Brief Genetics Report

Hepatic Lipase Gene Variant −514C>T Is Associated With Lipoprotein and Insulin Sensitivity Response to Regular Exercise

The HERITAGE Family Study

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We investigated the associations between the hepatic lipase gene (LIPC) −514C>T polymorphism and lipases, lipoproteins, and insulin sensitivity (S_i) responses to exercise training. Hepatic lipase and lipoprotein lipase activities, plasma lipoprotein levels, and S_i were measured in the sedentary state and post–exercise training in the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study (n = 662). The LIPC −514C allele frequency was 0.516 (blacks) and 0.796 (whites). Baseline and post–exercise training hepatic lipase activities were 40% higher in CC homozygotes (P < 0.0001) in both races. Black CC homozygotes had lower baseline lipoprotein lipase activity, HDL cholesterol, HDL_3, and apolipoprotein (apo)A-1 concentrations. White CC homozygotes had lower baseline HDL cholesterol, apoA-1, LDL cholesterol, and apoB levels that remained low post–exercise training. Baseline S_i was not associated with the LIPC genotypes. However, training-induced improvements in S_i both in blacks and whites were greater in CC homozygotes (+1.25 ± 0.2 and +0.22 ± 0.2 $\mu U \cdot min^{-1} \cdot ml^{-1}$) than in the TT genotype (+0.27 ± 0.3 and −0.97 ± 0.3 $\mu U \cdot min^{-1} \cdot ml^{-1}$) ($P$ = 0.008 and P = 0.002, respectively). The LIPC −514C allele was associated with higher hepatic lipase activity in sedentary and physically active states and better S_i responses to regular exercise both in black and white individuals. The benefits from an exercise program on S_i are likely to be substantial in the general population given the high frequency of the LIPC −514C allele, particularly in whites. *Diabetes* 54:2251–2255, 2005

Hepatic lipase hydrolyzes triglyceride and phospholipids from high-, intermediate-, and low-density lipoproteins, transforming them into smaller and denser particles, and promotes the cellular uptake of HDL cholesterol (1). The hepatic lipase gene (LIPC), located on chromosome 15q21-q23, is expressed in the liver. Hepatic lipase has been the subject of recent reviews for its molecular (1) and pathophysiologic significance in obesity, dyslipidemia, and atherogenesis (2). There is familial resemblance for plasma postheparin lipoprotein lipase (LPL) and postheparin hepatic lipase activities (3), and exercise training–induced improvement in insulin sensitivity (S_i) correlates with decreased postheparin hepatic lipase activity.

Genetic polymorphisms in the LIPC gene are associated with postheparin hepatic lipase activity (4–6). Four frequently reported genetic variants in the LIPC promoter are in almost complete linkage disequilibrium, forming two haplotypes (2). The less common T allele in the −514C>T variant has been associated with a 30–40% decrease in postheparin hepatic lipase activity and higher HDL cholesterol levels (4). However, the relevance of this polymorphism for the transcriptional regulation of the LIPC gene remains controversial (7–10).

The benefits of regular physical activity in decreasing the risk of developing insulin resistance and coronary heart disease (CHD) are well documented, although individual responses vary considerably (11,12). Regular exercise affects lipid-lipoprotein profiles and peripheral glucose utilization (12,13). We investigated associations between the LIPC −514C>T variant and plasma lipoprotein levels, S_i and postheparin hepatic lipase, and postheparin

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apo, apolipoprotein; CHD, coronary heart disease; HERITAGE, Health, Risk Factors, Exercise Training, and Genetics; LPL, lipoprotein lipase.

