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Association of Two Genetic Variations of Lipoprotein Lipase, S447X and Hind III, with Coronary Artery Disease and Hypertriglyceridemia

Daria Pašalić[1], Goran Ferenčak[1], Branka Gršković[1], Mihajlo Šesto[2] and Ana Stavljenić-Rukavina[1]

[1] Department of Chemistry and Biochemistry, School of Medicine, University of Zagreb, Zagreb, Croatia
[2] Specialized Hospital for Cardiovascular Surgery and Cardiology »Magdalena«, Krapinske Toplice, Croatia

A B S T R A C T

This study was performed to assess the effect of the S447X and Hind III lipoprotein lipase gene polymorphisms on development of coronary artery disease and hypertriglyceridemia. The study included 132 patients and 98 healthy control subjects of Croatian descent. The lipoprotein lipase S447X polymorphism was associated with coronary artery disease and hypertriglyceridemia, as indicated by the lower frequency of S447 allele in the patient group (p=0.005) and odds ratio (O.R=0.40, p=0.006). The patient and control groups also showed a significant difference in the distribution of Hind III/S447X genotype combinations (p=0.013). There were no significant associations with lipid parameters for any genotype or genotype combination in the patient group. Frequencies of the S447X polymorphism and S447X/Hind III combinations differed between the CAD/TG and control group, thus these polymorphisms may be associated with CAD and hypertriglyceridemia.

Key words: *coronary artery disease, hypertriglyceridemia, lipoprotein lipase, polymorphism, Croatia*

Introduction

Lipoprotein lipase (LPL) hydrolyzes the triacylglycerol component of chylomicrons and very low-density lipoproteins (VLDL), and indirectly participates in the reverse transport of cholesterol[1]. Abnormal LPL expression takes part in some pathophysiological processes, which include chylomicronemia, atherosclerosis, obesity, diabetes, etc.[2] It is also well known that hypertriglyceridemia itself can be a risk factor for the development of coronary artery disease (CAD), as well as of its lowering effect on the levels of high-density lipoprotein cholesterol (HDL-C)[3]. The genetic background in the interaction with many other factors determines some changes of the phenotype characteristics and influences some epidemiological events[4]. Several common genetic variants in LPL gene with different epidemiological effects have been reported[5–7]. Summary statistics of multiple studies have yielded statistically significant effects of some LPL polymorphisms on the development of CAD. These include a twofold increase in CAD risk associated with the lipoprotein lipase D9N and/or the –93T to G polymorphism, a marginal increase in CAD risk for N291S allele-S carriers among individuals from six different studies, and association of S447X allele-X carriers with a decrease in CAD in four different studies[7]. Polymorphisms affecting the noncoding region of LPL gene are also implicated in the development of hypertriglyceridemia and/or CAD. The most common and most widely investigated are the Pvu II and Hind III polymorphisms[6,8].

Over the last several years, many researchers have investigated allelic distribution of different LPL gene variants and their effect on lipid profiles in various patient populations. In a previous study, we also investigated the polymorphisms associated with CAD (–93T/G, D9N, N291S and S447X)[9]. Recent studies have demonstrated that LPL447X mutation was associated with higher postheparin LPL activity in patients[10]. The S447X and Hind III polymorphisms of the LPL gene represent two variant sites that are within 600 bp of each other in the gene[11]. It is also well known that these two polymorphisms are in the strong linkage disequilibrium[11]. Some European studies showed a favorable effect of the 447X allele on lipid traits, while some of them did not find any significant influence on lipid parameters[12]. The EARS

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study showed that H-X447 haplotype was associated with significantly lower concentrations of plasma triglycerides (TG)[11].

The aim of our study was to explore the possible effects of these two polymorphisms and their combinations in CAD patients with elevated TG levels (CAD/TG group). We therefore compared the frequencies of the S447X and Hind III polymorphisms individually and the frequencies of S447X/Hind III genotype combinations between the CAD/TG and control groups. We have also investigated the association between these two polymorphisms and levels of plasma lipids.

