International Journal of Biomedicine 14(1) (2024) 104-109
http://dx.doi.org/10.21103/Article14(1)_OA16

ORIGINAL ARTICLE

Population Genetics

INTERNATIONAL JOURNAL OF BIOMEDICINE

The Association of Leptin Receptor Gene Q223R Polymorphism with Obesity in the Yakut Population

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Abstract

Background: This study aimed to compare the frequencies of alleles and genotypes of the *LEPR* Q223R SNP in the Yakut population in samples with normal BMI and obesity and compare the data obtained with other populations worldwide.

Methods and Results: The study included 336 DNA samples from volunteers of Yakut nationality (117 women and 219 men) without chronic diseases, whose average age was 47.4±0.06 years. All volunteers were divided into two groups: Group 1 (n=151) with normal BMI and Group 2 (n=185) with obesity (BMI ≥30 kg/m^2). Group 2 was divided into two subgroups: Group 2A (n=156) with BMI ≥30 kg/m^2 plus abdominal obesity and Group 2B (n=29) with BMI ≥30 kg/m^2 and without abdominal obesity.

The study of the *LEPR* Q223R SNP was performed using the PCR-RFLP method. The frequency of the G allele of the *LEPR* Q223R SNP was 79.5% in Group 1 and 82.7% in Group 2. Analysis showed a high frequency of genotype GG: 64.2% and 69.7% in Group 1 and Group 2, respectively. The frequency of the GA genotype was 30.5% in Group 1 and 25.9% in Group 2. The frequency of alleles and genotypes does not differ in the sample of Yakuts with normal BMI and those with obesity. There are also no differences in the frequency of alleles and genotypes based on gender and the presence of abdominal obesity.

The high frequency of the G allele in the Yakut population is close to that observed in East Asian populations (86.9%). There was no statistical difference in allele frequencies in comparison with the populations of Han Chinese from Beijing, Japanese from Tokyo, and Vietnamese from Ho Chi Minh City. In European, African, American, and South Asian populations, the G allele occurs with a frequency of 43.7% to 59.2%.

Conclusion: The *LEPR* Q223R SNP does not affect BMI in the Yakut population. In this study, Q223R allele frequencies were like allele frequencies in East Asian populations but not in Caucasians, reflecting racial diversity in the allele distribution of this polymorphism.**(International Journal of Biomedicine. 2024;14(1):104-109.)**

Keywords: body mass index • *LEPR* gene • Q223R SNP • Yakut population

For citation: Pavlova NI, Bochurov AA, Alekseev VA, Krylov AV, Sydykova LA, Kurtanov KA. The Association of Leptin Receptor Gene Q223R Polymorphism with Obesity in the Yakut Population. International Journal of Biomedicine. 2024;14(1):104-109. doi:10.21103/Article14(1)_OA16

Abbreviations

AO, abdominal obesity; **BMI**, body mass index; **PCR**, polymerase chain reaction; **SNP**, single nucleotide polymorphism.

Introduction

Over the past few decades, the prevalence and incidence of obesity have increased rapidly worldwide and reached epidemic proportions. Obesity is associated with many adverse consequences, such as type 2 diabetes, hypercholesterolemia, hypertension, or coronary heart disease, and is directly associated with increased mortality and reduced life

expectancy.[1] With the completion of the Human Genome Project and the first large genome-wide association studies, an increasing number of risk alleles associated with obesity have been identified, some in genes not previously known to be associated with obesity. However, genome-wide association studies have identified a small percentage of genetic variations significantly associated with obesity or body mass index (BMI) for most ethnic groups.

The mechanisms and genetic basis of the influence of diet and habitat remain unclear. One widely studied candidate gene for obesity, the leptin receptor (*LEPR*) gene, is located in the biological pathway to obesity (leptin-insulin pathway). Leptin is a hormone primarily produced by the adipose tissue in proportion to the size of fat stores. Besides adipose tissue, leptin is also produced by other tissues, such as the stomach, placenta, and mammary gland. It is known to have pleiotropic effects, including regulating several neuropeptides involved in appetite control and thermogenesis. Numerous studies have tested two nonsynonymous single nucleotide polymorphisms of the *LEPR* gene (Q223R and K109R) for association with obesity and type 2 diabetes, with inconclusive results.[2,3] Recently, many studies have been published on the association between *LEPR* variants and obesity, including studies of the interaction of these variants with gender or other factors. Of these two polymorphisms, the Q223R (rs1137101) SNP occurs as a result of a non-conservative A to G substitution at codon 223 resulting in a glutamine to arginine amino acid change. This functional variant reduces leptin binding and thus impairs leptin signaling. Data from studies of the Q223R polymorphism are very contradictory, considering the results obtained in patients from different ethnic groups. This makes further studies of polymorphic loci of the *LEPR* gene relevant.

