ORIGINAL RESEARCHES

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POLYMORPHIC MARKER RS137100 OF THE *LEPR* GENE AND METABOLIC DISORDERS IN THE INDIGENOUS POPULATION OF YAKUTIA

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The aim of the study was the search for associations of polymorphic marker rs1137100 of *LEPR* gene with lipid specter, metabolic syndrome and its components among indigenous population of Yakutia. The study involved 227 representatives of the Yakut nationality, permanently residing in the village of Berdigestyakh, Gorny Ulus of Yakutia. We found a significant relationship between allelic variant A, genotypes AA/AG of *LEPR* gene with hypoalphacholesterolemia. No association with metabolic syndrome or its components was found.

Keywords: *LEPR* gene, polymorphic marker rs 1137100, obesity, metabolic syndrome, population, genetics, dyslipidemia, indigenous population, Yakutia, North.

Introduction. Leptin is a hormone produced in adipocytes and is involved in the regulation of satiety, energy balance, and fat metabolism. In recent studies it was shown that leptin stimulates glucose uptake and fatty acid oxidation, participates in the secretion of insulin through *LEPR* receptors, which are localized in the β-cells of the pancreatic gland, adipose tissue, and muscle [10]. Leptin receptor is a transmembrane protein belonging to the superfamily of cytokine receptors; it has several alternative isoforms.Leptin receptors form homodimers that can activate paths JAK2/STAT3, which regulate food intake and energy balance. The *LEPR* gene localized on chromosome 1 (1p31.3) has been studied in various ethnic groups [9]. We describe polymorphic variants of the *LEPR* gene associated with obesity, insulin resistance, diabetes, and increased risk of cardiovascular and oncologic disease [7]. However, the results of studies in different ethnic populations are contradictory.

In polymorphism of rs1137100 (K109R), lysine is replaced by arginine (AGG by AAG) at codon 109, exon 4 (K109R). Currently, there are many studies focusing on the role and relationship of K109R polymorphism with lipoproteins, metabolic syndrome [15, 17], obesity [4, 8, 10, 12], diabetes mellitus [16], increased risk of developing cardiovascular diseases [6], but the research results are ambiguous.

This study aims to study the association of *LEPR* gene polymorph marker (rs1137100, K109R) with lipid profile, metabolic syndrome and its components in a sample of representatives of the Yakut population.

Materials and Methods. The sample was formed in the course of a one-stage observational study among the unorganized population of the village Berdigestyakh, Gorny Ulus of the Sakha (Yakutia) Republic. The genetic study was carried out in 227 representatives of the Yakut nationality, permanently residing in this settlement. The age of the respondents was 18 and older, the av-

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Table 1

Distribution of Alleles and Genotypes of *LEPR* Gene Polymorphic Marker (Rs137100) In A Group of Yakut Nationality*

Group	n (%)			R
	Allele			
	A	G		
Men Women	28 (30.8) 71 (34.6)	63 (69.2) 134 (65.4)		0.515
Both sexes	99 (33.4)	197 (66.6)		
20-39 years old 40-59 years old 60 years and older	39 (32.5) 43 (35) 17 (32.1)	81 (67.5) 80 (65) 36 (67.9)		0.896
Genotype				
	AA	AG	GG	
Men Women	8 (11.2) 22 (14.1)	20 (28.2) 49 (31.4)	43 (60.6) 85 (54.5)	0.675
Both sexes	30 (13.2)	69 (30.4)	128 (56.4)	
20-39 years old 40-59 years old 60 years and older	9 (10) 13 (14) 8 (18.2)	30 (33.3) 30 (32.2) 9 (20.4)	51 (56.7) 50 (53.8) 27 (61.4)	0.453

Note: * Distribution of genotypes in all groups is consistent with the Hardy-Weinberg law of equilibrium; p is the achieved level of statistical significance of differences when comparing groups using the Pearson $\chi 2$ test.

erage age was 43±17.5. Gender-wise the respondents were primarily women with 156 (68.4%), with 72 men (31.6%). The research project was approved by the local Committee on Bioethics of the Yakutsk Scientific Center for Complex Medical Problems (extract from Minutes No. 39 dated June 26, 2014). All participants signed informed voluntary consent to participate in the study.

