Genetic influences on lipid metabolism trait variability within the Stanislas Cohort

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Abstract The contribution of 17 polymorphisms within 13 candidate genes on lipid trait variability was investigated by a multiplex assay in 772 men and 780 women coming for a health checkup examination. The studied genes were APOE, APOB, APOC3, CETP, LPL, PON, MTHFR, FGB, GpIIIa, SELE, ACE, and AGT. We found that APOB-Thr71Ile, APOE-(112/158), APOC3-1100C/T, and SELE-98G/T polymorphisms had a significant effect on lipid traits ($P \leq 0.001$ to $P \leq 0.01$). Genetic effects accounted for 3.5–5.7% of variation in apolipoprotein B (apoB)-related traits among men, and for 5.7–9.0% among women. The contribution of APOE polymorphism on apoB-related traits variability was two to three times more important in women than in men. We found suggestive evidence for interactive effects between genetics and age, smoking status, and oral contraceptives. Increase of LDL-cholesterol and apoB concentrations with age was stronger among the ε4 carriers in women, and apolipoprotein A-I (apoA-I) concentration decreased with age in ε4 male carriers. The effect of ε2 allele on LDL-cholesterol was more important in the oral contraceptive users. In nonsmokers only, the APOC3-1100C allele in women was related to lower apoB-related traits concentrations, and in men to higher apoA-I and HDL-cholesterol concentrations. In conclusion, this work, in addition to the reinforcement of the already known associations between APOB, APOE, and APOC3 genes and lipids, leads to new perspectives in the complex relationships among genes and environmental factors. The newly observed relationships between E-selectine gene and lipid concentrations support the hypotheses of multiple metabolic pathways contributing to the complexity of lipids variability.—Pallaud, C., R. Gueguen, C. Sass, M. Grow, S. Cheng, G Siest, and S. Visvikis. **Genetic influences on lipid metabolism trait variability within the Stanislas Cohort. *J. Lipid Res.* 2001.** 42: **1879–1890.**

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There is accumulating evidence that plasma concentrations of lipids, lipoproteins, and apolipoproteins are risk factors for coronary artery diseases, although the exact mechanisms remain unclear (1–4). Nevertheless, it has been established that elevated plasma concentrations of total cholesterol (TC), LDL-cholesterol (LDL-C), apolipoprotein B (apoB), TGs, and decreased plasma concentrations of HDL-cholesterol (HDL-C) and apolipoprotein A-I (apoA-I) can be considered atherogenic factors, by influencing several mechanisms participating in the initiation and/or progression of atherosclerosis. Knowledge of lipid profile could predict the potential victims of cardiovascular diseases before they become ill (5); therefore, it is very important to identify factors that could influence blood lipid concentrations.

It has been demonstrated that lipid levels are influenced by both genetic and environmental factors, and by interactions between them (6).

In the present study, we sought to investigate the association of several candidate genes with serum lipid trait variability, in a middle-aged adult population coming for a routine checkup examination in a center for preventive medicine, to determine genetic profiles associated with atherogenic or antiatherogenic lipid profile in this population. In addition to candidate genes directly involved in lipid metabolism known to play an important physiological role in the regulation of cholesterol and TG homeostasis, we also considered genes involved in other pathways liable to contribute to lipid variability, such as blood pressure regulation, platelet aggregation, homocysteine metabolism, and leukocyte adhesion (**Table 1**).

Indeed, familial clustering of hyperlipidemia with hypertension has been described (7). Furthermore association of lipid levels with blood pressure has been described in several epidemiological studies (8). This suggests that they may share common genetic determinants. The renin-angiotensin system is important in blood pressure regula-

Abbreviations: ACE, angiotensin converting enzyme; AngII, angiotensin II; AT1R, AngII type 1 receptor; BMI, body mass index; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; OC, oral contraceptive; PON, paraoxonase; TC, total cholesterol; TRL, TG-rich lipoprotein.

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TABLE 1. Panel of markers included in the study

Gene	Polymorphism(s)	Association With: Lipid Traits	References
Lipid metabolism			
APOE	Codons (112 and 158)	TC, LDL-C, apoB	(38)
APOB	Thr71Ile	LDL-C, apoB	(43)
APOC3	−482C/T, −455T/C	TG	(34, 55, 56)
	3206T/G, 3175C/G	TG	(34, 55, 56)
	1100C/T	TG, apoC-III	(35, 27)
CETP	Ile405Val	HDL-C, apoA-I, CETP	(57, 58)
PON	Gln192Arg	PON activity	(59)
LPL	Ser447Ter	TG, HDL-C	(60)
Renin-angiotensin system			
AT1R	1166A/C	—[b]	
AGT	Met235Thr	TG, TC	(61)
ACE	Ins/Del	LDL-C	(11)
Platelet aggregation			
GpIIIa	GpIIIa $p1^{A1/A2}$	TG, VLDL-TG	(23)
Fibrinogen[a]	−455G/A	TC, HDL-C, LDL-C, TG	(21, 22)[a]
Homocysteine metabolism			
MTHFR[a]	677C/T	TC, TG	(16, 17)[a]
Molecular adhesion			
SELE[a]	98G/T	LDL-C	(12)[a]

[a] Association with the concentration of the gene product.
[b] No data.

tion, and several data indicate complex interactions between angiotensin II (AngII) and lipids. AngII increases induced macrophage-mediated oxidation of LDL, cellular uptake of oxidized LDL by macrophages (9). Furthermore, Keidar et al. (10) have shown that AngII increases macrophage cholesterol biosynthesis via interaction with the AngII type 1 receptor (AT1R). Conversely, associations between polymorphism of the angiotensin converting enzyme (ACE) and lipids variability were reported (11).

Adhesion molecules and homocysteine have been related to lipid variability. Increase levels of E-selectin has been reported in hypercholesterolemic patients (12). Conversely, Sampietro et al. (13) found that LDL apheresis induced a reduction of E-selectin level, and Barter (14) showed that HDLs have the ability to inhibit cytokine-induced expression of E-selectin. Elevated homocysteine levels increase oxidative stress and can promote LDL oxidation. Oxidation of lipids and/or apolipoproteins may disturb lipid metabolism. Hulten et al. (15) showed that oxysterols decreased the expression of the LPL. Association between homocysteine and cholesterol or TG levels have been described in some studies (16, 17). We hypothesized that polymorphisms of genes linked to E-selectin or homocysteine levels could influence lipids variability. The Ser128Arg mutation in the E-selectin gene and the C677T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) have been related to E-selectin and homocysteine levels, respectively (18, 19).

