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ORIGINAL RESEARCHES

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LIPOPROTEIN LIPASE GENE POLYMORPHISM rs320 AND METABOLIC SYNDROME IN NATIVE PEOPLE OF YAKUTIA

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The **aim** of the study was investigation the relationship of allelic variants and genotypes of the rs 320 polymorphism of the LPL gene with the metabolic syndrome and its components in adult population of the Yakut ethnic group. In the studied group, it was not possible to establish a direct connection between the allelic variants, the genotypes of the LPL rs320 gene with the metabolic syndrome and its components. However, it is important to note individuals with the TT genotype had somewhat higher level of triglycerides in the blood. It may be associated with a small sample size. We assume that the T allele is associated with low enzyme activity in this population, and plays a key role in the development of diseases associated with metabolic disorders.

Keywords: obesity, metabolic syndrome, multiple metabolic risk factors, population, genetics, rs320 polymorphism of the LPL gene, dyslipidemia, indigenous population, Yakutia, North.

One of the variants of the LPL gene, which encodes the enzyme lipoprotein lipase, is the replacement of thymine (T) by guanine (G) at position 495 in intron 8. The Hind III (rs320) polymorphism changes the recognition site of the Hind III restriction enzyme and affects the activity of the enzyme. In recent studies, it was shown that the polymorphism rs320 of the LPL gene has a significant effect on the structure of the precursor RNA [9]. The frequency of minor G allele in different world populations varies from 24 to 38%, the highest frequency is observed among the population of Saudi Arabia (37,6%) [3, 5]. The literature presents conflicting data on the role of Hind III (rs320) polymorphism in the development of diseases associated with lipid metabolism disorders. In some studies, the presence of a minor allele was associated with a lower risk of diseases associated with impaired lipid metabolism [4, 10, 12, 16], in other studies the presence of this polymorphism was a risk factor for the development of metabolic disorders and related diseases [7, 13].

In early studies the significant association between LPL rs320 with type 2 diabetes in the Yakut population has shown [1, 2, 3]. However, the mechanism of the influence of polymorphism on the development of metabolic disorders has not been studied enough. It is known that the inhabitants of the North from time immemorial adapted to a diet rich in fats. Currently, there is an intensive increase in the incidence of metabolic disorders in the Yakut population. In this regard, the study of the mechanisms of the influence of the LPL gene on the metabolism of indigenous peoples is a very interesting.

The purpose of this study was to estimate of the allele and genotype frequency of LPL gene rs 320 polymorphism and its association with metabolic parameters and components of the metabolic syndrome in the adult population of Yakut nationality living in Central Yakutia.

Materials and methods: The genotype frequency of the LPL gene rs320 was estimated among the unorganized population of the Central region (Gorny ulus, village Berdigestyakh) of the Sakha Republic (Yakutia). The research project was approved by the local bioethics committee of the Yakut Scientific Center for Complex Medical Problems (Protocol No. 39 dated June 26, 2014). Participation in the study was completely voluntary. Obtained clinically useful information was available to study participants. The initial participant's selection was based on household lists. The study included persons of the Yakut nationality (by self-determination) at the age of 18 and older, regardless of whether they have any somatic disease (n = 363).

Analyze of rs320 polymorphism was performed in 189 representatives (142 women and 47 men aged 18 years and older) who gave voluntary informational consent to conduct genetic studies. The average age was 52.7 (13.7) years. All participants were examined by a single program, including anthropometric examination by the standard method, analysis of body composition for bio-impedance analysis "Tanita" (Japan) SSC 330, twofold blood pressure measurement (BP), fasting venous blood sampling. The content of glucose, total cholesterol (cholesterol), triglycerides, high density lipoproteins (HDL cholesterol) was determined on the express analyzer Cardiochek PA, USA. The concentration of low-density lipoprotein cholesterol (LDL cholesterol)

was calculated using the Friedwald formula with a blood triglyceride level of less than 4.5 mmol/l.

