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ASSOCIATION OF THE *FTO* GENE POLYMORPHISM (RS9939609) WITH BODY MASS INDEX IN THE YAKUT POPULATION

DOI 10.25789/YMJ.2024.86.08

UDC 616-036

The study is devoted to studying the relationship between the rs9939609 polymorphism of the *FTO* gene and body mass index (BMI) in the Yakut population. The sample consisted of 521 participants of Yakut nationality without diabetes mellitus and not registered with a dispensary, aged from 18 to 75 years, 222 women and 299 men. An analysis of the distribution of frequencies of occurrence of alleles and genotypes was carried out, as well as an analysis of BMI indicators in groups with different genotypes of the rs9939609 polymorphism of the *FTO* gene, during which similarities were found in the ratios of allele frequencies with populations of East and South Asia. Statistical analysis using the Kruskal-Wallis test with multiple analysis Dunn's test with Bonferroni correction and the odds ratio (OR) with the significance test with Yates' correction within the study showed a weak association of obesity with the risk allele A when comparing the group with normal BMI and the combined group of obesity + pre-obesity $p = 0.043$.

Keywords: obesity, *FTO*, rs9939609 polymorphism, Yakut population, BMI.

Introduction. Obesity is one of the most common health problems throughout the world, including the population of Yakutia. It is characterized by excess accumulation of fat in the body, which can have serious consequences for a person's health. Obesity is caused by a combination of genetic, psychological, behavioral and environmental factors, such as diet, level of physical activity and lifestyle. Large weight gain leads to the risk of developing a variety of serious diseases, including diabetes, cardiovascular disease and some types of cancer [11]. Addressing the problem of obesity requires a comprehensive approach, in-

cluding lifestyle changes, a balanced diet and increased physical activity. Developing and implementing effective interventions to prevent obesity is a critical public health challenge [4, 5].

Genome-wide association studies (GWAS) have identified at least 52 obesity susceptibility loci at the population level [10]. The *FTO* (Fat Mass and Obesity-Associated) gene encodes a protein that plays a role in regulating appetite and metabolic processes. *FTO* belongs to the superfamily of Fe(II)- and 2-oxoglutarate-dependent dioxygenases and plays a role in the demethylation of RNA and single-stranded DNA [9, 15]. A number of animal studies have shown that *FTO* expression occurs in the hypothalamus, predominantly in the arcuate, paraventricular, dorsomedial and ventromedial nuclei, which are key brain regions that control appetite [13, 15]. The rs9939609 polymorphism is one of the most studied variants in the *FTO* gene and is associated with the risk of obesity [8]. The association of *FTO* variants with obesity was confirmed by a study by Church Ch. et al. (2010) in mice, they found that increased *FTO* expression leads to increased fat mass and obesity due to hyperphagia. The authors suggest that at-risk single nucleotide polymorphisms (SNPs) in the human *FTO* gene may enhance *FTO* expression [12]. Research by Daya M et al. (2019) found that individuals with the T to A polymorphism of the *FTO* rs9939609 gene show a preference for high-calorie foods, such as high-fat foods, which leads to weight gain due to changes in gene expression *FTO* in the hypothalamus [11].

Although there has been a lot of research into genetic susceptibility to obesi-

ty in recent years, research findings may also differ among different peoples and ethnic groups. Studying individuals from different ethnic groups can help us better understand the genetic factors that influence susceptibility to obesity and improve our understanding of the different findings across different populations [1, 3].

The purpose of this study was to study the association of T/A polymorphism rs9939609 of the *FTO* gene in the Yakut population and its relationship with BMI in people without diabetes.

Materials and research methods.

The study was conducted in the laboratory of hereditary pathology of the department of molecular genetics of the Yakut Scientific Center for Complex Medical Problems (YSC KMP). For the study, DNA samples were used from the biorepository collection of the YSC KMP using the UNU "Genome of Yakutia" (reg. No. USU_507512). All study participants gave written consent. The study protocol was approved by the local biomedical ethics committee at the YSC KMP.

The sample consists of 521 randomly selected participants of Yakut nationality without diabetes, aged from 18 to 75 years, 222 women and 299 men. The main criterion for dividing into groups was body mass index (BMI) and the absence of diabetes mellitus. Body mass index (BMI) was assessed using the Western Pacific Region (WPRO) criteria for Asian residents [16]. With a BMI <18.5, body weight was considered insufficient, within 18.5–22.9% – normal, within 23.0–24.9 kg/m² – overweight. In the range of 25.0–29.9 kg/m², class I obesity was diagnosed, ≥ 30.0 kg/m² – class II obesity, ≥ 35.0 kg/m² – class III obesity, ≥ 40.0 kg/m² – obesity IV degree. Three groups

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were formed: a group with normal BMI, a group with overweight and a general group with obesity of all degrees.

For molecular genetic analysis, DNA extraction was carried out from whole blood using a commercial DNA extraction kit "Newteryx" (Russia, Yakutsk).

The study of single nucleotide polymorphisms was carried out using the polymerase chain reaction (PCR) followed by restriction fragment length analysis (RFLP). The conditions for amplification and restriction are presented in Table 1.

