

Common Hepatic Lipase Gene Promoter Variant Determines Clinical Response to Intensive Lipid-Lowering Treatment

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Background—The common $-514 C \rightarrow T$ polymorphism in the promoter region of the hepatic lipase (HL) gene affects HL activity. The *C* allele is associated with higher HL activity, more dense and atherogenic LDL, and lower HDL₂ cholesterol. Intensive lipid-lowering therapy lowers HL activity, increases LDL and HDL buoyancy, and promotes coronary artery disease (CAD) regression. We tested the hypothesis that subjects with the *CC* genotype and a more atherogenic lipid profile experience the greatest CAD regression from these favorable effects.

Methods and Results—Forty-nine middle-aged men with dyslipidemia and established CAD who were undergoing intensive lipid-lowering therapy were studied. Change in coronary stenosis was assessed by quantitative angiography, HL polymorphism by polymerase chain reaction amplification, HL activity by ¹⁴C-labeled substrate, and LDL buoyancy by density-gradient ultracentrifugation. The response to lipid-lowering therapy was significantly different among subjects with different HL promoter genotypes. Subjects with the *CC* genotype had the greatest decrease in HL activity ($P < 0.005$ versus *TC* and *TT* by ANOVA) and the greatest improvement in LDL density ($P < 0.005$) and HDL₂-C ($P < 0.05$) with therapy. These subjects had the greatest angiographic improvement, with 96% of them experiencing CAD regression, compared with 60% of *TC* and none of the *TT* patients ($P < 0.001$).

Conclusions—In middle-aged men with established CAD and dyslipidemia, the HL gene $-514 C \rightarrow T$ polymorphism significantly predicts changes in coronary stenosis with lipid-lowering treatment that appear to involve an HL-associated effect on LDL metabolism. This study identifies a gene polymorphism that strongly influences the lipid and clinical response to lipid-lowering drugs. (*Circulation*. 2001;103:792-798.)

Key Words: coronary artery disease ■ liver ■ genes ■ lipoproteins ■ pharmacogenetics

Cardiovascular disease is the leading cause of death worldwide in both men and women. Recent coronary artery disease (CAD) prevention trials have unequivocally confirmed the importance of lowering plasma total and LDL cholesterol (LDL-C) for reducing cardiovascular morbidity and mortality.¹⁻⁴ These studies suggested that not all the reduction in coronary events could be attributed to lowering the LDL-C concentration.^{5,6} A substantial number of patients treated still experienced either no benefit or even CAD progression, resulting eventually in myocardial infarction and other cardiovascular events. Our understanding is limited as to why lipid and CAD response to lipid-lowering therapy varies among different subjects.

Both lipoprotein metabolism and atherogenesis are modulated by genetic and environmental factors that interact to determine individual responsiveness to lipid-lowering intervention. Hepatic lipase (HL), a key component of lipoprotein metabolism, represents one such factor. HL is a plasma lipolytic enzyme that plays a pivotal role in the metabolism of

both LDL^{7,8} and HDL.⁹ Increased HL is associated with small, dense LDL particles and lower levels of the antiatherogenic large HDL particles (HDL₂).⁷⁻⁹ Patients with small, dense LDL have a 3-fold increased risk of premature CAD.^{10,11} Recently, 4 common sequence polymorphisms in the HL gene promoter were shown to be associated with variation in the HL activity.¹²⁻¹⁶ These 4 polymorphisms were observed to be in complete linkage disequilibrium in white men,¹⁷ defining a single haplotype. The presence of a $C \rightarrow T$ substitution at position -514 with respect to the transcription start site of the HL gene accounts for 20% to 30% of the variance in HL activity in men and women.¹³⁻¹⁸ The presence of the *C* allele has been significantly associated with higher HL activity; smaller, denser, and more atherogenic LDL particles; and inversely with lower levels of antiatherogenic HDL₂ lipoproteins.¹⁶ Lipid-lowering treatment results in a significantly greater CAD improvement in patients with a lipid profile similar to that found in patients with the *CC* genotype (ie, more small, dense LDL and lower

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HDL-C).¹⁹ In addition to lowering LDL-C levels, pharmacologically induced changes in HL activity increase LDL particle buoyancy, leading to CAD regression.²⁰ Therefore, we hypothesize that CAD patients will respond differently to therapeutic intervention, depending on the HL gene promoter polymorphism.

