships among the study members using Proc Genmod in SAS. We also tested for interactions between the different genetic variants and hypertension, smoking, obesity and diabetes on carotid IMT and stenosis whenever there was a sufficiently large sample size (>30 subjects in each of the defined subgroups). A two-tailed $p$-value < 0.05 was considered as statistically significant. The SAS program (Version 8.0) was used for statistical analysis. Dominant, recessive and additive genetic models were defined when the frequency of the rare allele was <0.10, whereas a dominant model was defined when this frequency was 0.10, whereas a dominant model was defined when this frequency was <0.10.

To evaluate power we used a conservative approach based on the smallest available sample ($n = 1621$) and as the analyses were stratified by sex we assumed a sample size of 800 subjects. Assuming this sample size, 1.7% significance level (applying the Bonferroni correction for comparison between three genotype groups) and 80% power we found that we could detect differences of 0.86, 0.62, 0.42 and 0.34 standard deviations when the rare allele frequency was 0.10, 0.20, 0.30 and 0.40, respectively. When the rare allele frequency was 0.01 we could detect differences of 0.53 standard deviations between two genotype groups.

### 3. Results

The characteristics of the 3380 participants who underwent B-mode carotid ultrasonography, and of the 1621 participants who had at least one of the determined genetic variants by sex, are shown in Table 1.

<table>
<thead>
<tr>
<th>Characteristics of the sample: mean (standard deviation) or percentage</th>
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<tr>
<td>Age (years)</td>
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<td>Smoking (%)</td>
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<td>Hypertension (%)</td>
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<td>Diabetes (%)</td>
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<td>Obesity (%)</td>
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<td>SBP (mmHg)</td>
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<td>BMI (kg/m²)</td>
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<td>Triglycerides (mmol/L)</td>
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<td>HDL cholesterol (mmol/L)</td>
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<td>LDL cholesterol (mmol/L)</td>
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<tr>
<td>ICA IMT (mm)</td>
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<tr>
<td>CCA IMT (mm)</td>
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<tr>
<td>Carotid stenosis ≥ 25% (%)</td>
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</tbody>
</table>

**Diabetes:** fasting glucose ≥ 126 mg/dL or use of insulin or hypoglycemic medication. **Obesity:** BMI ≥ 30 kg/m².

**Abbreviations:** SBP, systolic blood pressure; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; ICA IMT, internal carotid artery intimal medial thickness; CCA IMT, common carotid artery intimal medial thickness.

The multivariate-adjusted mean of the ICA IMT are presented in Table 2 for men and women across genotypes according to different genetic models. The CETP-TaqIB rare allele was marginally associated with lower ICA IMT in men according to an additive genetic model (Table 2), even after adjusting for lipids (data not shown, $p = 0.042$). The homozygote of the FABP2 A54T rare allele was marginally associated with lower ICA IMT in men ($p = 0.049$) according to a recessive model. These associations were unchanged after further adjustment including the APOE genotype in the multivariable model.

There was a marginally statistically significant interaction in men between APOCIII Sst-1 genetic variant and hypertension on ICA IMT ($p = 0.041$); hypertension was significantly associated with higher ICA IMT in G allele carriers but not in CC homozygotes (Fig. 1A). There were no other significant interactions noted.

LPL N291S was the only variant associated with stenosis in men. No other statistically significant associations were observed (Table 3). The group of male carriers of the LPL S variant ($n = 30$) showed a higher prevalence of ICA stenosis (40.0% versus 23.8%; $p = 0.041$). The crude, age-adjusted, and multivariable-adjusted carotid stenosis odds ratio for S carriers are presented in Fig. 1B. This association persisted even after adjustment for lipids.