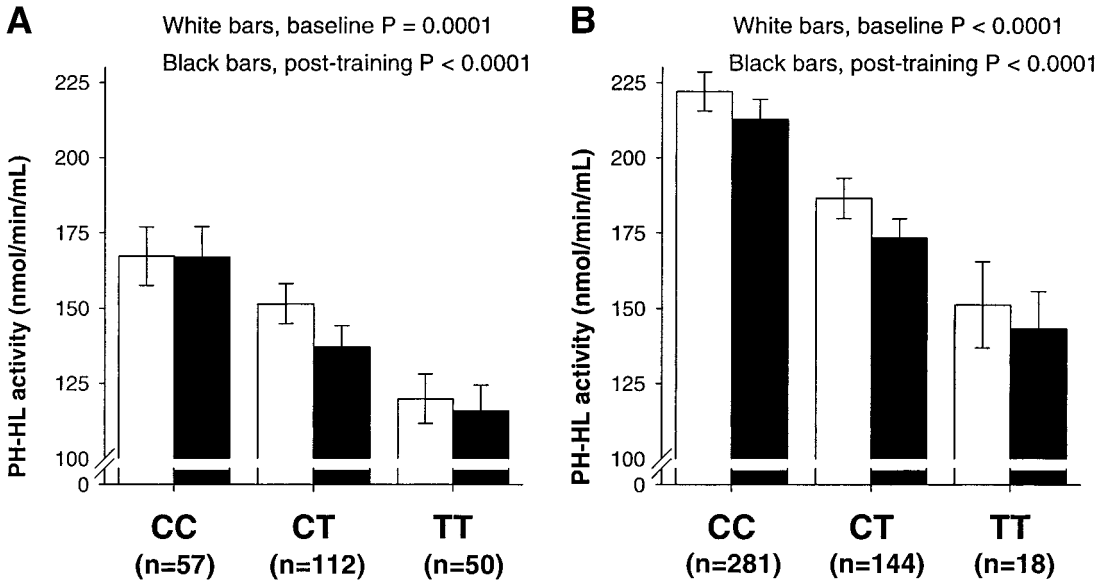

FIG. 1. Postheparin hepatic lipase (PH-HL) activity according to the LIPC −541C>T genotype in blacks (*A*) and whites (*B*). Pretraining (□) and post-training (■) columns represent the data adjusted for age, sex, and BMI. Error bars represent SE. *P* values are for the genotype differences.

arin LPL activities in a biracial cohort under sedentary-state conditions and their responses to endurance exercise training.

RESEARCH DESIGN AND METHODS

The Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study design and methods have been described previously (14). Briefly, the HERITAGE Family Study was designed to investigate the role of genetic factors in cardiovascular, metabolic, and hormonal responses to endurance training in white and black families. All subjects were required to be sedentary and in good health to participate in the HERITAGE Family Study, as well as to fulfill a series of inclusion criteria (14). For the present study we only excluded individuals without genotype or phenotype data. Data from 219 black adults (79 males and 140 females) and 443 white adults (218 males and 225 females) were available. Each institutional review board of the HERITAGE Family Study research consortium approved the study protocol. Written informed consent was obtained from each participant.

Exercise training program. The exercise training program has been described in detail previously (14,15). Briefly, the exercise intensity of the 20-week program was customized for each participant based on the heart rate–oxygen uptake relationship measured at baseline. During the first 2 weeks, the subjects trained at a heart rate corresponding to 55% of $V\mathrm{O}_{2\mathrm{max}}$ for 30 min per session. Duration was gradually increased to 50 min per session and intensity to the heart rate associated with 75% of the baseline $V\mathrm{O}_{2\mathrm{max}}$. These conditions were then sustained for the last 6 weeks. Training frequency was three times per week, and all training sessions were performed under supervision on cycle ergometers at the participating clinical centers. The subjects were instructed not to change their diet during the intervention.

Phenotype measurements. All phenotypes were measured at baseline and after the 20-week exercise training program.

Measurement of S_i. A frequently sampled intravenous glucose tolerance test was performed as described (16) in the morning after a 12-h overnight fast and no less than 24 h after the last exercise session. From the frequently sampled intravenous glucose tolerance test data, S_i was derived using the MINMOD Millennium computer program (17). S_i measures the ability of plasma insulin to enhance the net disappearance of glucose from plasma. These analyses were described previously (16).