Interpretation of genotyping results was performed based on different band patterns of the region with the rs9939609 polymorphism (Figure).

The analysis of the obtained data was carried out using the Microsoft Office Excel 2010 program. To examine the association between unfavorable allele frequency and obesity, we used a four-field contingency Table and applied the χ -square test with Yates' correction. To assess the significance of the odds ratio, the boundaries of the 95% confidence interval (CI 95%) were calculated.

Comparison of mean BMI values depending on the genotype was carried out using the Kruskal-Wallis test with the method of multiple comparisons according to Dunn's test using the Bonferroni correction. For the analysis, we used the online calculator Statistics Kingdom [6]. Results were considered significant at $p < 0.05$.

Results and discussions. Analysis of the odds ratio of allele frequencies showed some connection between allele A in the compared groups of obesity and normal BMI (OR = 1.643; CI 1.083-2.492; $p = 0.054$), but did not reveal significant differences between samples with pre-obesity and normal BMI (OR = 1.65; CI = 0.967-2.816; $p = 0.174$). At the same time, in the combined sample of obesity + preobesity, an association of the A allele with obesity was revealed (OR = 1.644; CI 1.101-2.455; $p = 0.043$). (Table 2).

In the analysis of BMI scores (Table 3), the Kruskal-Wallis H test indicated that there was a significant difference in mean BMI scores between genotypes in the entire sample ($p = 0.037$). However, when considering each individual sample, no significant differences were found.

Table 4 presents the frequencies of alleles and genotypes of the rs9939609 polymorphism in various populations; data were taken from a database of 1000 genomes [7]. On average, in all populations, the A allele occurs in 34% of cases, and the T allele in 66%.

When comparing the obtained fre-

quencies of alleles and genotypes of other populations of the world [7] with the Yakuts, similarities were revealed with the Vietnamese population of Ho Chi Minh City in East Asia, the Pakistani population of Lahore, the Gujarati Indian population in Houston and the Bengali population in Bangladesh in South Asia (Table 4).

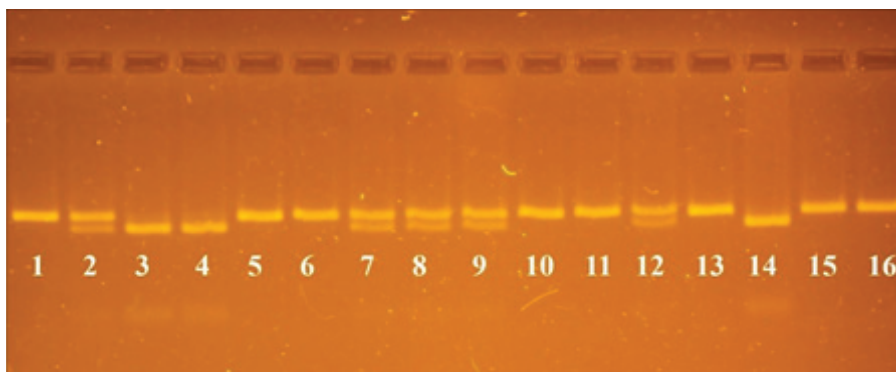
The association of the rs9939609 FTO polymorphism with BMI and other indicators associated with obesity has im-

portant clinical implications, as it may be associated with the presence of several components of the metabolic syndrome [3]. A study by Boyarinova M.A. et al (2018) found that the presence of the A allele reduced the likelihood of metabolic health in obese patients. The presence of the TT genotype of the FTO gene in obesity is probably associated with the formation of a metabolically healthy obesity phenotype [2]. Our study involved only healthy individuals who were not regis-

Table 1

Conditions for PCR-RFLP analysis

Gene	Primer sequence	Length of amplification bp.	Annealing temperature	Restriction endonuclease	Length of restriction fragments bp.
<i>FTO</i>	5'-TGGGCCTGAAGTCCGAGGGT-3'	182 п.н.	65°C	<i>Zrm I</i>	TT- 182 AT - 182, 154, 28 AA - 154, 28



Electrophoregram of polymorphism rs9939609 of the FTO gene on 4% agarose gel after RFLP: 1, 5, 6, 10, 11, 13, 15 and 16 – TT genotype (182 bp); 2, 7, 8, 9 and 12 – AT genotype (182, 154, 28 bp); 3, 4 and 14 – AA genotype (154, 28 bp)

Table 2

Frequency distribution of alleles and genotypes of polymorphism rs9939609 of the FTO gene with odds ratios (OR)

Sample	n	Genotypes, %			Alleles, %		OR (ДИ 95 %)	p
		TT	AT	AA	T	A		
Pre-obesity	93	51.6	40.9	7.5	72.0	28.0	1.65	0.17
Normal BMI	138	63.8	29.7	6.5	78.6	21.4	(0.967-2.816)	
Obesity	290	51.7	41.4	6.9	72.4	27.6	1.643	0.05
Normal BMI	138	63.8	29.7	6.5	78.6	21.4	(1.083-2.492)	
Pre-obesity + Obesity	383	51.7	41.3	7.0	72.3	27.7	1.644	0.04
Normal BMI	138	63.8	29.7	6.5	78.6	21.4	(1.101-2.455)	

Note: OR (95% CI) – odds ratio with 95% confidence interval, p – significance with Yates correction, BMI – body mass index.