This study aimed to compare the frequencies of alleles and genotypes of the *LEPR* Q223R SNP in the Yakut population in samples with normal BMI and obesity and compare the data obtained with other populations worldwide.

Materials and Methods

The study included 336 DNA samples from volunteers of Yakut nationality (117 women and 219 men) without chronic diseases, whose average age was 47.4±0.06 years.

BMI was calculated and categorized as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30 kg/m^2), based on WHO classification.[4] Abdominal obesity (AO) was diagnosed when the waist circumference (WC) exceeded 88 cm in women and 102 cm in men.

All volunteers were divided into two groups: Group 1 (n=151) with normal BMI and Group 2 (n=185) with obesity. Group 2 was divided into two subgroups: Group 2A (n=156) with BMI ≥30 kg/m^2 plus OA and Group 2B (n=29) with BMI ≥30 kg/m^2 and without OA.

Genomic DNA samples were isolated from whole blood using a commercial kit for DNA isolation (Newteryx, Yakutsk, Russia). The study of the *LEPR* Q223R SNP was performed using the PCR-RFLP method. Amplification of the gene region containing the polymorphic variant was carried out with standard pairs of primers. Forward: 5′-ACCCTTTAAGCTGGGTGTCCCAAATAG-3 and Reverse: 5′ - AATGTCAGTTCAGCCCATAAATATGG -3′. PCR temperature conditions were as follows: 94°C for 4 min, followed by 35 cycles at 94°C for 1 min, 62°C for 1 min, and 72°C for 1 min, and a final extension at 72°C for 5 min. The RFLP mixture with a volume of 20 µl consisted of: amplifier - 7 µl, deionized water - 10.9 µl, restriction buffer - 2 µl and restriction endunuclease MspI (2 u.a.).

Interpretation of the genotyping results was performed based on different patterns of gene region bands (Fig 1).

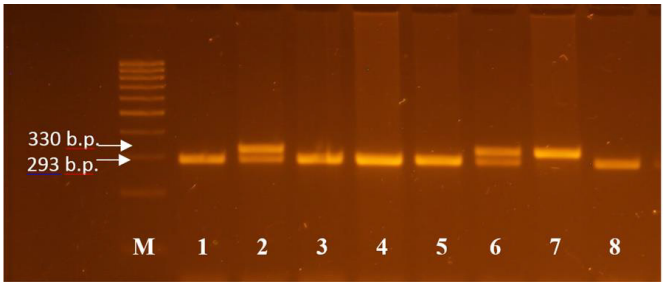

Fig 1. *The electropherogram of the LEPR gene region in a 4% agarose gel after RFLP. 1 - Step 100 marker; 7 – genotype AA (330 bp); 2 and 6 – genotype AG (330, 293 bp); 1, 3,4,5,8 – genotype GG (293 bp).*

Statistical analysis was performed using Microsoft Excel 2010. Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±SD for continuous variables. Genetic markers for HWE were tested. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Differences in the allele and genotype distribution between the groups were assessed by χ2-test with Yates correction. The Mann-Whitney U-test tested differences in continuous variables. Four inheritance models were analyzed (the dominant model, the codominant model, the recessive model of inheritance, and the multiplicative model). A probability value of P<0.05 was considered statistically significant.

Results

The variability of the *LEPR* Q223R SNP in the Yakut population and the associations of the study SNP with obesity in Yakuts were studied.

The distribution of polymorphic markers of the *LEPR* Q223R SNP in Groups 1 and 2 was in HWE. The frequency of the G allele of the *LEPR* Q223R SNP was 79.5% in Group 1 and 82.7% in Group 2. Analysis showed a high frequency of genotype GG: 64.2% and 69.7% in Group 1 and Group 2, respectively. The frequency of the GA genotype was 30.5% in Group 1 and 25.9% in Group 2. The frequency of alleles and genotypes does not differ in the sample of Yakuts with normal BMI and those with obesity. There are also no differences in the frequency of alleles and genotypes based on gender and the presence of abdominal obesity. Thus, our analysis did not reveal a significant positive association between the *LEPR* Q223R SNP and the risk of obesity across the studied inheritance models (Table 1)

Table 1.

