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COMPARISON OF VARIANTS OF LEPR, *FADS1, FADS2* AND *FABP2* GENES IN THE POPULATION OF THE REPUBLIC OF SAKHA (YAKUTIA)

This study is devoted to studying the frequencies of gene variants (*LEPR, FADS1, FADS2, FABP2*) in Yakuts, Russians, and Evenks, as well as their relationship to body mass index (BMI). The study included 776 volunteers from the Republic of Sakha (Yakutia): There are 211 Russians, 140 Evenks and 425 Yakuts. The participants had no chronic diseases. Based on body mass index (BMI), participants were divided into three groups: normal BMI (18.5–24.9 kg/m2), pre-obese (25-29.9 kg/m2) and obese (≥30 kg/m2). The study of variants rs174537 of the enhancer genes *FADS1, FADS2*, rs1137101 of the *LEPR* gene and rs1799883 of the *FABP2* gene in populations of Russians (n=211), Evenks (n=140) and Yakuts (n=425) revealed significant population-specific differences.

Keywords: obesity, nutrition, Yakuts, Russians, Evenks, BMI, *LEPR, FADS1, FADS2, FABP2*

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Introduction. Obesity is one of the key public health problems of the 21st century, associated with an increased risk of cardiovascular diseases, type 2 diabetes, metabolic syndrome, and other chronic conditions [25]. Despite the fact that obesity is caused by the interaction of genetic, environmental, and behavioral factors, the role of genetic polymorphism in regulating metabolism and fat accumulation attracts special attention.

Numerous studies have attempted to understand the genetic basis of human adaptation to various environmental conditions and diets, and with the development of molecular genetic technologies, an understanding of the contribution of genetic variability to nutritional needs among various human subpopulations has emerged [20].

The nutritional history of the Yakut population provides an excellent opportunity to study the effect caused by the interaction between genes and food, which could exert selective pressure on certain SNPs associated with metabolism. Until the middle of the 17th century, agriculture was not practiced in Yakutia, respectively, the main food was animal and vegetable products. The beginning of grain farming in Yakutia dates back to 1652, when 6 exiled peasants took up farming [1], and potatoes were first imported in 1776 [3]. It has been established that under the influence of low temperatures in plants growing in Yakutia, the content of polyunsaturated fatty acids (PUFA) increases, among which 18:3n-3, 16:0 and 18:2n-6 dominate [18]. This, in turn, plays an important role in regulating the resistance of herbivores to prolonged low-temperature stress and the high content of 18:3n-3 in their meat, liver, and fat [10, 21].

Also, a distinctive feature of the Yakuts was the lack of a diet, they mostly ate once or twice a day, compensating for the large intake of it in the morning and evening hours. Animal and vegetable products were consumed in significant quantities in their natural raw form, which made it possible to preserve its nutritional properties [5].

According to physiological and biochemical studies, the entire indigenous population of Northeast Asia differs from the more southern Siberian peoples in a special "polar" type of metabolism, which was formed on the basis of a lipid-protein diet and is characterized by an increased role of lipids as an energy source [2].

In recent years, with changes in the eating habits of the population of Yakutia, the number of people with obesity and other metabolic diseases, such as type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), etc. has increased.

With the help of Human Genome Association Studies (GWAS), researchers from various parts of the world have currently identified a huge number of single nucleotide polymorphisms (SNPs) associated with obesity, some of which were not previously known to be associated with obesity. However, of all the identified SNPs for most ethnic groups, only a small percentage are significantly associated with obesity or body mass index (BMI).

The leptin receptor gene (*LEPR*), one of the widely studied candidate genes for increased BMI, is on the biological pathway to obesity (leptin-insulin pathway). Leptin is produced in adipose tissue in proportion to its mass, and is also produced in other organs. It is known that leptin has a multifaceted effect, including the regulation of several neuropeptides involved in appetite control and thermogenesis [8].

Polymorphisms in genes related to lipid metabolism, such as *FADS* (Fatty Acid Desaturase), play a key role in modulating polyunsaturated fatty acid (PUFA) levels, which affect energy balance and the risk of obesity [14].