Hypertriglyceridemia was established with triglycerides ≥1.7 mmol/l, hypoalphalesterolemia - at HDL cholesterol concentrations <1.0 mmol/l in men and <1.3 mmol/l in women; elevated blood pressure — with CAD ≥130 mmHg and/or DBP ≥85 mmHg; fasting hyperglycemia - with blood plasma glucose ≥5.6 mmol/l. Persons received specific medical treatment for these conditions were also referred to patients with metabolic disorders. Multiple metabolic disorders were established with 2 or more of the 4 above-mentioned risk factors. The following criteria were used to diagnose obesity: body mass index ≥30 kg/m2; the ratio of waist circumference to height ≥0.5; waist circumference by IDF criteria (IDF1) for European populations (more than 80 cm in women and 94 cm in men); IDF (IDF2) for Asian populations (more than 80 cm in women and 90 cm in men) [13].

LPL rs320 SNP was genotyped by the PCR-RFLP method. Amplification was performed with specially selected primers and ready-made commercial reaction mixtures on the T-100 amplifier (Bio-Rad). Next, the PCR products were subjected to Hind III restriction enzyme (New England Biolabs) according to the manufacturer's protocol. Restriction products were visualized using electrophoresis in a 3% agarose gel on the gel documentation system BDA digital system 20 (Biometra). Each reaction was carried out in triplicate.

The verification of the distribution of genotypes to the equilibrium state of Hardy-Weinberg was carried out using an online calculator at https://wpcalc.com/en/equilibrium-hardy-weinberg / [6]. Statistical data analysis was carried out in the IBM SPSS STATISTICS 22 package. The comparison of groups was performed using Mann-Whitney and Pearson χ2 criteria depending on the type of data. The critical value of the level of statistical significance of differences (p) was 5%.

Results and discussion. The distribution of genotypes, both in general among all examined, and in groups by age and sex, did not correspond to the Hardy-Weinberg equilibrium (Table 1). This is probably due to due to insufficient size of the studied group. However, an attempt to assess the relationship between lipid, anthropometric parameters and LPL rs320 was made as the part of exploratory research.

In the studied group, the T allele frequency was 68%, and the G allele - 32%. The TT genotype (58.7%) was the most common; GG (12%) was a rare genotype. The frequency of the heterozygous variant was 29%. Thus, homozygous genotypes were more common than heterozygous (table 1). These distributions are consistent with data from other European and Asian populations [3]. Table 2 presents the quartile distribution of some biochemical and anthropometric data depending on the genotype and allelic variants of the rs320 polymorphism. The triglycerides level in the blood of individuals with the TT genotype was slightly higher than that of GG homozygotes. The GT genotype was associated with lower diastolic pressure values compared to homozygotes. There were no statistically significant differences in the levels of other indicators.

Metabolic syndrome was observed in 27 studied patients (14.3%). The most common variant of the metabolic syndrome was a combination of central type of obesity, high blood pressure and dyslipidemia. The frequency of the metabolic syndrome and its components did not depend on the genotypes and allelic variants of the studied polymorphism (table 3). This result may be due to the limited number of observations with metabolic syndrome and lipid disorders. To date, the effect of rs320 polymorphism on the enzyme lipoprotein lipase activity and metabolic processes in the human body is not completely clear. Most studies have shown that allele G is associated with a low risk of developing metabolic syndrome, acute cardiovascular conditions (strokes, heart attacks), and a lower risk of developing hypertension [4, 10, 15]. But at the same time, there are works indicating that carriers of the GG genotype have a high risk of diabetic dyslipidemia and type 2 diabetes [11, 13]. There are studies that suggest the association of the genotype and nutrition in the form of greater sensitivity to the diet of carriers of the T allele, compared with carriers of G [7, 8, 15, 17].

Early studies in the Yakut population showed association of T alleles with an increased risk of type 2 diabetes [1, 2, 3]. Our data show that the TT genotype may be associated with low enzyme activity and an increase in triglyceride levels in the blood. Contradictory results of the different authors may be related to the fact that, the functioning of a gene is significantly affected by the lifestyle, physical activity of a person and the type of food, because the gene product associated with energy metabolism [1, 2]. The lower prevalence of diabetes and cardiovascular diseases among the indigenous people of the North in historical past is probably associated with a change in the energy balance of modern man.

Conclusion. In the studied indigenous population of Yakutia, we did not reveal an association of the rs320 polymorphism of the LPL gene and metabolic parameters, which may be due to limitations in the formation of the group. The allele and genotype frequency were close to those described for rs320 in other groups of the world's population. The obtained data and the analysis of literature suggest that the T allele carrier, associated with a low activity of the enzyme that hydrolyzes triglycerides in chylomicrons and LDL, may increase the risk of metabolic disorders under conditions of changes of energy balance.