Platelet aggregation also may influence lipid levels. Indeed, it has been reported that plasma lipoproteins specifically bind to the plasma membrane of human blood platelets via the fibrinogen receptor GPIIb-IIIa (20), and that fibrinogen levels were correlated with lipids variability (21, 22). Conversely, variation at the GpIIIa locus was associated with lipids (23), and polymorphism in the fibrinogen gene was related to fibrinogen levels (24).

Therefore, we hypothesized that genetic variation in the ACE, AGT, SELE, MTHFR, fibrinogen and GpIIIa genes together with genes directly implicated in lipid metabolism, that is, apolipoproteins B (APOB), E (APOE), CIII (APOC3), CETP, LPL, and paraoxonase (PON) genes, could influence lipids variability.

Therefore, for the present investigations we have selected the following gene polymorphisms: APOB Thr71Ile; APOE (112/158); APOC3 −482C/T, −455T/C, 1100C/T, 3175C/G, 3206T/G; CETP Ile405Val; LPL Ser447Ter; PON Gln192Arg; GpIIIa $P1^{A1/A2}$; fibrinogen −455G/A, ACE I/D, AGT Met235Thr, MTHFR 677C/T and SELE 98G/T, Ser128Arg, Leu554Phe.

Therefore, supposing that several genetic markers, frequent in the population, with small individual effects may interact together and with environmental factors to determine lipid levels and increase predisposition of a given individual to develop dyslipidemia, we tested putative gene-gene and gene-environmental factor interactions. This approach was possible thanks to the use of a multilocus genotyping assay (25, 26). Some of the genetic polymorphisms investigated here already have been studied by others (Table 1); however, these studies generally focused on only one candidate gene and frequently were conducted in subjects with cardiovascular diseases and/or on medication. Few studies investigated more than one gene, and very often those genes were involved only in lipid metabolism (27, 28–31).

To our knowledge, this is the first study in which so many genetic markers were simultaneously investigated in a large middle-aged and supposedly healthy adult population of caucasian origin for identifying genetic markers of lipids profile.

MATERIALS AND METHODS

Population

The study included 772 men and 780 women selected from the Stanislas Cohort designed to investigate factors related to cardiovascular disease. The Stanislas Cohort previously was described by Siest et al. (32). Individuals were recruited during a detailed checkup examination, and informed consent was obtained from all participants. Specifically for this study, we selected subjects who were not under treatment with lipid-lowering, antihypertensive, or anti-inflammatory drugs. In this relatively young population, all women were premenopausal.

Lipid measurements and DNA polymorphism determinations

Blood samples were collected after an overnight fast. Serum cholesterol and TG levels were measured using standard enzymatic methods (Merck, Darmstadt, Germany), automated on AU5021 (Olympus; Merck). Serum apoA-I and B were determined by immunonephelometry on Behring Nephelometer Analyser, with Behring reagents (Rueil-Malmaison, France). Serum apoE was determined by turbidimetry and serum HDL-C by phosphotungstate precipitation on a Cobas-Mira (Roche). LDL-C was obtained according to the Friedwald (1972) formula: LDL-C = TC − HDL-C − TG/2.18. None of the subjects studied exhibited TG concentrations ⩾400 mg/dl.

Personal and medical history, medication, smoking habits, and alcohol consumption were recorded using a standardized questionnaire. Smokers were defined as those who were current smokers.

Genomic DNA was extracted from peripheral blood samples by the salting out method (33). The complete multiplex assay has been described previously by Cheng et al. (25, 26).

Using this multiplex assay, we genotyped all individuals for all polymorphisms presented in Table 1. Additional mutations or polymorphisms [APOB3500, CETP442, LPL (−93, −39, 9, 291), factor V506, CBS278, SELE554] having a frequency of the less frequent allele below 8% were not analyzed in this study. For technical reasons, we were unable to genotype all individuals for APOC3-625 and AT1R 1166A/C polymorphisms, and these polymorphisms also were not included in the analyses.

Statistical approach

Data for TGs and apoE were log transformed before statistical analysis to reduce the skewness of the data. Analyses were done separately for men and women using BMDP® software (University of California, Los Angeles).

ANOVA was performed to determine significant genetic factors of variation for lipid traits. In our population, the SELE 98G/T and SELE Ser128Arg are in complete concordance (data not shown); therefore, we studied only one of the two markers: the SELE 98G/T polymorphism. Each phenotype-genotype association with a significance of $P \leqslant 0.01$ was kept in the multiple regression analyses.

Multiple regression analysis was used to test the influence of the APOB, APOE, APOC3, and SELE gene polymorphisms and several covariates [i.e., age, body mass index (BMI), smoking, alcohol, oral contraceptive (OC) use] on lipid traits. Three different models of regression were tested; one genotypic model G and two allelic models A1 and A2.

The genotypic model G allowed a direct estimation of the effect of each genotype and the covariates listed above. It includes indicator variables for each genotype. It means that for a biallelic polymorphism (A,a), model G includes I_{Aa} and I_{aa}, which are 0–1 variables for corresponding genotypes, the common homozygote genotype I_{AA} being used as the reference group for each polymorphism. For the APOE gene, because there are only a few carriers of the less frequent genotypes, we introduced E2 as the indicator variable of two genotypes, $\varepsilon2\varepsilon2$ and $\varepsilon3\varepsilon2$, E4 as the indicator variable of genotypes $\varepsilon4\varepsilon4$ and $\varepsilon3\varepsilon4$ and E24 as the indicator variable of genotype $\varepsilon2\varepsilon4$. Consequently, the reference group is implicitly $\varepsilon3\varepsilon3$ genotype. Restricted to these two polymorphisms, model G can be written:

$$Y = \beta_0 + \beta_1 I_{Aa} + \beta_2 I_{aa} + \beta_3 E2 + \beta_4 E4 + \beta_5 E24$$

The allelic model A1 was designed to estimate the allelic effects of all the studied polymorphisms; this allelic model A1 was nested in model G. The model A1 uses indicator variables for each allele: I_a for a biallelic polymorphism. Concerning the APOE alleles, the A1 model pooled genotypes $\varepsilon3\varepsilon2$, $\varepsilon2\varepsilon4$, and $\varepsilon2\varepsilon2$ to define the variable "presence of the $\varepsilon2$ allele," named $\varepsilon2$, and pooled genotypes $\varepsilon4\varepsilon4$ with $\varepsilon3\varepsilon4$ and $\varepsilon2\varepsilon4$ to define the variable "presence of the $\varepsilon4$ allele," named $\varepsilon4$. So Model A1 is then written as: $Y = \gamma_0 + \gamma_1 I_a + \gamma_2 I_{\varepsilon2} + \gamma_3 I_{\varepsilon4}$. The covariates of this A1 model were those found significant in model G.