The *FABP2* gene encodes Fatty Acid Binding Protein 2, which is involved in lipid absorption and transport in enterocytes. The rs1799883 polymorphism (G>A substitution), which causes the amino acid substitution Ala54Thr in this protein, is associated with changes in lipid and carbohydrate metabolism – carriers of the Thr allele have higher triglyceride levels and a tendency to insulin resistance [19]. The associations of Ala54Thr with obesity, type 2 diabetes mellitus, and metabolic syndrome have been repeatedly described in different populations [11, 13]

The purpose of this study is to compare the gene variants (*LEPR*, *FADS1*, *FADS2*, and *FABP2*) involved in lipid metabolism and their relationship to BMI in Yakuts, Russians, and Evenks.

Materials and research methods. The criteria for inclusion in the study sample were age 18 and over and written informed consent to the study. Criteria for non-inclusion:

- Presence of decompensated chronic pathology;
- Serious or uncontrollable physical or mental illnesses;
- Taking medications for the treatment of obesity in the postoperative period.
- The onset of pregnancy;
- The patient's refusal to continue participating in the study.

The study included 776 volunteers from the Republic of Sakha (Yakutia): There are 211 Russians, 140 Evenks and 425 Yakuts. The average age was 47.4±0.99 years for Russians, 50.7±1.65 years for Evenks, and 48.1±0.58 years for Yakuts. Bioassays and questionnaires of volunteers, including anthropometric indicators, were selected from various regions of the republic during field expeditions and business trips with doctors and laboratory technicians. DNA of the volunteers is included in the bioresource collection of the Yakut Scientific Center for Complex Medical Problems (YANC KMP) UNU "Genome of Yakutia" (reg. no.USU_507512). The desk work was carried out in the laboratory of Hereditary pathology of the Department of Molecular Genetics of the YANGTS KMP. The study was approved by the local biomedical ethics committee, and all participants provided written informed consent.

The sample was divided into three ethnic groups, followed by body mass index (BMI) categories, according to the criteria of the World Health Organization (WHO): normal BMI (18.5–24.9 kg/m2), pre-obesity (25-29.9 kg/m2) and obesity (≥30 kg/m2). SNP genotyping was performed using classical polymerase chain reaction (PCR) and restriction fragment length polymorphism (RDF). The conditions for amplification of the gene region containing polymorphic variants, indicating the sequence of oligonucleotide primers, the restrictase used, and the length of the extraction fragments, were described in early works [4, 16].

Statistical analysis: Statistical data processing was carried out using Micro-

Table 1

Percentage of BMI categories of ethnic groups

	Russians	Yakuts	Evenks
Normal	30.3	35.3	32.9
Pre-obesity	32.2	22.8	30.0
Obesity	37.4	41.9	37.1

Table 2

Frequencies of genotypes and alleles in Russians, Yakuts and the Evenks

Population	Frequency of genotypes (%)			Frequency of alleles (%)		Chi-square	p
rs174537 *FADS1, FADS2*	TT	GT	GG	**T**	G		
Russians	21.8	44.1	34.1	43.8	56.2	108.79	**0.00**
Evenki	70.7	25.7	3.6	83.6	16.4		
Russians	21.8	44.1	34.1	43.8	56.2	122.08	**0.00**
Yakuts	57.4	36.0	6.6	75.4	24.6		
Evenki	70.7	25.7	3.6	83.6	16.4	7.56	**0.01**
Yakuts	57.4	36.0	6.6	75.4	24.6		
rs1137101 *LEP*R	AA	AG	GG	A	**G**	**Chi-square**	**p**
Russians	21.3	49.8	28.9	46.2	53.8	44.98	**0.00**
Evenki	6.4	29.3	64.3	21.1	78.9		
Russians	21.3	49.8	28.9	46.2	53.8	109.24	**0.00**
Yakuts	4.0	28.5	67.5	18.2	81.8		
Evenki	6.4	29.3	64.3	21.1	78.9	0.93	0.34
Yakuts	4.0	28.5	67.5	18.2	81.8		
rs1799883 *FABP2*	CC	CT	TT	C	**T**	**Chi-square**	**p**
Russians	43.1	40.3	16.6	63.3	36.7	0.63	0.43
Evenki	39.3	41.4	19.3	60.0	40.0		
Russians	43.1	40.3	16.6	63.3	36.7	49.08	**0.00**
Yakuts	24.5	35.5	40.0	42.2	57.8		
Evenki	39.3	41.4	19.3	60.0	40.0	26.00	**0.00**
Yakuts	24.5	35.5	40.0	42.2	57.8		

