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POLYMORPHISMS RS738409 AND RS2294918 OF THE *PNPLA3* GENE IN THE YAKUT POPULATION

DOI 10.25789/YMJ.2022.78.02

УДК 575.176

The article presents the frequency of polymorphic variants of the PNPLA3 gene (rs2294918 and rs738409) in Yakuts (n=150) living in the Republic of Sakha (Yakutia) (RS (Y)).

Genotyping of PNPLA3 (rs738409 and rs2294918) was performed by PCR – RFLP. Single nucleotide polymorphism rs738409 (I148M) of the PNPLA3 gene in the Yakut population is characterized by a high frequency of the risk G allele (72%). From the data of the 1000 Genomes project, it follows that the G allele (148M) is found with a high frequency in the populations of Latin American countries (Peruvians - 71.8%, Mexicans - 55.5%, Colombians - 41%). Analysis of the distribution of the genotype frequency of the rs2294918 polymorphism showed that the G allele is found with a high frequency in all populations in the world. So in the studied sample of Yakuts, it was - 89.3%; in African populations it averages 91.3%; in the populations of Central and South America (Colombians, Mexicans, Peruvians and Puerto Ricans) on average - 78.8%, in the populations of East Asians (Chinese, Japanese and Vietnamese) on average - 81.8%; Europeans (Finns, British, Iberians, Tuscans and Utah residents of northern and Western European descent) on average - 62.9%; South Asians (Indians and Pakistanis) have an average of 77.2%.

In the studied sample of Yakuts, two diplotypes [GG] [GG] and [CG] [GG] are more common. These diplotypes carry the mutant allele G (rs738409) and do not carry the A allele (rs2294918), which has a weakening effect on 148M, which in turn promotes the accumulation of triglycerides in hepatocytes. Perhaps in the Yakuts, the accumulation of fat in the liver in the past did not lead to NAFLD, since the accumulated fat was quickly converted into energy to generate heat. In modern realities, this diplotype has its detrimental effect by increasing the frequency of metabolic diseases, including non-alcoholic fatty liver disease (NAFLD).

The data obtained on the frequencies of the markers rs738409 and rs2294918 of the *PNPLA3* gene can be used in the diagnosis of susceptibility to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) to study the genetic mechanisms of human adaptation to cold, as well as the formation of risk groups for these diseases.

Keywords: gene, polymorphism, NAFLD, *PNPLA3*, liver.

Yakutia is the coldest region of Russia, whose territory is located in the permafrost zone. Preservation of heat in the body has been relevant for almost the entire history of mankind, especially in the northern regions of the planet. The body of indigenous people has adapted to living in harsh climatic conditions [1]. But in the modern world, people live in warm houses all year round, dress in warm clothes and are exposed to minimal effects of cold on the body. In addition to changing the effect of temperature on the body of the indigenous population, with the development of agriculture and road communications, the diet has also changed. Just a few generations ago, the basis of the diet was mainly protein and lipid products (meat, fish, dairy products), in modern conditions, the basis of the diet is carbohydrate products (potatoes, pasta and flour products, rice, buckwheat, etc.). Until recently, among the indigenous population, traditional high-fat foods were considered beneficial for the body and keeping warm, but at the moment this food has become the main source of various metabolic diseases, including type 2 diabetes mellitus, atherosclerosis, non-alcoholic fatty liver disease (NAFLD) and others [2].

NAFLD is characterized by changes in liver tissue due to excessive deposition of fat droplets in hepatocytes. If before industrialization and the use of modern approaches to maintaining heat in the body, under the influence of cold, this accumulated fat was converted into energy to generate heat, then at the moment it leads to various pathological changes in the liver.

Many foreign and domestic researchers indicate that the rs738409 polymorphism of the *PNPLA3* gene is the main determinant of liver fat and affects the development and progression of NAFLD [3,4]. Variant G (rs738409) of the *PNPLA3* gene leads to the accumulation of triglycerides in hepatocytes. The rs2294918 polymorphism of the *PNPLA3* gene reduces the expression of the PNPLA3 protein, reducing the effect of variant G (rs738409) on the predisposition to steatosis and liver damage [5].