The criteria of the International Diabetes Federation (IDF, 2005) were used to verify the metabolic syndrome. All participants were examined according to a single program, which included: anthropometric examination according to the standard method, analysis of body composition using a Tanita Bioimpedance Analyzer (Japan) SSC 330, double measurement of blood pressure (BP), and fasting venous blood sampling. The content of glucose, total cholesterol (TC), triglycerides, high density lipoproteins (HDL cholesterol) was determined on an Express Analyzer CardioChek PA, USA. We have also taken into account the conducted medicinal treatment for hypertension, diabetes, and lipid disorders. The following criteria were used to diagnose obesity: body mass index ≥ 30 kg/m2; the size of the waist circumference more than 80 cm in women and 94 cm in men (according to the IDF criteria for European populations) [13]. Obesity was diagnosed in 46 (20.8%) individuals. The metabolic syndrome was detected in 36 respondents, which amounted to 16.4% of the total number of those surveyed. Among women, metabolic syndrome occurred significantly more often than among men – 20.7 and

Table 2

Frequency of Allelic Variant G of the *LEPR* Gene Polymorphic Marker (Rs137100) In Different Ethnic Groups*

Authors, year	Country	Population	N	Floor	Allele frequency G (95% CI)
Data from this study, 2017	Russia	Yakuts	228	Both sexes	0.66 (0.68; 0.72)
Matsuoka et al., 1997.	Japan	Asians	115	Both sexes	0.78 (0.70; 0.85)
Koh et al., 2002	Korea	Asians	220	Men	0.83 (0.78; 0.88)
Gotoda et al., 1997	England	Europeans	322	Both sexes	0.27 (0.22; 0.31)
Mamme's et al., 2001	France	Europeans	566	Both sexes	0.25 (0.21; 0.28)
Wauters et al., 2001	Belgium	Europeans	280	Women	0.28 (0.22; 0.33)
Yiannakouris et al., 2001	Greece	Europeans	118	Both sexes	0.12 (0.06; 0.18)

Note: N – the number of examined; CI – confidence interval.

Table 3

Anthropometric and Metabolic Characteristics of Respondents Depending on the Allelic Variant and Genotypes of The *LEPR* Gene Polymorphic Marker (rs137100)

Indicators	Genotype	Me (Q_1;Q_3)	p	Allele	Me (Q_1;Q_3)	p
SBP, mm Hg	AA и AG	112.7 (106.7; 126.7)	0.143	A	112.6 (106.6; 126.6)	0.508
	GG	120 (108.3; 134.0)		G	115.8 (107.3; 130.0)	
DBP, mm Hg	AA и AG	75.3 (70.0; 82.0)	0.195	A	75.3 (70.0; 82.0)	0.603
	GG	77.7 (70.0; 88.5)		G	76.1 (70.0; 85.0)	
Total cholesterol, mmol/l	AA и AG	4.2 (3.6; 5.3)	0.358	A	4.1 (3.5; 5.2)	0.452
	GG	4.4 (3.6; 5.2)		G	4.4 (3.5; 5.2)	
HDL cholesterol, mmol/l	AA/AG	1.7 (1.47; 2.1)	0.300	A	1.6 (1.4; 2.0)	0.370
	GG	1.7 (1.4; 2.2)		G	1.7 (1.4; 2.2)	
Triglycerides, mmol/l	AA / AG	0.9 (0.8; 1.1)	0.683	A	0.8 (0.7; 1.0)	0.810
	GG	0.9 (0.8; 1.118)		G	0.8 (0.7;1.0)	
LDL cholesterol, mmol/l	AA / AG	2.7 (1.7; 4.0)	0.244	A	2.6 (1.6; 4.0)	0.529
	GG	2.3 (1.7; 3.5)		G	2.3 (1.6; 3.8)	
Fasting glucose, mmol/l	AA /AG	5.1 (4.6; 5.5)	0.322	A	5.1 (4.6; 5.5)	0.352
	GG	5.0 (4.6; 5.446)		G	5 (4.5; 5.5)	
Body weight, kg	AA/AG	59.5 (51.9; 71.7)	0.606	A	59.4 (51.9; 71.6)	0.797
	GG	60.8 (53.8; 70.7)		G	59.8 (53.2; 70.6)	
Body mass index, kg/m^2	AA/AG	23.5 (20.3;27.3)	0.550	A	23.5 (20.3; 27.3)	0.816
	GG	23.6 (21.6; 28.3)		G	23.5 (20.9; 27.5)	
Waist circumference, cm	AA/AG	85.50 (76.2; 96.2)	0.344	A	85.5 (76.2; 96.2)	0.578
	GG	87.2 (79.8; 96.5)		G	85.9 (77.7; 96.2)	
Atherogenic index	AA/AG	1.5 (1.0; 2.2)	0.937	A	1.5 (0.9; 2.2)	0.911
	GG	1.4 (1.0; 1.9)		G	1.4 (1.0; 2.0)	
Fat percentage	AA/AG	15.8 (9.5; 22.6)	0.897	A	15.8 (9.5; 22.6)	0.960
		16.6 (10.2; 22.8)		G	16.4 (9.7; 22.6)	

