Interaction Effect of Serine447Stop Variant of the Lipoprotein Lipase Gene and C-514T Variant of the Hepatic Lipase Gene on Serum Triglyceride Levels in Young Adults: The Bogalusa Heart Study

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The opposing effects of lipoprotein lipase (LPL) Serin447Stop (S447X) polymorphism and hepatic lipase (HL) C-514T polymorphism on serum triglyceride (TG) levels have been known. However, little is known about the interaction effect of these 2 functional gene variants on serum triglyceride levels. This aspect was examined in a community-based sample of 902 whites and 389 blacks aged 18 to 41 years, using a repeated measures analysis in a mixed model. The frequency of the LPL X447 allele was higher in whites than blacks (16% *v* 11%, *P* < .05); whereas the frequency of HL T-514 allele was higher in blacks than whites (77% *v* 40%, *P* < .001). The combined genotype distribution was also different between whites and blacks (*P* < .001). Although the frequency of carriers of both variants was similar in whites and blacks (7% *v* 8%), more whites carried the LPL X447 allele only (9% *v* 3%), and more blacks carried the HL T-514 allele only (70% *v* 33%). Mean levels of TG adjusted for age, sex, and body mass index (BMI) in carriers versus noncarriers of the LPL X447 allele were lower by 13.5% (*P* < .0001) in whites, 15.8% (*P* < .01) in blacks and 16.0% (*P* < .0001) in the total sample. No such phenotypic effect was noted with respect to HL T-514 allele either in blacks or whites, although the mean level in carriers was marginally (*P* = .08) higher in the total sample. The interaction effect of LPL and HL variants on TG levels was significant in the total sample (*P* = .016) and marginal in whites (*P* = .079). In the total sample, the decrease of TG in carriers versus noncarriers of the LPL X447 was 1.8-fold greater in carriers versus noncarriers of the HL T-514 allele (13.6 mg/dL *v* 7.4 mg/dL, *P* = .016). Whites tended to show a similar trend (16.8 mg/dL *v* 6.1 mg/dL, *P* = .079). Blacks also showed a similar, but nonsignificant, trend (10.4 mg/dL *v* 8.6 mg/dL, *P* = .45). These results by showing modulation of association between S447X variant of the LPL gene and serum TG by C-514T variant of the HL gene underscore the importance of gene-gene interactions in the assessment of genetic effects on complex traits.

AN ELEVATED LEVEL of serum triglycerides (TG) is increasingly being recognized as an important risk factor for coronary heart disease (CHD).[1] Parameters of lipoprotein metabolism that determine serum lipid and lipoprotein levels are modulated by multiple genes and their interaction with each other and with the environment. Lipoprotein lipase (LPL) as a lipolytic enzyme hydrolyzes TG of very low-density lipoproteins and chylomicrons and as a ligand protein mediates the cellular binding and uptake of lipoproteins.[2-4] Although hepatic lipase (HL), unlike LPL, plays no rate-limiting role in the catabolism of triglyceride-rich lipoproteins,[5,6] it hydrolyzes TG and phospholipids contained in lipoproteins, forming smaller denser particles, and facilitates the hepatic uptake of lipoproteins by acting as a ligand.[2,7-9] In the general population, increased LPL activity is associated with a favorable lipid profile, including relatively lower TG; whereas the opposite is true with respect to HL activity.[2,3,10-12] It has been suggested that LPL and HL may be metabolically linked, albeit inversely in their metabolic effect.[13]

Of the common LPL gene variants described within the coding region, the 447 Serine Stop substitution (S447X) located in exon 9 produces a truncated protein lacking 2 amino acids at the carboxy terminus.[14] This variant, which promotes increases in the secretion of LPL mass without affecting lipolytic activity,[15] is generally associated with lower TG.[16-19] The promoter region of the HL gene contains C-514T polymorphism in complete linkage disequilibrium with 3 other common polymorphisms.[20-23] The HL promoter variant, C-514T, has been associated with lower HL activity and, in some studies, higher TG.[20-26] Although the effects of S447X variant of the LPL gene and C-514T variant of the HL gene on serum TG have been studied extensively, evidence is lacking for the interaction effect of these 2 functional gene variants on serum TG. As part of the Bogalusa Heart Study, a biracial (black-white) community-based study of early natural history of cardiovascular disease,[27] the present study examines (1) the black-white difference in frequency of carriers of both X447 and T-514 variants and (2) the interaction effect of these 2 variants on serum TG.