Materials and Methods

Study subjects

Study subjects were recruited among patients who underwent coronarography at Magdalena Specialized Hospital for Cardiovascular Surgery and Cardiology in Krapinske Toplice near Zagreb. The blood samples were collected from 2001 to 2004. The subjects were divided into two groups based on coronarography findings and TG concentrations. The CAD/TG group included 132 patients with at least 50% stenosis of any of the major coronary arteries and TG levels greater than 2.2 mmol/L (98 males, median age 59, range 34–82; and 34 females, median age 61.5, range 38–73). The control group included 98 subjects with <10% stenosis of major coronary arteries, TG levels lower than 2.0 mmol/L, and without evidence of any chronic disease (60 males, median age 52.5, range 18–76; and 38 females, median age 61, range 26–76). Patients who had a family history of acute or chronical pancreatitis were excluded from the study because of known relationships between changes in LPL activities and pancreatitis[6]. We used WHO criteria to define diabetes in both study groups[13]. We have also excluded patients with extremely high lipid concentrations, because they would complicate statistic analysis. Patients gave an informed consent to participate in the study, which was approved by the Ethics Committee of Magdalena Specialized Hospital for Cardiovascular Surgery and Cardiology in Krapinske Toplice and of the Zagreb University School of Medicine.

Determination of plasma lipid and lipoprotein subclass concentrations

Blood samples were collected after an overnight fast. The concentrations of total cholesterol (TC) and TG were measured by standard enzymatic methods on an Olympus AU-640 (Olympus, Tokyo, Japan). HDL-C was determined by selective precipitation (Immuno AG, Vienna, Austria), and also measured on an Olympus AU-640. Low density lipoprotein cholesterol (LDL-C) was calculated using Friedewald equation[14]. If TG concentration was greater than 3.0 mmol/l, HDL-C was measured by direct immunoinhibition method (Olympus Diagnostica GmbH, Lismeehan, Ireland), and LDL-C by homogeneous assay (Randox Laboratories, Crumlin, United Kingdom). Apolipoproteins (apo) A–I and B were measured by the nephelometric method (Dade Behring, Marburg, Germany).

PCR amplification and RFLP analysis

DNA was extracted from peripheral whole blood by the salting out method[15]. Polymerase chain reaction (PCR) for exon 9 of LPL gene was performed using primers previously described by Monsalve et al[16]. The reactions were performed in a DNA thermocycler (Eppendorf Mastercycler 3350, Hamburg, Germany), as described elsewhere[17]. S447X polymorphism was genotyped by digestion of exon 9 with Hinf I restriction endonuclease (Roche, Mannheim, Germany). Hind III locus was genotyped using Eppendorf Mastercycler 3350 and oligonucleotides, PCR and restriction conditions as previously described[17,18].

Statistical analysis

Statistical analysis was performed by use of StatSoft, Inc. (2003) STATISTICA (data analysis software system) version 6.1, and MedCalc 4.10 (Frank Schoonjans, Mariakerke, Belgium). Genotype frequencies were calculated by counting. Group comparisons of categorical variables were performed using Pearson's χ^2 or Fisher's exact test. Hardy-Weinberg equilibrium was tested by χ^2-test. Odds ratios were calculated for assessment of association between LPL gene polymorphisms and CAD. All continuous data were expressed as X±SD. Differences between the two groups studied were evaluated by Student's t-test or Mann-Whitney test, depending on distribution normality. Multivariate analysis (MANOVA) with age, gender and diabetes as covariates were used for testing of the effects of LPL gene polymorphisms on lipid parameters. TG values were not normally distributed and were therefore log-transformed. The level of significance was set at 0.05.

Results

The characteristics and lipid parameters of the two groups are presented in Table 1. There were more males, diabetics and smokers in the CAD/TG group. HDL-C was significantly lower and LDL-C higher in the CAD/TG group.

Table 2 shows genotype frequencies in the two study groups. The observed genotypes were in Hardy-Weinberg equilibrium for all the genetic variants examined. Carriers of the 447X allele were more frequent in the control group, while there was no significant differences between groups in genotype frequencies for the Hind III polymorphism. The odds ratio for the association of S447X polymorphism with CAD and hypertriglyceridemia (O.R.) was 0.40 (p=0.006). The frequencies of genotype combinations for the S447X and Hind III polymorphisms are also presented in Table 2. There are nine possible combinations but only six of them were observed. There was a statistically significant difference between the CAD/TG and control group in the distribution of different Hind III/S447X genotype combinations. As

TABLE 1
CHARACTERISTICS OF CAD/TG AND CONTROL GROUP[a]