Note: p – significance with the Yates correction for alleles.

Table 3

Associations of genetic variants with BMI categories of Russians, Yakuts, and Evenks

Russians								Yakuts								Evenks							
Polymorphism/ sampling	**Frequence of genotypes (%)**			**Frequence of alleles (%)**		**OR**	**p**	**Polymorphism/ sampling**	**Frequence of genotypes (%)**			**Frequence of alleles (%)**		**OR**	**p**	**Polymorphism/ sampling**	**Frequence of genotypes (%)**			**Frequence of alleles (%)**		**OR**	**p**
rs174537 *FADS1, FADS2*	**TT**	**GT**	**GG**	**T**	**G**	**Regarding the T allele**		**rs174537 *FADS1, FADS2***	**TT**	**GT**	**GG**	**T**	**G**	**Regarding the T allele**		**rs174537 *FADS1, FADS2***	**TT**	**GT**	**GG**	**T**	**G**	**Regarding the T allele**	
Normal	15.6	34.4	50	32.8	67.2	1.988 (1.207-3.275)	**0.01**	Normal	61.3	34.0	4.7	78.3	21.7	1.359 (0.894-2.065)	0.18	Normal	73.9	19.6	6.5	83.7	16.3	1.027 (0.463-2.278)	0.89
Pre-obesity	23.5	51.5	25	49.3	50.7			Pre-obesity	53.6	38.1	8.2	72.7	27.3			Pre-obesity	69.0	28.6	2.4	83.3	16.7		
Obesity	25.3	45.6	29.1	48.1	51.9	1.898 (1.171-3.077)	**0.01**	Obesity	56.2	36.5	7.3	74.4	25.6	1.242 (0.863-1.786)	0.28	Obesity	69.2	28.8	1.9	83.7	16.3	1.003 (0.470-2.143)	0.85
Normal	15.6	34.4	50	32.8	67.2			Normal	61.3	34.0	4.7	78.3	21.7			Normal	73.9	19.6	6.5	83.7	16.3		
Pre-obesity	25.3	45.6	29.1	48.1	51.9	0.954 (0.603-1.510)	0.94	Pre-obesity	56.2	36.5	7.3	74.4	25.6	0.914 (0.615-1.357)	0.73	Pre-obesity	69.2	28.8	1.9	83.7	16.3	0.977 (0.450-2.119)	0.89
Obesity	23.5	51.5	25	49.3	50.7			Obesity	53.6	38.1	8.2	72.7	27.3			Obesity	69.0	28.6	2.4	83.3	16.7		
Normal	15.6	34.4	50	32.8	67.2	1.939 (1.256-2.993)	**0.00**	Normal	61.3	34.0	4.7	78.3	21.7	0.780 (0.558-1.089)	0.17	Normal	73.9	19.6	6.5	83.7	16.3	0.987 (0.503-1.936)	0.90
Pre-obesity + Obesity	24.5	48.3	27.2	48.6	51.4			Pre-obesity + Obesity	55.3	37.1	7.6	73.8	26.2			Pre-obesity + Obesity	69.1	28.7	2.1	83.5	16.5		
rs1137101 *LEPR*	**AA**	**AG**	**GG**	**A**	**G**	**Regarding the G allele**		**rs1137101 *LEPR***	**AA**	**AG**	**GG**	**A**	**G**	**Regarding the G allele**		**rs1137101 *LEPR***	**AA**	**AG**	**GG**	**A**	**G**	**Regarding the G allele**	
Normal	25.0	42.2	32.8	46.1	53.9	1.116 (0.687-1.814)	0.75	Normal	5.3	30.7	64.0	20.7	79.3	1.319 (0.823-2.112)	0.30	Normal	10.9	32.6	56.5	27.2	72.8	1.866 (0.895-3.891)	0.13
