APOA5 genotype modulates 2-y changes in lipid profile in response to weight-loss diet intervention: the Pounds Lost Trial[1–3]

Xiaomin Zhang, Qibin Qi, George A Bray, Frank B Hu, Frank M Sacks, and Lu Qi

ABSTRACT

Background: The apolipoprotein A5 gene (*APOA5*) is a major gene that regulates lipid metabolism and is modulated by dietary factors. A novel variant rs964184 in *APOA5* was identified to be associated with lipids in genome-wide association studies.

Objective: We examined whether this variant modified changes in lipid concentrations in response to a 2-y weight-loss diet intervention in a randomized trial.

Design: The current analyses were secondary analyses of a data set from the Pounds Lost Trial. We genotyped *APOA5* rs964184 in 734 overweight or obese adults who were randomly assigned to one of 4 diets that differed in percentages of energy derived from fat, protein, and carbohydrate for 2 y. We evaluated changes in fasting serum concentrations of total cholesterol (TC), LDL cholesterol, HDL cholesterol, and triglyceride from baseline to 2 y of follow-up.

Results: After a 2-y dietary intervention, we showed significant interactions between the *APOA5* rs964184 polymorphism and dietary fat intake (low compared with high) in the determination of changes in TC, LDL cholesterol, and HDL cholesterol (*P*-interaction = 0.007, 0.017, and 0.006, respectively). In the low-fat intake group (20% of energy derived from fat), carriers of the risk allele (G allele) exhibited greater reductions in TC and LDL cholesterol than did noncarriers (*P* = 0.036 and 0.039, respectively), whereas in the high-fat diet group (40% of energy derived from fat), participants with the G allele had a greater increase in HDL cholesterol than did participants without this allele (*P* = 0.038).

Conclusion: Our data showed better improvement in lipid profiles from long-term low-fat diet intake in the *APOA5* rs964184 risk allele. The Pounds Lost Trial was registered at clinicaltrials.gov as NCT00072995.   *Am J Clin Nutr* 2012;96:917–22.

INTRODUCTION

Unfavorable blood lipid concentrations, including high triglyceride, total cholesterol (TC), and LDL cholesterol and low HDL cholesterol, have been associated with increased risk of cardiovascular disease (1–3). Lipid profiles are determined by interactions between genetic and environmental factors, such as diet and lifestyle (4). Genetic variants in the apolipoprotein A5 gene (*APOA5*), which are located in the *APOA1-APOC3-APOA4-APOA5* gene cluster on human chromosome 11q23, are widely studied in relation to lipid profiles in candidate gene studies (5–8). In addition, observational studies and short-term (<3 mo) intervention trials have shown that several common variants in the *APOA5* gene interact with dietary factors, especially dietary fat, in the determination of blood lipid concentrations (5, 9–17). However, gene-diet interactions in long-term randomized intervention settings have been rarely explored.

In genome-wide association studies, a novel variant rs964184 in the *APOA5* locus was identified to be associated with increased triglyceride, TC, and LDL cholesterol and decreased HDL cholesterol for the risk allele (18–21). Furthermore, this variant showed the strongest associations with serum triglyceride concentrations in a dyslipidemic population (22). rs964184 resides 11 kb upstream of *APOA5* and in the 5′ untranslated region of a zinc finger protein, which may be involved in signal transduction and have multiple physiologic functions (22). However, to our knowledge, no study has examined the effect of rs964184 on protein function or availability. In the current study, we aimed to investigate whether the *APOA5* rs964184 genotype may interact with weight-loss diets that vary in macronutrients on 2-y changes in lipid concentrations in the randomized intervention study the Pounds Lost Trial (www.clinicaltrials.gov; NCT00072995).