Parameter	CAD/TG group (n=132)	Control group (n=98)	Significance, p
Age, years (range)	59 (34–82)	56.5 (18–76)	
Sex (male), n (%)	98 (74.2)	60 (61.2)	0.035
Hypertension, n (%)	68 (51.5)	51 (52.0)	0.937
Diabetes, n (%)	28 (21.2)	3 (3.1)	<0.001
Smoking, n (%)	44 (33.3)	22 (22.4)	0.071
Glucose, mmol/L (X±SD)	6.61±3.26	5.19±1.26	<0.001
TC, mmol/L (X±SD)	6.1±1.6	5.33±1.05	0.414
TG, mmol/L (X±SD)	3.09±0.85	1.24±0.35	Not done[b]
HDL-C, mmol/L (X±SD)	0.95±0.24	1.21±0.33	<0.001
LDL-C, mmol/L (X±SD)	3.98±1.27	3.35±0.90	0.002
Apo A-I, g/L (X±SD)	1.26±0.29	1.43±0.34	0.161
Apo B, g/L (X±SD)	1.25±0.31	1.02±0.25	0.244

[a] Differences between groups were evaluated by Student's t-test or Mann-Whitney test, depending on distribution normality.
[b] TG values were used to define the CAD/TG group (TG >2.2 mmol/l) and control groups

hypertriglyceridemia can be a consequence of diabetes, we examined the effect of excluding diabetic subjects. Without diabetic subjects, the S447X genotype frequencies, as well as the Hind III/S447X genotype combination frequencies were still significantly different between the CAD/TG and control groups.

To explore possible mechanisms for this protective effect, the associations between LPL genotypes and genotype combinations and some plasma lipid traits (TC, TG, HDL-C, LDL-C, apo A–I and apo B) were examined in the CAD/TG group. The results are presented in table 3. Due to the low frequency of the H-H– genotype, the H-H– and H-H+ genotypes were pooled together as a single subgroup (H–&+) and compared with the subgroup consisting of the H+H+ genotype. There was no significant genotype effect on lipid parameters for any of the genotypes or genotype combination.

Discussion

When investigating possible LPL genotype effects, one has to take into account that the LPL enzyme can have both pro- and anti-atherogenic roles[1]. The main role of the LPL is its catalytic activity that includes hydroly-

TABLE 2
FREQUENCIES OF GENOTYPES AND GENOTYPES COMBINATIONS IN CAD/TG AND CONTROL GROUP

Genotype	CAD/TG group	Control group	p	Odds ratio (95% C.I.)	p	Odds ratio (95% C.I.)
			Diabetics included		Diabetics excluded	
S447X				0.40		0.43
SS, n (%)	113 (85.6)	69 (70.4)		(0.21, 0.77)		(0.21, 0.85)
SX, n (%)+ XX, n (%)	19 (14.4)+0 (0)	28 (28.6)+1 (1)	0.005	p=0.006	0.015	p=0.016
Hind III						
H-H–, n (%) H-H+,	8 (6.1)+46 (34.8)	6 (6.1)+45 (45.9)		1.57		1.49
n (%)H+H+, n (%)	78 (59.1)	47 (48.0)	0.084	(0.93, 2.65)	0.163	(0.85, 2.61)
				p=0.094		p=0.164
Hind III/S447X						
H-H–/SS, n (%)	6 (4.5)	0 (0)				
H-H–/SX, n (%)	28 (21.2)	22 (22.4)				
H-H–/XX, n (%)	79 (59.8)	47 (48.0)	0.013		0.050	
H-H+/SS, n (%)	2 (1.5)	5 (5.1)				
H-H+/SX, n (%)	17 (12.9)	23 (23.5)				
H+H+/SS, n (%)	0 (0)	1 (1.0)				

[a] Comparison of study groups were performed by using Pearson's χ^2 or Fisher's* exact test.