By comparing the residual variances of these two nested models using F-ratio, we tested the hypothesis of additivity of the allelic effects. Allelic effects were found to be additive for all lipid parameters (TC, LDL-C, apoB, apoE, apoA-I, TG, HDL-C) both in men and in women.

Therefore, the allelic model A2 was used to specify the effect of the APOE alleles. Model A2 is the same as model A1 with an extra-variable to indicate the presence of ε_3 allele and can be written as: $Y = \gamma'_0 + \gamma'_1 I_a + \gamma'_2 I_{\varepsilon2} + \gamma'_3 I_{\varepsilon4} + \gamma'_4 I_{\varepsilon3}$. The model A1 was nested in model A2. With this model, we tested the hypothesis of no difference between the carriers and the noncarriers of the $\varepsilon3$ allele.

Models A1 and A2 were found significantly different ($P \leqslant 0.001$) only in men for apoE concentrations. We therefore used the allelic model A1 for all lipid traits excepted for apoE concentration in men.

We then included, systematically for each lipid trait, in multiple regression models (A1, A2) putative interactions between environmental (BMI, smoking, alcohol, OC use, and age) and genetics factors found significantly associated with a trait in regression analysis, and interactions between genes also were tested. Interactions were parameterized through products of variables (i.e., indicator variables for alleles), putting all possible interactions in the list of covariates in the stepwise regression procedure. Significant interactions were kept for further analysis.

Also, the final model A1 included the following determinants: BMI, age, smoking, alcohol intake, and allelic effects of the APOB 71Ile, APOC3 1100T, APO$\varepsilon2$, APO$\varepsilon4$, SELE 98T gene polymorphisms and interactions APO$\varepsilon4$ × age, APOC3 1100C × no-smoker and in women only APO$\varepsilon2$ × OC. The determinants of the model A1 were tested for all lipid traits by using a forward stepwise regression analysis. To take into account correction for multiple testing, we set P value to enter to 0.01 at each step.

RESULTS

Table 2 presents the mean characteristics of the studied population. Women were slightly, but significantly, younger than men ($P \leqslant 0.001$). The means of all traits were significantly lower in women than in men, with the exception of HDL and apoA-I concentrations, which were higher in women ($P \leqslant 0.001$). **Table 3** presents allele frequencies. The genotype distributions for each marker were in Hardy-

TABLE 2. Characteristics of the studied population

Trait	Men (n = 772) (Mean ± SD)	Women (n = 780) (Mean ± SD)	Comparison Between Gender *P*
Age (years)	41.5 ± 4.6	39.5 ± 4.4	<0.001
Body mass index (kg/m^2)	25.3 ± 3.1	23.5 ± 3.6	<0.001
Smoker %	33	21	<0.001
Alcohol intake (g/day)	23.5 ± 26.5	4.4 ± 8.7	<0.001
ApoB (g/l)	1.14 ± 0.26	0.97 ± 0.21	<0.001
ApoA-I (g/l)	1.55 ± 0.23	1.69 ± 0.26	<0.001
ApoE (mg/l)	48.6 ± 13.2	43.8 ± 10.5	<0.001
TG (mmol/l)	1.29 ± 0.79	0.83 ± 0.39	<0.001
Cholesterol total (mmol/l)	5.96 ± 1.05	5.49 ± 0.88	<0.001
HDL cholesterol (mmol/l)	1.26 ± 0.33	1.56 ± 0.40	<0.001
LDL cholesterol (mmol/l)	4.11 ± 0.97	3.55 ± 0.83	<0.001

Weinberg equilibrium, and no significant difference in allele frequencies between gender were observed (data not shown); therefore, allele frequencies were given for men and women pooled together.

Table 4 (for men) and **Table 5** (for women) indicate *P* values for significant associations between lipid traits and the 13 loci given by ANOVA. The polymorphisms in four genes, (APOB, APOE, APOC3, and SELE) showed significant association with a $P \leqslant 0.01$ value for at least one trait (**Table 6** and **Table 7**) and were kept for further analyses. No biochemical trait was significantly associated with genotypic variation in CETP, LPL, PON, ACE, AGT, MTHFR, GpIIIa, or fibrinogen ($P > 0.01$).

Multiple regression analysis (**Tables 8–12**) showed that the following gene polymorphisms were associated with at least one lipid trait variability: APOB Thr71Ile; APOE codons 112/158; APOC3 1100C/T and SELE 98G/T.

The results of the final multiple regression models, as explained in Materials and Methods, are shown in Tables 8–12 (Tables 8, 9, and 10 for men; Tables 11 and 12 for women). In men, the covariates and the gene polymorphisms effects explained 14.6%, 9.3%, 9.5%, 16.2%, 15.5%, 11.3%, and 12.8% of the variability of apoB, LDL-C, TC, apoE, TG, HDL-C, and apoA-I, respectively, and in women they explained, respectively, 14.9%, 15.5%, 8.9%, 26.4%, 19.4%, 16.4%, and 15.3%.

TABLE 3. Allele frequencies observed within the sample population studied

Gene	Allele (A/a)	a		
APOE	Codons (112/158)	ε2	ε4	ε3
		0.09	0.13	0.79
APOB	Thr71Ile	0.32		
	Arg3500Gln	0.00		
APOC3	−482C/T	0.27		
	−455T/C	0.38		
	1100C/T	0.26		
	3175C/G	0.09		
	3206T/G	0.37		
LPL	Ser447Ter	0.12		
	−93T/G	0.02		
	−39T/C	0.00		
	Asp9Asn	0.02		
	Asn291Ser	0.02		
CETP	Ile405Val	0.29		
	Asp442Gly	0.00		
PON	Gln192Arg	0.30		
ACE	I/D	0.56		
AGT	Met235Thr	0.40		
MTHFR	677C/T	0.36		
CBS	Ile278Thr	0.08		
GpIIIa	$P1^{A1/A2}$	0.15		
Fibrinogen	−455G/A	0.20		
Facteur V	Arg506Gln	0.02		
SELE	98G/T	0.08		
	Ser128Arg	0.08		
	Leu554Phe	0.04		

APOB Thr71Ile

The APOB 71Ile allele was associated with elevated LDL-C, apoB ($P \leqslant 0.001$) and TC concentrations ($P \leqslant 0.01$) in women, whereas in men we found no significant association with the lipid traits studied. This polymorphism accounts for 1.5% and 1.3% of the LDL-C and apoB variability, respectively, and for 0.9% of the TC variability in women.

APOC3 1100C/T

The APOC3 1100T allele was associated with elevated concentrations of apoB-related traits (TC, LDL-C, apoB; $P \leqslant 0.001$) and TG ($P \leqslant 0.001$) in men. The contribution of this polymorphism in men was 1.7% for apoB-related traits variability and 1.2% for TG concentrations.