SUBJECTS AND METHODS

Study population

The Pounds Lost Trial was conducted from October 2004 through December 2007 at the following 2 sites: the Harvard School of Public Health and Brigham & Women's Hospital (Boston, MA) and the Pennington Biomedical Research Center of the Louisiana State University System (Baton Rouge, LA). The study design and sample collection have been previously described in detail (23). Briefly, the study population was composed of 811 overweight or obese participants who were aged 30–70 y and had a BMI [in kg/m^2 (weight in kilograms divided by the square of the height in meters)] of 25–40. Major criteria for exclusion were the presence of diabetes treated with oral medications or insulin, unstable cardiovascular disease, the use of medications that affect body weight, and insufficient motivation as assessed by an interview and questionnaire. Individuals with type 2 diabetes controlled with diet or with hypertension or hyperlipidemia treated with diet or drugs were eligible to participate. Participants were randomly assigned to one of 4 diets that constituted a 2-by-2 factorial design; target percentages of energy derived from fat, protein, and carbohydrate in the 4 diets were 20%, 15%, and 65%, respectively; 20%, 25%, and 55%, respectively; 40%, 15%, and 45%, respectively; and 40%, 25%, and 35%, respectively. After 2 y, 645 participants (80% of the total population) completed the trial. The study was approved by the human subjects committee at each institution and by a data and safety monitoring board appointed by the National Heart, Lung, and Blood Institute. All participants provided written informed consent.

The current analyses were secondary analyses of a data set obtained from the Pounds Lost Trial, which was not designed for testing the hypothesis in the current analysis. A total of 734 participants with APOA5 rs964184 genotype data available were included in the current study (90.5% of participants in the Pounds Lost Trial). Consistent with the entire Pounds Lost Trial, the mean (±SD) age of participants in the current analysis was 50.9 ± 9.2 y, and the mean BMI (±SD) was 32.7 ± 3.9 kg/m^2. There was no significant difference in basic characteristics between participants with and without APOA5 rs964184 genotype data.

Measurements

Body weight and waist circumference were measured in the morning before breakfast on 2 d at baseline, 6 mo, and 2 y. Dietary intake was assessed in a random sample of 50% of participants by a review of the 5-d diet record at baseline and by a 24-h recall during a telephone interview on 3 nonconsecutive days at 6 mo and 2 y. Fasting blood samples, 24-h urine samples, and measurement of the resting metabolic rate were obtained on 1 d, and blood pressure was measured on 2 d at baseline, 6 mo, and 2 y. Analyses of serum lipids, glucose, and urinary nitrogen were performed at the Clinical Laboratory at Pennington Biomedical Research Center of the Louisiana State University System. The respiratory quotient was obtained by using the DeltaTrac II metabolic cart (Datex-Ohmeda) (23). Triglyceride, TC, LDL cholesterol, and HDL cholesterol were measured by using the Beckman Synchron CX7 analyzer (Beckman Coulter). LDL cholesterol was calculated for each participant according to the following formula (24):

$$\text{LDL cholesterol} = \text{TC} - \text{HDL cholesterol} - \text{triglyceride} \div 5 \qquad (1)$$

except when the triglyceride concentration was >400 mg/dL, in which case LDL cholesterol was measured directly on all samples of the participant.

Genotyping

As indicated in the Introduction, we selected APOA5 single nucleotide polymorphism (SNP) rs964184 because it was identified to be associated with multiple lipid traits (18–21), and previous evidence has shown potential interactions between this locus and dietary intakes, especially of fat in relation to lipids (11, 14, 16, 25). With consideration of genotyping cost, we focused on this specific variant rather than all of the reported lipid-associated SNPs. DNA was extracted from the buffy coat fraction of centrifuged blood by using the QIAmp Blood Kit (Qiagen). APOA5 rs964184 was genotyped successfully in 734 total participants, including 587 white subjects, with DNA samples made available by using the OpenArray SNP Genotyping System (BioTrove). The genotype success rate was 99%. Replicated quality-control samples (10%) were included in every genotyping plate with >99% concordance (26). The genotype distribution was in Hardy-Weinberg equilibrium in all participants or in white subjects ($P > 0.05$).