Note: p is the achieved level of statistical significance of differences when comparing groups using the Mann-Whitney test; data are presented as median and interquartile range in Me format (Q_1; Q_3).

7.2%, respectively (Fisher's exact test, p = 0.017).

For SNP genotyping, we have used TaqMan probes specific to the regions containing the SNPs of interest. Samples and primers were developed using PREMIER Biosof's Beacon Designer 8 software. FAM and R6G dyes were used as reporters, and BHQ-1 was used as a quencher. Real-time polymerase chain reaction was performed in a CFX96 system from Bio-Rad. The volume of the reaction mixture was 25 µl. Each reaction was performed in triplicate. Reaction conditions: activation stage was carried out at 95°C for 3 minutes, course of one cycle consisted of three temperature-time intervals – 95°C (30 sec), 54°C (20 sec) and 72°C (20 sec). The total number of cycles was 40.

The verification of the correspondence of the distribution of genotypes to the Hardy-Weinberg equilibrium state law was carried out using an online calculator at https://wpcalc.com/en/equilibrium-hardy-weinberg/ [11]. Statistical analysis of the data was carried out in the IBM SPSS STATISTICS 22 software suite. When comparing groups depending on the type of data, we used the Mann-Whitney and Pearson χ2 tests. The critical value of the level of statistical significance of differences (p) was taken equal to 5%.

Results and Discussion. The distribution of allelic variants and genotypes of polymorphic markers of the LEPR gene (rs137100) in the group of Yakut people is shown in Table 1. The distribution of genotypes in subgroups is consistent with the Hardy-Weinberg equilibrium state law. In the studied sample, the GG 128 genotype was more common (56.4 %), with the AA 30 genotype being less common (13.2%).

Table 2 shows frequency of polymorphic allelic variant G in different ethnic populations. This variant is significantly more frequent in Asian populations than the European populations. The frequency of allelic variants of G in the Yakut population is similar to other Asian populations [10].

When comparing quartile distribution anthropometric and metabolic until exponent depending on allelic variants and genotypes of rs137100 in LERP gene, we did not detect statistically significant differences (Table 3).

Frequency analysis of metabolic risk factors depending on the presence of allele and genotypes rs137100 of LEPR gene allowed us to detect associative relationship between genotypes AA/AG with hypoalphacholesterolemia (p = 0.021) (Table 4). Also, the frequency of hypoalphacholesterolemia was higher in carriers of the A allele (p = 0.038). There is no statistically significant relationship with other components of the metabolic syndrome. The findings differ from literature data, where allele connected with pathological signs of lipid metabolic imbalance, is the G allele [5, 8, 14, 18], whereas in the present study is the abnormal A allele.