Postheparin lipase activities, lipids, and lipoproteins. Postheparin LPL and postheparin hepatic lipase activities were measured by the modified Nilsson-Ehle and Ekman method, as previously reported (13). Activity is expressed as nanomoles of free fatty acid released divided by milliliters of plasma divided by minutes. Lipid, lipoprotein, and apolipoprotein (apo) assays have been reported previously in detail (3).

Genetic analyses. Genomic DNA was extracted from lymphoblastoid cell lines using standard procedures. Genotyping for the LIPC −514C>T polymorphism (dbSNP rs#1800588) was performed using the TaqMan allelic discrimination method. Details for PCR conditions and primer/probe sequences are available upon request.

Statistical analyses. All statistical analyses were performed with the SAS Statistical Software Package (release 8.2; SAS Institute, Cary, NC). A χ^2 test was used to compare allele frequencies and to test whether the genotype distributions were in Hardy-Weinberg equilibrium. Associations between the LIPC −514C>T genotypes and phenotypes were analyzed using a MIXED procedure. Nonindependence among family members was adjusted using a "sandwich estimator" as described in previous HERITAGE publications. Because of the skewed distributions, baseline plasma triglyceride, VLDL cholesterol, and HDL cholesterol were normalized with log transformation. The S_i data derived from the MINMOD Millennium model required a square root transformation to approximate a normal distribution. All analyses were done separately in blacks and whites. All baseline data were adjusted for age, sex, and BMI, whereas the training responses were also adjusted for the respective baseline values.

RESULTS

The LIPC −514C allele frequency was 0.516 (blacks) and 0.796 (whites). Genotype distributions were in Hardy-Weinberg equilibrium. The LIPC −514C>T polymorphism showed a strong association with postheparin hepatic lipase activity, which was ~40% higher in the CC homozygotes at baseline ($P \leq 0.0001$) and posttraining ($P \leq 0.0001$) in both ethnic groups (Fig. 1).

The LIPC −514C>T polymorphism was also associated with postheparin LPL activity. The black CC homozygotes had 32 and 21% lower postheparin LPL activity before and after exercise training than the LIPC TT homozygotes ($P = 0.0005$ and 0.009, respectively). White CC homozygotes had 12 and 19% lower postheparin LPL activity before and after exercise training than TT homozygotes ($P = 0.0004$ and <0.0001, respectively) (Fig. 2).

Associations of LIPC −514C>T genotypes with lipids and lipoprotein concentrations in the sedentary state and their training responses in blacks and whites are shown in Table 1. In blacks, the TT homozygotes exhibited higher baseline HDL cholesterol, HDL_3, and apoA-1 concentrations than the CC homozygotes. The LIPC −514 polymorphism was also associated with apoB ($P = 0.04$) training response, with the greatest reduction observed in the TT