MATERIAL AND METHODS

Study Subjects

From 1978 to 1996, 6 cross-sectional surveys of young adults were performed approximately every 3 years in the biracial (65% non-Hispanic white, Caucasians and 35% non-Hispanic black, African Americans) community of Bogalusa, LA. The age of young adults ranged from 18 to 20 years in the 1978 to 1979 survey and from 18 to 41 years in the 1995 to 1996 survey. This panel design resulted in multiple observations. Subjects were eligible for the present study if they had at least 1 examination between 1988 and 1996, when blood samples were collected specifically to obtain DNA for genotyping. Accordingly, 1,291 young adults (69.8% white, 30.2% black; mean age, 25.8 years) who had LPL S447X and HL C-514T genotypes data formed the study sample for this report. The number of observations,

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Table 1. Number of Times Examined by Race and Sex: The Bogalusa Heart Study

No. of Examinations	White Male	Black Male	White Female	Black Female	Total
1	106	39	168	84	397
2	108	45	133	69	355
3	65	39	77	34	215
4	51	13	83	40	187
5	35	10	45	11	101
6	12	3	16	1	32
7	1	1	2	0	4
Subjects	378	150	524	239	1,291
Observations	975	373	1,332	545	3,225

totaling 3,225, made on 1,291 members (an average of 2.5 observations/subject) of this cohort is given in Table 1. The study was approved by the Institutional Review Board, and all subjects gave informed consent at each examination.

Examinations

All examinations were conducted by trained examiners closely following standard protocol.[28] Participants were instructed to fast for 12 hours before venipuncture, and compliance was ascertained by interview on the morning of examination. Height and weight were measured twice to ± 0.1 cm and to ± 0.1 kg, respectively. Body mass index (BMI), a measure of overall adiposity, was calculated as weight in kilograms divided by the square of the height in meters.

Laboratory Analysis

From 1978 to 1986, serum triglyceride levels were measured using chemical procedure on Technicon Auto Analyzer II (Technicon Instrument, Tarrytwon, NY), according to the protocol developed by the Lipid Research Clinics Program.[29] Since then, it was measured enzymatically on an Abbottt VP instrument (Abbott Laboratories, North Chicago, IL). Both chemical and enzymatic procedures met the performance requirements of the Lipid Standardization Program sponsored by the Center for Disease Control and Prevention (CDC), Atlanta, GA. The laboratory has been monitored for precision and accuracy of lipid measurements by the agency's surveillance program since 1973. Approximately 10% random blind duplicates of individuals were selected daily to assess the reproducibility of the laboratory analyses. Intraclass correlation coefficient between the blind duplicate values ranged from 0.97 to 0.99 for serum TG.

Genotyping of the LPL S447X and HL C-514T polymorphisms was performed using the TaqMan assay.[30] The forward and reverse polymerase chain reaction (PCR) primers sequences for LPL genotyping were CGGTATTTGTGAAATGCCATGA and AAGCTCAGGATGCCCAGTCA, respectively; for HL genotyping GGGCATCTTTGCTTCTTCGT and TCAAAGTGTGGTGCAGAAAACC, respectively. Allele-specific fluorogenic probes, labeled with different reporter dyes, were hybridized to the target DNA in a sequence-specific manner. The allele-specific probes for LPL genotyping were 6FAM-TGCTCACCAGCCTGACTTCTTATTCAGA and VIC-TGCTCACCAGCCTCACTTCTTATTCAGA; for HL genotyping 6FAM-TTCACCCCCGTGTCAAAAGGAGC and VIC-CTTCACCCCCATGTCAAAAGGAGCT. After PCR amplification, the increase in fluorescent intensity of the reporter dyes is detected using the ABI 7700 fluorescence plate reader (Applied Biosystems, Foster City, CA). Genotyping was determined by automated analysis of the fluorescent signals. Based on the analysis of 63 pairs of blind duplicates, there was a 100% concordance in both LPL S447X and HL C-514T genotyping.

Statistical Analysis

All analyses were conducted using SAS version 8 (SAS, Cary, NC).[31,32] Gene counting was used to estimate allele frequencies within each race. Race differences in the distribution of genotype and allele frequencies were tested in 2-way contingency table using chi-square statistic. When the expected frequency of any 1 genotype was less than 5, Fisher's exact test was used instead. Deviation from Hardy-Weinberg equilibrium was tested using 1-way goodness-of-fit chi-square statistic.