Interactions were found between the APOC3 C1100 allele and smoking status. Indeed, in men, the apoC-III C1100 allele was associated with increased apoA-I ($P \leqslant 0.001$) and HDL-C ($P \leqslant 0.01$) concentrations in nonsmokers only. In women, the apoC-III C1100 allele was related to lower concentrations of apoB ($P \leqslant 0.001$), LDL-C ($P \leqslant 0.01$) and TC ($P \leqslant 0.01$) in nonsmokers only.

SELE 98G/T

The SELE 98T allele was found associated with higher HDL concentrations in women and explained 0.7% of HDL-C variability ($P \leqslant 0.01$), whereas in men this polymorphism was associated with none of the studied lipid traits.

APOE codons112/158

The APOE ε2 allele was related to lower concentrations of apoB-related traits and with elevated concentrations of apoA-I and apoE in both men and women ($P \leqslant 0.001$ to $P \leqslant 0.01$), and with elevated HDL-C concentrations in women only ($P \leqslant 0.001$). The apoE ε4 allele was associated with lower concentrations of apoE ($P \leqslant 0.001$) in both men and women, whereas in women it also was related to higher TC concentrations ($P \leqslant 0.01$). In women, the APOE ε2 allele showed a significant interaction ($P \leqslant 0.01$) with OC use regarding the LDL-C variability ($P \leqslant 0.01$). This interaction leads to a more important effect of APOE ε2 allele in the OC users.

Significant interactions were found between APOE ε4 allele and age on apoA-I ($P \leqslant 0.001$) concentrations in men, and on apoB ($P \leqslant 0.001$) and LDL-C ($P \leqslant 0.001$) concentrations in women. In men, apoA-I concentrations decrease with age in ε4 carriers only. In women, the con-

TABLE 4. *P* values of significant associations from ANOVA analyses in men (n = 772)

Gene Polymorphisms	Chol	TG	ApoB	ApoA-I	ApoE	HDL	LDL
APOE (codons 112/158)	⩽0.001	—	⩽0.001	⩽0.01	⩽0.001	—	⩽0.001
APOB Thr71Ile	—	—	—	—	—	—	—
APOC3 −482C/T	—	⩽0.01	—	—	—	⩽0.01	—
APOC3 −455T/C	—	—	—	—	—	—	—
APOC3 1100C/T	⩽0.001	⩽0.01	⩽0.001	—	⩽0.01	—	⩽0.001
APOC3 3206T/G	—	—	—	—	—	—	⩽0.01
APOC3 3175C/G	—	—	—	—	—	—	—
CETP Ile405Val	—	—	—	—	—	—	—
LPL Ser447Ter	—	—	—	—	—	—	—
PON Q192R	—	—	—	—	—	—	—
ACE ID	—	—	—	—	—	—	—
AGT Met235Thr	—	—	—	—	—	—	—
GPIIIa $P1^{A1/A2}$	—	—	—	—	—	—	—
Fibrinogen −455G/A	—	—	—	—	—	—	—
MTHFR 667C/T	—	—	—	—	—	—	—
SELE 98G/T	—	—	—	—	—	—	—

Long dashes indicate nonsignificant association.

centrations of apoB and LDL-C increase with age and more strongly among the ε4 carriers.

DISCUSSION

The aim of this study was to look for associations between lipid metabolism phenotypes and 13 genes related to cardiovascular diseases, in a middle-aged adult population coming for a routine checkup examination, to determine genetic profiles associated with lipid traits concentration in this population. This is the first report in which so many loci involved in many metabolic pathways were simultaneously studied in relation to lipid trait variability in a large population (772 men, 780 women).

Among the 13 investigated genes, four of them showed statistically significant association with at least one lipid trait (APOB, APOC3, APOE, and SELE genes). Most of these associations were highly significant with a *P* level ⩽ 0.001. Because of the high number of associations tested, we preferred to ignore weak associations ($P > 0.01$).

The APOC3 and the APOE genes appeared to be the two main genes involved in lipid trait variability in our population; indeed, they exhibited associations with most of the lipid traits studied.

In men, the APOC3 C1100 allele was found to be strongly related ($P \leqslant 0.001$) to lower concentrations of apoB, LDL-C, TC, and TG and also was related to higher concentrations of apoA-I and HDL-C in nonsmokers only. In women, apoC-III C1100T polymorphism was strongly modulated by smoking status. Indeed, the allele C1100 was related to lower apoB-related traits ($P \leqslant 0.001$, $P \leqslant 0.01$) in nonsmokers only. Therefore, our results together with the literature data suggest that the APOC3 C1100 allele is associated with a benefit lipid profile. Several studies have shown association of the APOC3 C1100 allele with decreased apoC-III and TG concentrations (34, 35). However, few data are available concerning the association between the APOC3 C1100T polymorphism and other lipid traits than TG and TG-rich lipoprotein (TRL) or apoC-III. Peacock et al. (27) did not find a significant association between the APOC3 C1100T polymorphism and apoA-I and HDL-C concentrations in either Icelander men or women, and Xu et al. (34) observed no association with

TABLE 5. *P* values of significant associations from ANOVA analyses in women (n = 780)

Gene Polymorphisms	Chol	TG	ApoB	ApoA-I	ApoE	HDL	LDL
APOE (codons 112/158)	⩽0.001	—	⩽0.001	—	⩽0.001	—	⩽0.001
APOB Thr71Ile	—	—	⩽0.01	—	—	—	⩽0.01
APOC3 −482C/T	—	—	—	—	—	—	—
APOC3 −455T/C	—	—	—	—	—	—	—
APOC3 1100C/T	—	—	—	—	—	—	—
APOC3 3206T/G	—	—	—	—	—	—	—
APOC3 3175C/G	—	⩽0.01	—	—	—	—	—
CETP Ile405Val	—	—	—	—	—	—	—
LPL Ser447Ter	—	—	—	—	—	—	—
PON Q192R	—	—	—	—	—	—	—
ACE ID	—	—	—	—	—	—	—
AGT Met235Thr	—	—	—	—	—	—	—
GpIIIa $P1^{A1/A2}$	—	—	—	—	—	—	—
FGB −455G/A	—	—	—	—	—	—	—
MTHFR 667C/T	—	—	—	—	—	—	—
SELE 98G/T	—	—	—	—	—	⩽0.01	—

Long dashes indicate nonsignificant association.