Pre-obesity	14.7	57.4	27.9	43.4	56.6			Pre-obesity	1.0	30.9	68.0	16.5	83.5			Pre-obesity	2.4	28.6	69.0	16.7	83.3		
Obesity	24.1	49.4	26.6	48.7	51.3	0.899 (0.564-1.435)	0.74	Obesity	4.5	25.3	70.2	17.1	82.9	1.260 (0.851-1.865)	0.29	Obesity	5.8	26.9	67.3	19.2	80.8	1.567 (0.802-3.062)	0.25
Normal	25.0	42.2	32.8	46.1	53.9			Normal	5.3	30.7	64.0	20.7	79.3			Normal	10.9	32.6	56.5	27.2	72.8		
Pre-obesity	14.7	57.4	27.9	43.4	56.6	0.806 (0.508-1.278)	0.42	Pre-obesity	4.5	25.3	70.2	17.1	82.9	0.955 (0.598-1.527)	0.94	Pre-obesity	5.8	26.9	67.3	19.2	80.8	0.840 (0.396-1.784)	0.13
Obesity	24.1	49.4	26.6	48.7	51.3			Obesity	1.0	30.9	68.0	16.5	83.5			Obesity	2.4	28.6	69.0	16.7	83.3		
Normal	25.0	42.2	32.8	46.1	53.9	0.993 (0.655-1.506)	0.941	Normal	5.3	30.7	64.0	20.7	79.3	1.280 (0.895-1.830)	0.21	Normal	10.9	32.6	56.5	27.2	72.8	1.690 (0.936-3.051)	0.11
Pre-obesity + Obesity	19.7	53.1	27.2	46.3	53.7			Pre-obesity + Obesity	4.3	27.7	68.1	18	82			Pre-obesity + Obesity	3.2	21.0	75.8	13.7	86.3		
rs1799883 *FABP2*	**CC**	**CT**	**TT**	**C**	**T**	**Regarding the T allele**		**rs1799883 *FABP2***	**CC**	**CT**	**TT**	**C**	**T**	**Regarding the T allele**		**rs1799883 *FABP2***	**CC**	**CT**	**TT**	**C**	**T**	**Regarding the T allele**	
Normal	37.5	50	12.5	62.5	37.5	1.316 (0.804-2.153)	0.31	Normal	26.7	28.7	44.7	41.0	59.0	1.079 (0.746-1.560)	0.76	Normal	37.0	43.5	19.6	58.7	41.3	1.125 (0.621-2.039)	0.95
Pre-obesity	36.8	38.2	25	55.9	44.1			Pre-obesity	17.5	43.3	39.2	39.2	60.8			Pre-obesity	38.1	38.1	23.8	57.1	42.9		
Obesity	53.2	34.2	12.7	70.3	29.7	0.706 (0.430-1.157)	0.21	Obesity	26.4	37.1	36.5	44.9	55.1	0.851 (0.624-1.161)	0.35	Obesity	42.3	42.3	15.4	63.5	36.5	0.818 (0.460-1.455)	0.59
Normal	37.5	50	12.5	62.5	37.5			Normal	26.7	28.7	44.7	41.0	59.0			Normal	37.0	43.5	19.6	58.7	41.3		
Pre-obesity	53.2	34.2	12.7	70.3	29.7	0.536 (0.332-0.867)	**0.02**	Pre-obesity	26.4	37.1	36.5	44.9	55.1	0.789 (0.553-1.126)	0.22	Pre-obesity	42.3	42.3	15.4	63.5	36.5	0.768 (0.426-1.382)	0.46
Obesity	36.8	38.2	25	55.9	44.1			Obesity	17.5	43.3	39.2	39.2	60.8			Obesity	38.1	38.1	23.8	57.1	42.9		
Normal	37.5	50	12.5	62.5	37.5	1.049 (0.682-1.611)	0.92	Normal	26.7	28.7	44.7	41.0	59.0	1.082 (0.813-1.439)	0.64	Normal	37.0	43.5	19.6	58.7	41.3	1.084 (0.652-1.801)	0.86
Pre-obesity + Obesity	45.6	36.1	18.4	63.6	36.4			Pre-obesity + Obesity	23.3	39.3	37.5	42.9	57.1			Pre-obesity + Obesity	40.4	40.4	19.1	60.6	39.4		