Statistical analysis

The primary outcomes were 2-y changes in blood lipids. Because APOA5 is sensitive to dietary fat ingestion (17, 27–30), we compared low-fat (20%) with high-fat (40%) diets in the primary analysis and compared average-protein (15%) with high-protein (25%) diets in the secondary analysis. Triglyceride concentrations were log transformed to normalize the distribution of the data. The Hardy-Weinberg equilibrium and comparison of categorical variables were assessed by using the chi-square test. Differences in continuous variables at baseline by genotypes were tested by using general linear models, with adjustment for age, sex, and ethnicity. The main effects of genotype and diet intervention on 2-y changes of lipids were analyzed by using multivariate linear regression models. Moreover, to analyze potential interactions between genotype and diet intervention, an interaction product term was included in the model. Appropriate adjustments, such as age, sex, ethnicity, the baseline value for the respective outcome, baseline BMI, lipid-lowing medication use, and weight loss, were used in the analysis. With the use of time as a repeated variable, linear mixed models were applied to test genetic associations with the trajectory of changes in outcomes according to diet intervention during the 2 y of follow-up by including genotype-time interaction terms. Additive genetic models were used in the analyses. A partial Pearson's correlation was computed to examine the relation between weight loss and changes in lipid profiles. Because the majority of the study population was white (80%), similar analyses were repeated in white participants. All reported P values were 2-sided, and a $P = 0.05$ was considered statistically significant. All data were analyzed with SAS version 9.1 software (SAS Institute Inc).

RESULTS

Characteristics of study population

Baseline characteristics of participants according to the *APOA5* rs964184 genotype are shown in **Table 1**. Genotype frequencies were similar in men and women but differed by ethnicity ($P < 0.0001$). HDL cholesterol and triglyceride were significantly different across the genotype after adjustment for age, sex, and ethnicity, and the G allele of the rs964184 was associated with lower HDL-cholesterol and higher triglyceride concentrations; whereas other variables such as weight, BMI, TC, LDL cholesterol, dietary intake, and biomarkers of adherence (urinary nitrogen and respiratory quotient) were not associated with genotype at baseline. In addition, we did not find any significant difference in weight loss at 6 mo and ∼2 y across the rs964184 genotype (all $P > 0.05$).

Interactions between *APOA5* rs964184 genotype and dietary fat on 2-y changes in lipids

No significant gene-diet interaction on weight loss was shown during the intervention (data not shown). At 2 y, after adjustment for age, sex, ethnicity, baseline BMI, baseline values for respective outcomes, and lipid-lowing medication use, we showed significant interactions between the *APOA5* rs964184 genotype and dietary fat intervention (low compared with high) on changes in TC and LDL cholesterol (P-interaction = 0.007 and 0.017, respectively). In the low-fat diet group, participants with the risk allele (G allele) had greater reductions in TC and LDL-cholesterol concentrations than did noncarriers ($\beta \pm$ SE = −9.3 ± 4.4 for TC and −7.5 ± 3.6 for LDL cholesterol; P = 0.036 and 0.039, respectively) (**Figure 1**), but the genetic variant was not related to changes in TC and LDL cholesterol in the high-fat diet group. Because changes in TC and LDL cholesterol were highly correlated in study samples ($r^2 \sim$ 0.90; $P < 0.0001$), we further assessed the independence of the genetic effects on these 2 markers. We showed that the genetic effects on change in TC were attenuated to be nonsignificant after additional adjustment for LDL cholesterol in the model ($P > 0.1$).

In addition, we also observed the gene-diet interaction on the change in HDL cholesterol (P-interaction = 0.006), and carriers of risk allele had a greater increase in HDL cholesterol response to the high-fat diet ($\beta \pm$ SE = 1.7 ± 0.8; P = 0.038). We did not find significant interaction between diet fat and the *APOA5* rs964184 genotype in relation to changes in serum concentrations of triglyceride (Figure 1). Additional adjustment for weight loss did not substantially change the results.

TABLE 1
Baseline characteristics of the study participants according to *APOA5* rs964184 genotypes[1]