The primary goals of this study were to test (1) whether in men with established CAD, intensive lipid-lowering therapy can normalize the adverse lipid profile in subjects with the *CC* genotype at position -514 of the HL gene promoter and (2) whether these changes lead to greater improvement in angiographically documented CAD, thus defining a common genetically determined responsiveness to drug-associated CAD regression. Data addressing these questions will have remarkable potential clinical relevance, given the high frequency of the HL gene polymorphism among white (20% to 25%)¹²⁻¹⁶ and particularly among black (\approx 45%)¹⁶⁻¹⁸ and Japanese (\approx 47%)¹⁶ populations.

Methods

Patients

The study included 49 dyslipidemic men with elevated apoB levels (\geq 125 mg/dL). The subjects had completed a clinical intervention trial,²¹ were \leq 62 years old at entry, had CAD diagnosed by coronary angiography, and had DNA available to evaluate HL gene polymorphism. Patients were studied at baseline and after 2.5 years of intensive lipid-lowering therapy with either lovastatin (40 mg/d) and colestipol (30 g/d) (LC) or niacin (4 g/d) and colestipol (NC). Twenty-one patients who in the original clinical trial²¹ were randomized to receive placebo (AHA step 2 diet) were not included.

Blood Collection

Blood specimens were collected in 0.1% EDTA after a 12- to 14-hour fast for plasma lipid measurements and density-gradient ultracentrifugation. Blood was collected in iced lithium-heparin tubes for measurement of HL and lipoprotein lipase activity. Blood samples were immediately processed and stored at -70°C for HL, lipoprotein lipase, and LDL buoyancy evaluation.

Lipid and Lipoprotein Determinations

Plasma, LDL, HDL, and HDL₂ cholesterol, triglycerides, and apolipoproteins apoB, AI, and AII were measured at the Northwest Lipid Research Laboratories as previously described.²¹ Density-gradient ultracentrifugation for apoB-containing lipoproteins separates lipoprotein particles by the rate of flotation (Rf) of lipoproteins in a salt density gradient and is designed to optimize the resolution of apoB-containing lipoproteins into 38 fractions as previously described.^{20,22} LDL Rf, a measure of LDL buoyancy, is calculated as the fraction number of the major peak of LDL divided by the total number of fractions collected.

Postheparin Plasma Lipase Activity

Total lipolytic activity was measured in plasma as previously described²³ by use of glycerol tri[1-¹⁴C]oleate emulsified with lecithin. HL activity, in nanomoles of fatty acids released per minute per milliliter of plasma, is defined as the activity remaining in the postheparin sample after incubation with a specific monoclonal antibody (5D2) that selectively inhibits lipoprotein lipase.

DNA Analysis

Screening for the *LIPC* -514 C \rightarrow T polymorphism was carried out by polymerase chain reaction amplification using the primer pair as previously described.²⁴

Coronary Angiography

Quantitative coronary angiography was performed, and angiograms were analyzed as previously described.²¹ In each subject, an estimate of percentage proximal disease severity was obtained by averaging the severity of the worst lesion found in each of the 9 standard proximal coronary segments. Disease changes were calculated as the difference between percentage proximal disease severity at baseline and after treatment.