TABLE 6. Lipid traits according to APOB, APOC3, APOE, and SELE polymorphisms in men (n = 772)

					P
APOB Th71Ile	11 (n = 343)	12 (n = 347)	22 (n = 82)		
Chol	5.94 ± 1.06	5.96 ± 1.05	6.11 ± 1.10		0.001
TG	1.28 ± 0.76	1.29 ± 0.83	1.32 ± 0.79		—
ApoB	1.13 ± 0.26	1.14 ± 0.26	1.20 ± 0.28		0.001
ApoA-I	1.56 ± 0.22	1.54 ± 0.23	1.50 ± 0.23		0.010
ApoE	47.6 ± 13.0	49.4 ± 13.3	49.1 ± 14.1		0.001
HDL	1.28 ± 0.32	1.25 ± 0.34	1.22 ± 0.36		—
LDL	4.08 ± 0.99	4.11 ± 0.95	4.28 ± 1.03		0.001
APOC3 −482C/T	11 (n = 404)	12 (n = 312)	22 (n = 56)		
Chol	5.88 ± 1.05	6.06 ± 1.07	6.06 ± 1.05		—
TG	1.21 ± 0.72	1.36 ± 0.86	1.47 ± 0.87		0.010
ApoB	1.12 ± 0.26	1.16 ± 0.26	1.18 ± 0.26		—
ApoA-I	1.55 ± 0.24	1.54 ± 0.22	1.50 ± 0.19		—
ApoE	48.0 ± 12.5	49.2 ± 14.1	49.1 ± 14.1		—
HDL	1.29 ± 0.34	1.24 ± 0.33	1.17 ± 0.27		—
LDL	4.04 ± 0.95	4.20 ± 0.99	4.22 ± 0.98		—
APOC3 1100C/T	11 (n = 424)	12 (n = 300)	22 (n = 48)		
Chol	5.83 ± 1.04	6.11 ± 1.07	6.26 ± 1.04		0.001
TG	1.21 ± 0.75	1.38 ± 0.82	1.47 ± 0.96		0.010
ApoB	1.11 ± 0.26	1.17 ± 0.26	1.24 ± 0.25		0.001
ApoA-I	1.54 ± 0.23	1.57 ± 0.23	1.48 ± 0.19		—
ApoE	47.3 ± 12.7	50.3 ± 13.7	48.8 ± 14.0		0.010
HDL	1.27 ± 0.34	1.25 ± 0.33	1.16 ± 0.27		—
LDL	4.00 ± 0.95	4.22 ± 0.99	4.43 ± 0.93		0.001
APOC3 3175C/G	11 (n = 643)	12 (n = 121)	22 (n = 8)		
Chol	5.93 ± 1.06	6.12 ± 1.02	6.83 ± 0.97		—
TG	1.26 ± 0.79	1.40 ± 0.80	1.83 ± 0.96		—
ApoB	1.14 ± 0.26	1.17 ± 0.24	1.35 ± 0.29		—
ApoA-I	1.55 ± 0.23	1.54 ± 0.22	1.46 ± 0.12		—
ApoE	48.2 ± 13.1	50.4 ± 13.9	53.8 ± 16.4		—
HDL	1.26 ± 0.33	1.24 ± 0.32	1.16 ± 0.24		—
LDL	4.08 ± 0.97	4.24 ± 0.94	4.82 ± 1.09		—
APOC3 3206T/G	11 (n = 317)	12 (n = 364)	22 (n = 91)		
Chol	5.84 ± 1.06	6.04 ± 1.02	6.11 ± 1.16		—
TG	1.21 ± 0.77	1.33 ± 0.80	1.40 ± 0.86		—
ApoB	1.11 ± 0.26	1.16 ± 0.26	1.18 ± 0.28		—
ApoA-I	1.54 ± 0.23	1.56 ± 0.23	1.51 ± 0.22		—
ApoE	47.5 ± 13.1	49.5 ± 13.6	48.7 ± 12.2		—
HDL	1.27 ± 0.33	1.26 ± 0.33	1.19 ± 0.31		—
LDL	4.01 ± 0.98	4.17 ± 0.94	4.28 ± 1.07		0.010
SELE 98G/T	11 (n = 662)	12 (n = 100)	22 (n = 10)		
Chol	5.98 ± 1.06	5.98 ± 1.05	5.83 ± 1.21		—
TG	1.29 ± 0.77	1.29 ± 0.91	1.41 ± 1.06		—
ApoB	1.14 ± 0.26	1.14 ± 0.27	1.13 ± 0.29		—
ApoA-I	1.54 ± 0.23	1.58 ± 0.24	1.55 ± 0.19		—
ApoE	48.5 ± 13.2	49.1 ± 14.0	47.1 ± 10.5		—
HDL	1.25 ± 0.32	1.32 ± 0.36	1.23 ± 0.36		—
LDL	4.13 ± 0.98	4.07 ± 0.92	3.95 ± 1.17		—
APOE (codons112/158)	2/2 + 3/2 (n = 111)	3/3 (n = 493)	3/4 + 4/4 (n = 154)	2/4 (n = 14)	
Chol	5.58 ± 0.99	6.02 ± 1.06	6.09 ± 1.04	6.00 ± 1.17	0.001
TG	1.27 ± 0.73	1.28 ± 0.77	1.32 ± 0.93	1.48 ± 0.78	—
ApoB	1.00 ± 0.26	1.16 ± 0.25	1.20 ± 0.26	1.09 ± 0.24	0.001
apoA-I	1.62 ± 0.24	1.55 ± 0.23	1.49 ± 0.21	1.54 ± 0.31	0.010
ApoE	58.0 ± 14.4	47.4 ± 11.7	44.8 ± 14.2	55.9 ± 11.0	0.001
HDL	1.33 ± 0.35	1.25 ± 0.32	1.22 ± 0.33	1.21 ± 0.34	—
LDL	3.66 ± 0.87	4.17 ± 0.97	4.26 ± 0.97	4.11 ± 0.97	0.001

TC concentrations but did in familial combined hyperlipidemia. Our results are mechanistically plausible. Evidence is accumulating that apoC-III regulates TRL metabolism by modulating their lipolysis (36) and their receptor-mediated uptake (37). Inhibition of the LPL by apoC-III leads to a slow turnover of VLDL resulting to an inefficient conversion of VLDL to IDL and to LDL and an increase in TG levels. ApoC-III by inhibiting apoE-dependent hepatic uptake of TRL leads to a slow turnover of VLDL and to an efficient conversion of apoB in VLDL to LDL and an increase in apoB-related traits.