Note: OS is the odds ratio, p is the significance with the Yates correction for alleles.

soft Excel 2010 software. The comparison of allele and genotype frequencies between populations was performed using the χ2-Yates-corrected test. When analyzing the conjugation of the frequency of the unfavorable allele with obesity, a four-field conjugation table and the Yates-adjusted square criterion were used. To assess the significance of the odds ratio, the boundaries of the 95% confidence interval (95% CI) were calculated. The results were considered significant at $p<0.05$.

Results and discussion. In all ethnic groups, there is a predominance of obese people, the percentage of BMI categories among Russians and Evenks did not differ significantly from each other, unlike the Yakuts, where obese people are most common and least obese. (Table 1).

The distribution of genotypes for each SNP (rs174537, rs1137101, rs1799883) did not deviate from the Hardy-Weinberg equilibrium ($p>0.05$), except for the Yakut group in variant rs1799883 of the *FABP2* gene (chi2-31.41; p=0.00), which is probably due to the large predominance of carriers of the T allele.

Russian Russians (n=211), Evenks (n=140), and Yakuts (n=425) revealed statistically significant differences in the variants rs174537 of the enhancer genes *FADS1*, *FADS2*, rs1137101 of the *LEPR* gene and rs1799883 of the *FABP2* gene (Table 2) (Table 2). The frequencies of genotypes and alleles in Russians, Yakuts, and Evenks (n=140) revealed statistically significant differences (Table 2).

According to the rs174537 polymorphism of the *FADS1* and *FADS2* gene enhancer, the highest frequency of the ancestral T allele was recorded in the Evenk population – 84%, followed by the Yakuts – 75%, while the Russian T allele is less common (44%). The Evenks have the TT genotype (71% of the sample), and the Yakuts have a similar high proportion of TT (57%), while the Russians have the GT and GG genotypes (only 22% have the TT genotype).

The *LEPR* (Gln223Arg) gene shows a similar pattern: the “unfavorable” Arg allele (G) dominates in Yakuts (82%) and Evenks (79%) compared with 54% in Russians. Russian Russians have only 29% of the GG genotype, while 21% of Russians have the protective AA (Gln/Gln) genotype, and homozygotes for Arg (GG) make up two–thirds of the sample of Yakuts (67.5%) and Evenks (64%). Russian Russians and Yakuts ($p<0.001$) and Evenks and Russians ($p<0.001$) differ significantly in the frequencies of the Arg allele, while Yakuts and Evenks do not differ (p=0.34).

FABP2 also significantly outweighs the unfavorable Thr54 allele in Yakuts (58% versus 40% in Evenks and 37% in Russians). The Thr/Thr genotype is found in 40% of Yakuts – more than twice as often as in Russians (17%) and Evenks (19%). Differences in the frequencies of the Thr allele between the Yakuts and both other groups are significant ($p<0.001$), whereas the Evenks and Russians have no significant difference in this variant (p=0.43).