Frequency distribution of alleles and genotypes of the LEPR rs1137101 SNP with inheritance models.

Groups	Alleles		Genotypes					
			Codominant model of inheritance		Dominant model of inheritance		Recessive model of inheritance	
	A [% (n)]	G [% (n)]	AG [% (n)]	GG [% (n)]	AA [% (n)]	AG+GG [% (n)]	AA+AG [% (n)]	GG [% (n)]
Group 1 (normal BMI) (n=151)	20.5 (62)	79.5 (240)	30.5 (46)	64.2 (97)	5.3 (8)	94.7 (143)	35.8 (54)	64.2 (97)
Group 2 (BMI ≥30 kg/m^2) (n=185)	17.3 (64)	82.7 (306)	25.9 (48)	69.7 (129)	4.3 (8)	95.7 (177)	30.3 (56)	69.7 (129)
OR (95% CI)	1.23 (0.8-1.8)		1.04 (0.4-3)	1.33 (0.5-3.7)	1.24 (0.4-3.4)		1.28 (0.8-2)	
P	0.33		0.85	0.77	0.87		0.34	
Men with normal BMI (n=105)	20.5 (43)	79.5 (167)	31.4 (33)	63.8 (67)	4.8 (5)	95.2 (100)	36.2 (38)	63.8 (67)
Men with BMI ≥30 kg/m^2 (n=114)	15.4 (35)	84.6 (193)	27.2 (31)	71.1 (81)	1.8(2)	98.2(112)	28.9(33)	71.1(81)
OR (95% CI)	1.42 (0.9-2.3)		2.35 (0.4-13)	3.02 (0.6-16.1)	2.8(0.5-14.7)		1.39 (0.8-2.5)	
P	0.2		0.55	0.33	0.38		0.32	
Women with normal BMI (n=46)	20.7 (19)	79.3 (73)	28.3 (13)	65.2 (30)	6.5 (3)	93.5 (43)	34.8 (16)	65.2 (30)
Women with BMI ≥30 kg/m^2 (n=71)	20.4 (29)	79.6 (113)	23.9 (17)	67.6 (48)	8.5 (6)	91.5(65)	32.4 (23)	67.6 (48)
OR (95% CI)	1.01 (0.5-1.9)		0.65 (0.1-3.1)	0.8 (0.2-3.4)	0.76 (0.2-3.2)		1.1 (0.5-2.4)	
P	0.9		0.88	0.95	0.98		0.95	
Croup 1 (normal BMI) (n=151)	20.5 (62)	79.5 (240)	30.5(46)	64.2 (97)	5.3 (8)	94.7 (143)	35.8 (54)	64.2 (97)
Group 2A (BMI ≥30 kg/m^2 + OA) (n=156)	17.6 (55)	82.4 (257)	25.0 (39)	69.9 (109)	5.1 (8)	94.9 (148)	30.1 (47)	69.9 (109)
OR (95% CI)	1.21 (0.8-1.8)		0.85 (0.3-2.5)	1.12 (0.4-3.1)	1.03 (0.4-2.8)		1.29 (0.8-2.1)	
P	0.42		0.98	0.97	0.85		0.35	
Group 2B (BMI ≥30 kg/m^2 without OA (n=29)	15.5 (9)	84.5 (49)	31.0 (9)	69.0 (20)	0	100 (29)	31.0 (9)	69.0 (20)
Group 2A (BMI ≥30 kg/m^2 +OA) (n=156)	17.6 (55)	82.4 (257)	25.0 (39)	69.9 (109)	5.1 (8)	94.9 (148)	30.1 (47)	69.9 (109)
OR (95% CI)	0.86 (0.4-1.8)		0.74 (0.3-1.8)	1.04 (0.4-2.5)	0		1.04 (0.4-2.5)	
P	0.84		0.41	0.49	0.45		0.9	

OA - abdominal obesity; BMI - body mass index

Analysis of the association between the *LEPR* Q223R SNP and the BMI values and abdominal obesity is presented in Table 2.

When analyzing the average anthropometric values depending on the genotype, we found that the BMI in carriers of the heterozygous AG genotype was greater than in carriers of the GG genotype. Moreover, in the obese sample, carriers of the AA genotype had the highest BMI. However, differences in BMI indicators depending on genotype in all samples were not statistically significant.

The *LEPR* gene emerged as the most promising candidate gene, likely undergoing natural selection, represented by three variants (*rs1137100*, *rs1137101*, and *rs1805096*) that strongly distinguish East Asian populations from all other populations described in the literature (Table 3).

