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Effects of Lipoprotein Lipase and Peroxisome Proliferator-Activated Receptor-γ Gene Variants on Metabolic Syndrome Traits

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A B S T R A C T

Peroxisome proliferator activated receptor-γ (PPARG) and lipoprotein lipase (LPL) play important role in lipid homeostasis, insulin resistance and adipogenesis, and their gene variability could be considered as predictive genetic markers for metabolic syndrome (MetSy). The aim of the study was to estimate possible associations of PPARG (Pro12Ala) and LPL PvuII (+/–) polymorphisms with MetSy and its traits. Study included 527 subjects. According to the modified National Cholesterol Education Program Adult Treatment Panel III definitions, subjects were classified into the metabolic syndrome group and control group. Genotyping was performed using polymerase chain reaction-restriction fragment length polymorphism methods. In the total sample, LPL variants were associated with waist circumference (χ^2= 7.263, d.f.=2, p=0.026) and with BMI (χ^2=6.549, d.f.=2, p=0.038), where PvuII (+/+) genotype carriers had the highest risk for increased waist circumference (specific PvuII (+/+) vs. others analysis χ^2=7.033, p=0.008) and increased BMI (specific Pvu II(+/+) vs. others analysis χ^2=5.154, p=0.023). LPL gene variants were also associated with HDL-C levels (χ^2=6.901, d.f.=2, p=0.032), where PvuII (–/–) genotype carriers had higher HDL-C values in comparison to others (specific Pvu (+/+) vs. others analysis χ^2=6.504, p=0.011). Furthermore, PvuII (–) allele carriers had significantly lower glucose (allele based analysis Add Value=–0.0878, χ^2=5.878, d.f.=1, p=0.015). Significant interaction was detected between PPARG and LPL that affected HDL-C levels in male population (χ^2=11.790, d.f.=1, p=0.0006) in the manner that Ala/PvuII(+) contributed to the lowest HDL-C values (Specific Ala/ Pvu(+) vs. others analysis was χ^2=11.750, p= 0.0006). According to obtained results LPL and PPARG gene variants could be susceptibility factors of obesity and lipid status, contributing to development of MetSy, particularly in males. Because of antiatherogenic function of HDL-C, the identification of genetic variants associated with HDL-C can provide useful information related to genotype-phenotype relationships. Since the interplay between PPARG and LPL gene and gender seems to be significant it could point to the personalized behavioural recommendations for prevention of metabolic and cardiovascular diseases.

Key words: *metabolic syndrome, genetic polymorphisms, peroxisome proliferator-activated receptor γ gene, lipoprotein lipase gene*

Introduction

Metabolic syndrome (MetSy) is a rising global public health problem because of its role in increasing the risk of cardiovascular disease and type 2 diabetes mellitus (T2DM). It is a cluster of modifiable risk factors including hypertension, abdominal obesity, dyslipidemia and insulin resistance, and of nonmodifiable risk factors, such as age, sex and genetic background[1]. The underlying determinants of individual susceptibility to MetSy form a complex network of interactions between genetic and environmental risk factors, as a consequence of their

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multi-factorial nature. Although considerable efforts have been made toward controlling all these risk factors, progress seems to be most prominent in the field of dyslipidemia. Serum lipid levels, including high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs), two components of the MetSy, are highly heritable, with estimates consistently over 50%[2,3]. While the importance of genetic factors to the development of MetSy has been widely recognized, the contribution of genes has not yet been fully clarified. Many association studies have been conducted with inconsistent results[4,5].

Peroxisome proliferator activated receptor-γ (PPARG) and lipoprotein lipase (LPL) are the two important proteins that play a key role in lipid homeostasis, insulin resistance and adipogenesis, and their gene variability could be considered as predictive genetic markers for MetSy.

