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Association between hepatic lipase –514 C/T promoter polymorphism and myocardial infarction is modified by history of hypercholesterolemia and waist circumference[☆]

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KEYWORDS

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Effect modification

Abstract *Background and aims:* To examine whether the association between the –514 C/T polymorphism of the hepatic lipase gene and myocardial infarction (MI) is modified by history of hypercholesterolemia and increased waist circumference.

Methods and results: A total of 1940 pairs of nonfatal MI cases and population-based controls were genotyped. Multiple conditional logistic regression was used for data analyses. The –514T variant was not associated with MI in the whole population. However, among people with history of hypercholesterolemia the T allele increased MI risk for heterozygous and homozygous carriers, respectively [OR = 1.25 (95%CI = 0.92–1.70) and OR = 1.59 (95%CI = 1.09–2.32)]. In contrast, the T allele decreased MI risk among people with no history of hypercholesterolemia [OR = 0.85 (95%CI = 0.70–1.03) and OR = 0.76 (95%CI = 0.60–0.97)], *p* for interaction = 0.004. Among subjects with normal waist circumference there was no association between the –514T allele and MI for heterozygous and homozygous carriers, respectively [OR = 1.04 (95%CI = 0.86–1.25) and OR = 0.96 (95%CI = 0.77–1.21)], while among subjects with waist circumference above the limits of the metabolic syndrome definition there was a protective association [OR = 0.63 (95%CI = 0.45–0.90) and OR = 0.81 (95%CI = 0.53–1.25)] *p* for interaction = 0.04].

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Conclusion: The -514 T allele is associated with MI in opposite directions depending on the background of the studied population. This could explain what seem like inconsistent results across studies.

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Introduction

Hepatic Lipase (HL) is a major determinant of HDL cholesterol, an established independent predictor of coronary heart disease (CHD) [1]. However, the role of HL in atherosclerosis remains uncertain. Overexpression of HL in transgenic and knockout animal models has resulted in both antiatherogenic and pro-atherogenic effects [2]. Although low HL activity in humans has been identified as a risk factor for CHD [3] the net effect of HL on CHD is hard to establish given its role in lipoprotein metabolism as both a lipolytic enzyme and as a ligand that facilitates uptake of lipoproteins [4].

Four linked polymorphisms (-250 G to A, -514 C to T, -710 T to C, -763 A to G) have been identified in the promoter region of the HL gene [5]. These four polymorphisms are in complete linkage disequilibrium and together define a common HL allele designed as -514 T allele. The T allele at position -514 of the HL gene is consistently associated with lower HL activity, higher HDL cholesterol, particularly HDL₂ cholesterol, higher remnant-like particles, and triglyceride content and size of HDL and LDL particles [6]. Nevertheless, evidence of the effect of the -514 T allele on CHD is inconsistent. Some studies have shown no association [7–14], while others have shown an increased risk of CHD for carriers of the -514 T allele [15–19]. Surprisingly, the -514 T allele has not been inversely associated with CHD.

Conflicting results are suggestive of diverse effects under different metabolic situations. It has been proposed that high HL activity is antiatherogenic in familial hypercholesterolemia and pro-atherogenic in hypertriglyceridemia [6]. We evaluated the association of the -514 C/T polymorphism with myocardial infarction (MI), under the hypothesis that the association of the -514 T with risk of MI would differ by history of hypercholesterolemia and waist circumference, using waist as a surrogate measure of increased triglyceride levels.

Methods

Study population

The study design and population have been described previously [20,21]. Briefly, eligible case subjects were men and women who were diagnosed as survivors of a first acute MI by two independent cardiologists at any of the six recruiting hospitals in the Central Valley of Costa Rica for the period 1994–2004. All cases met the World Health Organization criteria for MI, which require typical symptoms plus either elevations in cardiac enzyme levels or diagnostic changes in the electrocardiogram [22]. Enrollment was carried out while cases were in the hospital's

step-down-unit. One free-living control subject for each case, matched for age (± 5 years), sex, and area of residence (county), was randomly selected using the information available at the National Census and Statistics Bureau of Costa Rica. Participation was 98% for cases and 88% for controls. The Costa Rican Central Valley population fulfills two major prerequisites necessary for the effective search of susceptibility genes for human diseases. It derives from a relatively small number of founders, and the expansion of the population has occurred by reproduction rather than by immigration.