Table 3

BMI indicators for different genotypes of the rs9939609 polymorphism of the *FTO* gene

Показатель		Генотип			p
		TT	AT	AA	
Normal BMI	Number of patients	88	41	9	0.536
	Body mass index (kg/m ²)	21.0±0.174	21.0±0.175	21.4±0.541	
Pre-obesity	Number of patients	48	38	7	0.075
	Body mass index (kg/m ²)	23.9±0.187	23.8±0.194	24.3±0.192	
Obesity	Number of patients	150	120	20	0.192
	Body mass index (kg/m ²)	29.8±0.073	30.7±0.082	31.9±1.247	
Pre-obesity+ Obesity	Number of patients	198	158	27	0.435
	Body mass index (kg/m ²)	28.4±0.066	29.1±0.070	29.9±1.126	
Entire sample	Number of patients	286	199	36	0.037
	Body mass index (kg/m ²)	27.1±0.056	27.4±0.066	27.8±0.185	

Note: p according to the Kruskal-Wallis test

Table 4

Frequency of occurrence of alleles and genotypes of the rs9939609 polymorphism of the *FTO* gene in different populations

Population	Subpopulation	Alleles. %		Genotypes. %		
		T	A	TT	TA	AA
All		66	34	45.7	40.6	13.7
African (AFR)		51	49	25.6	50.1	24.4
	African Caribbean in Barbados	51	49	27.1	46.9	26
	African Ancestry in Southwest US (ASW)	54	46	29.5	49.2	21.3
	Esan in Nigeria (ESN)	54	46	27.3	52.5	20.2
	Gambian in Western Division. The Gambia (GWD)	55	45	33.6	42.5	23.9
	Luhya in Webuye. Kenya (LWK)	44	56	21.2	46.5	32.3
	Mende in Sierra Leone (MSL)	49	51	18.8	61.2	20
	Yoruba in Ibadan. Nigeria (YRI)	48	52	21.3	53.7	25
American (AMR)		74	26	54.8	38	7.2
	Colombian in Medellin. Colombia (CLM)	66	34	43.6	44.7	11.7
	Mexican Ancestry in Los Angeles. California (MXL)	77	23	57.8	39.1	3.1
	Peruvian in Lima. Peru (PEL)	92	8	85.9	11.8	2.4
	Puerto Rican in Puerto Rico (PUR)	64	36	37.5	52.9	9.6
East Asian (EAS)		83	17	70	26.2	3.8
	Chinese Dai in Xishuangbanna. China (CDX)	85	15	73.1	23.7	3.2
	Han Chinese in Beijing. China (CHB)	84	16	72.8	23.3	3.9
	Southern Han Chinese. China (CHS)	86	14	76.2	20	3.8
	Japanese in Tokyo. Japan (JPT)	83	17	68.3	28.8	2.9
	Kinh in Ho Chi Minh City. Vietnam (KHV)	77	23	59.6	35.4	5.1
European (EUR)		59	41	37.2	19.9	42.9
	Utah residents with Northern and Western European ancestry (CEU)	56	44	30.3	50.5	19.2
	Finnish in Finland (FIN)	61	39	41.4	38.4	20.2
	British in England and Scotland (GBR)	61	39	37.4	47.3	15.4
	Iberian populations in Spain (IBS)	63	37	43.9	37.4	18.7
	Tosceni in Italy (TSI)	54	46	32.7	42.1	25.2
South Asia (SAS)		71	29	50.1	42.1	7.8
	Bengali in Bangladesh (BEB)	72	28	50	44.2	5.8
	Gujarati Indian in Houston. TX (GIH)	76	24	57.3	36.9	5.8
	Indian Telugu in the UK (ITU)	70	30	49	41.2	9.8
	Punjabi in Lahore. Pakistan (PIL)	72	28	51	42.7	6.2
	Sri Lankan Tamil in the UK (STU)	66	34	43.1	46.1	10.8
Yakut population		74	26	54.9	38.2	6.9

tered for any diseases, which could have played some role in the obtained results on the frequencies of alleles and genotypes of the rs9939609 polymorphism of the FTO gene. A limitation of the study is also the lack of data, particularly on lifestyle factors such as diet and daily activity patterns.

Conclusion. This study showed similarity in the frequencies of alleles and genotypes of the rs9939609 polymorphism of the FTO gene between the populations of South and East Asia with the Yakut population. Also, an analysis of the odds ratio of allele frequencies showed a significant association of allele A with the risk of obesity, while the analysis of BMI indicators for different genotypes did not reveal statistically significant differences in individual groups, however, when multiple analysis of Dunn's test with Bonferroni correction in the entire sample, there was a significant association between the risk allele A and also BMI indicators. From the results of the study, we can assume a weak connection between obesity and the studied polymorphism in the Yakut population.

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