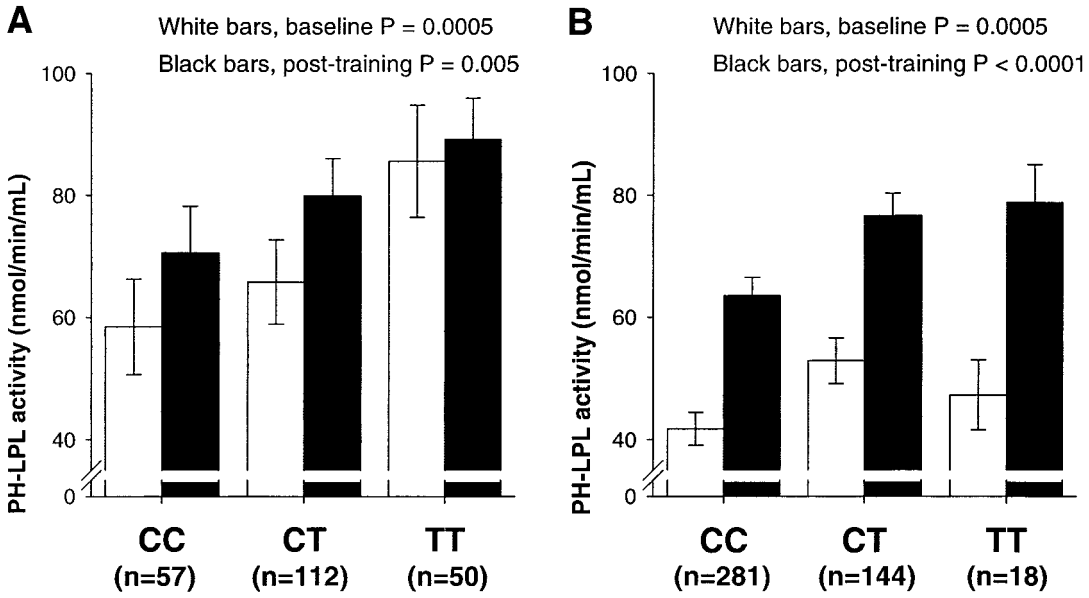

FIG. 2. Postheparin lipoprotein lipase (PH-LPL) activity according to the LIPC −541C>T genotype in blacks (*A*) and whites (*B*). Pretraining (□) and post-training (■) columns represent the data adjusted for age, sex, and BMI. Error bars represent SE. *P* values are for the genotype differences.

homozygotes. White TT homozygotes also had higher HDL cholesterol and apoA-1 concentrations in the sedentary state, as well as significantly higher plasma trigylceride, VLDL cholesterol, LDL cholesterol, and apoB concentrations.

There were no differences in S_i between the LIPC −514 genotypes in blacks and whites in the sedentary state (Table 2). However, training–induced improvements in S_i in blacks and whites were greater in the CC homozygotes ($+1.25 \pm 0.2$ and $+0.22 \pm 0.2$ $\mu U \cdot min^{-1} \cdot ml^{-1}$) than in the TT genotype ($+0.27 \pm 0.3$ and -0.97 ± 0.32 $\mu U \cdot min^{-1} \cdot ml^{-1}$), with heterozygotes showing intermediary values.

DISCUSSION

Our data demonstrate significant associations between the LIPC −514C>T polymorphism and plasma postheparin

TABLE 1
Associations between the LIPC −514C>T genotype and plasma lipids and lipoproteins

	Blacks				Whites			
Variable*	CC	TC	TT	*P*	CC	TC	TT	*P*
n	57	112	50		281	144	18	
Triglycerides (mmol/l)								
Pretraining	0.95 ± 0.06	0.90 ± 0.05	0.93 ± 0.06	0.60	1.12 ± 0.04	1.13 ± 0.05	1.38 ± 0.10	**0.02**
Training response	0.03 ± 0.05	−0.04 ± 0.05	−0.04 ± 0.06	0.41	−0.07 ± 0.05	−0.01 ± 0.04	−0.02 ± 0.10	0.21
VLDL cholesterol (mmol/l)								
Pretraining	0.05 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.19	0.09 ± 0.01	0.08 ± 0.01	0.15 ± 0.04	**0.04**
Training response	0.01 ± 0.02	−0.03 ± 0.02	−0.02 ± 0.02	0.35	−0.03 ± 0.02	−0.001 ± 0.02	−0.01 ± 0.04	0.13
LDL cholesterol (mmol/l)								
Pretraining	2.80 ± 0.14	2.93 ± 0.10	2.97 ± 0.12	0.37	2.79 ± 0.06	3.01 ± 0.07	3.18 ± 0.15	**0.009**
Training response	0.06 ± 0.07	0.08 ± 0.06	−0.02 ± 0.06	0.29	−0.01 ± 0.04	−0.02 ± 0.04	−0.005 ± 0.10	0.98
HDL cholesterol (mmol/l)								
Pretraining	1.02 ± 0.04	1.06 ± 0.03	1.17 ± 0.05	**0.009**	0.95 ± 0.02	1.00 ± 0.03	1.01 ± 0.04	**0.05**
Training response	0.06 ± 0.02	0.07 ± 0.01	0.05 ± 0.03	0.57	0.05 ± 0.05	0.07 ± 0.02	0.05 ± 0.03	0.57
HDL_2 (mmol/l)								
Pretraining	0.35 ± 0.04	0.38 ± 0.03	0.44 ± 0.04	0.08	0.35 ± 0.02	0.37 ± 0.02	0.35 ± 0.03	0.22
Training response	0.03 ± 0.02	0.06 ± 0.01	0.06 ± 0.02	0.09	0.02 ± 0.01	0.04 ± 0.01	0.02 ± 0.03	0.36
HDL_3 (mmol/l)								
Pretraining	0.70 ± 0.02	0.72 ± 0.01	0.78 ± 0.03	**0.02**	0.65 ± 0.01	0.67 ± 0.01	0.69 ± 0.03	0.17
Training response	0.02 ± 0.02	0.01 ± 0.01	0.01 ± 0.02	0.81	0.02 ± 0.01	0.03 ± 0.01	0.03 ± 0.03	0.77
ApoA-I (mmol/l)								
Pretraining	1.14 ± 0.03	1.18 ± 0.02	1.23 ± 0.02	**0.02**	1.10 ± 0.02	1.15 ± 0.02	1.20 ± 0.03	**0.005**
Training response	0.04 ± 0.02	0.04 ± 0.01	0.04 ± 0.02	0.79	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.03	0.88
ApoB (mg/dl)								
Pretraining	0.81 ± 0.04	0.83 ± 0.03	0.83 ± 0.03	0.76	0.80 ± 0.02	0.85 ± 0.02	0.90 ± 0.05	**0.04**
Training response	0.02 ± 0.02	0.01 ± 0.02	−0.03 ± 0.02	**0.04**	0.004 ± 0.01	0.01 ± 0.01	0.02 ± 0.02	0.58