	CC (n = 526)	CG (n = 194)	GG (n = 14)	P
Age (y)	51.0 ± 9.3[2]	50.6 ± 9.1	53.4 ± 6.7	0.384
Sex [n (%)]				0.687
F	323 (71.9)	119 (21.5)	7 (1.6)	
M	203 (71.2)	75 (26.3)	7 (2.5)	
Race or ethnicity [n (%)]				<0.0001
White	439 (74.8)	134 (22.8)	14 (2.4)	
Black	73 (65.8)	38 (34.2)	0 (0.0)	
Hispanic or other	14 (38.9)	22 (61.1)	0 (0.0)	
Weight (kg)	93.4 ± 15.6	93.4 ± 15.4	91.4 ± 15.9	0.669
BMI (kg/m^2)	32.7 ± 3.9	32.9 ± 3.8	31.4 ± 3.9	0.941
Waist circumference (cm)	103.8 ± 13.2	103.6 ± 12.8	101.3 ± 11.6	0.471
Glucose (mg/dL)	91.8 ± 11.1	92.3 ± 13.9	90.4 ± 7.4	0.977
SBP (mm Hg)	119.4 ± 13.1	119.9 ± 14.5	122.0 ± 11.0	0.674
DBP (mm Hg)	75.4 ± 9.3	76.2 ± 9.5	77.1 ± 9.9	0.253
TC (mg/dL)	201.5 ± 36.7	204.9 ± 37.5	204.2 ± 39.3	0.131
HDL cholesterol (mg/dL)	49.6 ± 14.3	46.9 ± 13.8	46.5 ± 11.3	0.028
LDL cholesterol (mg/dL)	125.3 ± 31.1	126.7 ± 34.0	127.3 ± 39.5	0.380
Triglyceride (mg/dL)[3]	136.9 ± 85.5	160.4 ± 84.6	152.3 ± 78.0	0.002
Dietary intake per day				
Energy (kcal)	1806 ± 790	1742 ± 833	2187 ± 965	0.949
Carbohydrate (%)	41 ± 8	41 ± 7	39 ± 6	0.189
Fat (%)	39 ± 8	40 ± 7	41 ± 7	0.090
Protein (%)	18 ± 3	18 ± 3	18 ± 2	0.160
Dietary fiber (g)	12.9 ± 6.3	12.1 ± 5.9	14.5 ± 6.1	0.309
Saturated fat (%)	13.8 ± 3.2	13.8 ± 3.0	14.9 ± 3.0	0.283
Biomarkers of adherence				
Urinary nitrogen (g)	12.1 ± 4.4	12.3 ± 4.3	13.1 ± 4.6	0.448
Respiratory quotient	0.84 ± 0.04	0.84 ± 0.04	0.83 ± 0.04	0.054
Weight loss at 6 mo (kg)	−6.9 ± 5.8	−5.8 ± 5.4	−8.7 ± 5.7	0.351
Weight loss at 2 y (kg)	−4.3 ± 7.7	−3.0 ± 6.9	−7.6 ± 8.2	0.768

[1] P values were calculated by using the chi-square test for categorical variables and general linear models for continuous variables after adjustment for age, sex, and ethnicity. DBP, diastolic blood pressure; SBP, systolic blood pressure; TC, total cholesterol.
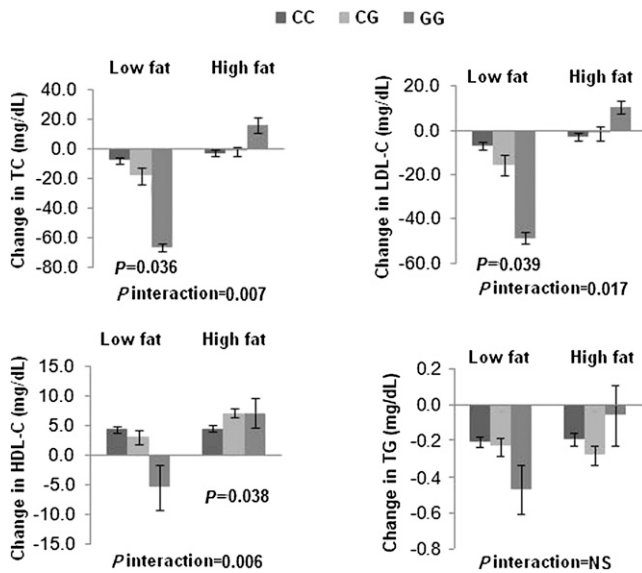[2] Mean ± SD (all such values).
[3] Log transformed before analysis.

FIGURE 1. Effects of *APOA5* rs964184 genotype and fat intervention on mean (±SE) changes in lipid profile at 2 y. Data included 219 and 176 (CC), 50 and 77 (CG), and 3 and 9 (GG) participants in low- and high-fat groups, respectively, at 2 y (total *n* = 534). *P* values were calculated by using general linear models with adjustment for age, sex, ethnicity, baseline BMI, baseline values for respective outcomes, and lipid-lowing medication use. HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TC, total cholesterol; TG, triglyceride.