Table 4

Frequency of Metabolic Syndrome and Its Components Depending on the Allelic Variant and Genotypes of the *LEPR* Gene Polymorphic Marker (rs137100)

Genotype	MS Component, n (%)		χ^2, p	Allele	Component MC, n (%)		χ^2, p
	Yes	No			Yes	No	
High blood pressure							
AA/ AG	36 (36.7)	62 (63.3)	χ=0.273 p=0.601	A	36 (36.7)	62 (63.3)	χ=0.029 p=0.865
GG	51 (40.2)	76 (59.8)		G	74 (37.8)	122 (62.2)	
Hypoalphacholesterolemia							
AA/AG	13 (13.3)	85 (86.7)	χ=5.304 **p=0.021**	A	13 (13.3)	85 (86.7)	χ=4.284 **p=0.038**
GG	6 (4.7)	122 (95.3)		G	12 (6.1)	184 (93.9)	
Hypertriglyceridemia							
AA/AG	6 (6.1)	92 (93.9)	χ=0.241 p=0.623	A	6 (6.1)	92 (93.9)	χ=0.107 p=0.743
GG	10 (7.8)	118 (92.2)		G	14 (7.1)	182 (92.9)	
Fasting hyperglycemia							
AA/AG	24 (24.7)	73 (75.3)	χ=0.224 p=0.636	A	24 (24.7)	73 (75.3)	χ=0.154 p=0.695
GG	28 (22)	99 (78)		G	44 (22.7)	150 (77.3)	
Obesity by body mass index							
AA/AG	21 (21.6)	56 (57.7)	χ=0.284 p=0.868	A	21 (21.6)	76 (78.4)	χ=0.07 p=0.791
GG	25 (20.3)	69 (56.1)		G	39 (20.3)	153 (79.7)	
IDF_1 central obesity							
AA/AG	49 (51)	47 (49)	χ=2.542 p=0.11	A	49 (51)	47 (49)	χ=1.213 p=0.314
GG	76 (61.8)	47 (38.2)		G	110 (57.9)	80 (42.1)	
Metabolic syndrome							
AA/AG	16 (16.5)	81 (83.5)	χ=0.243 p=0.622	A	16 (16.5)	81 (83.5)	χ=0.0048 p=0.826
GG	24 (19)	102 (81)		G	34 (17.5)	160 (82.5)	
High and atherogenic index							
AA/AG	6 (6.1)	93 (93.9)	χ=0.210 p=0.647	A	6 (6.1)	93 (93.9)	χ=0.305 p=0.581
GG	6 (4.7)	122 (95.3)		G	9 (4.6)	188 (95.4)	
GG	3 (2.4)	124 (97.6)		G	8 (4.1)	188 (95.9)	

Note. χ2* – Pearson Chi-square test, p – significance level.

Conclusion. At the moment, the world carried on a lot of research devoted to study of the rs1137100 LEPR gene polymorphic variant (K109R) in different ethnic groups. Despite this, the role of the polymorph variants in the development of diseases related to lipid metabolism disorders are contradictory. Thus, when conducting a meta-analysis with the inclusion of 7 studies such as case-control study, we do not establish association of this polymorph marker with type 2 diabetes (type 2 (patients with type 2 diabetes – 3319, healthy – 2844) [16]. Also, a meta-analysis of 7 studies did not establish a clear association of rs1137100 with obesity [10]. A systematic review (analyzed 10 publications, with the included and it in the data analysis of 1989 people with coronary heart disease and 2601 healthy) did not confirm associative connection of this polymorph variants with coronary heart disease [6]. But at the same time there are studies which found associative connection of the polymorphic marker with ischemic stroke [5], obesity [8, 18], the risk of cardiovascular disease [14].

The conflicting results of the studies are probably related not only to the genetic characteristics of ethnic groups, but also with the influence of various factors of the environment, especially climatic conditions, physical activity, and dietary features. Several studies have noted the high level of leptin in the blood of the population living in northern latitudes. We relate this feature to thermoregulation processes [22]. Also, in recent studies it was shown that when respondents (carriers of negative genotype polymorphic marker Lys656Asn/rs8179183 in *LEPR* gene) changed their diets and physical activity, they saw increased sensitivity to insulin and better anthropometric characteristics. In recent years, studies are actively looking at the role of polyunsaturated fatty acids in leptin genes expression, because experiments on animals, humans, and cell cultures showed the impact of fatty acids on the expression of the gene and the concentration of leptin [15] .

