RESEARCH ARTICLE

Study and Investigation of Ser447Ter *Lipoprotein Lipase* Gene Polymorphism, and Obesity in Children and Adolescents

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ABSTRACT

Objectives: Obesity raises the risk for many chronic illnesses. Clinically, obesity is determined using the body mass index (BMI). The *lipoprotein lipase* (*LPL*) gene was linked to the metabolism and obesity of lipoproteins. This study aimed to study investigate the Ser447ter (C-G) polymorphisms of the *LPL* gene and rs9939609 of the FTO gene and obesity in children and young Rostov people from Russia.

Methods: The research investigated the relationship between the Ser447Ter in the *LPL* gene with obesity in 870 participants of both sexes aged (3– 17) years: the major group consisted of 540 obese, and the control group - had 330 participants without obesity. Genotyping of the gene *LPL* Ser447Ter polymorphisms rs328 was performed using polymerase chain reaction (PCR)-allele-specific primers. Polymorphisms (rs328) of the *LPL* gene in donor DNA samples were typed by the electrophoretic method using commercial test systems from the Litekh research and production company (Russia).

Results: The relationship between the *LPL* Ser447Ter gene obesity ($p > 0.05$) was not significant established between the main and control groups in the frequency of occurrence of the genotype SerSer ($p = 0.381$) and allele Ser447 ($p = 0.404$; OR 1.17; 95% CI 0.82 – 1.67) of the rs328 polymorphism of the *LPL* gene. Even though recessive and dominant models are constructed, for *LPL* gene was statistically not significant TerTer vs SerTer + SerSer ($p = 1.000$ OR 1.84; 95% CI 0.07– 45.05).

Conclusions: An observed absence of an association between the gene Ser447Ter of the *LPL* gene with the obesity. However, more studies are needed to confirm these findings.

Keywords: Children and adolescents, *Lipoprotein Lipase*, Obesity, Ser447Ter polymorphism.
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INTRODUCTION

Obesity prevalence has increased all over the world as a pandemic.[1] Obesity is a complex disease that is based on the interaction of environmental factors and genetic predisposition. To date, more than 30% of the world's population is obese (WHO, 2014). Along with an increase in the number of adults who are overweight and obese, there is an increase in the number of children and adolescents with established diagnoses of obesity.[2,3] The question of the role of heredity in the formation of obesity is still controversial.[4] Obesity can be defined as the biological case resulting from the accumulation of excess fat or these fats which have little use as a source of bio-energy due to the weakness of human activity or individual tendency to avoid movement, work, or environmental interaction.[5]

Lipoprotein lipase (*LPL*) is a key enzyme involved in the process of removing triglycerides from plasma. *LPL* catalyzes the hydrolysis of triglycerides in very low-density lipoprotein (VLDL) particles and chylomicrons. The maximum amount of *LPL* is determined in skeletal muscle and adipose tissue. Apolipoprotein CII is involved in *LPL* activation.[6] LPL plays a significant role in lipid metabolism and lipid transport. Therefore, chylomicrons and VLDLs produce chylomicron and lipoprotein intermediate density residues (IDLs); accordingly,

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it is considered the enzyme responsible for the hydrolysis of core triglycerides.[7]

The *LPL* is located on chromosome 8p22, consists of 10 exons, and encodes a 474 amino acid precursor for the enzyme. Two mutations of the *LPL* gene are known. This is a point mutation 1595C> G (Ser447Stop), which leads to the formation of a stop codon at the site of serine-447, and thus an abridged copy of the enzyme is synthesized. The polymorphic marker Ser447Ter is located in exon 9. The presence of the 447Ter allele, which leads to the loss of two C-terminal amino acids, is associated with an increase in the catalytic activity of *lipoprotein lipase* and, as a result, an 8% decrease in the average level of triglycerides in blood plasma.[6]

On the other hand, Ser447X polymorphism is associated with increased HDL-C and decreased triglyceride levels in certain populations and, thus, may be associated with protective effects in atherogenesis via its favorable lipoprotein profile.[8] A study done among Italian patients showed that carriers of the Ser447X polymorphism presented with higher HDL-C concentration as well as significantly reduced risk of high triglyceride/low HDL-C dyslipidemia.[9] A study of a homogenous Caucasian population likewise showed significantly lower levels of triglyceride levels among those with Ser447X polymorphism.[10] In this study, we investigated and correlations the Ser447Ter polymorphism within obesity. Estimate the *LPL* gene in association with obesity and obesity-associated phenotypes.

METHODS

Subjects

In 870 children and adolescents of both 3 and 17-year-olds, an example study investigated the relation between *LPL* gene polymorphisms of the Ser447Ter (S447X) and obesity. The obese group consisted of 540 participants. Group control: 330 healthy individuals, children, and adolescents. The major selection criterion for the study was the BMI. The obese population included children and adolescents people with BMI>30 kg/ m^2, while participants of children and adolescents without obesity (BMI range 18.5 to 24.9 kg per m^2). Genotypes study have been undertaken in the Genetics Institute of the South Federal University. Patients were recruited to the Center of Science Medicine (Rostov region, Russia).