The PNPLA3 protein belongs to the family of patatin-like phospholipases. It has hydrolase activity against triglycerides, catalyzes the conversion of lysophosphatidic acid to phosphatidic. A mutation in the gene results in the replacement of isoleucine with methionine at position 148 of the amino acid sequence, which leads to the loss of these functions and the accumulation of triglycerides and retinol palmitate in the liver. [6].

We previously found a high frequency of the G allele (rs738409) of the *PNPLA3* gene in the Yakut population (73%) [7]. The adaptation mechanisms listed above, such as the accumulation of fat in the liver, probably left their mark on the Yakut gene pool, in particular, in the genes that have an effect on metabolism. In this regard, the purpose of our study was to study the distribution of frequencies of alleles, genotypes, haplotypes and diplotypes of polymorphic variants of the PNPLA3 gene (rs2294918 and rs738409) in Yakuts.

Materials and research methods. Genotyping of polymorphisms rs2294918 and rs738409 of the PNPLA3 gene was carried out in the Laboratory of Hereditary Pathology of the Department of Molecular Genetics of the Yakut Scientific Center for Complex Medical Problems (YSC CMP). DNA samples from 150 healthy volunteers from the biomaterial collection of the YSC CMP were used for the study using the USU "Genome of Yakutia" (reg. No. USU_507512). All participants in the study were ethnically Yakuts and lived on the territory of the Republic of Sakha (Yakutia). For comparison, the data of

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the 1000 Genomes project [8] were used. The study was conducted with the written consent of the participants. The study protocol was approved by the local committee on biomedical ethics at the YSC CMP.

Isolation of DNA from peripheral blood lymphocytes was carried out using a commercial kit for the isolation of nucleic acids from whole venous blood produced by OOO Excell Biotech (Yakutsk, Russia). Primer selection was performed using the National Center for Biotechnology Information (NCBI) primer design tool, Primer-BLAST. The study site sequence for the primer selection matrix and primer specificity check were taken from the UCSC Genome Browser database (GRCh38/hg38). The primers were synthesized by Lumiprobe RUS Ltd, Moscow. The reaction mixture for PCR contained: primer forward and reverse, 10 pmol/μl (1 μl); Dream Taq PCR master mix -12.5 μl; deionized water 9.5 μl and DNA in the amount of 100 μg/ml - 1 μl. The total volume of the reaction mixture for amplification was 25 μl. The mixture for RFLP with a volume of 20 μl consisted of: amplificate - 7 μl, deionized water - 10.9 μl, restriction buffer - 2 μl and for polymorphism rs738409 restriction endunuclease BstF5 I (2 u), and for polymorphism rs2294918 - Ama87I (2 u).

Detection of PCR and RFLP products was carried out using horizontal electrophoresis in a 4% agarose gel plate with the addition of ethidium bromide, a specific intercalating fluorescent DNA (RNA) dye, using a standard tris-acetate buffer at a field voltage of ~ 20 V/cm for 30 minutes. The correspondence of genotype distributions to the expected values under Hardy-Weinberg equilibrium and the comparison of the frequencies of allelic variants/genotypes were performed using the χ2 test (chi-square). The frequency of haplotypes was determined using the EM algorithm. Linkage disequilibrium (LD) between SNP pairs was calculated using Lewontin's proposed D' coefficient and Pearson's r2 coefficient. Linkage disequilibrium blocks were determined using the "Solid spine LD" algorithm (D'>0.75).

Haploview software (v4.2) was used to evaluate *PNPLA3* haplotypes and frequencies based on genotyping data and to test the association between alleles and haplotypes of the *PNPLA3* gene [9].

Results and discussions. The PNPLA3 gene in the Yakut population according to the rs738409 polymorphism is characterized by a high frequency of the risky allele G (72%). From the data of the 1000 Genomes project [8], it follows that the G allele is found with a high frequency in the populations of Central and South America (Peruvians - 71.8%, Mexicans - 55.5%, Colombians - 41%). Europeans have an average G allele frequency of 22.6%. Among Asians, the high frequency of the G allele is in the Japanese (41.8%). The owners of the lowest frequency of the G allele are Africans, on average 11.8%. In the population sample of Yakuts for rs738409 due to the shift of genotypes towards the homozygous genotype GG, a deviation from the Hardy-Weinberg equilibrium was revealed, which may be evidence of the accumulation of this genotype as an adaptive mechanism to a cold climate (Table 1).