In Yakut population there is a high frequency of the G allele, similar to data from other Asian races [10]. Interestingly, in the investigated sample the A allele is negative and is associated with hypoalphacholesterolemia, which does not match the data from other studies, where the G allele is pathological [5, 8, 14, 18]. According to epidemiological studies, the Yakut population, like many other populations of the North, is characterized by a fairly high level of HDL cholesterol [1, 2, 17, 19]. The population of Yakutia has a special genotype formed for centuries, which is adapted to long-term exposure to cold, with diet rich in proteins and fats [3, 20, 21]. Changes in diet and lifestyle are accompanied by an increase in the frequency of metabolic disorders in the population, including a decrease in the concentration of HDL cholesterol, thus hypoalphacholesterolemia is one of the main components of MS in 70% of cases [2, 3]. It is possible that changes in metabolic parameters and an increase in the frequency of their disorders in the population are associated with changes in gene expression under the influence of living conditions and nutrition. In this regard, a further study of the functioning of the genes under the influence of these factors is particularly relevant and has fundamental scientific importance in research. It may reveal more data on the mechanism of human adaptation habitat conditions.

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Литература

1. Гыргoлькау Л. А. Содержание липидов в крови и частота дислипопротеинемий у коренных жителей Чукотки / Гыргoлькау Л. А., Щербакова Л. В., Иванова М. В. // Бюл. СО РАМН. -2011 - Т. 31, № 5 - С. 79–83 [Gyrgolkau L.A., Shcherbakova L.V., Ivanova M.V. The Content of Lipids In the Blood and the Frequency of Dyslipoproteinemia In the Indigenous Inhabitants of Chukotka. *Bulletin of the Siberian Branch of the Russian Academy of Medical Sciences*. Tomsk. 2011; 31(5) 79–83].

2. Липидный профиль и дислипопротеинемии у коренного сельского населения Якутии / Климова Т. М. [и др.]. // Сибирский медицинский журнал (Томск) - 2012. - Т. 27 - № 3 - С. 142–146. [Lipid Profile and Dyslipoproteinemia In the Indigenous Rural Population of Yakutia. *Sibirskij medicinskij zhurnal* [*Siberian Medical Journal (Tomsk)*]. 2012; 27 (3):142-146

3. Метаболический синдром среди коренной женской популяции Якутии / Климова Т.М. [и др.]. // Якутский медицинский журнал – 2019 -3 (25) - С. 66-70 [Klimova T.M., Egorova A.G., Zakharova R.N., Ammosova E.P., Baltakhinova M.E., Fedorov A.I., Romanova A.N. Metabolic Syndrome Among the Indigenous Female Population of Yakutia. *YAkutskij medicinskij zhurnal [Yakut Medical Journa]l*. 2019; 3 (25): 66-70.

4. Nicole Bender, Noe¨mi Allemann, Diana Marek et.al. Association between variants of the leptin receptor gene (LEPR) and overweight: a systematic review and an analysis of the CoLaus study. *PLoS ONE* . 2011; 6 (10):1-14 e26157.

5. Hui Tang, Zhen Zhang, Zheng-Ke Li [et. al.]. Association of leptin receptor gene polymorphisms with genetic susceptibility to ischemic stroke. *Journal of Stroke and Cerebrovascular Diseases*. 2015; 24(9): 2128-2133.

6. Hui Shi, Hexi Shu, Changjia Huang [et.al.]. Association of LEPR K109R polymorphisms with cancer risk: a systematic review and pooled analysis. *JBUON*. 2014; 19(3): 847-854.

7. Rubina Tabassum, Yuvaraj Mahendran, Om Prakash Dwivedi [et.al.] Common variants of IL6, LEPR, and PBEF1 are associated with obesity in indian children. *Diabetes;*. 2012; 61: 625-631.