In addition, all study participants of children and adolescents were informed, and consent was given in accordance with the Helsinki Declaration of the World Medical Association "Ethical Principles for Medical Science and Human Participation" (as amended from 2000) and the "Rules of Clinical Practice in the Russian Federation" (approved by order of the Ministry of Health Russia dated June 19, 2003 No. 266).

Genotyping Methods

Genomic DNA using blood expression reagent was extracted from whole blood leukocytes (NPF Litech, Russia). In addition, Spectrophotometer NanoDrop 2000c has checked the purity of DNA samples (Thermo Scientific, USA). Therefore, DNA samples have used commercial NPF-Liteh test equipment with electrophoretic detection for the type of the *LPL* gene Ser447Ter (C>G) polymorphism.

The SNP-Express reagent kit was used to study the allelic variant *LPL* Ser447Ter gene (Lytech, Russia). The study is based in two pairs of allel allele-specific primers on amplification reactions. Horizontal electrophoresis in 3% agarose gel separated amplification products.

Statistical Analysis

The parametric data for normality is analyzed, though significant variations in the genotyping and alleles frequencies were computed using the online Hardy-Weinberg.[11]

Compatibility with the theoretically expected distribution in the equilibrium of Hardy-Weinberg of alleles and genotypes variant of the *LPL* Ser447Ter gene was analyzed with the $\chi 2$ test. Continuity and odds Ratio (OR) and confidence intervals were adjusted (95% CI). The association between obesity and genotypes was estimated using the odd-ratio (OR) and 95% (CI)confidence interval in assessing obesity risk associated with investigated alleles, where was using version 11.65 of WinPepi computer software.[12]

RESULTS

The study associating the analyzed gene *LPL* Ser447Ter with obesity has been performed in obese and control groups of children and adolescents. Table 1 shows the comparison between genotypes and frequencies of the distributions for Ser447Ter polymorphisms in the patients and controls. The SerSer genotype was observed in 463 patients (85.7%) in the obesity community for the Ser447Ter genotype, while 76 patients (14.1%) carried the SerTer genotype. The SerSer and Ser447Ter genotypes were found in the control group in 275 (83.3%) and 55 (16.7%). We have detected no TerTer genotypes for this gene in the control group, while in other group detected TerTer genotypes 1 (0.2%) only. In the obesity group, a higher frequency of the SerSer genotype and a lower frequency of the Ser447Ter genotype, and the absence of the TerTer genotype were observed compared with the control group.

Table 1: *LPL* Ser447Ter Polymorphisms frequency and percentage in the studied groups.

Gene/Genotypes		*Obesity n = 540(%)*	*Controls n = 330(%)*	χ^2	*P*
LPL Ser447Ter	SerSer	463 (85.7)	275 (83.3)	1.665	0.496
	SerTer	76 (14.1)	55 (16.7)		
	TerTer	1 (0.2)	0 (0.0)		

X^2: Pearson chi-square, *P*: Fisher's probability (two-tailed).

Table 2: The frequency distribution analysis of the *LPL* Ser447Ter genotypes in the obese and control groups.

Genotypes LPL Ser447Ter	*Obese n =540*	*Controls n = 330*	χ^2	*P*	*OR 95% CI*
SerSer	463	275	0.922	0.381	1.20 (0.83–1.75)
SerTer	76	55	1.076	0.329	0.82 (0.56–1.19)
TerTer	1	0	0.612	1.000	1.84 (0.07 – 45.05)
Allele frequency	n = 1080(%)	n = 660(%)			
Ser	1002 (92.8)	605 (91.7)	0.716	0.404	1.17 (0.82 – 1.67)
Ter	78 (7.2)	55 (8.3)			0.86 (0.60 – 1.23)

P: Fisher's exact probability (two-tailed), X^2: Pearson chi-square, OR: odds ratio, 95% CI: 95% confidence interval.

Table 3: frequencies of the genotyping of *LPL* Ser447Ter in the patients' group compared to the control group.

Genotyping Ser447Ter	*Obesity n=540(%)*	*Chi-squared (chi2*	*Controls n = 330(%)*	*Chi-squared (chi2*
SerSer	463 (85.7)	1.361	275 (83.3)	2.727
SerTer	76 (14.1)		55 (16.7)	
TerTer	1 (0.2)		0 (0.0)	
P-HWE	0.243		0.098	

P-HWE: the probability of Hardy-Weinberg equilibrium, X^2: Chi-squared value – HWE.

Table 4: The *LPL* Ser447Ter gene frequency genotypes of recessive and dominant in both groups.