TABLE 3
LIPID PARAMETERS ACCORDING TO GENOTYPES IN CAD/TG GROUP

	TC X±SD (mmol/L)	TG X±SD (mmol/L)	HDL-C X±SD (mmol/L)	LDL-C X±SD (mmol/L)	Apo A–I X±SD (g/L)	Apo B X±SD (g/L)
Hind III genotype						
H–&+	6.38±1.18	3.10±081	1.00±0.25	4.25±1.25	1.29±0.29	1.31±0.31
H+	5.92±1.32	3.07±0.87	0.93±0.22	3.79±1.26	1.24±0.29	1.21±0.31
Significance, p	0.813	0.813	0.176	0.080	0.063	0.065
S447X						
SS	6.05±1.30	3.09±0.84	0.96±0.23	3.92±1.23	1.27±0.29	1.25±0.31
SX	6.44±1.13	3.10±0.92	0.96±0.30	4.37±1.29	1.23±0.26	1.29±0.32
Significance, p	0.136	0.913	0.427	0.137	0.075	0.142
Genotype combinations						
SS/– –	6.30±0.57	2.72±0.50	1.04±0.13	4.50±0.88	1.33±0.24	1.33±0.15
SS/–+	6.36±1.32	3.19±0.78	1.02±0.24	4.14±1.30	1.33±0.31	1.32±0.34
SS/++	5.92±1.32	3.08±0.87	0.93±0.22	3.79±1.26	1.24±0.29	1.21±0.31
SX/– –	6.45±0.64	3.20±1.03	1.14±0.20	4.65±1.06	1.40±0.11	0.94±0.25
SX/–+	6.44±1.19	3.08±0.94	0.94±0.30	4.34±1.34	1.21±0.27	1.32±0.31
Significance, p	0.262	0.817	0.336	0.241	0.155	0.087

[a] Differences between groups were evaluated by multivariante analysis and TGs were log-transformed before testing.
[b]P-values were calculated after adjustment for age, sex and diabetes.

sis of TGs from TG-rich lipoproteins. This main catalytic activity is involved in antiatherogenic effects. Namely, diminishing TGs in blood can limit reduction of HDL-cholesterol mediated by cholesteryl ester transfer protein[19]. This leads to low HDL-C concentrations as reported in hypertriglyceridemic humans[1]. We have also reported on inverse correlations between concentrations of HDL-C and TGs[20]. In contrast to the anti-atherogenic role, pro-atherogenic effects have also been well defined in some animal models[21]. In the vessel wall, LPL activity may be associated with lipoprotein retention because of foam cell formation[22]. As a consequence of its transferase activity, LPL possibly induces cholesteryl ester accretion in smooth muscle cells during atherogenesis[21]. The anti-atherogenic role is mostly due to plasma LPL, whereas the pro-atherogenic role is mediated by LPL from vessel wall epithelial cells and macrophages.

The present study investigated the S447X and Hind III lipoprotein lipase polymorphisms and lipid profiles in patients with CAD and TGs greater than 2.2 mmol/l relative to control subjects. These two different polymorphisms proved relevant and comparable with many similar studies. It is well known that lowering of LPL activity can influence the development and progression of atherosclerosis[1]. Diabetes mellitus may be secondary cause of hypertriglyceridemia[23], because individuals with impaired glucose tolerance and with diabetes mellitus have a slower plasma reduction of TGs[24]. Consequently, we have calculated and analyzed the frequencies between the CAD and the control group with and without diabetics to exclude the influence of hyperglycemia. Many studies report on a decrease in CAD risk in individuals carrying 447X-allele, in European and American populations, as well as Japanese[7,25]. The frequency of the X447 gene variant was also significantly lower in over than 1,300 myocardial infarction survivors than in the same number of the control subjects from the Central Valley of Costa Rica[26]. We similarly observed a significantly lower frequency of 447X-carriers among those with CAD.

Studies of *in vitro* expression showed both increased or unchanged activity and mass of LPL-X447 relative to S447[12] and studies of *in vivo* activity yield inadequate data for any general conclusion[12]. Many lipid association studies indicated a lowering effect on TGs and/or higher HDL-C concentrations in X447 carriers[5, 27–31]; therefore this beneficial LPL 447-X gene variant was considered for a gene therapy investigation[32]. Other recent studies, which include English[33] and Welsh[34] populations, did not indicate significant changes of TGs or HDL-C. These latter findings are in agreement with our study results. A lower LPL-X447 allele frequency was found in the LPL deficient cohort compared to Quebec population-based cohort, suggesting that beneficial LPL-X447 allele in combinations with some mutant alleles do not provide protective effect against the risk to develop CAD[35]. The HERITAGE family study showed that the relationships between the X447 allele and beneficial lipid profile were observed in obese but not in normal-weight subject[36] probably due to a higher LPL activity in obese people. The association of LPL gene mutations with CAD appeared to be exacerbated by the presence of additional risk factors, gene-gene, gene-environmental interactions

and lifestyle habits. Those facts, as well as inclusion criteria in the design of our study, such as CAD+hypertriglyceridemia, may modify the effect of polymorphisms on the lipid traits. Therefore we were unable to show expected benefits on lipid profiles such as lower TG concentrations.