PPARs (PPAR-α, PPAR-δ and PPAR-γ) are transcription factors that belong to the nuclear hormone receptor superfamily that regulate various genes involved in lipid and glucose metabolism, fatty acid transport, adipocyte differentiation, carcinogenesis, and inflammation[6]. The *PPARG* gene is located on chromosome 3p25 (OMIM number 601487). Because of alternative mRNA splicing, two protein isoforms occur: PPARG1 and PPARG2. While PPARG1 is found ubiquitously in the body, PPARG2 is largely found in adipose tissue and the large intestine. Among several variants in the *PPARG* gene, the Pro12Ala variant (rs1801282) has been most extensively examined in epidemiologic studies. The frequency of the 12Ala allele has been found to range from 2 to 18% in healthy people[7]. The substitution from proline to alanine at codon 12 has been found to modulate transcriptional activity. Ala variant has been shown to have a reduced affinity for the response element in target genes, which leads to the less efficient stimulation of PPARG target genes[8]. PPARG function appears to be a key factor in mediating conditions such as dyslipidemia, obesity, and insulin resistance[9,10], and has also been implicated in the development of cardiovascular diseases[11].

LPL belongs among different PPARG target genes and play the major role in the metabolism and transport of lipids. It is the enzyme responsible for the hydrolysis of core TGs. LPL has many physiological functions by which it regulates the supply of fatty acids to various tissues. Its interaction with lipoproteins facilitate lipoprotein particle uptake in the vessel wall. LPL also takes part in the kinetics of the majority of plasma lipoprotein particles, supporting the exchange of lipids between lipoproteins. To enhance lipoprotein uptake LPL molecules can even serve as ligands for lipoprotein receptors. In adipose tissue during adipocyte differentiation insulin increase LPL gene transcription enhancing considerably LPL activity[12]. Glucose also increases adipose tissue LPL activity.

The *LPL* gene has been mapped to human chromosome 8p22. Several *LPL* mutation loci have been detected and investigated for their associations with plasma lipid level and the development of cardiovascular diseases[13]. Polymorphism *LPL* Pvu II (–/+) (rs285) is caused by the absence (–) or presence (+) of a C>T transition at position 497 in intron 6, and may interfere with correct splicing of mRNA, diminishing the enzyme activity.

Results of association studies of *PPARG* and *LPL* gene polymorphisms with MetSy and its traits have been inconsistent.

Assuming a modest role of single polymorphisms as markers of complex traits and diseases, the study of variant gene combinations could provide complementary information that could be clinically important. Besides, the influence of gene variants on phenotype expression seems to be population specific because of possible variations in genetic and environmental factors and interpopulation differences in genetic background[14]. Here we consider the relations between the *PPARG* and *LPL* gene polymorphisms and MetSy traits in Croatian population. We also tested if the modulation of clinical and biochemical parameters of MetSy by interplay between *PPARG* and *LPL* genes is gender specific.

Subjects and Methods

Subjects

The required sample size was calculated for the targeted power of 80%, and the confidence level of 95%. A Chi-square (χ^2) test was used for testing of the first hypothesis: difference in prevalence of one (or more) metabolic syndrome parameters between subjects with different *LPL* variants PvuII (–/–), (–/+) and (+/+). The smallest effect size to be detected by Chi-square test was set at 0.15. Under these assumptions, the required final sample size was estimated at n=429. Initially required sample size was increased by 10% and was estimated at n =472 subjects. Finally a total of 527 subjects (343 female, 184 male) of Croatian origin, participated in the study. Participants were recruited among outpatients admitted to the University Hospital Center Zagreb, and among hospital staff and other Zagreb citizens, appointed for routine check up. MetSy was defined using the criteria established in the third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment in Adults[15]. An individual with a combination of any three or more of the following risk factors was classified as having MetSy: waist circumference, male >102 cm, female >88 cm; TG ≥1.7 mmol/L; HDL-C <1.0 in men and <1.3 mmol/L in women; systolic blood pressure (SBP) or diastolic blood pressure (DBP) ≥130/85 mm Hg, or use of anti-hypertensive medications; and fasting blood glucose ≥6.1 mmol/L or use of antidiabetic medication with the age of diagnosis of T2DM ≥40 years. In the case of participants' use of medications, formulas were applied that were based on previous research[16] which involved corrections of a participant's medicated traits according to the mean values of many summarized clinical trials. TG and HDL-C for the subjects treated with antihyperlipidemics were corrected to new values based on the following formula: TG/(1–15.2/

100), HDL-C/(1+6.1/100). The SBP and DBP for subjects using antihypertensives were corrected to new values according to the formula: SBP+14.8 and DBP+10.5 (mm Hg). Data were collected from each participant on clinical variables including age, height, weight, and waist circumference. Body mass index (BMI) was calculated as weight (kg) / height (m^2). Blood samples for biochemical analyses (total cholesterol, TG, LDL-C, HDL-C, and glucose) were collected after overnight fasting and analyzed by using routine laboratory methods. All participants signed informed consent forms, and the study protocol was approved by Ethics Committee of the University Hospital Center Zagreb.