Data are means ± SE, unless otherwise indicated. *Data adjusted for age, sex, and BMI. Data in boldface are significant ($P < 0.05$).

TABLE 2
S_i ($\mu U \cdot min^{-1} \cdot ml^{-1}$) in relation to the LIPC −514C>T genotype

	LIPC −514C>T genotype			
	CC	TC	TT	*P* value
Blacks (*n*)	49	93	42	
S_i*†				
Pretraining	2.58 ± 0.4	2.69 ± 0.2	2.47 ± 0.3	0.72
Training response	1.25 ± 0.2	0.41 ± 0.2	0.27 ± 0.3	**0.008**
Whites (*n*)	275	135	19	
S_i*†				
Pretraining	4.26 ± 0.3	3.81 ± 0.3	3.58 ± 0.4	0.28
Training response	0.22 ± 0.2	0.09 ± 0.2	−0.97 ± 0.3	**0.002**

Data are means ± SE, unless otherwise indicated. *Data adjusted for age, sex, and BMI. †Based only on complete baseline and posttraining data. Data in boldface are significant ($P < 0.05$).

hepatic lipase and postheparin LPL activities and lipoprotein levels in the sedentary state as well as with endurance training–induced changes in S_i. Several studies have shown that DNA sequence variations at the LIPC locus contribute to postheparin hepatic lipase plasma levels and the lipoprotein profile (2,6). A recent meta-analysis concluded that the LICP −514C>T polymorphism is important in determining hepatic lipase activity and HDL concentration (18). However, associations between this polymorphism and changes in lipoprotein levels or S_i in response to exercise training have not been addressed before.

The LIPC −514TT homozygotes had 30% lower postheparin hepatic lipase activity compared with the CC homozygotes, and the genotype accounted for 7–8% of the variation in postheparin hepatic lipase activity. This association remained after exercise training. Blacks had lower postheparin hepatic lipase activity, an ethnic difference found in both sexes and concordant with previous observations (19,20). Several in vitro studies have reported a 30–40% reduction in transcriptional activity in cells transfected with the T allele compared with the C allele (rev. in 2). Other studies found no functional effects of this allelic variant, perhaps because of differences in cell lines, transfection efficiencies, and reporter vectors used (7,8,10). Overall, our data strengthen reports that associate postheparin hepatic lipase activity with the LIPC −514C>T polymorphism (4,7,9). Recently, a prospective cohort study found that the TT genotype had increased susceptibility to CHD in sedentary or moderately physically active subjects but not among the vigorously active (21).