An analysis of the frequency distribution of the rs2294918 polymorphism genotypes according to the 1000 Genomes project [8] showed that the G allele occurs with a high frequency in all populations in the world. Thus, in the studied sample of Yakuts, it amounted to 89.3%; in African populations, it averages 91.3%; in the populations of Central and South America (Colombians, Mexicans, Peruvians and Puerto Ricans) on average - 78.8%, in the populations of East Asians (Chinese, Japanese and Vietnamese) on average - 81.8%; Europeans (Finns, British, Iberians, Tuscans and residents of Utah of northern and Western European origin) on average - 62.9%; South Asians (Indians and Pakistanis) have an average of 77.2%. According to the polymorphism rs2294918 of the PNPLA3 gene, which suppresses the negative effect of rs738409, the protective allele A in Yakuts was only 10.7%. According to the 1000 Genomes project [8], the protective allele A (rs2294918) is more common in Europeans than in other populations (32.3%). In the populations of the Negroid population from Barbados (ACB), Puerto Ricans (PUR) and the Telugu Indian population from England (ITU), the frequencies of the risk allele G rs738409 and the protective allele A rs2294918 are close in value (13.13%; 32.31% and 25.23 % respec-

Table1

The frequency of allele variants and missense mutations of the PNPLA3 gene in the Yakut population and in the populations of the 1000 genomes project

Population	Sub-population	SNP	Mutation	MAF	Ho	He	p
1	2	3	4	5	6	7	8
Россия	YKT (n=150)	rs738409	G (148M)	**0.720 (G)**	0.293	0.403	0.0019
		rs2294918	A (434K)	0.107 (A)	0.173	0.191	0.4386
Африка	AFR (n=661)	rs738409	G (148M)	0.118 (G)	0.188	0.208	0.0244
		rs2294918	A (434K)	0.104 (A)	0.174	0.186	0.1581
	ACB (n=96)	rs738409	G (148M)	0.13 (G)	0.219	0.227	0.9781
		rs2294918	A (434K)	0.13 (A)	0.219	0.227	0.9781
	ASW (n=61)	rs738409	G (148M)	0.172 (G)	0.213	0.285	0.1216
		rs2294918	A (434K)	0.115 (A)	0.164	0.203	0.3196
	ESN (n=99)	rs738409	G (148M)	0.126 (G)	0.192	0.221	0.3542
		rs2294918	A (434K)	0.056 (A)	0.111	0.105	1.0
	GWD (n=113)	rs738409	G (148M)	0.106 (G)	0.177	0.19	0.7074
		rs2294918	A (434K)	0.124 (A)	0.195	0.217	0.4458
	LWK (n=99)	rs738409	G (148M)	0.086 (G)	0.131	0.157	0.2819
		rs2294918	A (434K)	0.106 (A)	0.212	0.19	0.6110
	MSL (n=85)	rs738409	G (148M)	0.112 (G)	0.176	0.199	0.5317
		rs2294918	A (434K)	0.100 (A)	0.153	0.18	0.3655
	YRI (n=108)	rs738409	G (148M)	0.116 (G)	0.213	0.205	1.0
		rs2294918	A (434K)	0.097 (A)	0.157	0.176	0.5046