Statistical Analyses

Data on and off treatment within the same group were analyzed by paired Student's *t* test or the Wilcoxon signed rank test if not normally distributed. Analyses among groups with different HL gene polymorphism were performed by ANOVA and the pairwise multiple comparison procedures (Tukey test). Whenever the data were not normally distributed, the Kruskal-Wallis 1-way ANOVA on ranks was used, as well as the pairwise multiple comparison procedures (Dunn's method). Relationships between quantitative variables were tested by multiple linear regression analysis. The assumption of Hardy-Weinberg equilibrium was tested in the study groups by means of gene counting and χ^2 analysis. The significance level was set at $P < 0.05$.

Results

Of the 49 patients studied, 25 had the *CC*, 20 the *CT*, and 4 the *TT* genotype at position -514 of the HL gene promoter. The observed genotypic frequency in this CAD population was consistent with Hardy-Weinberg equilibrium ($\chi^2 = 0.018$, $P = 0.99$). Twenty-five subjects were randomly assigned to receive LC and 24 NC. The numbers of patients treated with LC compared with NC in each HL genotype group were similar (13/12, 10/10, and 2/2 in the *CC*, *TC*, and *TT* groups, respectively). No significant differences were observed between the 2 treatment groups when the effect of different HL genotypes on changes in coronary stenosis, HL activity, LDL concentration and LDL buoyancy (Rf), apoB and A-I levels, total HDL and HDL₂ cholesterol, body weight, and systolic and diastolic blood pressure was evaluated. In addition, in a multivariate analysis, drug treatment, considered as an independent variable, did not significantly affect the association between HL gene polymorphism and changes in coronary stenosis. Data from the LC and NC groups were therefore pooled and analyzed together.

HL Gene Promoter Polymorphism, Lipids, Lipolytic Activity, and CAD at Baseline

Body weight and systolic and diastolic blood pressure were not different at baseline and did not change with treatment in all groups (data not shown). All patients in this population selected for high apoB and CAD had the atherogenic lipoprotein abnormalities to be expected in such patients. The nature of the abnormalities appeared to differ, however, depending on the HL promoter genotype. At baseline, those with the *CC* genotype had greater HL activity compared with the *TT* (283 versus 169 nmol \cdot min⁻¹ \cdot mL⁻¹, $P < 0.05$, Table 1), lower HDL₂-C (0.05 versus 0.21 mmol/L, $P < 0.005$) despite virtually identical HDL₃-C levels across genotypes, and lower LDL buoyancy (0.245 versus 0.283, $P < 0.01$) (Table 2). By contrast, those with the *TT* promoter variant had higher LDL-C (5.67 versus 4.64 mmol/L, $P = 0.05$) and borderline higher apoB levels (178 versus 152 mg/dL, $P = 0.08$). These high levels and the differences in LDL-C and apoB levels

TABLE 1. Plasma HL and LPL Activity

	HL Gene Promoter Polymorphism								
	CC (n=25)			TC (n=20)			TT (n=4)		
	Baseline	Treatment	Δ, %	Baseline	Treatment	Δ, %	Baseline	Treatment	Δ, %
HL, nmol · min ⁻¹ · mL ⁻¹	283±60	231±52	-18*	196±62†	178±71‡	-9 (P=0.07)	169±71†	160±77‡	-5
LPL, nmol · min ⁻¹ · mL ⁻¹	187±86	189±70	1	192±67	196±79	2	147±77	180±98	22

Values are expressed as mean±SD. LPL indicates lipoprotein lipase.

*P<0.01 vs baseline.

†P<0.05 vs baseline CC.