We did not find significant interactions between the *APOA5* rs964184 genotype and protein intake on changes in lipid concentrations (all *P* > 0.05). Similar interactions were observed when the analysis was restricted to the white participants.

Trajectory of changes in lipids by the *APOA5* rs964184 genotype

We further examined the dynamic pattern of changes in lipid by *APOA5* genotypes through the 2-y intervention period. We observed significant genotype-time interactions on changes in TC and LDL cholesterol in the low-fat diet group (*P*-interaction = 0.0005 and 0.002, respectively). Differences in reductions of TC and LDL cholesterol by *APOA5* genotypes displayed a continued, cumulative pattern throughout the intervention and reached maximum values at 2 y (**Figure 2**). A similar pattern was shown in the white population.

DISCUSSION

In this 2-y randomized, weight-loss intervention trial, we observed a significant interaction between the *APOA5* rs964184 polymorphism and dietary fat intake in relation to changes in TC, LDL-cholesterol, and HDL-cholesterol concentrations. Compared with noncarriers, individuals with the G allele exhibited a greater reduction in TC and LDL-cholesterol responses to a low-fat diet but had a greater increase in HDL cholesterol when assigned a high-fat diet. These findings suggest that the genetic variation of *APOA5* may modulate the effect of long-term dietary fat intake on blood cholesterol concentrations.

Evidence for an *APOA5*-diet interaction on lipids in previous studies was focused on the 2 most common tag SNPs T-1131>C (rs662799) and Ser19>Trp (rs3135506) (11, 14, 16, 25), which

are related to translation efficiency or gene expression, that contribute to the production and function of apolipoprotein AV (31–33). The Ser19>Trp variant in the *APOA5* gene was shown to modulate changes in plasma TC in men with a low-fat and -cholesterol and high-fruit and -vegetable diet for 8 y (11, 25), which is in partial agreement with our results. However, several short-term trials generated inconsistent results regarding *APOA5*-diet fat interactions on cholesterol (14, 16). In a 3-mo intervention trial with a low-fat diet, reductions of TC and LDL cholesterol concentrations were not associated with the T-1131>C polymorphism in hyperlipemic and overweight individuals (*n* = 606) (14). Conversely, in another study, *APOA5* variants (Ser19>Trp and T-1131>C) had a decrease in plasma LDL cholesterol concentrations in 98 overweight and obese women with 9 wk of lifestyle modification that consisted of a reduction of fat and cholesterol intakes and physical activity changes (16). In the current study, we showed that the genotype difference of TC and LDC cholesterol in response to a low-fat diet showed a continued, cumulative pattern throughout the intervention and reached maximum values at 2 y. These findings suggest that the gene-diet interactions on the changes of cholesterol concentrations are more likely to be detected after a long-term intervention. In addition, it is known that about two-thirds of circulating TC is attributable to LDL cholesterol (34). After additional adjustment for the change in LDL cholesterol, the genetic effect on the change in TC was abolished, suggesting that the effect of the variant on change in TC might be mainly driven by change in LDL cholesterol.

In this study, a significant gene-diet interaction was observed in the change in HDL cholesterol. Different from TC and LDL cholesterol, the changes in HDL cholesterol were more likely to be modulated by the high-fat diet in which individuals carrying the risk allele had a greater increase in HDL cholesterol. Several previous studies have shown that changes in HDL cholesterol concentrations in response to high-fat diets varied across different samples (35–38). Our data suggest that *APOA5* genotype may partly account for the interindividual heterogeneity in high-fat-diet induced HDL cholesterol changes, although the underlying mechanisms remain to be determined.