End of table 1

1	2	3	4	5	6	7	8
American	AMR (n=347)	rs738409	G (148M)	0.484 (G)	0.478	0.499	0.4795
		rs2294918	A (434K)	0.212 (A)	0.360	0.334	0.1942
	CLM (n=94)	rs738409	G (148M)	0.41 (G)	0.564	0.484	0.1772
		rs2294918	A (434K)	0.229 (A)	0.457	0.353	0.0037
	MXL (n=64)	rs738409	G (148M)	**0.555 (G)**	0.422	0.494	0.3260
		rs2294918	A (434K)	0.172 (A)	0.312	0.285	0.8301
	PEL (n=85)	rs738409	G (148M)	**0.718 (G)**	0.376	0.405	0.6473
		rs2294918	A (434K)	0.100 (A)	0.153	0.180	0.3655
	PUR (n=104)	rs738409	G (148M)	0.317 (G)	0.519	0.433	0.0742
		rs2294918	A (434K)	0.312 (A)	0.471	0.43	0.482
East Asian	EAS (n=504)	rs738409	G (148M)	0.350 (G)	0.419	0.455	0.0855
		rs2294918	A (434K)	0.182 (A)	0.284	0.297	0.3711
	CDX (n=93)	rs738409	G (148M)	0.231 (G)	0.333	0.355	0.6981
		rs2294918	A (434K)	0.21 (A)	0.312	0.331	0.7308
	CHB (n=103)	rs738409	G (148M)	0.383 (G)	0.456	0.473	0.8413
		rs2294918	A (434K)	0.141 (A)	0.282	0.242	0.2011
	CHS (n=105)	rs738409	G (148M)	0.39 (G)	0.438	0.476	0.3900
		rs2294918	A (434K)	0.238 (A)	0.343	0.363	0.238
	JPT (n=104)	rs738409	G (148M)	**0.418 (G)**	0.394	0.487	0.0736
		rs2294918	A (434K)	0.087 (A)	0.135	0.158	0.3183
	KHV (n=99)	rs738409	G (148M)	0.308 (G)	0.475	0.426	0.3992
		rs2294918	A (434K)	0.237 (A)	0.354	0.362	0.9730
Europian	EUR (n=503)	rs738409	G (148M)	0.226 (G)	0.344	0.349	0.7937
		rs2294918	A (434K)	**0.371 (A)**	0.479	0.467	0.6294
	CEU (n=99)	rs738409	G (148M)	0.217 (G)	0.354	0.340	0.9869
		rs2294918	A (434K)	0.323 (A)	0.438	0.438	0.8946
	FIN (n=99)	rs738409	G (148M)	0.172 (G)	0.303	0.284	0.8459
		rs2294918	A (434K)	0.369 (A)	0.495	0.466	0.7196
	GBR (n=99)	rs738409	G (148M)	0.253 (G)	0.374	0.378	1.0000
		rs2294918	A (434K)	0.346 (A)	0.473	0.453	0.8988
	IBS (n=107)	rs738409	G (148M)	0.257 (G)	0.364	0.382	0.7739
		rs2294918	A (434K)	**0.407 (A)**	0.551	0.483	0.2177
	TSI (n=107)	rs738409	G (148M)	0.229 (G)	0.327	0.353	0.5769
		rs2294918	A (434K)	**0.402 (A)**	0.449	0.481	0.5878
South Asian	SAS (n=489)	rs738409	G (148M)	0.246 (G)	0.354	0.371	0.3412
		rs2294918	A (434K)	0.228 (A)	0.350	0.352	0.9561
	BEB (n=86)	rs738409	G (148M)	0.244 (G)	0.419	0.369	0.3697
		rs2294918	A (434K)	0.198 (A)	0.349	0.317	0.6170
	GIH (n=103)	rs738409	G (148M)	0.311 (G)	0.388	0.428	0.4391
		rs2294918	A (434K)	0.209 (A)	0.32	0.33	0.9265
	ITU (n=102)	rs738409	G (148M)	0.221 (G)	0.324	0.344	0.6985
		rs2294918	A (434K)	0.225 (A)	0.373	0.349	0.7539
	PJL (n=96)	rs738409	G (148M)	0.198 (G)	0.271	0.317	0.2419
		rs2294918	A (434K)	0.297 (A)	0.406	0.417	0.9327
	STU (n=102)	rs738409	G (148M)	0.255 (G)	0.373	0.38	0.9960
		rs2294918	A (434K)	0.211 (A)	0.304	0.333	0.5155