Comparison of the frequencies of minor alleles (MAF) of genes of the studied ethnic groups with other populations of the world, according to the database "1000 Genomes Project Phase 3" [25, 26, 27] revealed the following:

– *FADS1*, *FADS2* (rs174537) MAF (T) in Russians 0.44 is similar to populations CLM 0.43 (Colombians in Medellin) and FIN 0.46 (Finns in Finland), Evenks 0.84 and Yakuts 0.75 are similar to populations CDX 0.78 (Chinese of the Dai population in Xishuangbanna) and KHV 0.82 (Kinh in Ho Chi Minh City);

– *LEPR* (rs1137101) MAF (G) in Russians is 0.54 similar to populations of ACB 0.56 (Afro-Caribbean origin in Barbados), PEL 0.50 (Peruvians in Lima), SAS 0.50 (South Asian populations), Evenks 0.79 and Yakuts 0.82 closer to populations of EAS 0.87 (East Asian populations);

– *FABP2* (rs1799883) MAF (T) in Russians 0.37 is similar to populations FIN 0.33 (Finns in Finland), BEB 0.33 (Bengalis in Bangladesh), GIH 0.39 (Gujarati Indians) and CHB 0.32 (Han Chinese in Beijing), Evenks 0.40 are similar to GIH 0.39 (Gujarati Indians), Yakuts 0.58 showed no similar frequencies with any of the populations.

The discrepancy and convergence of statistical indicators of genotype and allele frequencies between ethnic groups may reflect an adaptive strategy to food scarcity or extreme conditions, also with traditional nutrition.

The calculation of the odds ratio showed a reliable association of the rs174537 polymorphism of the *FADS1* and *FADS2* gene enhancer with BMI only in the sample of Russians. Thus, in Russians, the T allele was associated with pre–obesity (OR=1.99, 95% CI: 1.21–3.27, p=0.01), obesity (OR=1.89, 95% CI: 1.17-3.08, p=0.01) and pre-obesity + obesity (OR=1.94, 95% CI: 1.26-2.99, p=0.00) compared to the norm, which is confirmed by multidimensional logistic regression taking into account the population. A significant association of rs1799883 polymorphism was also found in the Russian sample (OR=0.536, 95% CI: 0.332–0.867, p=0.02) (Table 3).

In the samples of Evenks and Yakuts, there was no significant association of BMI with any of the polymorphisms studied. Some researchers also do not find associations of the rs174537 polymorphism of the *FADS1* and *FADS2* gene enhancer with BMI Wang C et al. (2021) [23]. Studies of the rs1799883 associations of the *FABP2* gene by Raisa Sipiläinen et al. (1997), Han TK et al. (2019) and Albala C et al. (2004) also disagree [7, 13, 21]. A similar pattern is observed for the LEPR (Gln223Arg) gene, the results of other researchers differ from Boumaiza I et al. (2012), Becer E et al. (2013), Illangasekera, Y.A. et al. (2020), Thi Tuyet Le et al. (2025), Tkhakushinov R.A. et al. (2020) [6, 9, 10, 12, 22] The lack of statistically significant associations between different BMI categories with polymorphisms within each ethnic group may be due to heterogeneity and low variability. However, the results remain contradictory and require further study.

Conclusion. The study revealed statistically significant differences in the frequencies of alleles between ethnic groups of Russians, Yakuts and Evenks for all three polymorphisms (rs174537, rs1137101, rs1799883), however, the frequencies in the *LEPR* gene variant (rs174537) did not differ statistically between the Yakut and Evenk groups, similar is observed in the *FABP2* gene variant (rs1799883), where the group already Russians did not differ statistically from the group of Evenks. The high frequency of the ancestral T allele (*FADS1*, *FADS2* rs174537) in Evenks and Yakuts may indicate its role in adapting to a diet high in PUFA (meat and fish). The high prevalence of the "unfavorable" G allele (*LEPR* rs1137101) may reflect an adaptive strategy to food scarcity or extreme conditions. *FABP2* (rs1799883) is associated with the metabolism of fatty acids, which could be important for energy storage during periods of abundance of food.

The relationship between the studied polymorphisms and BMI categories in three groups was established only in the Russian group in the variant of the *FADS1* and *FADS2* genes (rs174537), the other two groups (Yakuts and Evenks) showed no associations. Further research is needed on a larger sample, taking into account biochemical parameters, as well as the use of additional other approaches.

The authors declare that there is no conflict of interest.

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