Serum triglyceride levels were transformed to natural logarithms to improve normality. Because curvilinear relationships between serum triglyceride levels and age, as well as BMI, were observed in this sample, both their linear and quadratic terms were included in the model. However, having both linear and quadratic terms of age and BMI can cause colinearity problem in modeling, and the estimates of the coefficients can be unstable.[33] To obviate this, age and BMI values were centered by subtracting their means of the total sample (age = 25.8 years; BMI = 25.3 kg/m^2).

Associations between the HL C-514T and LPL S447X polymorphisms and triglyceride levels based on 1 or more measurements (Table 1) were examined using repeated measures analyses in mixed models. Because these serial measurements were highly interrelated, a time–series covariance structure in which correlations of the repeated measurements decline as a function of time (age) was used. Likelihood ratio tests were used to compare the relative fit of different models. The best model was selected based on improvement chi square tests. Adjusted mean levels of TG by genotype were computed by weighting equally for each subject. The mean differences for genotypes were calculated by subtracting the adjusted mean levels of the carriers from noncarriers. In the total sample, the mean differences for genotypes were also adjusted for the genotype distribution differences in blacks and whites. Maximum likelihood estimates were obtained for all fixed effect parameters. For testing main effects and interaction, we used a significance level of $\alpha = 0.05$.

RESULTS

Characteristics of the study cohort are shown in Table 2 by race and sex, as background. White males (*v* black males) and black females (*v* white females or black males) were significantly older among the race-sex groups. The race- and sex-related trends for BMI and lipoprotein variables were in the expected directions based on previous findings in the US population of young adults.[27,34-36] BMI was higher in white males (*v* white females) and black females (*v* white females or black males); LDL cholesterol higher in whites than blacks; HDL cholesterol higher in blacks than whites and in white females

Table 2. Characteristics of Study Cohort by Race and Sex: The Bogalusa Heart Study

	White Male (n = 378)	Black Male (n = 150)	White Female (n = 524)	Black Female (n = 239)
Age (yr)	25.1 ± 2.5[a]	23.3 ± 1.7	25.1 ± 1.8	25.5 ± 2.3[a,x]
BMI (kg/m^2)	26.2 ± 4.9[x]	26.2 ± 6.1	24.3 ± 5.5	27.8 ± 7.1[a,x]
LDL cholesterol (mg/dL)	115.8 ± 28.2[a]	107.6 ± 30.1	115.9 ± 28.8[a]	110.1 ± 25.8
HDL cholesterol (mg/dL)	43.5 ± 10.9	55.2 ± 15.5[a]	50.9 ± 12.4[x]	57.6 ± 13.3[a]
Triglycerides (mg/dL)	114.1 ± 67.8[a,x]	95.2 ± 74.1[x]	109.9 ± 59.3[a]	69.2 ± 39.4

NOTE. Values are mean ± SD.

Race-sex difference (adjusted for age/BMI): the superscripts a (for race) and x (for sex) denote significantly ($P < .05$) higher value compared with other race or sex.

than white males; TG higher in whites than blacks and in white males than white females.

The genotype distributions of the LPL S447X and HL C-514T polymorphisms separately and in conjunction are shown in Table 1 by race. The genotype distribution of each of the polymorphism differed significantly between blacks and whites in the study cohort. The carrier frequency for the LPL X447 allele was higher in whites than blacks (16% *v* 11%, $P < .05$). On the other hand, the carrier frequency for the HL T-514 allele was higher in blacks than whites (77% *v* 40%, $P < .0001$). The genotype distribution of both polymorphisms was in accordance with Hardy-Weinberg equilibrium expectations in whites ($P = .5$) and blacks ($P = .76$). When both polymorphisms were examined jointly as carriers of both LPL and HL variants, carriers of LPL variant only, carriers of HL variant only, and noncarriers of either variant, the combined genotype distribution was also different between blacks and whites ($P < .0001$). Noncarriers of either variant constituted a higher percentage of whites than blacks (51% *v* 19%), while the percentage of carriers of both variants was similar in both races (7% *v* 8%). Further, more whites than blacks carried the LPL X447 allele only (9% *v* 3%). On the other hand, more blacks than whites carried the HL T-514 allele only (70% *v* 33%). Although the proportion of blacks and whites varied significantly among the 4 combined genotype groups, the proportion of males and females, age (adjusted for race and sex), BMI (adjusted for age, race and sex) remained similar among the 4 genotype groups (data not shown).