Notes: MAF - is the frequency of the minor allele; Ho - observed heterozygosity; He is the expected heterozygosity; high frequencies of the minor allele are indicated in bold; YKT - Yakuts from Yakutia, Russia; AFR - Africans; ACB – African Carribian in Barbados; ASW - African Ancestry in Southwest US; ESN - Esan in Nigeria; GWD - Gambians in Western Division, The Gambia; LWK - Luhya in Webue, Kenya; MSL - Mende in Sierra-Leone; YRI - Yoruba in Ibadan, Nigeria; AMR - American; CLM - Colombian in Medellin, Colombia; MXL – Mexican Ancestry in Los Angeles, California; PEL - Peruvians in Lima, Peru; PUR - Puerto Rican in Puerto Rico; EAS - East Asian; CDX - Chinese Dai in Xishuangbanna, China; CHB - Han Chinese in Beijing, China; CHS - Southern Han Chinese, China; JPT - Japanese in Tokyo, Japan; KHV - Kinh in Ho Chi Minh City, Vietnam; EUR - European; CEU - Utah residents with Northern and Western European ancestry; FIN - Finnish in Finland; GBR – British in England and Scotland; IBS - Iberian population in Spain; TSI - Toscani in Italy; SAS - South Asian; BEB - Bengali in Bangladesh, India; GIH - Gujarati Indian in Houstan, Texas; ITU - Indian Telugu in the UK; PJL - Punjabi in Lahore, Pakistan; STU - Sri Lankan Tamil in The UK

tively). At the same time, in the populations of East Asia and America, the frequency of the risky allele G (rs738409) is significantly higher than the frequency of the protective allele A (rs2294918), while in the populations of Western Europe, a higher frequency of the protective allele A (rs2294918) is observed.

A weak linkage disequilibrium (LD) was observed between the two SNPs (D' = 0.096; r 2 = 0.003 in Yakuts. In other samples, strong linkage D' = 1, r 2 = 0.015 in Africans, D' = 0.98, r 2 = 0.242 in Americans, D' = 1, r 2 = 0.12 in East Asians, D' = 1, r 2 = 0.172 in Europeans, and D' = 1, r 2 = 0.097 in South Asians.

Analysis of the frequency distribution of genotypes in the studied sample of Yakuts showed the predominance of carriage of the GG genotype (57.3%). Genotypes AA and AG carrying the protective A allele are more common in European populations (13.1% and 47.9%, respectively).

The distribution of PNPLA3 gene haplotype frequencies for two SNPs (rs738409, rs2294918) based on all detected variants is presented in Table 2.

We identified two major haplotypes whose frequency was >0.1. One of the most common haplotypes carries the G variant (148M), the other carries the C variant (148I) and both carry the same G variant (434E). In other words, the more common two haplotypes carry the G (434E) allele, while the protective A (434K) allele does not occur in the major haplotypes found. The protective allele A (434K) is carried by both rare haplotypes. Haplotype G-A (148M-434K) was found only in Yakuts and Mexicans (6.9% and 1.1%, respectively).

The distribution of diplotype frequencies for two SNPs (rs738409-rs2294918) of the PNPLA3 gene showed 8 diplotypes out of nine possible variants. In Yakuts, two diplotypes [GG][GG] and [CG][GG] are more common. Both diplotypes carry the G allele (rs738409) (45.3% and 28%) and do not carry the protective A allele (rs2294918). The same distribution of diplotype frequencies was found in Peruvians (52.9% and 24.7%), Mexicans (32.8 and 23.4%) and Japanese (22.1 and 32.7%). Diplotypes carrying the protective allele A (rs2294918) occur at a low frequency (Table 3). Diplotypes [GG][AA] and [CG][AA] are absent in all 25 population samples, except for the diplotype [GG][AA] found in Yakuts (1.3%). In the Yoruba tribe, among the seven discovered diplotypes, [CC][GG] is more common (63.9%). This diplotype does not carry the pathological G allele (rs738409) and does not carry the protective A allele (rs2294918).

NAFLD is a multifactorial disease, timely developed patient management tactics will avoid the formation of complicated forms of the disease. The rs738409 polymorphism of the PNPLA3 gene is a major determinant of liver fat and predisposes to the full spectrum of liver damage in NAFLD. Many researchers have concluded that the G allele (rs738409) can increase the development of non-alcoholic fatty liver disease, while increasing serum ALT levels [2,5,6]. In their study, Donati, Motta, Pingitore, et al. (2016) found that carriers of the A (rs2294918) allele had lower levels of PNPLA3 protein in the liver ($P < 0.05$), thus this allele prevents the negative effects of the allele G (rs738409) [5].