The high frequency of the G allele in the Yakut population is close to that observed in East Asian populations (86.9%). There was no statistical difference in allele frequencies in comparison with the populations of Han Chinese from Beijing, Japanese from Tokyo, and Vietnamese from Ho Chi Minh City.

In European, African, American, and South Asian populations, the G allele occurs with a frequency of 43.7% to 59.2%.[5] Interestingly, the frequency of the G allele in populations of South and Middle America (43.7%) is similar to populations of Europeans (46.9%) and South Asians (50.3%). These data do not fit into modern views that the Indian and East Asian populations (86.9%) have the same roots.

Table 2.

Average BMI values depending on the LEPR Q223R SNP

Genotypes	n	BMI/ AO	Mann Whitney U test	*P*
BMI ≥30 kg/m^2				
AA	8	34 ± 1.22	215.5 (AA/AG)	>0.05
AG	48	33.4 ± 0.15	3063 (AG/GG)	>0.05
GG	129	33.1 ± 0.07	601 (AA/GG)	>0.05
BMI:18.5-24.9 kg/m^2				
AA	8	22.1 ± 0.69	145 (AA/AG)	>0.05
AG	46	22.7 ± 0.18	2128 (AG/GG)	>0.05
GG	97	22.6 ± 0.12	332.5 (AA/GG)	>0.05
Abdominal obesity				
AA	8	34 ± 1.22	161.5 (AA/AG)	>0.05
AG	39	33.9 ± 0.17	2247 (AG/GG)	>0.05
GG	109	33.5 ± 0.08	475 (AA/GG)	>0.05

Table 3.

Frequency distribution of alleles and genotypes of the LEPR rs1137101 SNP in the Yakut population and the populations of the 1000 Genomes project.

Populations	Alleles (%)		Genotypes (%)			χ^2-test	*P*
	A	G	AA	AG	GG		
Yakutia (this study)	18.8	81.2	4.8	28.0	67.3	-	-
Average frequency in the world	41.6	58.4	19.6	43.8	36.5	51.52	0.00
South and Middle America	56.3	43.7	29.7	53.3	17.0	107.39	0.00
Europe	53.1	46.9	30.2	45.7	24.1	97.92	0.00
South Asia	49.7	50.3	25.6	48.3	26.2	78.97	0.00
Africa	40.8	59.2	15.7	50.1	34.2	42.35	0.00
East Asia	13.1	86.9	1.6	23.0	75.4	9.6	0.00
Chinese Dai inXishuangbanna	11.3	88.7	0.0	22.6	77.4	5.2	0.02
Han Chinese in Beijing	13.1	86.9	2	22.3	75.7	3.11	0.08
Southern Han Chinese	12.4	87.6	1.9	20.9	77.1	4.12	0.04
Japanese in Tokyo	15.4	84.6	1.0	28.8	70.2	1.00	0.32
Kinh in Ho Chi Minh City	13.1	86.9	3.0	20.2	76.8	2.97	0.09

P – significance of differences in allele frequencies between listed populations and this study.

Discussion

Previously, several studies of the *LEPR* Q223R and K109R polymorphisms in the Yakut population were carried out. Ammosova et al.[6] investigated the relationship between the rs1137100 polymorphism of the *LEPR* gene and the lipid spectrum, metabolic syndrome and its components in the Yakuts. They found that the frequency of the G allele was 66.6%. No association with metabolic syndrome and its components has been identified. Asekritova et al.[7] conducted a study of rs1137101 polymorphism in Yakuts. They found that the frequency of the G allele in patients with metabolic syndrome was 87% and in patients without metabolic syndrome 91%. Ievleva[8] came to significant results and found that the risk markers for the implementation of disorders of carbohydrate and energy metabolism against the background of overweight and obesity in Caucasian adolescents (Russians) are the carriage of alleles of the polymorphic loci of the *LEPR* rs1137101 and rs1137100, and in Mongoloid adolescents (Buryats), carriage of the *FTO* rs9939609 and *FTO* rs8050136 alleles. A study in the Malaysian population did not reveal an association between the rs1137101 and rs1137100 polymorphisms and obesity.[9] Okada et al.[10] found an association between the A allele and the incidence of childhood obesity and overweight in the Japanese population. The GENYAL study in Spain assessed 11 SNPs associated with high BMI in children and found a significant association between *LEPR* Q223R and high weight gain.[11] The researchers observed a north-south gradient in Q223R allele frequency in Europeans, with a higher frequency of derived alleles in the north and a lower frequency in the south. The same phenomenon for SNPs of other genes was reported in the Framingham Heart Study[12] and a pan-European analysis.[13] In a study of residents of Sri Lanka, Illangasekera et al.[14] found a connection between the G allele and BMI and waist circumference; they also found that living in an urban area neutralized the protective effect of the non-risk AA genotype in the development of obesity.