All subjects gave informed consent on documents approved by the Human Subjects Committee of the Harvard School of Public Health and the University of Costa Rica.

Data collection

Trained personnel visited all study participants at their homes for data collection, biological specimen collection, and anthropometric measurements. Socio-demographic characteristics including income, medical history including self-reported history of hypercholesterolemia, and lifestyle habits, were collected using a general questionnaire. Smoking was assessed using questions about history and frequency of cigarette smoking. Alcohol was assessed using questions on history of alcohol consumption from the general questionnaire and intake of alcohol during the last year using information from a food frequency questionnaire. Physical activity was assessed by asking subjects the average frequency and time spent on several occupational and leisure time activities during the last year. These activities were grouped into six categories according to their intensity, or METS (metabolic equivalents). Self-reported history of high cholesterol was used to define hypercholesterolemia. Two questions were used: (1) before your myocardial infarction, did the doctor ever tell you that you have high cholesterol? (2) How long ago was the first time they told you that you had high cholesterol? Self-reported history of hypercholesterolemia is associated with increased risk of MI in this population (OR = 1.25, 95%CI: 1.08, 1.44). Furthermore, LDL cholesterol concentrations among controls after excluding people on lipid lowering drugs were 141 ± 36 vs. 124 ± 35 mg/dl when comparing people with and without history of hypercholesterolemia. These results suggest that regardless of potential misclassification, this variable is a good proxy of hypercholesterolemia. Unfortunately, plasma cholesterol levels could not be used to identify individuals with high cholesterol because measurements were conducted after the MI and therefore they are affected by use of medications. The average total cholesterol level in cases is lower (186 ± 42 mg/dl) than in the controls (208 ± 41 mg/dl). All anthropometric parameters were taken by trained fieldworkers who were acquainted with standardized methods, with subjects wearing light clothing but not shoes. All

measurements were performed in duplicate and were averaged for analyses. Waist circumference was measured at the umbilical level [23]. Because self-reported history of hypertriglyceridemia was not included in the study, we used waist circumference as a surrogate measure of history of high plasma triglyceride levels. Plasma triglyceride levels could not be used for reasons described above. The correlation between waist circumference and plasma triglycerides was 0.31, $p < 0.0001$. We used the NCEP-ATPIII cutoffs for metabolic syndrome definition for waist circumference, greater than 102 cm for men and greater than 88 cm for women. In women the average triglyceride level among those with waist circumference above 88 cm was 222 mg/dL compared to 188 mg/dL in those with a waist circumference equal to or less than 88 cm. In men the average triglyceride level was 258 mg/dL compared to 220 mg/dL in those with a waist circumference of greater than 102 cm vs. those with a waist circumference equal to or less than 102 cm. Thus, the use of waist circumference could be used as an indicator of higher triglyceride levels in this population. Dietary intake, including alcohol, was collected using a food frequency questionnaire that has been developed and validated specifically for the Costa Rican population [24,25]. Plasma triglycerides, total cholesterol and HDL cholesterol levels were assayed with enzymatic reagents (Boehringer-Mannheim). Cholesterol measurements were standardized according to the program specified by the Centers for Disease Control and Prevention, Atlanta, GA and the National Heart, Lung and Blood Institute.

Genotyping

Genotyping was carried out using the GenomeLab™ SNPstream Genotyping System developed by Beckman Coulter (<http://www.beckmancoulter.com/genomelab>). This system uses multiplexed PCR in conjunction with tagged array multiplexed single-base primer extension technology. Genotyping is carried out in three steps:

- Step 1 12-Plex PCR is performed in 384-well plates at a volume of 5 μ L per reaction. PCR primers are pooled and added to the PCR mix. After PCR thermal cycling, cleanup reagents are added to remove the residual amount of PCR primers and dNTP.
- Step 2 Single-base extension reactions are carried out using dye-labeled dideoxynucleotides (ddNTPs). The extension mix cocktail is prepared using the SNPware Core Reagent Kit and each SNP primer has a unique tagged sequence.
- Step 3 Separation of the extension products by hybridization to a tag array plate. The different SNPs are visualized using the GenomeLab SNPstream™ Genotyping System (Beckman Coulter).