Genes	*Genotypes*	*Obesity n = 540*	*Controls n = 330*	χ^2	*P*	*OR (95% CI)*
LPL Ser447Ter	[a]TerTer + SerTer	77	55	0.922	0.381	0.83 (0.57–1.21)
	vs SerSer	463	275			
	[b]TerTer *vs*	1	0	0.612	1.000	1.84 (0.07– 45.05)
	SerTer + SerSer	539	330			

P: Fisher's probability (two-tailed), X2: Pearson chi-square, OR: odds ratio, 95% CI: confidence interval, (a) dominant model, (b) recessive model.

We were analyzing the distribution of Ser447Ters polymorphism genotype locus, which showed that the SerSer g enotype of 83% of obese participants was typical. But it was observed that the polymorphism locus Ser447Ter of the *LPL* gene has not been confirmed for obesity ($p > 0.05$). The alleles results shown comparing the *LPL* gene alleles distribution, the frequency of the ser44 allele was found to be greater in both groups (92.8 and 91.7%) respectively compared to the 447Ter allele frequency (7.2 and 8.3%). Simultaneously, our findings showed that no substantial variation had been detected in the distribution of the *LPL* Ser447Ter gene alleles in both groups ($p > 0.05$) (Table 2).

Table 3 shows the genotypes of the frequencies observed. The distribution of the genotypes yielded from the Hardy-Weinberg equilibrium was calculated for Ser447Ter polymorphism in the patients and controls.

While constructing dominant and recessive models, for polymorphism Ser447Ter (rs328) of the *LPL* gene, the genotypes frequencies of SerSer and SerTer had been no longer differed within the analyzed corporations a dominant and recessive fashions TerTer + SerTer vs SerSer ($p = 0.381$); OR: OR: 0.83; 95% (CI: 0.57–1.21)) and ($p = 1.000$); OR: 1.84; 95% CI: (0.07–45.05)) respectively as in Table 4. In the construction of dominant and recessive models, there was similarly no statistically significant difference between the two groups (Table 4).

DISCUSSION

This research represents the first report in the Rostov-on-Don population on the frequency of *lipoprotein lipase* polymorphisms Ser447Ter genotypes of participations that have obesity. Some studies have suggested that *LPL* activity in obesity is high in adipose tissue.[13,14] *LPL* has dual main functions: hydrolase triglyceride and lipoprotein absorption by the receptor.[15] The S447X of the *LPL* gene variation is linked to differences in plasma lipids in different populations.[16] In addition, a gene *LPL* imbalance may change the TG plasma partition between the adipose tissue and the muscle and so affect resistance to insulin and obesity.[13,14]

The study investigated the frequencies of genotype and allelea associated with overweight of the gene Ser447Ter *Lipoprotein lipase* and association with overweight in the Rostov on Don of children and adolescents from Russia. As also, and as far as of our knowledge, this is the first related study for the Rostov region. And therefore, found that *LPL* Ser447Ter SNP was not significantly associated with obesity. The observed results were consistent with similar earlier investigations that were conducted in other populations.[17,18] In addition, in the present study, the Ser447Ter polymorphism frequencies (CC, 85.50; CG, 13.50 and GG, 0.0) were similar to those observed in different ethnic groups, And the Ser447Ter polymorphism (C) and (G) allele frequencies in this sample

were similar to those observed in other populations of Zhichun Z. *et al*.[17]

In addition, there are several meta-analysis studies on stroke risk and hypertension, and blood pressure with the *LPL* gene is considered to be a protective factor.[19–21] There are also several original studies on coronary heart disease, stroke, hyperinsulinemia and insulin resistance with a gene *LPL* considered to have an effect on plasma lipid levels,[22] while an original study showed that the *lipoprotein lipase* gene has no association with coronary heart disease.[23,24] There is also an original study on hyperinsulinemia and insulin resistance with a gene *LPL* that is not considered to be associated with hyperinsulinemia and insulin resistance in the Kazakh population.[25] Therefore, there are few studies on the association of the gene *LPL* Ser447Ter polymorphism with obesity to be discussed with our current study, which showed in our study that there is no association with obesity.

In this study, however, there was no association between *LPL* rs328 and obesity in children and adolescents, and also this corresponds to Arezoo A. K. *et al*.[26] Therefore, It could be explained by the ethnic differences, eating habits, and limitations that may affect the study. In this case, it is advisable to study the prevalence and associations of the above gene polymorphisms in different ethnic groups. Giving regard to the ethnic characteristics of the population within examination, The mutation's interaction with the phenotype in order to establish subsequent causal relationships in disease development. In addition, to study the pathogenesis of obesity, a comprehensive study of the polymorphisms of different genes is needed to develop the disease.

CONCLUSIONS

In conclusion, the investigation in this study observed the absence of an association of the *LPL* gene in the Ser447Ter polymorphisms with obesity. Therefore, a study of domestic and foreign literature suggests that further research is needed to investigate the genetic aspects of obesity pathogenesis.

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