Although a large number of studies have shown strong relation between *APOA5* genetic variants and triglyceride concentrations (19, 20, 39–43), the genetic effects on long-term change in triglyceride were NS and not modified by dietary intakes in our study. Of note, a similar result was also shown in an 8-y follow-up study (11, 25) in which changes in plasma triglyceride concentrations in response to dietary composition changes were not affected by *APOA5* genetic variation. In contrast, several short-term studies observed that genetic variants at the *APOA5* locus could affect the triglyceride concentration response to a dietary intervention. For example, 2 trials in small samples showed that *APOA5* −1131 C-allele carriers had higher triglyceride concentrations in response to a 6-d high-carbohydrate and low-fat diet and high-fat experimental meal (12, 27). In contrast, Suchanek et al (16) showed that the reduction of triglyceride concentrations by the 3-mo low-fat intervention was not associated with the *APOA5* T-1131>C. The reasons for the differential genetic effects on various lipid components are not clear. rs964184 is independent (22) and is not strongly correlated with T-1131>C and Ser19>Trp (linkage disequilibrium r^2 = 0.339 and 0.246, respectively). It is currently unknown
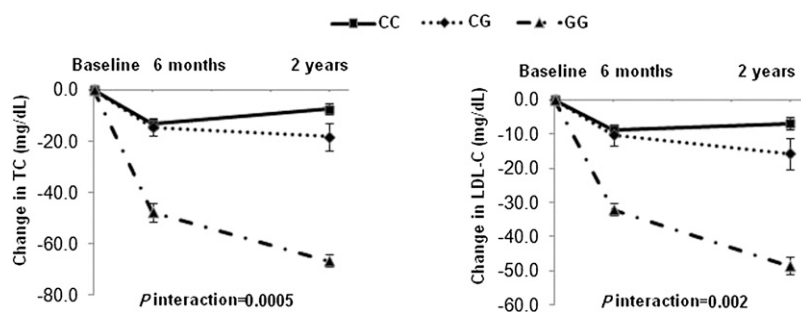
FIGURE 2. Changes in TC and LDL-C in the low-fat diet intervention group according to *APOA5* rs964184 genotype from baseline to 6 mo and 2 y under intervention. Data included 283, 250, and 219 (CC); 81, 65, and 50 (CG); and 4, 3, and 3 (GG) participants at baseline, 6 mo, and 2 y, respectively. *P*-interaction was tested by using linear mixed models between genotype and intervention time after adjustment for age, sex, ethnicity, baseline BMI, baseline values for respective outcomes, and lipid-lowering medication use. LDL-C, LDL cholesterol; TC, total cholesterol.

whether rs964184 is a functional variant or a marker in linkage disequilibrium with other possible functional variants that causally affect lipid homeostasis. Our results suggest that some serum lipid variables were partly affected by the interactions of the *APOA5* genetic variant and fat intake; therefore, we assume that different mechanisms might drive the observed gene-diet interactions for various lipid phenotypes.

In this study, we did not find parallel gene-diet interactions on weight loss and changes in lipids profiles. After additional adjustment for weight loss, the interaction and genetic effect had no substantial change on lipid profiles. The findings suggest that these effects on changes in lipid profiles might be independent of weight loss, and weight loss was not involved in the genotype-lipid interaction. Although weight loss was shown to have long-term beneficial effects on lipids, especially on LDL and TC concentrations (44), in our study samples and different subgroups, weight loss was significantly correlated only with triglyceride and HDL cholesterol and not with TC and LDL cholesterol at the 2-y intervention. Thus, to some extent, it is not surprising that we did not observe a statistically meaningful effect of weight loss on interaction and genetic effects.

This study had several limitations. First, although our study was, to our knowledge, the largest and longest diet intervention trial in which the genetic effects on changes in lipid profiles were tested, the analyses were based on secondary analyses, and the sample size in certain genotype such as GG was relatively small. An original design and larger samples are required to confirm our findings. Second, our analyses were restricted to only the *APOA5* rs964184 variant; however, as indicated, the selected rs964184 has been most consistently reported in several genome-wide association studies and is related to all of the lipid traits (18–21). Third, we did not adjust for multiple testing because of a high correlation between outcomes and the repeated measurements. Overadjustment for multiple comparisons may increase the type II error, which reduces the power to detect significant differences. Furthermore, because the participants were all overweight or obese, our results may not be generalized to the general population with a normal range of body weight. Finally, because the majority of our study samples were from white participants, and all of the 14 homozygous variant cases were white, future studies are warranted to verify the gene-diet interactions in other minority groups.

In conclusion, we showed that *APOA5* polymorphism might modify dietary fat–induced changes of lipid profiles, especially of LDL cholesterol and TC, in overweight or obese subjects.

These findings may provide information to the development of an effective diet intervention in prevention and treatment of obesity-related disorders. However, these findings need to be verified in future intervention studies with large sample sizes.

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