Mean serum triglyceride levels in carriers versus noncarriers of LPL X447 and HL T-514 alleles are given in Table 3 for whites, blacks, and the total sample. The levels among carriers versus noncarriers of the LPL X447 allele were significantly lower by 13.5% in whites, 15.8% in blacks, and 16.0% in the total sample. No such phenotypic effect was noted with respect to the HL T-514 allele either in blacks or whites, although triglyceride values in carriers were marginally ($P = .08$) higher in the total sample.

Parameter estimates for the interaction effect of LPL X447 and HL T-514 alleles on serum triglyceride levels are provided in Table 4. Although the coefficients of the interaction terms were similar in whites, blacks, and the total sample, the interaction effect was significant in the total sample ($P = .016$) and marginal in whites ($P = .079$). Figure 1 showing the covariate-adjusted mean difference in TG levels between noncarriers and carriers of the LPL X447 allele by HL genotype illustrates this further. In the total sample, the decrease of TG levels in carriers versus noncarriers of the LPL X447 allele was 1.8-fold greater in carriers versus noncarriers of the HL T-514 allele (13.6 mg/dL *v* 7.4 mg/dL, $P = .016$). Whites tended to show a similar trend (2.8-fold decrease; 16.8 mg/dL *v* 6.1 mg/dL, $P = .079$). Blacks also showed a similar, but nonsignificant, trend (1.2-fold decrease; 10.4 mg/dL *v* 8.6 mg/dL, $P = .455$).

The likelihood of a male-female differential in the observed gene-gene interaction effect was examined by adding a 3-way interaction term in the hierarchical model. No significant 3-way interaction was found (data not shown).

DISCUSSION

Studies on combined or interaction effect of common, functionally relevant genetic variants on serum lipids are beginning to emerge.[37-40] The current study for the first time demonstrates the interaction effect of LPL S447X and HL C-514T polymorphisms on serum triglyceride levels in young adults. In addition, this study shows a significant black-white difference in the genotype distribution of these 2 polymorphisms, either separately or in conjunction. These observations are noteworthy in that the data are derived from an unselected community-based sample.

In this study, the carrier frequency for the LPL X447 allele among whites and blacks was similar to that observed in other populations,[18,19,41,42] with whites having a relatively higher frequency than blacks. On the other hand, the carrier frequency of the HL T-514 allele was higher in blacks than whites, consistent with earlier reports.[21,43,44] With respect to combined genotypes distribution, the observed frequency of carriers of both variants was similar in whites and blacks (7% *v* 8%).

Table 3. Serum Triglyceride Levels (mean ± SE) in Carriers Versus Noncarriers of LPL S447X and HL C-514T Variants in Whites, Blacks, and Total Sample: The Bogalusa Heart Study

	Serum Triglyceride (mg/dL)		
	Whites	Blacks	Total
LPL X447 allele			
Noncarriers	112.6 ± 1.9	89.2 ± 2.4	99.1 ± 1.7
Carriers	97.4 ± 4.0	75.1 ± 7.5	83.2 ± 3.7
	$P < .001$	$P = .002$	$P < .001$
HL T-514 allele			
Noncarriers	107.6 ± 2.2	88.7 ± 4.7	93.7 ± 2.3
Carriers	113.2 ± 2.6	87.8 ± 2.6	99.1 ± 2.0
	$P = .252$	$P = .511$	$P = .081$

NOTE. Mean values adjusted for age, age^2, BMI, BMI^2, and sex/race.

Table 4. Interaction Effect of LPL S447X and HL C-514T Variants on Serum Triglycerides: The Bogalusa Heart Study

Independent Variable	White		Black		Total	
	Regression Coefficient	*P* Value	Regression Coefficient	*P* Value	Regression Coefficient	*P* Value
Race	—	—	—	—	.305	.000
Sex	.024	.305	.137	.000	.070	.000
BMI	.041	.000	.017	.000	.033	.000
BMI^2	−.001	.038	−.000	.461	−.001	.000
Age	.011	.000	.021	.000	.014	.000
Age^2	−.001	.136	−.001	.045	−.001	.021
HL (T Allele)	.041	.099	.030	.464	.051	.014
LPL (X Allele)	−.074	.055	−.090	.398	−.074	.034
LPL*HL	−.105	.079	−.094	.455	−.122	.016

NOTE. Triglycerides Ln-transformed. LPL X447 allele: 1 = carrier, 0 = noncarrier; HL T514 allele: 1 = carrier, 0 = noncarrier; Race: 1 = white, 0 = black; Sex: 1 = male, 0 = female.