### 4. Discussion

In this community-based study we have analyzed the association of each of 12 well-characterized genetic variants related to lipoprotein metabolism with CCA IMT, ICA IMT and stenosis. We selected variants from genes in key lipoprotein pathways because most of these variants have been shown...
to be associated with significant alterations in lipoprotein levels in the Framingham Heart Study as well as multiple other cohorts. Consistent with the complex, multifactorial etiology of these phenotypes, no strong associations between these variants and carotid measures were observed. However, there were a few notable less strong statistically significant associations observed in men only. The \textit{CETP}-TaqIB variant was associated with lower ICA IMT, the \textit{LPL} N291S variant was associated with carotid stenosis, and there was a significant interaction between \textit{APOC3} Sst-1 genetic variant and hypertension on ICA IMT also in men. The homozygote for the \textit{FABP2} A54T rare allele variant was associated with lower ICA IMT.

\textit{CETP} facilitates the exchange of triglycerides and esters of cholesterol between lipoprotein particles. The rare allele of the TaqIB variant of the gene coding \textit{CETP} has been associated with a lower activity of this protein, higher HDL cholesterol and lower risk of prevalent coronary heart disease in men [4]. The results of our study support the protective role of this genetic variant against atherosclerosis and are concordant with other studies reporting a lower risk for coronary heart disease [17,18] among the carriers of this variant.

\textit{LPL} is a key enzyme in the metabolism of chylomicrons and very low density lipoproteins. The \textit{LPL} D9N and \textit{LPL} N291S variants have been consistently associated with an adverse lipid profile [8] but the association with cardiovascular disease has been less consistent [19,20]. We noted an association between the presence of the \textit{LPL} N291S rare allele with higher prevalence of carotid stenosis in men. In previous studies, this variant has not been associated with carotid plaque area [21] or stenosis [22], although the sample size of these cohorts was smaller than that of the current