‡P<0.005 vs on treatment CC.

between groups with different genotypes are not traits attributable to the genetic variation in HL activity.^{7,12,14-16}

Baseline parameters were not significantly associated with changes in CAD with therapy. Only LDL buoyancy showed a trend toward an association with changes in CAD ($r=0.27$, $P=0.06$), as we previously observed.²⁰

Association Between the HL Gene Polymorphism and Changes in HL Activity, LDL Buoyancy, and HDL₂ Cholesterol With Lipid-Lowering Therapy

Lipid-lowering therapy significantly reduced plasma cholesterol, triglyceride, LDL-C, and apoB concentration to a similar extent in all 3 subgroups of patients (Table 2). The HL gene promoter polymorphism was not associated with changes in cholesterol, triglycerides, LDL-C, and apoB levels with treatment. HDL-C increased significantly with therapy in the CC and TC groups (by 35% and 22%, respectively, $P<0.01$). A 14% increase in HDL-C was seen in the TT group. With lipid-lowering therapy, HL activity decreased significantly in the CC patients (-18%, $P<0.01$, Table 1), who also had a significant increase in LDL buoyancy (by

12%, $P<0.01$, Table 2). HL activity and LDL buoyancy did not change significantly in the TT patients.

The HL promoter polymorphism was significantly associated with the degree of changes in HL activity ($P<0.005$; ANOVA) and LDL buoyancy ($P<0.005$; ANOVA) with intensive lipid-lowering therapy (Figure 1). Patients with the CC genotype, who at baseline had higher HL activity and smaller, denser LDL particles, had a greater decrease in HL activity (Figure 1A) as well as a greater increase in LDL buoyancy (Figure 1B). The TT patients, who at baseline had lower HL and more buoyant, larger LDL particles, had no change in HL and LDL buoyancy with therapy. Intermediate changes were observed in the TC group. In addition, pairwise comparisons of these data indicated that both the TC and TT groups are significantly different from the CC subjects for changes in HL activity ($P<0.01$ for both comparisons) and changes in LDL buoyancy ($P<0.05$ for both comparisons). Finally, changes in HL activity were not significantly associated with changes in LDL-C or apoB with therapy.

With intensive lipid-lowering therapy, absolute changes in HDL₂-C were not significantly different among groups with

TABLE 2. Clinical and Lipid Parameters

	Hepatic Lipase Gene Promoter Polymorphism								
	CC (n=25)			TC (n=20)			TT (n=4)		
	Baseline	Treatment	Δ, %	Baseline	Treatment	Δ, %	Baseline	Treatment	Δ, %
Cholesterol, mmol/L	6.63±1.0	4.81±1.1	-27†	6.81±1.3	4.92±1.1	-28†	7.60±1.4	5.31±0.4	-30*
Triglyceride	2.43±1.3	1.97±1.0	-19†	2.15±1.5	1.76±0.8	-18*	1.93±1.3	1.43±0.4	-27*
LDL-C	4.64±0.8	2.87±1.0	-38†	4.84±1.4	3.03±1.0	-37†	5.67±1.4	3.42±0.6	-40*
HDL-C	0.88±0.1	1.19±0.3	35†	0.96±0.1	1.16±0.2	22†	1.09±0.2	1.24±0.3	14
HDL ₂ -C	0.05±0.02	0.22±0.15	335†	0.10±0.08	0.23±0.09	128†	0.21±0.11‡	0.31±0.24	49
HDL ₃ -C	0.85±0.1	0.94±0.1	11†	0.85±0.10	0.93±0.08	9	0.89±0.15	0.92±0.09	3
ApoB, mg/dL	152±23	104±25	-31†	157±33	108±26	-31†	178±39	115±23	-35*
ApoA-I, mg/dL	126±12	141±19	12†	129±15	143±20	11*	133±12	138±24	5
ApoA-II, mg/dL	29±6	28±3	-3	27±4	27±6	0	32±3	27±4	-15
LDL Rf	0.245±0.024	0.274±0.032	12†	0.254±0.047	0.268±0.039	6 (P=0.08)	0.283‡±0.043	0.287±0.044	1.4
Coronary stenosis, %S _{prox}	35.6±12.1	33.5±12.2	-2.1†	39.4±12.2	38.3±13.1	-1.1	31.1±3.3	35.1±6.1	4.0 (P=0.08)

Values are expressed as mean±SD. %S_{prox} indicates mean percent diameter reduction of worst lesions in each of the 9 standard proximal coronary segments.