Genotyping procedures

Genomic DNA was extracted from blood leukocytes and genotyping of *PPARG* (Pro12Ala) and *LPL* PvuII (–/+) was performed according to previously published methods[17,18].

Statistical analysis

The required sample size was calculated in 11th PASS Hintze, J. (2011), NCSS, LLC. Kaysville, Utah, USA. www.ncss.com. The statistical analysis was performed using SPSS for Windows version 13.0 (SPSS Inc., Chicago, IL, USA). Study subjects were described using means and standard deviations for interval measures and frequencies and percentages for categorical variables. For testing the normality of data distribution, Kolmogorov-Smirnov goodness of fit test was used (with $p>0.05$ considered as a non-significant departure from normality). Chi-square tests were used to compare different categorical variables, including genotypes between cases and controls and between males and females. To compare different continuous variables between cases and controls and between males and females we used Mann-Whitney or t-tests for independent samples where variables were non-parametric and parametric, respectively.

The association of *PPARG* and *LPL* gene variants with the MetSy components (the levels of TG, glucose, HDL-C, blood pressure and waist circumference) was tested using program UNPHASED ver. 3.0.10. We analyzed associations of MetSy components with alleles, genotypes, specific genotypes (estimating the odds ratios and additive values of individual genotype vs. others) and cis gene-gene interactions. The sequential Bonferroni adjustments were applied to correct for the effect of multiple tests using SAS Release 8.02 (SAS Institute, 1999). The equivalence of the genotype distribution to the Hardy-Weinberg equilibrium was tested using the online software (http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl).

TABLE 1
CLINICAL FEATURES OF STUDY PARTICIPANTS

		Patients Mean±SD	Controls Mean±SD	*p*
Age (yrs)		52.13±10.68	51.62±10.40	0.188
Gender (N of male participants/All)		98/263	85/264	0.222
BMI (kg/m^2)		32.20±4.75	24.57±3.36	<0.001
Waist circumference (cm)		107.29±11.24	86.25±11.74	<0.001
TG (mmol/L)		2.59±2.17	1.22±0.74	<0.001
Cholesterol (mmol/L)		5.76±1.27	5.52±1.02	0.039
HDL-C (mmol/L)		1.34±0.32	1.69±0.41	<0.001
LDL-C (mmol/L)		3.46±1.31	3.30±0.89	0.242
Glucose (mmol/L)		6.23±2.22	4.98±0.77	<0.001
High Blood pressure (N of subjects with high BP/All)		195/257	53/254	<0.001
Systolic blood pressure		152.4±26.0	124.8±14.24	<0.001
Diastolic blood pressure		94.4±15.87	79.5±8.60	<0.001
	Genotype	N	N	
	ProPro	198	201	
PPARG	ProAla	62	60	0.974
	AlaAla	3	3	
	PvuII(–/–)	63	70	
LPL	PvuII(–/+)	122	134	0.194
	PvuII(+/+)	78	60	

BMI – body mass index, TG – triglycerides, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, BP – blood pressure. Differences between groups were evaluated by t-test, Mann-Whitney test or chi-square test depending on distribution normality.

Results

Description of the sample

Clinical features of study participants are given in Table 1. A total of 527 subjects (343 female, 184 male) of Croatian origin, participated in the study, 263 participants met criteria for MetSy and 264 were without MetSy criteria and served as controls. Participants with MetSy had significantly higher blood pressure, BMI and waist circumferences and higher levels of TG, total cholesterol and glucose and lower levels of HDL-C compared to controls. MetSy and control group did not differ significantly with respect to age and sex. In comparison to males, females were younger, had smaller BMI and waist circumference, higher TG and glucose levels and had lower HDL-C. Males had significantly more often high blood pressure. No differences in genotype distribution according to gender were detected (Table 2).