\begin{table}
\centering
\begin{tabular}{|l|l|l|l|l|l|}
\hline
Genetic variant & Sample size (rare allele frequency) & \multicolumn{2}{c|}{Men} & \multicolumn{2}{c|}{Women} \\
\hline & & Common homozygote & Rare allele carriers & \(p\) & Common homozygote & Rare allele carriers & \(p\) \\
\hline Dominant model & \textit{APOA1} 75G > A & 1856 (0.17) & 0.91 (0.02) & 0.9 (0.03) & 0.864 & 0.72 (0.02) & 0.73 (0.03) & 0.799 \\
& \textit{APOA4} G360H & 2057 (0.07) & 0.88 (0.02) & 0.9 (0.05) & 0.676 & 0.72 (0.02) & 0.78 (0.04) & 0.179 \\
& \textit{APOC3} Sst-1 & 2115 (0.08) & 0.88 (0.02) & 0.9 (0.04) & 0.684 & 0.71 (0.02) & 0.69 (0.03) & 0.519 \\
& \textit{CETP}-TaqIB & 2632 (0.43) & 0.93 (0.03) & 0.87 (0.02) & 0.094 & 0.74 (0.02) & 0.72 (0.02) & 0.473 \\
& \textit{CYP71B} 204A > C & 1980 (0.41) & 0.92 (0.03) & 0.86 (0.03) & 0.142 & 0.68 (0.02) & 0.72 (0.02) & 0.122 \\
& \textit{FABP2} A54T & 1621 (0.27) & 0.87 (0.02) & 0.89 (0.03) & 0.570 & 0.72 (0.02) & 0.70 (0.02) & 0.513 \\
& \textit{LIPC} 514C > T & 2268 (0.28) & 0.91 (0.02) & 0.86 (0.02) & 0.191 & 0.71 (0.02) & 0.73 (0.02) & 0.620 \\
& \textit{LPL} D9N & 1980 (0.01) & 0.90 (0.02) & 0.77 (0.10) & 0.214 & 0.73 (0.02) & 0.66 (0.07) & 0.337 \\
& \textit{LPL} N291S & 1980 (0.01) & 0.89 (0.02) & 1.07 (0.10) & 0.071 & 0.72 (0.02) & 0.76 (0.09) & 0.713 \\
& \textit{LPL} S447X & 2445 (0.09) & 0.89 (0.02) & 0.91 (0.04) & 0.676 & 0.71 (0.01) & 0.74 (0.03) & 0.402 \\
& \textit{MTP} 493G > T & 2138 (0.08) & 0.89 (0.02) & 0.89 (0.02) & 0.989 & 0.71 (0.05) & 0.72 (0.01) & 0.963 \\
& \textit{PPAR} L162V & 2301 (0.06) & 0.89 (0.02) & 0.94 (0.05) & 0.309 & 0.73 (0.01) & 0.73 (0.04) & 0.951 \\
\hline
Recessive model & \textit{APOA1} 75G > A & 0.91 (0.02) & 0.94 (0.11) & 0.822 & 0.72 (0.02) & 0.88 (0.13) & 0.234 \\
& \textit{CETP}-TaqIB & 0.90 (0.02) & 0.84 (0.03) & 0.112 & 0.73 (0.02) & 0.71 (0.03) & 0.569 \\
& \textit{CYP71B} 204A > C & 0.85 (0.04) & 0.91 (0.03) & 0.253 & 0.73 (0.04) & 0.68 (0.02) & 0.192 \\
& \textit{FABP2} A54T & 0.89 (0.02) & 0.78 (0.05) & 0.049 & 0.71 (0.02) & 0.69 (0.06) & 0.699 \\
& \textit{LIPC} 514C > T & 0.89 (0.02) & 0.85 (0.09) & 0.679 & 0.72 (0.01) & 0.74 (0.07) & 0.738 \\
& \textit{MTP} 493G > T & 0.86 (0.02) & 0.89 (0.02) & 0.753 & 0.72 (0.02) & 0.71 (0.02) & 0.873 \\
\hline
Additive model & \textit{APOA1} 75G > A & 0.91 (0.02) & 0.90 (0.04) & 0.94 (0.11) & 0.961 & 0.72 (0.02) & 0.71 (0.03) & 0.88 (0.13) & 0.468 \\
& \textit{CETP}-TaqIB & 0.93 (0.03) & 0.88 (0.02) & 0.84 (0.03) & 0.045 & 0.74 (0.02) & 0.72 (0.02) & 0.71 (0.03) & 0.425 \\
& \textit{CYP71B} 204A > C & 0.92 (0.03) & 0.86 (0.02) & 0.86 (0.04) & 0.145 & 0.68 (0.02) & 0.72 (0.02) & 0.73 (0.04) & 0.176 \\
& \textit{FABP2} A54T & 0.87 (0.02) & 0.92 (0.03) & 0.78 (0.05) & 0.829 & 0.72 (0.02) & 0.70 (0.02) & 0.69 (0.06) & 0.497 \\
& \textit{LIPC} 514C > T & 0.90 (0.02) & 0.85 (0.03) & 0.84 (0.09) & 0.174 & 0.71 (0.02) & 0.70 (0.02) & 0.74 (0.07) & 0.981 \\
& \textit{MTP} 493G > T & 0.89 (0.02) & 0.88 (0.03) & 0.89 (0.06) & 0.801 & 0.71 (0.02) & 0.72 (0.02) & 0.71 (0.05) & 0.911 \\
\hline
\end{tabular}
\caption{Sample size, rare allele frequencies and multivariable-adjusted mean internal carotid artery intimal medial thickness in mm (standard error) across genotypes, in men and women, according to different genetic models.}
\end{table}

Adjusted for age, systolic blood pressure, hypertension treatment, diabetes mellitus, cigarette smoking and body mass index, as well as menopause status and estrogen replacement therapy in women.
Table 3
Multivariable-adjusted odds ratios (95% confidence interval) for carotid stenosis (≥25%) across genotypes, in men and women, according to different genetic models