*P<0.05 and †P<0.01 vs baseline, same genotype.

‡P<0.01 vs baseline CC.

TABLE 3. Multiple Regression Models for Changes in Coronary Stenosis

Δ Stenosis	Model 1		Model 2		Model 3		Model 4	
	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>
HL Poly	+0.423	0.001	+0.434	0.002	+0.202	0.167	+0.184	0.217
Δ ApoB			+0.521	0.024	+0.496	0.030	+0.498	0.023
Δ HL					+0.477	0.007	+0.182	0.338
Δ Rf							-0.790	<0.001
<i>R</i>	0.51		0.65		0.71		0.85	

HL Poly indicates HL gene promoter polymorphism. β -values are expressed as standardized coefficients. HL polymorphism was coded as CC=0, CT=1, and TT=2. All models include as independent variables drug treatment, changes in plasma cholesterol, triglycerides, HDL-C, HDL₂-C, and apoA-I, all not significantly associated with Δ Stenosis.

different genotypes. When changes in HDL₂-C were expressed as percent of baseline concentration, however, the carriers of the *C* allele had a significantly greater increase in HDL₂-C than subjects in the *TT* group (335%, 128%, and 49% in *CC*, *TC*, and *TT*, respectively, Table 3 and Figure 1C, $P < 0.05$ by ANOVA).

ApoA-I levels increased significantly in *CC* and *TC* subjects. Changes in apoA-I among groups with different genotypes failed to reach statistical significance ($P = 0.79$ by ANOVA).

HL Gene Promoter Polymorphism, Coronary Atherosclerosis, and Response to Treatment

Lipid-lowering therapy resulted in a significant improvement of coronary stenosis in *CC* patients ($\Delta\%S_{\text{prox}} -2.1$, $P < 0.01$) and to a lesser extent in the *TC* group (Table 2), whereas progression of stenosis was observed in the *TT* group ($\Delta\%S_{\text{prox}} 4.0$, $P = 0.08$).

The HL gene promoter polymorphism was associated with significantly different degrees of coronary stenosis regression with lipid-lowering therapy ($P = 0.01$ by ANOVA). In the *CC* group, 96% of patients (24 of 25) experienced no worsening or improvement in mean coronary stenosis severity, compared with 60% (12 of 20) in the *TC* and 0% (0 of 4) in the *TT* group ($\chi^2 = 16.43$; $P < 0.001$, Figure 2). Changes in coronary stenosis continued to be statistically different in the *CC* versus *CT* patients ($P = 0.01$) after exclusion of the *TT* subjects. In addition, after adjustment for baseline HL activity levels, the HL gene promoter polymorphism continued to be significantly associated with changes in coronary stenosis ($r = 0.45$, $P < 0.01$).

The analysis for linear trends in the proportion of subjects who experience progression or regression in coronary stenosis demonstrated a highly statistically significant difference in progression/regression based on genotype ($\chi^2 = 15.215$, $P < 0.0001$).

The association between HL gene polymorphism and CAD benefit remained significant ($P < 0.005$) after adjustment for drug-induced changes in cholesterol, triglycerides, HDL-C, HDL₂-C, apoA-I, and apoB levels, with the latter being the only significant predictor of CAD outcome in addition to HL genotype (Table 3, model 2). Finally, when changes in HL activity (Table 3, model 3) and changes in LDL buoyancy (Table 3, model 4) were included in the model, the associa-

tion between HL genotype and degree of CAD regression with treatment was no longer significant. This suggests that the association between HL gene polymorphism and CAD improvement with therapy is mediated by the effect of this polymorphism on HL activity and subsequently on LDL buoyancy.

HL gene promoter polymorphism continued to significantly predict changes in coronary stenosis, HL activity, LDL buoyancy, and HDL₂-C after the *TT* patient who presented the greatest CAD progression had been removed from the statistical analyses (Figure 2, $\Delta\%S_{\text{prox}}$, +14.6).