Genetic analysis

Frequencies of the *PPARG* (Pro12Ala) variants Pro-Pro, ProAla, AlaAla were 399 (75.7%), 122 (23.2%) and 6 (1.1%), respectively. Frequencies of the *LPL* variants PvuII (–/–), (–/+) and (+/+) were 133 (25.2%), 256 (48.6%) and 138 (26.2%), respectively. No departure from the Hardy-Weinberg equilibrium (*PPARG* controls p= 0.5267 and cases p=0.4446; *LPL* controls p=0.7873 and cases p=0.2617) was observed.

Associations of PPARG and LPL gene variants and MetSy

No differences in *PPARG* and *LPL* genotype distributions between MetSy cases and controls have been found (Table 2).

Associations of PPARG and LPL gene variants and MetSy components

No associations of *PPARG* variants and the components of MetSy have been observed (data not shown).

In the total sample, *LPL* variants were associated with waist circumference (χ^2=7.263, d.f.=2, p=0.026) and with BMI (χ^2=6.549, d.f.=2, p=0.038), where PvuII (+/+) genotype carriers had the highest risk for increased waist circumference (specific PvuII (+/+) vs. others analysis χ^2=7.033, p=0.008) and increased BMI (specific Pvu II(+/+) vs. others analysis χ^2=5.154, p= 0.023). *LPL* gene variants were also associated with HDL-C levels (χ^2=6.901, d.f.=2, p=0.032), where PvuII (–/–) genotype carriers had higher HDL-C values in comparison to others (specific Pvu (+/+) vs. others analysis χ^2=6.504, p=0.011) (Table 3). Furthermore, PvuII (–) carriers had significantly lower glucose (allele based analysis Add Value=–0.0878, χ^2=5.878, d.f.=1, p=0.015; genotype based analysis revealed an association of borderline statistical significance χ^2=5.821, d.f.=2, p= 0.054) (Table 3). These associations remained positive after sequential Bonferroni corrections (α was set at 0.05 for genotype and 0.025 for allele based analyses). No associa-

TABLE 2
CLINICAL AND GENETIC DATA ACCORDING TO GENDER

		Males (N=184) Mean±SD	Females (N=343) Mean±SD	p
Age (yrs)		53.56±12.32	50.98±9.35	0.014
BMI (kg/m^2)		29.00±5.28	28.13±5.78	0.042
Waist circumference (cm)		104.23±12.81	94.96±15.87	<0.001
TG (mmol/L)		2.46±2.63	1.67±1.09	<0.001
Cholesterol (mmol/L)		5.63±1.31	5.65±1.08	0.573
faautoHDL-C (mmol/L)		1.37±0.40	1.57±0.40	<0.001
LDL-C (mmol/L)		3.40±1.43	3.37±0.95	0.584
Glucose (mmol/L)		6.01±2.06	5.45±1.63	<0.001
High Blood pressure (N of subjects with high BP/All)		100/180	148/331	0.019
	Genotype	N	N	
	ProPro	132	267	
PPARG	ProAla	47	75	0.139
	AlaAla	4	2	
	PvuII(–/–)	46	87	
LPL	PvuII(–/+)	81	175	0.206
	PvuII(+/+)	56	82	

BMI – body mass index, TG – triglycerides, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, BP – blood pressure. Differences between groups were evaluated by t-test, Mann-Whitney test or chi-square test depending on distribution normality.