<table>
<thead>
<tr>
<th>Genetic variant</th>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Common homozygote</td>
<td>Rare allele carriers</td>
</tr>
<tr>
<td>Dominant model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOA1 75G &gt; A</td>
<td>1</td>
<td>0.92 (0.63–1.34)</td>
</tr>
<tr>
<td>APOA4 G360H</td>
<td>1</td>
<td>0.97 (0.58–1.63)</td>
</tr>
<tr>
<td>APOCIII Sst-1</td>
<td>1</td>
<td>0.92 (0.62–1.36)</td>
</tr>
<tr>
<td>CETP-TaqIB</td>
<td>1</td>
<td>0.93 (0.68–1.28)</td>
</tr>
<tr>
<td>CYP71B 204A &gt; C</td>
<td>1</td>
<td>0.95 (0.57–1.66)</td>
</tr>
<tr>
<td>FABP2 A54T</td>
<td>1</td>
<td>1.06 (0.74–1.51)</td>
</tr>
<tr>
<td>LIPC 514C &gt; T</td>
<td>1</td>
<td>0.67 (0.22–1.99)</td>
</tr>
<tr>
<td>LPL D9N</td>
<td>1</td>
<td>0.63 (0.21–1.93)</td>
</tr>
<tr>
<td>LPL N291S</td>
<td>1</td>
<td>2.59 (0.11–6.02)</td>
</tr>
<tr>
<td>LPL S447X</td>
<td>1</td>
<td>0.83 (0.55–1.25)</td>
</tr>
<tr>
<td>MTP 493G &gt; T</td>
<td>1</td>
<td>0.64 (0.34–1.18)</td>
</tr>
<tr>
<td>PPARA L162V</td>
<td>1</td>
<td>1.50 (0.95–2.35)</td>
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<tr>
<th>Genetic variant</th>
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<tr>
<td></td>
<td>Common allele carriers</td>
<td>Rare homozygote</td>
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<tr>
<td>Recessive model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOA1 75G &gt; A</td>
<td>1</td>
<td>0.66 (0.25–1.77)</td>
</tr>
<tr>
<td>CETP-TaqIB</td>
<td>1</td>
<td>0.94 (0.64–1.38)</td>
</tr>
<tr>
<td>CYP71B 204A &gt; C</td>
<td>1</td>
<td>0.95 (0.66–1.57)</td>
</tr>
<tr>
<td>FABP2 A54T</td>
<td>1</td>
<td>1.13 (0.54–2.38)</td>
</tr>
<tr>
<td>LIPC 514C &gt; T</td>
<td>1</td>
<td>0.91 (0.67–1.24)</td>
</tr>
<tr>
<td>MTP 493G &gt; T</td>
<td>1</td>
<td>0.88 (0.63–1.21)</td>
</tr>
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<tr>
<th>Genetic variant</th>
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<td>Common homozygote</td>
<td>Heterozygote</td>
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<td>Additive model</td>
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<tr>
<td>APOA1 75G &gt; A</td>
<td>1</td>
<td>0.97 (0.66–1.42)</td>
</tr>
<tr>
<td>CETP-TaqIB</td>
<td>1</td>
<td>0.94 (0.67–1.32)</td>
</tr>
<tr>
<td>CYP71B 204A &gt; C</td>
<td>1</td>
<td>0.96 (0.65–1.40)</td>
</tr>
<tr>
<td>FABP2 A54T</td>
<td>1</td>
<td>1.04 (0.71–1.52)</td>
</tr>
<tr>
<td>LIPC 514C &gt; T</td>
<td>1</td>
<td>0.86 (0.61–1.21)</td>
</tr>
<tr>
<td>MTP 493G &gt; T</td>
<td>1</td>
<td>0.93 (0.66–1.30)</td>
</tr>
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Adjusted for age, systolic blood pressure, hypertension treatment, diabetes mellitus, cigarette smoking and body mass index, as well as menopause status and estrogen replacement therapy in women. More frequent homozygote group risk as a reference.

study. Interestingly, this association between the LPL N291S variant with carotid stenosis was not attenuated by adjustment for lipids, suggesting that the mechanism of this association is independent of measured lipid levels. In fact, it is not yet clear to what extent this variant affects the catalytic function of LPL in humans [19]. Other LPL functions such as the lipoprotein bridging and selective cholesteryl ester uptake [19], could be related to this genetic variant and explain the reported association.