Discussion

In men with established CAD and dyslipidemia, the HL gene -514 *C*→*T* polymorphism significantly predicts coronary stenosis regression during intensive lipid-lowering treatment. This association appears to be mediated by the modulating effect of this polymorphism on specific drug-induced changes in lipoprotein metabolism. Homozygous *CC* patients exhibited a greater decrease in HL activity and a greater increase in LDL buoyancy with lipid-lowering therapy than both homozygous and heterozygous carriers of the *T* allele. Thus, the HL gene promoter polymorphism is responsible for a differential lipoprotein and angiographic response to lipid-lowering drugs.

Data from the 21 patients in the placebo group of the original clinical trial strongly support the presence of a specific, modulating effect of the HL gene polymorphism on CAD response to therapy. Regardless of their HL promoter genotype, these patients showed a similar degree of disease progression ($\Delta\%S_{\text{prox}}$: *CC* [n=12], +2.45; *CT* [n=7], +2.36; *TT* [n=2], +2.42) and no significant changes in HL activity, LDL density, and lipoprotein variables (data not shown).

Patients in the present study were middle-aged men selected for having dyslipidemia and CAD as diagnosed by angiography.²¹ When initially evaluated, the severity of coronary artery stenosis was not significantly different among groups with different HL promoter genotypes, in agreement with similar previous observations.^{15,18} Their lipoprotein profiles showed interesting differences, however, suggesting that the presence of CAD in these patients may have been accounted for by the presence of different lipid risk factors. Specifically, higher HL activity, small, dense LDL particles, and lower HDL₂-C levels characterized the atherogenic po-