The APOE common polymorphism was found to be strongly associated with variation of all the studied lipid traits except for TG concentration. The APOE ε2 allele was associated with lower concentrations of apoB-related traits, higher apoE, and apoA-I concentrations in men

TABLE 7. Lipid traits according to APOB, APOC3, APOE, and SELE polymorphisms in women (n = 780)

					P
APOB Thr71Ile	11 (n = 360)	12 (n = 340)	22 (n = 80)		
Chol	5.43 ± 0.89	5.51 ± 0.86	5.69 ± 0.88		—
TG	0.84 ± 0.42	0.82 ± 0.37	0.84 ± 0.36		—
ApoB	0.95 ± 0.21	0.98 ± 0.21	1.02 ± 0.22		0.010
ApoA-I	1.70 ± 0.28	1.69 ± 0.25	1.68 ± 0.24		—
ApoE	43.9 ± 10.7	43.8 ± 10.3	43.3 ± 10.6		—
HDL	1.58 ± 0.42	1.55 ± 0.39	1.55 ± 0.37		—
LDL	3.47 ± 0.81	3.58 ± 0.83	3.75 ± 0.87		0.010
APOC3 −482C/T	11 (n = 416)	12 (n = 312)	22 (n = 52)		
Chol	5.45 ± 0.86	5.56 ± 0.91	5.37 ± 0.85		—
TG	0.81 ± 0.39	0.85 ± 0.40	0.88 ± 0.47		—
ApoB	0.96 ± 0.21	0.99 ± 0.21	0.92 ± 0.22		—
ApoA-I	1.69 ± 0.27	1.70 ± 0.26	1.69 ± 0.28		—
ApoE	43.3 ± 10.3	44.6 ± 10.9	43.4 ± 9.80		—
HDL	1.58 ± 0.42	1.54 ± 0.38	1.57 ± 0.42		—
LDL	3.50 ± 0.81	3.64 ± 0.84	3.39 ± 0.84		—
APOC3 1100C/T	11 (n = 407)	12 (n = 315)	22 (n = 58)		
Chol	5.47 ± 0.89	5.48 ± 0.85	5.74 ± 0.90		—
TG	0.80 ± 0.35	0.87 ± 0.44	0.82 ± 0.45		—
ApoB	0.97 ± 0.21	0.97 ± 0.22	1.00 ± 0.22		—
ApoA-I	1.69 ± 0.26	1.70 ± 0.27	1.74 ± 0.26		—
ApoE	43.5 ± 10.0	43.9 ± 10.9	45.2 ± 11.3		—
HDL	1.56 ± 0.39	1.55 ± 0.41	1.66 ± 0.47		—
LDL	3.54 ± 0.83	3.52 ± 0.82	3.71 ± 0.84		—
APOC3 3175C/G	11 (n = 636)	12 (n = 141)	22 (n = 3)		
Chol	5.48 ± 0.89	5.53 ± 0.83	6.55 ± 0.60		—
TG	0.81 ± 0.37	0.89 ± 0.45	1.80 ± 1.01		0.010
ApoB	0.97 ± 0.21	0.99 ± 0.22	1.23 ± 0.17		—
ApoA-I	1.70 ± 0.26	1.69 ± 0.26	1.63 ± 0.20		—
ApoE	43.6 ± 10.4	44.7 ± 10.7	45.9 ± 6.4		—
HDL	1.57 ± 0.41	1.52 ± 0.38	1.29 ± 0.33		—
LDL	3.53 ± 0.84	3.60 ± 0.79	4.43 ± 0.76		—
APOC3 3206T/G	11 (n = 301)	12 (n = 362)	22 (n = 117)		
Chol	5.44 ± 0.87	5.47 ± 0.87	5.68 ± 0.90		—
TG	0.81 ± 0.36	0.85 ± 0.42	0.82 ± 0.40		—
ApoB	0.97 ± 0.21	0.97 ± 0.21	1.00 ± 0.28		—
ApoA-I	1.68 ± 0.26	1.69 ± 0.26	1.76 ± 0.26		—
ApoE	43.6 ± 10.0	44.4 ± 10.8	42.5 ± 10.6		—
HDL	1.54 ± 0.39	1.56 ± 0.41	1.64 ± 0.42		—
LDL	3.53 ± 0.83	3.53 ± 0.82	3.66 ± 0.86		—
SELE 98G/T	11 (n = 656)	12 (n = 118)	22 (n = 6)		
Chol	5.47 ± 0.87	5.62 ± 0.93	5.26 ± 0.43		—
TG	0.83 ± 0.40	0.84 ± 0.39	0.63 ± 0.19		—
ApoB	0.97 ± 0.21	1.00 ± 0.20	0.84 ± 0.12		—
ApoA-I	1.69 ± 0.26	1.71 ± 0.28	1.81 ± 0.26		—
ApoE	43.9 ± 10.4	42.8 ± 10.7	49.7 ± 9.99		—
HDL	1.55 ± 0.39	1.59 ± 0.42	2.03 ± 0.63		0.010
LDL	3.53 ± 0.83	3.65 ± 0.83	2.94 ± 0.42		—
APOE (codons112/158)	2/2 + 3/2 (n = 110)	3/3 (n = 468)	3/4 + 4/4 (n = 179)	2/4 (n = 23)	
Chol	5.05 ± 0.83	5.51 ± 0.86	5.71 ± 0.87	5.39 ± 0.76	0.001
TG	0.82 ± 0.33	0.83 ± 0.41	0.80 ± 0.36	1.04 ± 0.54	—
ApoB	0.83 ± 0.17	0.99 ± 0.21	1.03 ± 0.20	0.93 ± 0.19	0.001
ApoA-I	1.77 ± 0.28	1.68 ± 0.26	1.67 ± 0.25	1.76 ± 0.21	—
ApoE	52.8 ± 11.2	43.2 ± 9.47	38.5 ± 8.16	54.0 ± 8.95	0.001
HDL	1.69 ± 0.45	1.54 ± 0.40	1.54 ± 0.38	1.60 ± 0.33	—
LDL	2.99 ± 0.73	3.59 ± 0.80	3.81 ± 0.79	3.31 ± 0.77	0.001

and in women, and with higher HDL-C concentrations in women. These results are in accordance with those previously obtained (38), which showed APOE ε2 allele associated with favorable lipid profile and APO ε4 allele with unfavorable lipid profile (39–41). We observed also that the APOE ε2 allele lowering effect on apoB concentrations was most pronounced in the OC user. Consistent with this result, sex hormones have been reported to modulate the impact of apoE phenotype on apoB concentrations (42). The APOE ε4 allele was associated with lower apoE concentrations in both men and women, lower HDL-C concentrations in men, and higher TC in women. The results reported here are consistent with those of Sing and Davignon (38) and Kamboh et al. (40). We found that the APOE ε4 allele effect on apoA-I in men and on apoB and LDL-C in women was modulated by age with a more pronounced ef-