Individuals carrying the LIPC −514T allele had higher postheparin LPL activity at baseline and after exercise training. We have reported earlier higher postheparin LPL activity in blacks in the sedentary state (22) and that increased LPL activity was associated with an improved lipoprotein-lipid profile in response to an exercise training program (13). Here we report that the TT homozygotes had 25% higher LPL activity after exercise training than the CC homozygotes. The increase in LPL activity after endurance exercise training in combination with the higher HDL cholesterol observed in the TT homozygotes could impact CHD risk.

Hepatic lipase deficiency modifies the lipoprotein profile. It has been related to increased plasma cholesterol and trigylceride levels and mass redistribution within HDL particles (2). The most consistent finding in hepatic lipase deficiency is increased HDL_2. The LIPC −250G>A variant, which is in complete linkage disequilibrium with the LIPC −514C>T, also leads to decreased hepatic lipase activity in the A allele carriers and to buoyant LDL particles and high HDL cholesterol (4). We found associations between the LIPC −514C>T polymorphism and the lipoprotein profile in the sedentary state, with higher HDL cholesterol and apoA-1 levels in the TT homozygotes. Although there were no significant associations with other lipoproteins, the association for HDL cholesterol levels remained significant in the trained state. Increased risk of atherosclerosis has been associated with the LIPC −514T allele, and CC homozygotes benefit the most from intensive lipid-lowering therapy (4,23).

This study is the first to examine the associations between the LIPC −514C>T genotypes and S_i and the responses of postheparin lipase to an exercise training intervention. The LIPC −514C>T genotypes showed associations with S_i and postheparin hepatic lipase activity after exercise training. The enhanced S_i after exercise training, primarily in the CC homozygotes, was associated with higher postheparin hepatic lipases activity. Remarkably, these S_i differences appeared only in response to exercise training. The second European Atherosclerosis Research Study reported that T allele carriers have the lowest glucose tolerance (24). Recently, the LIPC-205G>A polymorphism, which is in complete linkage disequilibrium with the LIPC −514C>T, has been reported to predict the conversion from impaired glucose tolerance to type 2 diabetes in a 3-year follow-up lifestyle intervention (25).

The mechanisms behind the association of the LIPC −514C>T polymorphism and S_i are unclear. Changes in blood lipids in response to decreased postheparin hepatic lipase activity and increased postheparin LPL activity may accompany changes in intramyocellular lipid storage, affecting S_i (26). Several regulatory elements have been identified in the rat LIPC promoter, and consensus analysis with the human sequence suggests that the LIPC −514C>T variant may be in a DNA motif containing the sequences necessary for insulin/glucose responses. Insulin regulation of the LIPC gene could be mediated by either upstream stimulatory factor or sterol regulatory element–binding protein-1c transcription factors, which bind to the E-box motif located in the LIPC promoter region at −514 bp, although this has not been demonstrated (9). One could speculate that human variation in S_i response to exercise training associated with the LIPC genotype is the consequence of transcriptional effects on the LIPC gene by insulin and the binding (or lack of) of transcription factors to the E-box motif.

Finally, the present study suggests that regular exercise may not influence the lipoprotein profile or improve S_i at the same rate for all individuals and that the efficacy of regular exercise could be related in part to the LIPC −514C>T genotype. C allele carriers may not only have more clinical benefit from intensive lipid-lowering therapy, as reported (4), but are more likely to benefit from an exercise training program. The improvement in S_i with

regular exercise in individuals with the LIPC −514C allele has significant clinical applications due to its high frequency in various populations (4,5,7). Arguably, screening for T allele carriers may allow the identification of subjects at elevated risk requiring individualized therapeutic strategies to decrease cardiovascular and metabolic disease risks.

In summary, results from the HERITAGE Family Study indicate that the C allele at −514 in the promoter region of the LIPC gene is associated with higher postheparin hepatic lipase activity and better S_i response to regular exercise. The benefits on S_i from an exercise program could be of considerable importance in the general population given the high frequency of the LIPC −514C allele.

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