On the other hand, the LPL S447X rare allele has been previously associated with a better lipid profile and a lower risk of CHD [9,19,20] and atherothrombotic cerebral infarction [23]. While we did not find any significant association between this variant and carotid IMT or stenosis, the direction of the association with carotid stenosis was consistent with a protective pattern (Table 3).

Although the observed statistically significant interaction between APOCIII Sst-1 variant and hypertension on ICA IMT should be considered with caution given the multiple comparisons examined during our analyses, this result is consistent with the observed association between this variant and a worse lipid profile [3] and with previous reports suggesting a possible role for APOCIII gene in both lipid and blood pressure control [24].

The FABP2 A54T rare allele variant has been associated with a worse lipid profile [6]. Our hypothesis was that this rare allele would be also associated with higher carotid IMT or stenosis prevalence. However, the TT homozygote was associated with lower ICA IMT in men. This result, although marginally statistically significant, should also be considered with caution.

All the reported associations were observed only in men. This sex disparity could be related to differences in biological pathways, lack of power to detect the associations in women, or unmeasured context-dependent effects [25].
On the other hand, CETP and APOCIII variants were associated with ICA IMT whereas LPL N291S variant was associated with carotid stenosis. These two carotid phenotypes, IMT and stenosis, although correlated, represent two different stages in the process of atherosclerosis [13,15] and show different correlations with individual cardiovascular risk factors [26]. Our results could reflect the differential role of these proteins in different steps of this complex process.

There are some potential study limitations. First, although our study has a large sample size of subjects with carotid measures, it is possible we have not detected associations with a very small to modest magnitude of effect. Second, because we have not conducted extensive SNP genotyping across each gene and we have not measured other carotid atherosclerosis measures rather than IMT and stenosis, it is possible that we may have not completely accounted for the contribution of all possible genetic variation, in these or in other genes, with all possible carotid measures [15,27]. Other carotid phenotypes, such as carotid plaque area, have been reported to be more closely related to classical cardiovascular risk factors than carotid IMT, so they might have other genetic determinants compared with carotid IMT and stenosis [13]. Third, it is possible that some of our findings with marginal statistical significance represent false-positive findings. While several of these findings might not remain statistically significant after a conservative adjustment for multiple tests, several of these findings appear to replicate previous reports. Our findings clearly support further focused studies to replicate specific findings for CETP, LPL and possibly APOCIII. Moreover, we consider that it is important to report all positive and negative results and make public these results to try to replicate them in other populations and for future summaries of available information by meta-analysis or similar approaches.

In conclusion, we exclude the presence of a large association between a number of genetic variants for lipoprotein metabolism and carotid phenotypes. Our results confirm and extend evidence from prior studies for a role of CETP and LPL genetic variants in cardiovascular risk and a possible role for effect modification in the association between hypertension and carotid IMT by the APOCIII Sst-1 variant. Further studies are warranted to replicate these results in other populations, and to analyze the potential modifier effect of other genetic or environmental factors.

Acknowledgments

This work was supported by the National Heart, Lung and Blood Institute Contract N01-HC-25195, National Institute of Neurological Disorders and Stroke (NIH/NINDS 5R01-NS17950-22), and NIH/NHLBI Grant No. HL54776 and Contracts 53-K06-5-10 and 58-1950-9-001 from the US Department of Agriculture Research Service. Roberto Elosua received a grant from the Fulbright-Generalitat de Catalonia Program and from the Spanish Network of Cardiovascular Research Centers (RECA V A, FIS-C03/01).

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