Thus, in all samples of African origin, among the detected diplotypes, [CC][GG] is more common, which does not carry the pathological G allele (rs738409) and does not carry the protective A allele (rs2294918). An interesting fact is the absence of [GG][AA] and [CG][AA] diplotypes in all the 25 world samples studied, except for the Yakuts, in which we found the [GG][AA] diplotype with a frequency of occurrence of 1.3%. This diplotype may be found in the Yakut population due to the high prevalence of carriers of the homozygous GG variant (rs738409).

In our sample of Yakuts, two diplotypes [GG][GG] and [CG][GG] are more common. These diplotypes carry the mutant G allele (rs738409) and do not carry the A allele (rs2294918), which has a weakening effect on 148M, which in turn contributes to the accumulation of

Table2

The frequency of haplotypes I148M - E434K in the Yakut population and in the populations of the 1000 genomes project

Haplotypes	Protein	Haplotype frequency					
		YKT (n=150)	AFR (n=661)	AMR (n=347)	EAS (n=504)	EUR (n=503)	SAS (n=489)
G-G	148M-434E	**0.651**	0.118	**0.482**	0.350	0.226	0.246
C-G	148I-434E	0.243	**0.778**	0.306	**0.468**	**0.404**	**0.526**
G-A	148M-434K	0.069	0	0	0	0	0
C-A	148I-434K	0.037	0.104	0.210	0.182	0.371	0.228

Table3

Distribution of diplotypes by two SNP markers of the PNPLA3 gene in the Yakut population and in the populations of the 1000 genomes project

Genotype / SNP		Diplotype	Diplotype frequency					
rs738409	rs2294918		YKT (n=150)	AFR (n=661)	AMR (n=347)	EAS (n=504)	EUR (n=503)	SAS (n=489)
GG	GG	[GG][GG]	**0.453**	0.024	0.242	0.141	0.054	0.070
CG	GG	[CG][GG]	0.280	0.162	**0.282**	**0.317**	0.155	0.249
GG	AG	[GG][AG]	0.107	0.000	0.003	0.000	0.000	0.000
CG	AG	[CG][AG]	0.013	0.026	0.196	0.101	0.189	0.104
GG	AA	[GG][AA]	0.013	0.000	0.000	0.000	0.000	0.000
CC	AA	[CC][AA]	0.007	0.017	0.032	0.040	0.131	0.053
CC	AG	[CC][AG]	0.053	0.148	0.161	0.183	**0.290**	0.245
CC	GG	[CC][GG]	0.073	**0.623**	0.084	0.218	0.181	**0.278**
CG	AA	[CG][AA]	0.000	0.000	0.000	0.000	0.000	0.000

triglycerides in hepatocytes. The liver is responsible for the production of digestive bile, filtration of blood and processing of raw materials coming from food into the necessary chemical elements for the work of other organs. In his article Simcox J. and co-authors (2017) demonstrated in mice exposed to cold that acylcarnitines produced by the liver are necessary to maintain thermogenesis [10]. It is possible that in the Yakuts, the accumulation of fat in the liver in the past did not lead to NAFLD, as the accumulated fat was quickly converted into energy for heat generation. In modern realities, this diplotype has its detrimental effect by increasing the incidence of metabolic diseases, including NAFLD.

Conclusion. Thus, the high frequency of diplotypes [GG][GG] and [CG][GG] in Yakuts (45.3% and 25%, respectively) carrying mutant alleles G (rs738409) and not carrying allele A (rs2294918) which has a weakening effect on 148M indicates that these diplotypes in the past, they were probably adaptively favorable for the Yakuts. A normally functioning protein of the PNPLA3 gene regulates the activity of triglyceride hydrolase and acyltransferase of phosphatidic acid. Therefore, it can be assumed that the high frequency of the mutant allele G polymorphism rs738409, as well as the low frequency of the protective polymorphism rs2294918 of the PNPLA3 gene in Yakuts may be one of the reasons for the violation of the mechanism of lipid metabolism and lead to various liver diseases. The obtained data on the frequencies of markers rs738409 and rs2294918 of the PNPLA3 gene can be used in the diagnosis of susceptibility to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) for the prevention of these diseases, as well as in the study of the genetic mechanisms of human adaptation to cold.

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