Considering that this population is evolutionarily adapted to food rich in fats, study of the rate of utilization of dietary fats in individuals with different LPL rs320 genotypes could be of scientific interest.

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Table 1

Frequency distribution of alleles and genotypes of the rs 320 polymorphism of the *LPL* gene among the population

rs 320	n (%)	
Alleles		
G	78 (32)	
T	166 (68)	
Genotypes		
GG	23 (12.2)	χ^2= 12.47 p<0.001
GT	55 (29.1)	
TT	111 (58.7)	

Note: χ2 - Pearson Chi-square test; p - the achieved level of significance when checking compliance with the Hardy-Weinberg equilibrium distribution.

Table 2

Anthropometric and metabolic characteristics of the respondents depending on the allelic variant and the genotypes of the rs 320 polymorphism of the *LPL* gene

Genotypes						Аллель	
TT/GT		GT/GG		TT/GG		G/T	
Me (Q_1;Q_3)	p	Me (Q_1;Q_3)	p	Me (Q_1;Q_3)	p	Me (Q_1;Q_3)	p
Systolic blood pressure, mm Hg							
120 (110;130) 115 (100;129)	0.256	115 (100;129) 120 (107;138)	0.319	120 (110;130) 120 (107;138)	0.653	115 (100;130) 116 (110;130)	0.748
Diastolic blood pressure, mm Hg							
75 (70; 82) 70 (60; 80)	0.047	70 (60; 80) 80 (68; 90)	0.014	75 (70; 82) 80 (68; 90)	0.211	75 (63; 80) 75 (65; 80)	0.776
TC, mmol / l							
5.0 (4.2; 5.6) 4.7 (3.9; 5.7)	0.199	4.7 (3.9; 5.7) 4.9 (4.2; 5.6)	0.669	5.0 (4.2; 5.6) 4.9 (4.2; 5.6)	0.533	4.8 (4.1; 5.6) 4.9 (4.2; 5.7)	0.394
HDL-C, mmol / l							
1.7 (1.4;2.0) 1.8 (1.6;2.1)	0.096	1.8 (1.6; 2.1) 1.7 (1.4; 2.0)	0.308	1.7 (1.4; 2.0) 1.7 (1.4; 2.0)	0.959	1.8 (1.5; 2.0) 1.7 (1.5; 2.0)	0.439
TG, mmol / l							
0.9 (0.8; 1.2) 0.9 (0.6; 1.1)	0.265	0.9 (0.6; 1.1) 0.8(0.6; 1.0)	0.215	0.9 (0.8; 1.2) 0.8 (0.6; 1.0)	0.046	0.8 (0.6; 1.0) 0.8 (0.6; 1.2)	0.133
LDL-C, mmol / l							
2.8 (2.1; 3.4) 2.0 (2.5; 3.2)	0.112	2.0 (2.5; 3.2) 2.6 (2.2; 3.5)	0.338	2.8 (2.1; 3.4) 2.6 (2.2; 3.5)	0.924	2.5 (2.1; 3.2) 2.7 (2.1; 3.4)	0.450
Glucose, mmol / l							
4,7 (4,4; 5,1) 4,7 (4,4; 5,1)	0.853	4.7 (4.4; 5.1) 4.7 (4.2; 5.0)	0.541	4.7 (4.4; 5.1) 4.7 (4.2; 5.0)	0.368	4.7 (4.3; 5.1) 4.7 (4.4; 5.1)	0.260
Fat %							
18.4 (13.9; 26.5) 19.1 (12.8; 24.3)	0.903	19.1 (12.8; 24.3) 18.5 (14.5; 26)	0.938	18.4 (13.9; 26.5) 18.5 (14.5; 26)	0.946	19 (14.3;24.7)/19 (13.9;25.3)	0.973
BMI, kg / m2							
25.3 (22.7; 29.2) 24.7 (22.1; 27.5)	0.291	24.7 (22.1; 27.5) 25.1 (22.1; 28.5)	0.591	25.3 (22.7; 29.2) 25.1 (22.1; 28.5)	0.860	25.1 (22.1; 28.1) 25.1 (22.3; 28.4)	0.567
waist, sm							
91.9 (85.7; 101.8) 94.3 (83.2; 98.7)	0.802	94.3 (83.2; 98.7) 94.8 (83.8; 100.0)	0.967	91.9 (85.7; 101.8) 94.8 (83.8; 100.0)	0.791	93.3 (83.5; 99.3) 92.7 (85.4; 99.6)	0.824
Waist /growth							
0.58 (0.53; 0.65) 0.59 (0.54; 0.64)	0.99	0.59 (0.54; 0.64) 0.58 (0.53; 0.65)	0.697	0.58 (0.53; 0,65) 0.58 (0.53; 0.65)	0.755	0.8 (0.53; 0.64) 0.59 (0.53; 0.64)	0.862