Abbreviation: BMI, body mass index.

However, more whites carried the LPL X447 allele only, and more blacks carried the HL T-514 allele only, reflecting the black-white difference on genotype distribution of each variant. No corresponding combined genotypes distribution data are available for comparison. More population-based studies are needed in this regard.

The current study has confirmed the triglyceride-lowering effect of the LPL X447 allele noted in pervious studies,[16-19] but the mechanism behind this association is not completely understood. An in vitro expression study has found enhanced secretion of catalytically normal LPL 447 isoform.[15] Consistent with this in vitro finding, higher levels of postheparin LPL in X447 carriers versus noncarriers has been reported in CHD patients.[13] In the current study, the HL T-514 allele tended to be associated with higher triglyceride levels in the total sample. This is consistent with earlier studies showing association of the HL T-514 allele with higher triglyceride levels and lower HL activity.[20-26]

Of interest, the triglyceride-lowering effect of the LPL X447 allele was enhanced further in the presence of the HL T-514 allele, among whites and in the total sample, despite the fact that the HL T-514 allele had a marginal positive effect on triglyceride levels. The mechanism(s) by which both variant alleles interact to enhance the triglyceride-lowering effect is not clear. This observational study cannot address this issue. It is likely that the polymorphism of the HL gene promoter or another linked polymorphism within the HL gene may potentiate the expression of the LPL variant and related triglyceride-lowering effect, as previously demonstrated in vitro for the Trp64Arg variant of β3-adrenergic receptor and the Pro12Ala variant of peroxisome proliferator-activated receptor -γ2 genes.[45]

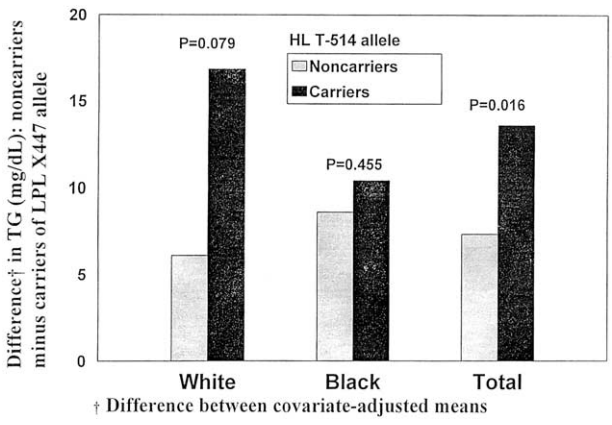

Fig 1. Differences in triglyceride levels between noncarriers and carriers of LPL X447 allele by HL C-514T genotype: The Bogalusa Heart Study. *P* values were adjusted for age, age^2, BMI, BMI^2, sex and/or race.

The basis for the observed lack of interaction effect of LPL S447X and HL C-514T variants on TG in blacks is not clear. Blacks compared with whites generally have lower TG, regardless of confounding factors, such as age, adiposity, and sex.[35,36,46,47] Studies, including our own, have shown that blacks versus whites have markedly higher LPL activity and lower HL activity.[12,21,48] Moreover, HL activity related positively to fasting and postprandial TG in whites, but inversely in blacks.[12] Because these metabolic parameters favor relatively lower TG trait intrinsically in blacks, the interaction effect of LPL and HL variants per se may not be apparent in this group. Furthermore, the sample size of blacks was relatively small and may not have adequate power to detect significant interaction effect, although the magnitude and direction of the parameter estimates (Table 3) were similar in both races.

In conclusion, the triglyceride-lowering effect of the LPL X447 variant was enhanced by the HL T-514 allele. Whether the magnitude of the observed decrease in TG has any pathobiologic significance in terms of CHD risk is not clear and can only be ascertained by prospective studies. Further, while the LPL X447 variant is generally considered protective against CHD,[16] the role of the HLC-514T variant in this regard has not been clearly established.[8] Nonetheless, these results underscore the importance of gene-gene interactions in the assessment of genetic effects on complex traits.

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