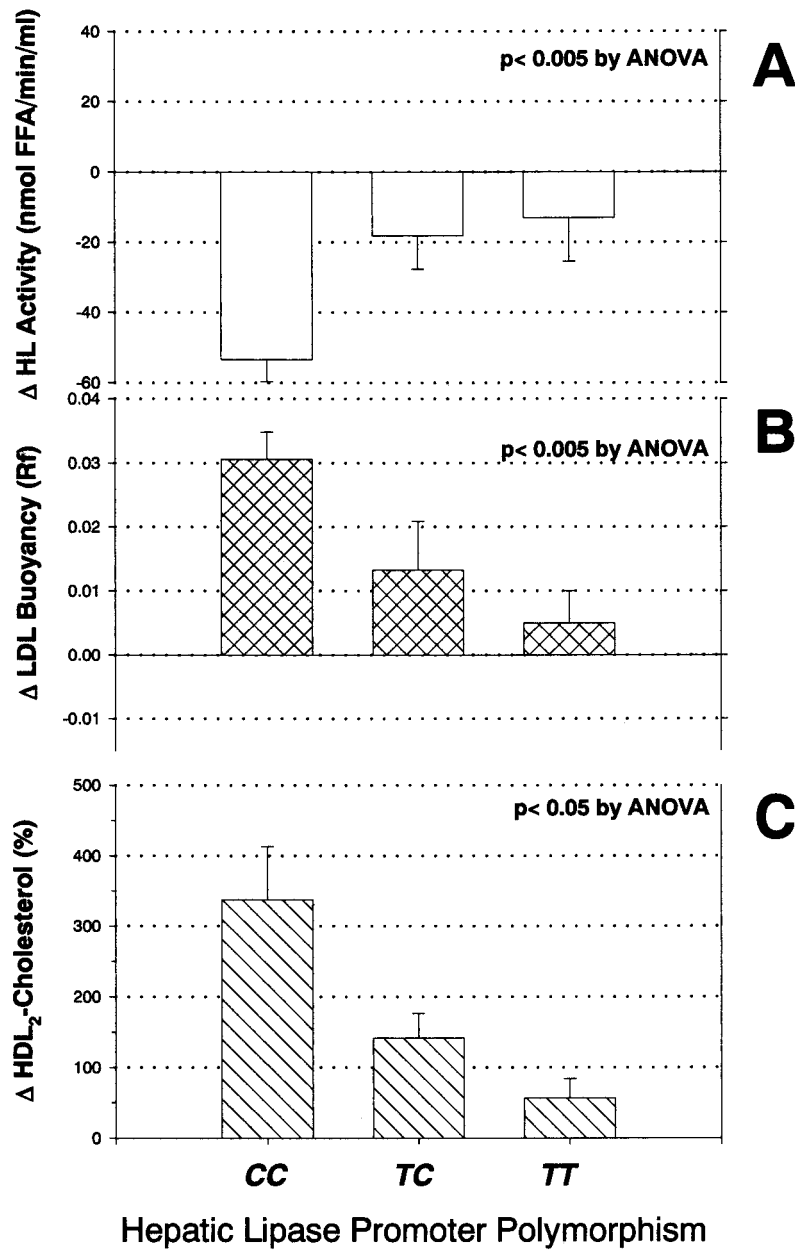


Figure 1. Change in HL activity (A), LDL buoyancy (B), and percent HDL₂-cholesterol (C) during intensive lipid-lowering therapy in patients with different HL gene promoter genotypes (CC, TC, and TT). Values are expressed as mean \pm SD (error bars). See Methods for details.

tential of the lipid profile in CC patients. Previous observations showed that high HL activity is indeed associated with smaller and denser LDL particles,^{7,8} as well as lower HDL₂-C,⁹ and large epidemiological studies have demonstrated that both low HDL-C (and HDL₂-C)²⁵ and the presence of small, dense LDL^{10,11} are risk factors for CAD. Conversely, patients with the TT genotype had significantly higher LDL-C and apoB levels and developed CAD despite the presence of more buoyant, less atherogenic LDL and higher HDL₂-C levels. Indeed, both LDL-C and apoB levels are strong independent risk factors for CAD²⁻⁶ and are not associated with HL activity levels.⁷

Our group recently reported that cholesterol-lowering therapy with an HMG-CoA reductase inhibitor or nicotinic acid in association with a resin not only affects lipoprotein levels (particularly LDL-C) but also significantly decreases plasma HL activity and increases LDL buoyancy.²⁰ HL-mediated

changes in LDL buoyancy strongly predicted CAD regression with therapy. Two concurrent and independent lipoprotein pathways accounting for drug-associated CAD regression were identified (Figure 3): the well-known one leading to changes in LDL-C and apoB levels and the new pathway of HL-mediated improvements in LDL buoyancy.²⁰ The present study was designed to investigate the genetic contribution to the HL-mediated pathway associated with CAD response to therapy. No significant association was seen between changes in LDL-C and apoB and changes in HL activity in this study. This observation, as well as previous data²⁰ showing that a decrease in both plasma LDL-C and apoB levels with colestipol was associated with increased HL activity (opposite of what was seen in the present study), suggests that these 2 pathways may be at least partly independent of each other. Conversely, the present experimental design does not allow testing of the possibility that lipoprotein changes associated

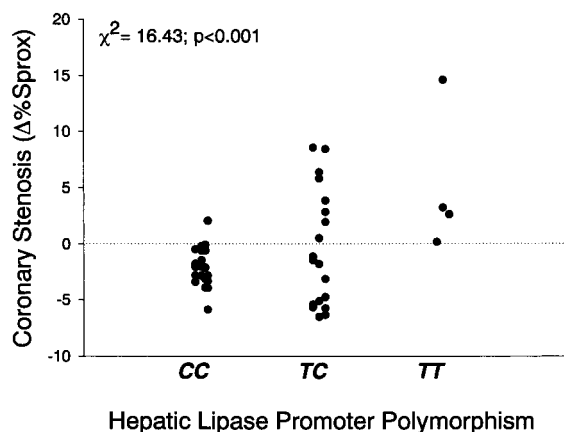


Figure 2. Change in coronary disease severity with intensive lipid-lowering therapy in patients with different HL gene promoter genotypes (CC, TC, and TT).

with drug-induced decrease in HL activity may also be beneficial if they were not associated with reduction in plasma concentration of atherogenic lipoprotein particles, and specific studies are needed to address this question.