Our studies in the Yakut population show a high prevalence of variants of the *PNPLA3* and *FABP2* genes associated with increased BMI and non-alcoholic fatty liver disease.[15] A study by Simcox et al.[16] found that the G allele of the *PNPLA3* gene is associated with adaptation to cold. The authors suggest that the sharply continental climate and specific diet were probably the reason for the high prevalence of variants of genes involved in the metabolism of lipids and carbohydrates, and the accumulation of risk alleles is a consequence of adaptation to living conditions in Yakutia.

LEPR is involved in fat storage, heat dissipation by mitochondria, and body weight regulation. Polymorphisms in the *LEPR* gene that exhibit some signatures of selection in East Asian populations have been reported to be involved in specific metabolic patterns and/or disorders. For example, rs1137100 is responsible for a nonsynonymous substitution (*K109R*) that is found to be associated with an increased respiratory quotient (i.e., increased basal metabolic rate), consistent with its important effect on nonshivering thermogenesis.

There is evidence of adaptation to cold in populations ancestral to anatomically modern humans. Sazini et al.[17]

analyzed genes associated with the function of brown adipose tissue, modifications of which contribute to increased heat dissipation by mitochondria, in the genomes of modern populations of East Asia and Europe, as well as in the genomes of fossil hominids (Neanderthals and Denisovans). They found evidence of positive selection for three SNPs in the *LEPR* gene in East Asians. The G variant of the *LEPR* gene (*rs1137101*), showing signs of positive selection, was found in the Neanderthal and Denisovan genomes, suggesting the evolution of independent mechanisms of adaptation to thermal efficiency in these fossil hominin populations. The variation surrounding *LEPR* rs1137100 appears to have actually been shaped by positive selection in East Asian populations, whereas only the potentially cold-adapted *LEPR* rs1137101 was observed in archaic species. This suggests that convergent evolution of modern and archaic increased thermogenesis mediated through brown adipose tissue or introgression of related archaic cold-adapted alleles into modern genomes is unlikely.[18]

Long-term consumption of fructose has also been shown to lead to leptin resistance. Recently, leptin was found to be associated with autophagy. Autophagy has been demonstrated to be involved in several interesting processes, such as fat storage in adipocytes and the liver.[19]

The mutant allele has also been reported to reduce leptin inhibition of insulin, leading to insulin dysregulation and increased insulin release, thereby accelerating glucose uptake and basal metabolic rate. Accordingly, this variant could potentially be detrimental in hot climates, in which it did maintain a low frequency, becoming increasingly beneficial in colder climates due to the associated increase in basal metabolic rate and, thus, heat dissipation, which is the basis of nonshivering thermogenesis. It appears that changes in the *LEPR* gene (*rs1137101* and *rs1137100*) were an advantage for Asian populations 6000–8000 years ago, corresponding to the introduction of agriculture in Asia. It has been suggested that the *LEPR* gene may be considered a "thrifty" gene, leading to the accumulation of adipose tissue in times of plenty and providing a reserve in times of famine. As an alternative explanation for the positive selection of *LEPR* in Asian populations, Hancock et al.[20] found associations of several *LEPR* variants with climate variables, suggesting a role for climate adaptation in the biological processes underlying cold adaptation and overweight. They suggest that variants such as Q223R and K109R may be harmful in hot equatorial climates and beneficial in colder climates.

In conclusion, our study shows that the *LEPR* Q223R SNP does not affect BMI in the Yakut population. Differences in allele frequencies between populations can be due to various environmental and genetic factors. In this study, Q223R allele frequencies were like allele frequencies in East Asian populations but not in Caucasians, reflecting racial diversity in the allele distribution of this polymorphism.

Competing Interests

The authors declare that they have no competing interests.

Ethical Considerations

The study was approved by the Ethics Committee of the Yakut Science Center of Complex Medical Problems (YSC CMP). Written informed consent was obtained from each research participant.

Acknowledgments

The study was carried out within the framework of the Scientific - Research Experimental - Design Work "Study of the genetic structure and burden of hereditary pathology of populations of the Republic of Sakha (Yakutia)" using the Unique scientific equipment (USE) "The Genome of Yakutia" (No. USU_507512).

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