Statistical analysis

All data were analyzed with the Statistical Analysis Systems software (SAS Institute Inc., Cary, NC). The significance of differences in health characteristics and potential confounders were assessed by McNemar's test and paired *t*-

tests, if normally distributed, or Wilcoxon signed-rank test, if not normally distributed. From the total of 4547 subjects of the original study, 4107 had DNA samples. After deleting missing genotypes, other missing values in the variables of interest and potential confounders, and deleting unmatched subjects, a complete matched dataset of 3880 subjects was used in the final analysis to evaluate the association between -514 T LIPC (hepatic lipase gene) genotype and risk of MI. Missing values for plasma lipids were 369 for LDL cholesterol, 78 for HDL cholesterol and, 14 for triglycerides. Odds ratios (OR) and 95% confidence intervals (CI) were estimated from multiple conditional logistic regression models. We present two conditional logistic regression models; the first one adjusted for matching factors (age, sex, and county of residence) and the second adjusted for other potential confounders. Although statistical criteria were used to guide the inclusion of potential confounders (i.e. association with the exposure and with the outcome conditional on the exposure), the final decision to include them in the model was based on the causal network linking the variables under study. Potential confounders entered in the final models include: saturated fat as a percentage of total energy intake (quintiles), total energy intake (quintiles), smoking (never, past, <10 cigarettes/day, 10–20 cigarettes/day, >20 cigarettes/day), physical activity (quintiles of METS), income (quintiles), alcohol intake (never, past, and tertiles of alcohol intake for current drinkers), and height (continuous). Likelihood ratio was used to test for interactions.

Results

General characteristics of the study population by case-control status are shown in Table 1. Genotype frequencies were in Hardy-Weinberg equilibrium in cases and controls.

The -514 T polymorphism increased significantly HDL concentrations, a finding that is consistent with a decrease in HL activity observed previously for this variant. Plasma lipid concentrations by genotype among controls are shown in Table 2.

The -514 T polymorphism was not associated with MI in univariate or multivariate analysis. Using the homozygous wild type in the promoter polymorphism as the reference, the ORs were: 0.99 (95%CI: 0.86, 1.15) for the heterozygous, and 0.92 (95%CI: 0.76, 1.10) for the homozygous for the variant. Multivariate adjustment was performed because even if potential confounders are expected to be equally distributed by genotype, it is possible that imbalances may occur by chance. However, after adjusting for smoking status, physical activity, and income, or other potential confounders (such as history of diabetes, history of hypertension, angina, BMI, etc.), the results did not change.

Table 3 shows that the risk of MI associated with the -514 T allele of the HL gene is modified by history of hypercholesterolemia. The OR and 95%CI for the heterozygous and homozygous carriers of the variant genotypes were 0.85 (0.70, 1.03) and 0.76 (0.60, 0.97) for people with no history of hypercholesterolemia, while they were 1.25 (0.92, 1.70) and 1.59 (1.09, 2.32) for people with history of hypercholesterolemia, p for interaction = 0.004. We also stratified by lipid lowering medication use as another proxy

Table 1 General characteristics of the study population by case control status.^a