TABLE 8. Model A1: determinants of lipid traits variability in men

Covariates	ApoB β	ApoB ±SE	ApoB Change in R^2	LDL-C β	LDL-C ±SE	LDL-C Change in R^2	TC β	TC ±SE	TC Change in R^2
BMI	0.0178[a]	0.0028	0.0553	0.0375[b]	0.0108	0.0130	0.0463[a]	0.0017	0.0269
Age	0.0083[a]	0.0019	0.0187	0.0299[a]	0.0074	0.0202	0.0300[a]	0.0081	0.0202
Tobacco	0.0681[a]	0.0185	0.0151	0.1991[b]	0.0710	0.0093	—[c]	—[c]	—[c]
Alcohol × 10^{E-3}	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	4.6[a]	1.4	0.0131
APOB 71Thr	—[c]	—[c]	—[c]				—[c]	—[c]	—[c]
APOC3 1100T	0.0592[a]	0.0143	0.0173	0.2093[a]	0.0549	0.0171	0.2320[a]	0.0596	0.0171
APOE ε2	−0.1460[a]	0.0238	0.0400	−0.4693[a]	0.0912	0.0332	−0.3985[a]	0.0992	0.0181
APOE ε4	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
SELE 98T	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
APOE ε4 × age				—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
$C3_1$ × no-smoking	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
Y-intercept		0.3156			2.0223			3.3868	
Total R^2		0.1464			0.0929			0.0954	

BMI, body mass index; β, standard regression coefficient, $C3_1$, APOC3 1100C. *P* value to enter was set to 0.01 at each step: [a] $P \leq 0.001$, [b] $P < 0.01$, [c] nonsignificant association.

fect of the APO ε4 allele with advancement of age. Jarvik et al. (41) showed also that ε4 allele effects on lipids may be age dependent, but they found that ε4 allele effects on TC and TG decreased over longitudinal examinations.

We found that the APOB 71Ile allele was related to elevated concentrations of LDL-C, apoB, and TC concentrations in women. Few data have been published concerning this gene polymorphism and lipid levels and its physiological significance. Tikkanen et al. (43) observed in children a significant association with this allele and apoB-related traits. Our results are mechanistically plausible given that apoB is both the structural protein for the LDL particle and the ligand for the LDL receptor (44), and this polymorphism is located in the N-terminal region of the protein that may participate in the binding to the LDL receptor (45). The presence of the APOB 71Ile allele or another polymorphism in desequilibrium may be related to lower affinity or lower binding to the LDL receptor resulting in a lower clearance of apoB-related traits from the plasma.

This study is the first one to our knowledge investigating the relationship between SELE polymorphisms and lipid levels. We found that the SELE 98T allele was strongly associated ($P \leq 0.01$) with higher HDL-C in women. This result suggests that this allele is associated with a benefit lipid profile at least in women. E-selectin mediates the adhesion of leukocytes to activated endothelium, and E-selectin level has been correlated with cholesterol and TG levels and with decreased HDL-C level (46). Very few data are available concerning the physiologic significance of the 98G/T polymorphism. The 98G/T polymorphism in the 5′ untranslated region may be related to regulatory aspects. Conversely, the SELE 98T allele has been associated previously with cardiovascular diseases (47). One possible explanation for our observed results may be a regulatory mechanism to maintain E-selectin homeostasis. Indeed, several studies (13, 14, 48) showed that lipids could regulate SELE expression; HDL-C especially can induce decreased SELE expression in cells culture. We can hypothesize that E-selectin could regulate its own level via HDL-C

TABLE 9. Model A1: determinants of lipid traits variability in men

Covariates	ApoA-I β	ApoA-I ±SE	ApoA-I Change in R^2	HDL-C β	HDL-C ±SE	HDL-C Change in R^2	TG β	TG ±SE	TG Change in R^2
BMI	−0.0130[a]	0.0025	0.0324	−0.0287[a]	0.0036	0.0698	0.0274[a]	0.0025	0.1326
Age	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]
Tobacco	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	0.0547[a]	0.0164	0.0109
Alcohol × 10^{-3}	2.2[a]	0.3	0.0537	2.4[a]	0.43	0.0335	—[b]	—[b]	—[b]
APOB 71Thr	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]
APOC3 1100T	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	0.0418[a]	0.0127	0.0119
APOE ε2	0.0553[c]	0.0210	0.0079	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]
APOE ε4	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]
SELE 98T	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]
APOE ε4 × age	−0.0016[a]	0.0004	0.0171	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]
$C3_1$ × no-smoking	0.0606[a]	0.0158	0.0168	0.0677[c]	0.0231	0.0098	—[b]	—[b]	—[b]
Y-intercept		1.7911			1.8857			−0.6342	
Total R^2		0.1279			0.1131			0.1554	

BMI, body mass index; β, standard regression coefficient; $C3_1$, APOC3 1100C. *P* value to enter was set to 0.01 at each step: [a] $P \leq 0.001$, [b] nonsignificant association, [c] $P < 0.01$.

TABLE 10. Model A2: determinants of lipid traits variability in men

	ApoE		
Covariates	β	±SE	Change in R^2
BMI	0.0078[a]	0.0012	0.0498
Age	0.0022[b]	0.0008	0.0083
Tobacco	—[c]	—[c]	—[c]
Alcohol × 10^{-3}	—[c]	—[c]	—[c]
APOB 71Thr	—[c]	—[c]	—[c]
APOC3 1100T	—[c]	—[c]	—[c]
APO ε2	0.0941[a]	0.0102	0.0935
APO ε4	−0.0281[b]	0.0091	0.0100
APO ε3	—[c]	—[c]	—[c]
SELE 98T	—[c]	—[c]	—[c]
$C3_1$ × no smoking	—[c]	—[c]	—[c]
APO ε4 × age	—[c]	—[c]	—[c]
Y-intercept		1.3723	
Total R^2		0.1616	

P value to enter was set to 0.01 at each step: [a] $P < 0.0091$, [b] $P < 0.01$, [c] nonsignificant association.

concentrations. The relation between SELE polymorphism and HDL-C was observed in women only. This may be related to the capacity of estrogens to regulate SELE expression as shown by Cid et al. (49).

Gender differences also were observed concerning the contribution of APOC3 and APOE genes to lipid trait variability. The APO ε2 allele explained twice as much of the apoB-related traits variability (TC, LDL-C, apoB) in women (4%, 7.6%, 7%, respectively) than in men (1.8%, 3.3%, 4%, respectively). These results support previous results showing that the contribution of the APOE polymorphism on lipid variability is larger in women than in men (40, 50). Conversely, the results obtained are very similar to those reported by Lussier-Cacan et al. (51) on LDL-C variability, showing that the three common APOE alleles explained 6% of LDL-C variation in women and 3.5% in men. In women, the effect of the APOC3 1100C/T polymorphism on apoB-related traits was observed only in nonsmokers, whereas in men it was independent of smoking status. This polymorphism explained 1.7% to the apoB-related traits variability in men, whereas in women it explained 1%.