The LPL Hind III polymorphism may affect RNA splicing because lies in intron eight, 495 bp from the splice-donor site[6]. It has been proposed that the H-allele of the Hind III polymorphism acts as a genetic marker for a functional mutation that could cause either enhanced enzyme activity or more efficient lipid binding[11]. It is in strong linkage disequilibrium with S447X polymorphism[11,12]. Therefore S447X and Hind III LPL polymorphisms are candidates that might be involved together in the development of CAD and hypertriglyceridema. We have also documented in this paper that almost all Croatian subjects with the Hind III H+H+ genotype had the 447SS genotype. This was comparable with the results from the European Atherosclerosis Research Study, which included university students from 12 European countries and investigated haplotype effects[11]. Although Hind III genotypes alone did not differ in frequencies between our two subgroups studied, there was a statistically significant difference in gene combinations with S447X. The H+H+/SS genotype combination was more prevalent in CAD/TG than in the control group. Namely, H+H+/SS genotype combination seems to be unfavorable and may be involved in the development of CAD.

The LPL-H+ and LPL S447 alleles have been associated with an increased risk for the development of CAD or hyperlipoproteinemia in a number of other studies. The H+H+ genotype was associated with predisposition to myocardial infarction in Russian patients[37] and the Hind III polymorphism correlated significantly with cerebrovascular disease in Japanese subjects[38]. Among German patients included in the MONICA study there was no difference in the frequencies of Hind III genotypes between patients and controls, but there were observed unfavorable lipid levels in homozygotes for H+ allele[4]. The H+ allele was also connected with some unfavorable lipid profiles in Spanish and US-American women[39,40]. By comparison, as in the study presented here, there was no observed association between the Hind III polymorphism and lipid profile among overweight, postmenopausal, US-American woman[41] nor in the Quebec family study[29,42]. Although we expected that patients with CAD and high TGs might have unfavorable lipid profile with LPL polymorphisms mentioned above, we did not find any significant influence of these polymorphisms. Data from the literature suggests that this effect may depend upon the specific patient population studied.

In summary, the S447X polymorphism and genotype combination of S447X and Hind III polymorphisms were shown to differ in frequencies between CAD/TG and control groups, suggesting their association with CAD and hypertriglyceridemia.

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D. Pašalić

Department of Chemistry and Biochemistry, School of Medicine, University of Zagreb, Šalata 3, 10000 Zagreb, Croatia
e-mail: daria.pasalic@mef.hr

POVEZANOST DVIJU VARIJANTI GENA ZA LIPOPROTEIN LIPAZU S KORONARNOM BOLESTI SRCA I HIPERTRIGLICERIDEMIJOM

S A Ž E T A K

Cilj ovog rada je bio ispitati učinak polimorfizama S447X i Hind III u genu za lipoprotein lipazu na razvoj koronarne bolesti srca i hipertrigliceridemiju. U istraživanje je uključeno 132 ispitanika s koronarnom bolesti srca i triacilglicerolom iznad 2.2 mmol/L i 98 zdravih ispitanika iz Hrvatske. U grupi ispitanika s koronarnom bolesti srca i povišenim triacilglicerolom učestalost S447 alela u genu za lipoprotein lipazu značajno je manja nego li kod kontrolne skupine ($p=0.005$) što potvrđuje i statistički značajan omjer vjerojatnosti (O.R.=0.40, $p=0.006$). Također je statistički značajna razlika učestalosti kombinacija gena Hind III/S447X između ispitivanih skupina ($p=0.013$). Genotipovi kao ni kombinacije genotipova nisu se značajno razlikovale u lipidnom profilu nijedne od ispitivanih skupina. Kako se učestalost S447X polimorfizma i kombinacije polimorfizama Hind III/S447X u genu za lipoprotein lipazu razlikuju između pacijenata i kontrolnih ispitanika može se zaključiti da su navedeni polimorfizmi mogu imati utjecaja na razvoj koronarne bolesti srca i hipertrigliceridemije.