	Controls (N=1940)		Cases (N=1940)		
	Mean	SD	Mean	SD	
Age (y)	58	11	58	11	
Sex (% women)	26		26		
Rural area (%)	26.4		26.4		
Waist circumference (cm)	90.7	10	90.8	9.2	
Height (cm)	163.6	9.2	162.8	9.2	a
Physical activity (MET)	1.56	0.7	1.52	0.7	a
Household income ^b (US\$)	571	425	500	394	a
History of diabetes (%)	13.9		24.4		a
History of hypertension ^b (%)	29.3		39.0		a
History of angina ^b (%)	4.3		13.1		a
History of hypercholesterolemia (%)	26.3		30.6		a
Lipid lowering medication use (%)	5.5		5.6		
Current smokers (%)	21		39.9		a
Total Calories (Kcal/d)	2448	746	2706	941	a
Saturated fat (% energy)	10.39	2.67	11.05	2.9	a
Monounsaturated fat (% energy)	11.86	3.9	11.88	3.49	
Polyunsaturated fat (% energy)	6.24	2.04	6.02	2.03	a
Trans fat (% energy)	1.15	0.61	1.19	0.57	a
Alcohol drinkers (%)	41.2		37.8		a
Triglycerides ^{b,c} (mg/dL)	219	130	230	120	a
Total cholesterol ^{b,c} (mg/dL)	208	42	186	41	a
HDL cholesterol ^{b,c} (mg/dL)	41	9	36	8	a
LDL cholesterol ^{b,c} (mg/dL)	128	36	108	36	a
Fasting glucose ^{b,c} (mg/dL)	83	33	85	35	
ApoE genotypes					
ε2ε2	0.22		0.27		
ε2ε3	6.38		6.88		
ε2ε4	0.82		0.38		
ε3ε3	75.12		74.55		
ε3ε4	16.86		16.73		
ε4ε4	0.60		1.19		
LIPC -514T allelic frequency	0.456		0.447		
LIPC -514T genotype frequency					
CC	29.9		30.5		
CT	49		49.7		
TT	21.1		19.8		

Values are means ± SD or percentages.

MET = metabolic equivalents; LIPC = hepatic lipase gene.

^a $p < 0.05$.

^b Missing values: income (290), history of hypertension (2), history of angina (7), triglycerides (14), total cholesterol (15), HDL (78), LDL (369), fasting glucose (437).

^c Post infarction measurements among cases.

for hypercholesterolemia. Results are consistent with Table 3 (Table 4). However the p -value for interaction is borderline and not significant in the adjusted model, likely due to the smaller sample size of the stratum using lipid lowering medications. Table 5 shows that the association between the -514 T allele and risk of MI was also modified by waist circumference. The OR and 95%CI for the heterozygous and homozygous carriers of the -514 T allele were 1.04 (0.86, 1.25) and 0.96 (0.77, 1.21) for people with normal waist circumference, while they were 0.63 (0.45, 0.90) and 0.81 (0.53, 1.25) for people with waist circumference above the limits of the metabolic syndrome definition, p for interaction = 0.04.

Previous studies have shown that saturated fat intake modifies the association of the -514 T allele on HDL cholesterol levels [26,27]. We examined whether similar associations would be evident with MI, but no significant interactions were observed. Using homozygous for the wild type as the reference, OR and 95%CI for heterozygous and homozygous for the variant were 0.92 (0.73, 1.16) and 0.84 (0.63, 1.12) among people with low saturated fat intake, and 1.00 (0.80, 1.25) and 1.06 (0.80, 1.41) among people with high saturated fat intake (p for interaction = 0.5). Similarly, although both saturated fat and the -514 allele were independently associated to HDL cholesterol levels (least square means were 40.4 mg/dl for people with low

Table 2 Plasma lipid concentrations by genotype among controls ($N = 1940$).

	LIPC genotype	Mean	SD	<i>p</i> -Value
LDL cholesterol	CC	127.6	36.2	0.38
	CT	127.2	37.1	
	TT	129.5	35.5	
HDL cholesterol	CC	40.0	8.9	0.0008
	CT	41.0	9.0	
	TT	41.7	8.2	
Triglycerides	CC	217.4	139.3	0.44
	CT	219.7	127.8	
	TT	220.5	121.5	

saturated fat intake and 41.4 mg/dl for people with high saturated fat intake, *p*-value 0.01, and 40.4 mg/dl for homozygous for the wild type, 41.4 mg/dl for heterozygous and 41.7 mg/dl for homozygous for the variant, *p*-value, 0.02), there was no significant interaction. HDL cholesterol least square means adjusted for smoking, physical activity, income, and total energy intake, were 39.2, 41.0, and 40.6 for homozygous for the wild type, heterozygous, and homozygous for the variant, among people with low saturated fat intake, and 41.4, 41.3, and 41.9 among people with high saturated fat intake (*p* for interaction = 0.5). We also evaluated a potential interaction between apoE genotypes and the hepatic lipase -514 T/C polymorphism. ApoE genotypes $\epsilon 3\epsilon 3$, $\epsilon 2\epsilon 3$, and $\epsilon 3\epsilon 4$ did not modify the association between hepatic lipase -514 T/C polymorphism and MI in this population (apoE genotypes $\epsilon 2\epsilon 2$, $\epsilon 2\epsilon 4$, and $\epsilon 4\epsilon 4$ were not evaluated due to small sample size).