8. Watowich SS, Wu H, Socolovsky M, [et al.]. Cytokine re ceptor signal transduction and the control of hematopoietic cell development. *Annu Rev Cell Dev Biol*. 1996; 12: 91–128.

9. Equilibrium Hardy-Weinberg [Online]. [cited 2017 June 15]. Available from: https://wpcalc.com/en/equilibrium-hardy-weinberg/.

10. Aline dos Santos Rocha, Rita de Cássia Ribeiro-Silva, Gustavo Nunes de Oliveira Costa et. al. Food Consumption as a Modifier of the Association between LEPR Gene Variants and Excess Body Weight in Children and Adolescents: A Study of the SCAALA Cohort. *Nutrients*. 2018; 101117: 1-14 doi:10.3390/nu10081117

11. International Diabetes Federation: IDF consensus worldwide definition of the metabolic syndrome [article online], 2006. URL: http://www.idf.org/webdata/docs/IDF_Meta_def_fi nal.pdf (accessed 15 August 2012).

12. Lei Wu, Dali Sun. Leptin receptor gene polymorphism and the risk of cardiovascular disease: a systemic review and meta-analysis. *Int. J. Environ. Res. Public Health* 2017; 14 375: doi:10.3390/ijerph14040375.

13. Catherine M. Phillips, Louisa Goumidi, Sandrine Bertrais [et. al.]. Leptin receptor polymorphisms interact with polyunsaturated fatty acids to augment risk of insulin resistance and metabolic syndrome in adults. *The Journal of Nutrition*. 2010; 14023: 244.

14. Boyer B., Mohatt G. V., Plaetke R. [et al.]. Metabolic syndrome in Yup'ik Eskimos: the Center for Alaska Native Health Research (CANHR) Study. *Obesity.* 2007; 15(11): 2535–2540.

15. Peilin Xiao, Jianli Shi, Xiaoli Liu. Associations of leptin and leptin receptor genetic variants with coronary artery disease: a meta-analysis. *Bioscience Reports*. 2019; 39 BSR20190466: 1-7 https://doi.org/10.1042/BSR20190466

16. Pramudji Hastuti, Izza Zukhrufia, Made Harumi Padwaswari [et. al.]. Polymorphism in leptin receptor gene was associated with obesity in Yogyakarta, Indonesia. *The Egyptian Journal of Medical Human Genetics*. 2016; 17: 271–276.

17. Young M.D., Bjerregaard P., Dewailly E.[et al.]. Prevalence of obesity and its metabolic correlates among the circumpolar Inuit in 3 countries. *Am. J. Publ. Health*. 2007; 97 (4): 691– 695.

18. Stephanie B Levy, William R Leonard, Larissa A Tarskaia [et al.]. Seasonal and socioeconomic influences on thyroid function among the Yakut (Sakha) of Eastern Siberia. *American Journal of Human Biology*. 2013; 25(6): 814-820. DOI: 10.1002/ajhb.22457.

19. Leonard WR, Levy SB, Tarskaia LA [et al.]. Seasonal variation in basal metabolic rates among the Yakut (Sakha) of Northeastern Siberia. *American Journal of Human Biology.* 2014; 26(4): 437-445. DOI: 10.1002/ajhb.22524.

20. Alena A. Nikanorova, Nikolay A. Barashkov, Sergey S. Nakhodkin [et. al.]. The Role of leptin levels in adaptation to cold climates. *Int. J. Environ. Res. Public Health*. 2020; 17- 1854; doi:10.3390/ijerph17061854.

21. Valentina Paracchini, Paola Pedotti, Emanuela Taioli. Genetics of leptin and obesity: A HuGE Review. *Am J Epidemiol.* 2005; 162: 101–114.

22. Yunzhong Yang, Tianhua Niu. Meta-analysis of associations of LEPR Q223R and K109R with T2D. *PLOS ONE*. 2018; 2 : 1-25 https://doi.org/10.1371/journal.pone.0189366.