TABLE 3
ASSOCIATIONS OF *LPL* PvuII (–/+) GENE VARIANTS AND METABOLIC SYNDROME TRAITS

Feature	LPL Genotype	N	Marginal Frequency	Additive value	CI	[a] Specific p	p
BMI	PvuII(–/–)	129	0.250	0	0	0.064	0.038
	PvuII(–/+)	250	0.484	0.022	–0.018 – 0.061	0.604	
	PvuII(+/+)	138	0.267	0.055	0.011 – 0.099	0.023	
Waist circumference	PvuII(–/–)	112	0.246	0	0	0.303	0.026
	PvuII(–/+)	217	0.476	0.0004	–0.015 – 0.016	0.120	
	PvuII(+/+)	127	0.279	0.019	0.002 – 0.036	0.008	
Glucose	PvuII(–/–)	125	0.249	0	0	0.024	0.054
	PvuII(–/+)	248	0.493	0.092	–0.080 – 0.265	0.704	
	PvuII(+/+)	130	0.258	0.176	0.0002 – 0.352	0.088	
HDL-C	PvuII(–/–)	125	0.249	0	0	0.011	0.032
	PvuII(–/+)	247	0.492	–0.609	–1.127 – (–0.090)	0.226	
	PvuII(+/+)	130	0.259	–0.708	–1.315 – (–0.102)	0.205	

BMI – body mass index, HDL-C – high-density lipoprotein cholesterol, CI – confidence interval
[a] Specific p – individual vs. others genotypes

TABLE 4
ASSOCIATIONS OF *LPL* PvuII (–/+) GENE VARIANTS AND METABOLIC SYNDROME TRAITS IN MALES

Feature	LPL Genotype	N	Marginal Frequency	Additive value	CI	[a] Specific p	p
BMI	PvuII(–/–)	46	0.251	0	0	0.015	0.012
	PvuII(–/+)	81	0.443	0.067	–0.053 – 0.139	0.871	
	PvuII(+/+)	56	0.306	0.119	0.040 – 0.199	0.018	

BMI – body mass index, CI – confidence interval
[a] Specific p – individual vs. others genotypes

tions between the *LPL* variants and other components of MetSy were found (data not shown).

Since significant associations were found for the whole sample, we conducted further analyses in the two gender-based subgroups. Significant associations were observed between *LPL* and the components of MetSy in the male subgroup only (Table 4). *LPL* variants were associated with BMI, and waist circumference where PvuII (+) allele carriers had increased risk for higher BMI (Add Value=0.0639, χ^2=9.724, d.f.=1, p=0.002 for allele based analysis and χ^2=8.901, d.f.=2, p=0.012 for genotype based analysis) and waist circumference (Add Value= 0.0202, χ^2=5.313, d.f.=1, p=0.021 for allele based analysis), although the later did not remain positive after sequential Bonferroni corrections (α was set at 0.025 for genotype and 0.0125 for allele based analyses).

Furthermore, significant gene interaction was detected between *PPARG* and *LPL* that affected HDL-C levels (χ^2=11.790, d.f.=1, p=0.0006) in the manner that Ala/PvuII(+) contributed to the lowest HDL-C values (Specific Ala/ Pvu(+) vs. others analysis was χ^2=11.750, p=0.0006). These associations remained positive after sequential Bonferroni corrections (α was set at 0.0125 and 0.00625, respectively) (Table 5).

However, no associations between the *LPL* variants and glucose levels were found when the two gender subgroups were analyzed separately (data not shown).

Discussion

The obtained results show independent and interacting effects of the *LPL* and *PPARG* polymorphisms on MetSy traits, as follows:

1. Presence of *LPL* PvuII (+/+) (low activity) genotype predisposes for increased waist circumference and BMI; showing a stronger effect in males,

2. Presence of *LPL* PvuII (–/–) (high activity) genotype predisposes for increased HDL-C,

3. Presence of *LPL* PvuII (–) (high activity) allele protects from elevated glucose level,

4. *LPL* and *PPARG* gene interaction confers to HDL-C levels, where Ala/Pvu(+) low activity allele combination predisposes for decreased HDL-C values, observed in males.