Discussion

In this study of 1940 cases of MI matched by age, sex and residence to 1940 population-based controls, the -514 T allele increased HDL concentrations but it was not associated with risk of MI. However, significant interactions were found between the -514 C/T polymorphism, hypercholesterolemia, waist circumference and risk of MI. That is, the -514 T allele was associated with lower MI risk among subjects with increased waist circumference, while among

people with history of hypercholesterolemia, the -514 T allele was associated with higher risk of MI.

The -514 T allele lowers HL activity, increases remnant-like apoB-containing particles, and triglyceride content and size of HDL and LDL particles [6]. Through these mechanisms, it would be expected that the -514 T allele increases the risk of CHD [6]. Some epidemiologic studies showing that the -514 T allele is associated with increased risk of CHD are consistent with this concept [15–19]. However, the -514 T allele also increases HDL cholesterol which plays an important role in protection against CHD [1], making possible that the overall effect of the -514 T allele is null. In fact, numerous studies, including our own have not been able to detect an association between the -514 T allele and risk of CHD [7–14].

Increased waist circumference is associated with high triglyceride levels and low HDL cholesterol [28]. In our study those with increased waist circumference had 17% higher plasma triglyceride levels and 5% lower HDL cholesterol than those with normal waist circumference. Among those with increased waist circumference the -514 T allele was associated with a decrease risk of MI, but no association was found among those with less waist circumference. These results suggest that individuals with increased adiposity are more likely to benefit from the HDL cholesterol raising properties of the -514 T allele, most likely because these individuals also have lower HDL cholesterol levels. Others have suggested that decreasing HL, another characteristic of the -514 T allele should benefit the lipid profile of obese subjects or those with high plasma triglycerides [6,29,30]. The results from our study contrast those from a previous report among diabetics, showing that the -514 T allele was associated with increased risk of MI among obese individuals [31]. The reasons for this discrepancy are uncertain, although it suggests that results within diabetic populations cannot be generalized to non-diabetic populations.

Despite of the lack of association between the -514 T allele and MI in the whole population, we found that the -514 T allele was associated with increased risk of MI among subjects with hypercholesterolemia. The -514 T allele lowers HL, and patients with CHD can have lower HL activity in some studies [6]. It is possible that the lower HL activity associated with the -514 T allele is atherogenic

Table 3 Interaction between LIPC -514 promoter polymorphism and history of hypercholesterolemia on risk of MI.

	LIPC -514 genotype	<i>N</i>	No history of hypercholesterolemia	<i>N</i>	History of hypercholesterolemia	<i>p</i> for Interaction
Model 1 ^a	CC	850	1.00	320	1.00	0.02
	CT	1358	0.91 (0.77, 1.08)	558	1.23 (0.92, 1.63)	
	TT	567	0.79 (0.64, 0.98)	227	1.36 (0.96, 1.92)	
Model 2 ^b	CC	850	1.00	320	1.00	0.004
	CT	1358	0.85 (0.70, 1.03)	558	1.25 (0.92, 1.70)	
	TT	567	0.76 (0.60, 0.97)	227	1.59 (1.09, 2.32)	

LIPC, hepatic lipase gene.

Further adjustments did not change the results, including waist circumference, other dietary factors, lipid lowering medication, medical history, etc.

^a Adjusted for matching factors (age, sex, and area of residence).

^b Model 1 + saturated fat, total energy intake, smoking, physical activity, and income.

Table 4 Interaction between LIPC –514 promoter polymorphism and use of lipid lowering medication on risk of MI.