Previous observations demonstrated that HL activity, LDL buoyancy, and HDL₂-C but not LDL-C or apoB levels are significantly associated with the -514 polymorphism of the HL gene promoter,^{13–16,18} making it an interesting candidate to study the contribution of genetic factors to individual susceptibility for CAD regression. Our data indeed demonstrated that this polymorphism had no significant impact on the lipoprotein pathway leading to changes in LDL-C and apoB levels (Figure 3). HL genotype strongly influenced the LDL buoyancy-mediated pathway, however, promoting CAD regression (Figure 3). Patients with the CC genotype, in addition to improving LDL-C and apoB concentrations, normalized their HDL₂-C levels and LDL buoyancy, which characterized the atherogenic potential of their lipid profile at baseline (ie, small, dense, atherogenic LDL and low HDL₂-C). The greater magnitude of the increase in LDL buoyancy and HDL₂-C (as percentage of baseline value) was accounted for by a greater decrease, with treatment, in HL activity among CC patients compared with both TC and TT subjects. A shift toward larger and more buoyant LDL particles

reduces their atherogenic potential because of diminished susceptibility to oxidative modification²⁶ in the subendothelial space, which triggers the sequence of inflammatory responses believed to be crucial for lipid accumulation and plaque destabilization in the atherosclerotic process.²⁷ In addition, normalization of HDL₂-C levels is consistent with a more efficient reverse cholesterol transport, a key pathway to reduce CAD risk and progression.²⁸

This study was not designed to provide clinical cardiovascular event end points; therefore, we do not have a direct measurement of the effect of HL gene promoter polymorphism on clinical CAD outcomes. The implications of our results, however, are most likely to be clinically relevant because a direct association between anatomic changes in coronary stenosis and future clinical events has been demonstrated by angiographic trials.²⁹

In summary, the present study provides compelling evidence that in white, middle-aged men with established CAD, the HL gene -514 C→T polymorphism significantly predicts changes in coronary stenosis with lipid-lowering therapy. In addition, this study provides the pathophysiological mechanism to account for the effect of this genetic polymorphism on CAD response to treatment, highlighting how current routine lipid measurements may not enable physicians to distinguish between responders and nonresponders. Screening for these variants in the HL gene promoter region identifies CAD patients who will benefit most from lipid-lowering strategies, as well as subjects who appear to be resistant to HL-mediated CAD regression. In these resistant patients, a more aggressive LDL-C-targeted and overall risk-reducing approach might be warranted. The relevance of these findings is emphasized by the high frequency of this polymorphism, ranging from 20% to 47%, depending on the population studied. Therefore, screening for this genetic variant could become an important parameter influencing the choice of treatment strategies for cardiovascular risk reduction and their cost-effectiveness.

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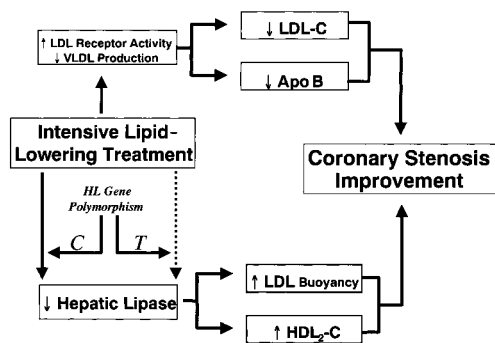


Figure 3. Differential effect of intensive lipid-lowering therapy on change in HL activity, LDL buoyancy, and HDL₂-cholesterol levels in carriers of the CC and TT genotypes at the HL promoter -514 locus.

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