The mechanism underlying these gender differences remains unknown, but similar effects have been reported in other studies (35, 52). These results presumably reflect hormonal effects on gene expression or possible gender-associated lifestyle effects such as diet or adiposity.

Despite these major gender differences in the genetic impact on lipid traits variation, the total contribution of the complete model to lipid variability was remarkably similar in men and in women. The total variability of each studied lipid trait explained by our models ranged from 9.3% to 16.2% in men and from 8.9% to 26.4% in women. As observed in other studies investigating quantitative variation in lipid traits (30, 35, 53), most of the variability in these lipid, lipoprotein, and apolipoprotein traits remains unexplained by the considered predictors. Other genetic markers and loci have to be considered in further studies as segregation analysis have shown that genetics factors explained ~40–50% of lipid variability (54). Our results emphasize what was observed already in many other analyses with a single gene: that each genetic factor explained a small part of lipid trait variability. However, small genetic effects can be expected because of the complexity of lipid metabolism. All together, our results reinforce the concept that the relation between genetic factors and lipid levels will be dependent of the context, that is, gender, age, and environmental factors, such as tobacco and OC. Interaction between genes also may be important, but in our study we did not find any significant interaction between APOE, APOC3, APOB, and SELE polymorphisms on lipid levels.

Finally, our results underline the importance of studying simultaneously the influence of several genetic markers. Our results show that the benefit effect of the APOE ε2 al-

Table 11. Model A1: determinants of lipid traits variability in women

	ApoB			LDL-C			TC		
Covariates	β	±SE	Change in R^2	β	±SE	Change in R^2	β	±SE	Change in R^2
BMI	0.0128[a]	0.0020	0.0419	0.0423[a]	0.0076	0.0297	0.0250[b]	0.0084	0.0090
Age	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	0.0243[a]	0.0070	0.0136
Tobacco	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
Pill	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
Alcohol × 10^{-3}	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
APOB 71Thr	0.0377[a]	0.0107	0.0126	0.1508[a]	0.0416	0.0145	0.1285[b]	0.0457	0.0087
APOC3 1100T	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
APOE ε2	−0.1465[a]	0.0188	0.0716	−0.4730[a]	0.0843	0.0760	−0.4315[a]	0.0805	0.0385
APOE ε4	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	0.2166[b]	0.0694	0.0099
SELE 98T	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
$C3_1$ × no-smoking	−0.0512[a]	0.0160	0.0112	−0.1810†	0.0622	0.0102	−0.1943[b]	0.0694	0.0092
APOE ε2 × OC	—[c]	—[c]	—[c]	−0.3879†	0.1471	0.0076	—[c]	—[c]	—[c]
APOE ε4 × age	0.001[a]	0.0004	0.0113	0.0065[a]	0.0016	0.0175	—[c]	—[c]	—[c]
Y-intercept		0.6955			2.6229			4.0223	
Total R^2		0.1487			0.1555			0.0890	

BMI, body mass index; OC, oral contraceptive; β, standard regression coefficient; C_{31}, APOC3 1100C. *P* value to enter was set to 0.01 at each step: [a] $P \leq 0.001$, [b] $P < 0.01$, [c] nonsignificant association.

TABLE 12. Model A1: determinants of lipid traits variability in women

Covariates	ApoA-I β	ApoA-I ±SE	ApoA-I Change in R^2	HDL-C β	HDL-C ±SE	HDL-C Change in R^2	TG β	TG ± SE	TG Change in R^2	ApoE β	ApoE ±SE	ApoE Change in R^2
BMI	−0.0146[a]	0.0024	0.0405	−0.0312[a]	0.0037	0.0835	0.0160[a]	0.0017	0.102	0.0039[a]	0.0009	0.0208
Age	0.0058[b]	0.0021	0.0085	—[c]	—[c]	—[c]	0.0043[b]	0.0013	0.0101	—[c]	—[c]	—[c]
Tobacco	−0.1159[a]	0.0220	0.0349	−0.1670[a]	0.0330	0.0270	0.0717[a]	0.0147	0.0189	—[c]	—[c]	—[c]
Alcohol	0.0046[a]	0.0010	0.0282	0.0087[a]	0.0015	0.0302	—[c]	—[c]	—[c]	−0.122[a]	0.0373	0.0102
Pill	0.1160[a]	0.0210	0.0292	—[c]	—[c]	—[c]	0.1167[a]	0.0141	0.0598	−0.0644[a]	0.0077	0.0612
APOB 71Thr	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
APOC3 1100T	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
APOE ε2	0.0769[b]	0.0231	0.0120	0.1350[a]	0.0352	0.0155	—[c]	—[c]	—[c]	0.1032[a]	0.0086	0.1387
APOE ε4	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	−0.0404[a]	0.0074	0.0327
SELE 98T	—[c]	—[c]	—[c]	0.0918[b]	0.0338	0.0075	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
$C3_1$ × no-smoking	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
APOE ε2 × OC	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
APOE ε4 × age	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
Y-intercept		1.6560			2.0873			−0.70657			1.5501	
Total R^2		0.1533			0.1642			0.1909			0.2637	

BMI, body mass index; OC, oral contraceptive; β, standard regression coefficient; $C3_1$, APOC3 1100C. *P* value to enter was set to 0.01 at each step: [a] $P \leq 0.001$, [b] $P < 0.01$, [c] nonsignificant association.

lele on apoB-related traits overcompensated for the unfavorable effects of the APOC3 1100T and APOB 71Thr alleles in men and in women, respectively. The favorable APOC3 common allele (1100C) effect in nonsmokers on apoB-related traits was important enough to compensate for the unfavorable APOB 71Thr effects on apoB-related traits concentrations in women.

To summarize, polymorphisms of four genes among the 13 genes studied were strongly associated with lipid metabolism ($P \leq 0.001$). Three of them (APOB, APOE, APOC3) are involved in lipid metabolism; the fourth one, SELE, is implicated in molecular adhesion. This result leads us to a new insight in the genetic of lipid regulation, even if further studies are needed to confirm the observed relationship between SELE and lipids. APOE codons 112/158 and APOC3 1100C/T polymorphisms appeared to be the most important sites affecting lipid trait variability in our population, and their effects appeared highly modulated by environmental factors. Our results emphasize the importance to analyze simultaneously several genes and to consider gene-environment interactions. Finally, our findings may contribute to a better understanding of the complex interactions between genes and environmental factors on lipid variability and may help for the identification of individuals at increased risk of cardiovascular diseases.

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