Our results pointed to the pleiotropic role of *LPL* gene with the influence on several MetSy traits: waist circumference, BMI, HDL-C and glucose. Previously published

TABLE 5
EFFECTS OF *PPARG* ProAla AND *LPL* PvuII(–/+) GENE INTERACTION ON HDL-C LEVEL IN MALES

Interactions/ feature	Haplo types	N	Marginal Frequency	Additive value	CI	[a] Specific p	p
LPLxPPARG/ HDL-C	PvuII(–)/Pro	135.9	0.414	0	0	0.806	0.0006
	PvuII(–)/Ala	19.14	0.058	1.544	0.447 – 2.642	0.173	
	PvuII(+)/Pro	141.1	0.430	0.185	–0.412 – 0.782	0.844	
	PvuII(+)/Ala	31.86	0.097	–1.786	–3.558 – (–0.013)	0.0006	

HDL-C – high-density lipoprotein cholesterol, CI – confidence interval
[a] Specific p – individual vs. others genotypes

results suggest the existence of interaction between *LPL* gene and central obesity[19,20], which is in accordance with our findings. LPL is an important marker for adipocyte differentiation, and LPL expression increases in parallel with cellular TG accumulation as preadipocytes differentiate. As both central obesity and serum lipids were found related with LPL activity, it is reasonable to assume that *LPL* gene variability contribute to the development of some of MetSy traits. Obese patients have a lower gene expression of factors (including LPL) related with lipid uptake and processing, in comparison with healthy lean persons[20]. This is concordant with our results showing that low activity *LPL* genotype predisposes for increased waist circumference and BMI. Considering the interplay between LPL, insulin and glucose, and the association of *LPL* and insulin resistance, our finding that *LPL PvuII* high activity allele protects from elevated glucose level is in agreement with published data[21,22]. Although LPL does not act directly on HDL, its action on triglyceride-rich lipoproteins has an important indirect effect on HDL metabolism[23]. The amount of cholesterol transported in HDL particles is measured as HDL-C and seems to be under considerable genetic control with heritability estimates of up to 80%[24]. However, the genes identified so far together explain only a small portion of the HDL-C variance. HDL-C loci discovered via genome-wide association studies (GWAS) for obesity, MetSy and multiple cardiovascular-related traits pointed to the *LPL*[4] and *PPARG* gene[25]. Some other literature data also point to the correlation of *LPL* with obesity and/or MetSy traits[26].

Frequency of *PPARG* Ala variant in Croatian population is estimated to be 12.7%, which is similar to other European populations[7]. While some studies have provided evidence for the association of the *PPARG* Ala variant with increased BMI, others have failed to confirm this finding. We found that common variants of *LPL* PvuII (–/+) and *PPARG* (Pro12Ala) could modulate some MetSy traits differentially in men and women. Gender-based dimorphism has been reported for several genes that affect MetSy traits and related diseases[27]. Possible explanations for this gender-based dimorphism include: 1. possible interaction of LPL with either sex-linked genes and/or sexual hormone effects[28]; 2. the effects of differentially expressed autosomal genes in males and females; 3. differential fat distribution patterns between genders; 4. differential gene-environment and gene-gene interactions. Gender influences the risk for many common diseases that affect both men and women, including atherosclerosis and diabetes and their preceding risk factors (e.g. hyperlipidemia, insulin resistance, and obesity)[29]. Although *PPARG Pro12Ala* variant in this study showed no influence on MetSy or its traits when tested separately, its interaction with *LPL* PvuII (–/+), variants seems to be relevant at least for HDL-C levels in male population. In their heritability estimation of sex-specific effects on human quantitative traits, Pan et al. have confirmed significant sex-specific autosomal effects on HDL-C[28]. Considering transcriptional regulation, the activity of the LPL promoter has been studied extensively. The 5' regulatory region contains a large number of specific *cis*-acting elements, among others the PPAR response element (PPRE)[30]. Because the *LPL* promoter was shown to be ~ 30% less efficiently transactivated in the presence of the *PPARG* Ala allele in a study in vitro, Schneider group proved that the Pro12Ala substitution may lead to decreased LPL activity in vivo[31]. Considering that LPL activity positively correlates with the plasma concentration of HDL-C, results of our study are in line with the Schneider group's hypothesis: we found a combination of the low activity alleles *PPARGAla*/*LPL PvuII* (+), adding 1.8 times higher risks for lower HDL-C values in males whereas the risk was not increased for the carriers of either of two genotypes when analyzed separately. Because of antiatherogenic function of HDL, the identification of genetic variants associated with HDL-C can provide useful information and we believe that our data pointed to the importance of studying *LPL* and *PPARG* interactions.