	LIPC –514 genotype	N	No lipid lowering medication	N	Lipid lowering medication	p for Interaction
Model 1 ^a	CC	1104	1.00	66	1.00	0.06
	CT	1813	0.97 (0.83, 1.13)	103	1.36 (0.73, 2.52)	
	TT	747	0.87 (0.72, 1.05)	47	2.27 (1.03, 4.99)	
Model 2 ^b	CC	1104	1.00	66	1.00	0.17
	CT	1813	0.93 (0.79, 1.10)	103	1.27 (0.65, 2.46)	
	TT	747	0.90 (0.73, 1.10)	47	2.04 (0.88, 4.76)	

LIPC, hepatic lipase gene.

Further adjustments did not change the results, including waist circumference, other dietary factors, medical history, etc.

^a Adjusted for matching factors (age, sex, and area of residence).

^b Model 1 + saturated fat, total energy intake, smoking, physical activity, and income.

Table 5 Interaction between LIPC –514 promoter polymorphism and waist circumference on risk of MI.

	LIPC –514 genotype	N	Normal waist circumference	N	Increased waist circumference ^a	p for Interaction
Model 1 ^b	CC	917	1.00	253	1.00	0.004
	CT	1258	1.10 (0.93, 1.30)	388	0.60 (0.44, 0.84)	
	TT	636	0.95 (0.77, 1.17)	158	0.75 (0.50, 1.11)	
Model 2 ^c	CC	917	1.00	253	1.00	0.04
	CT	1258	1.04 (0.86, 1.25)	388	0.63 (0.45, 0.90)	
	TT	636	0.96 (0.77, 1.21)	158	0.81 (0.53, 1.25)	

LIPC, hepatic lipase gene.

Further adjustments did not change the results, including history of hypercholesterolemia, other dietary factors, lipid lowering medication, other medical history, etc.

^a Defined as NCEP-ATPIII criteria for metabolic syndrome, greater than 102 cm for men and greater than 88 cm for women.

^b Adjusted for matching factors (age, sex, and area of residence) and height.

^c Model 1 + physical activity, total energy intake, alcohol intake, and smoking.

due to decreased reverse cholesterol transport [30]. It is also possible that hypercholesterolemics are more susceptible to the increases in remnant-like apoB-containing particles rich in triglyceride [32,33]. These particles are likely to contain apoCIII and have been associated with a 6.6-fold increase in CHD [34]. It is well established that carriers of the APOE4 allele have higher LDL cholesterol levels [35]. Carriers of the APOE4 allele also have higher risk of CHD when they are homozygous carriers of the –514 T allele, according to one study carried out among 9121 Caucasian adults [18]. However, we did not find any effect modification by ApoE genotypes. One study suggested that exercise protects against the detrimental association of the –514 T allele with CHD [36]. Our data suggest that among hypercholesterolemic individuals those with the –514 T allele would benefit the most from exercise. On the other hand, we found that the –514 T allele was associated with decreased risk among normocholesterolemic subjects. We could speculate that among normocholesterolemic subjects the increase in HDL cholesterol due to lower hepatic lipase activity prevails over other pro-atherogenic effects. In fact, our data show that the difference in HDL cholesterol levels between the –514TT and the –514CC homozygotes is only significant among those without history of hypercholesterolemia (+2.3 mg/dl, $p = 0.0001$ vs +1.3 mg/dl, $p = 0.09$).

The strength of our study includes the availability of a well-characterized population, a large sample size, and the high participation rate in cases and population-based

controls. As in all observational studies we cannot establish a causal relationship. Although our results are not likely to be confounded by age, sex, area of residence, diet, smoking, physical activity, and socioeconomic status, residual confounding or chance cannot be ruled out. We relied on self-reported history of hypercholesterolemia and waist circumference, because blood samples in cases were collected after the MI and plasma lipids do not necessarily reflect pre-MI lipid status. Therefore, misclassification is another potential limitation of our study.

In conclusion, we have shown that some genetic variants can have differing associations with MI that depend on the background of the studied population. These findings may explain in part the lack of consistency of previous reports. Further studies that replicate our results are warranted.

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