Note: p - the achieved level of statistical significance of differences when comparing groups using the Mann-Whitney test; Me (Q1; Q3) - median (25-75%); BMI - body mass index, OT-waist circumference;

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Table 3

The frequency of the metabolic syndrome and its components depending on the allelic variant and the genotypes of the rs 320 polymorphism of the *LPL* gene

Factor	Genotypes n (%)			χ^2, p	Alleles n (%)		χ^2, p
	GG n=23	GT n=55	TT n=111		G n=78	T n=166	
Raised blood pressure							
Yes	13 (10.9)	36 (30.3)	70 (58.8)	χ^2=0.776 p=0.67	49 (31.6)	106 (68.4)	χ^2=0.003 p=0.955
No	9 (14.1)	16 (25)	39 (60.9)		25 (31.3)	55 (68.8)	
Reduced HDL cholesterol							
Yes	4 (28.6)	3 (21.4)	7 (50)	χ^2=3.845 p=0.146	7 (41.2)	10 (58.8)	χ^2=0.713 p=0.425
No	19 (10.9)	52 (29.7)	104 (59.4)		71 (31.3)	156 (68.7)	
Raised triglycerides							
Yes	4 (16)	4 (16)	17 (68)	χ^2=2.468 p=0.291	8 (27.6)	21 (72.4)	χ^2=0.290 p=0.590
No	19 (11.6)	51 (31.1)	94 (57.3)		70 (32.6)	145 (72.4)	
Raised fasting plasma glucose							
Yes	4 (16)	4 (16)	17 (68)	χ^2=2.315 p=0.314	8 (27.6)	21 (72.4)	χ^2=0.287 p=0.675
No	19 (11.9)	49 (30.6)	92 (57.5)		68 (32.5)	141 (67.5)	
Obesity							
Yes	11 (12.4)	25 (28.1)	53 (59.6)	χ^2=0.087 p=0.957	36 (31.6)	78 (68.4)	χ^2=0.002 p=1.0
No	6 (11.3)	16 (30.2)	31 (58. 6)		22 (31.9)	47 (68.1)	
Abdominal obesity IDF_1							
Yes	14 (10.9)	37 (28.7)	78 (60.5)	χ^2=0.23 p=0.891	51 (30.7)	115 (69.3)	χ^2=0.124 p=0.732
No	5 (12.8)	12 (30.8)	22 (56.4)		17 (33.3)	34 (66.6)	
Abdominal obesity IDF_2							
Yes	14 (11.6)	36 (29.8)	71 (58.7)	χ^2=0.129 0.938	50 (31.8)	107 (68.2)	χ^2=0.069 p=0.871
No	5 (10.6 %)	13 (27.7)	29 (61.7)		18 (30)	42 (70)	
Multiple metabolic risk factors							
Yes	7 (18.4)	9 (23.7)	89 (58.9)	χ^2=2.013 p=0.366	16 (34)	31 (66)	χ^2=0.45 p=0.734
No	16 (10.6)	46 (30.5)	89 (58.9)		62 (31.5)	135 (68.5)	
Metabolic syndrome							
Yes	4 (14.8)	6 (22.2)	17 (63)	χ^2=0.945 p=0.623	10 (30.3)	23 (69.7 %)	χ^2=0.019 p=1.0
No	15 (10.6)	43 (31.5)	83 (58.9)		58 (31.5)	126 (68.5)	

Note: $\chi 2$ * - Pearson Chi-square test, p – significance level

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