Study Limitations

This study has some limitations: genetic association studies require very large cohorts to reach an acceptable power. Therefore the size of our population might be a limitation. Another limitation might be that the effects of environmental factors (e.g., physical activity, diet, and smoking) and controlling the risk of obesity and MetSy were not evaluated in this study.

In spite of these limitations, the data obtained confirm that *LPL* gene variability contributes in the modu-

lation of certain clinical and biochemical parameters of MetSy. Although further studies are needed to confirm the gender specificity of *LPL* and *PPARG* interaction, the interplay between genes and gender seems to be significant and could point to the personalized behavioural recommendations for prevention of metabolic and cardiovascular diseases.

Conflict of Interest

The authors declare that they have no conflict of interest.

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UTJECAJ POLIMORFIZAMA GENA ZA LIPOPROTEIN LIPAZU I RECEPTORA ZA AKTIVATOR PROLIFERACIJE PEROKSISOMA-GAMA NA SASTAVNICE METABOLIČKOG SINDROMA

S A Ž E T A K

Receptor za aktivator proliferacije peroksisoma tip g (PPARG) i lipoprotein lipaza (LPL) imaju važnu ulogu u lipidnoj homeostazi, inzulinskoj rezistenciji i adipogenezi i stoga se njihova genska varijabilnost može smatrati mogućim prediktivnim biljegom metaboličkog sindroma (MetSy). Cilj istraživanja bio je ispitati povezanosti između polimorfizma *PPARG* (Pro12Ala) i *LPL* PvuII (–/+) s MetSy i njegovim sastavnicama. U studiju je bilo uključeno 527 ispitanika. Prema kriterijima američkog programa za edukaciju o kolesterolu (National Cholesterol Education Program – Third Adult Treatment Panel, NCEP-ATP III) ispitanici su podijeljeni u skupinu s metaboličkim sindromom i kontrolnu skupinu. Genotipizacija je provedena metodama temeljenim na polimeraznoj lančanoj reakciji i analizi duljine restrikcijskih ulomaka (PCR-RFLP). U ukupnom uzorku LPL varijante su bile povezane s opsegom struka (χ^2=7.263, d.f.=2, p=0.026) i s BMI (χ^2=6.549, d.f.=2, p=0.038), pri čemu su nosioci genotipa *LPL* PvuII (+/+) imali najveći rizik za povećani struk (specifični PvuII (+/+) vs. ostali χ^2=7.033, p=0.008) i povećani BMI (specifični Pvu II(+/+) vs. ostali χ^2=5.154, p=0.023). *LPL* genske varijante su također povezane s razinom HDL-C (χ^2=6.901, d.f.=2, p=0.032), pri čemu su nosioci genotipa PvuII (–/–) imali više vrijednosti HDL-C u odnosu na ostale (specifični Pvu (+/+) vs. ostali χ^2=6.504, p=0.011). Nosioci alela PvuII (–) su također imali značajno niže vrijednosti glukoze (Add Value=–0.0878, χ^2=5.878, d.f.=1, p=0.015). Uočena je značajna interakcija između *PPARG* i *LPL* s utjecajem na razine HDL-C u muškoj populaciji (χ^2=11.790, d.f.=1, p=0.0006), pri čemu su nosioci Ala/PvuII(+) imali najniže vrijednosti HDL-C (specifični Ala/Pvu(+) vs. ostali χ^2=11.750, p=0.0006). Na osnovi dobivenih rezultata varijante gena *LPL* i *PPARG* bi se mogle ubrojiti u genetičke čimbenike povećane podložnosti za razvoj debljine i lipidnog statusa koji doprinose razvoju MetSy, posebno u muškoj populaciji. Zbog antiaterogene uloge koju ima HDL-C, identifikacija genetičkih varijacija povezanih s HDL-C može rezultirati korisnim podacima u svrhu procjene genetičkog rizika. U tom smislu dobiveni podaci podupiru važnost ispitivanja interakcija gena *LPL* i *PPARG* sa svrhom stvaranja personaliziranih preporuka ponašanja i s konačnim ciljem prevencije metaboličkih i kardiovaskularnih bolesti.