before endoscopic screening at the outpatient stage.

The authors declare no conflict of interest.

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VARIABILITY OF PNPLA3 AND GCKR GENES, AND THEIR INFLUENCE ON BIOCHEMICAL PARAMETERS IN RESIDENTS OF THE REPUBLIC OF SAKHA (YAKUTIA)

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The article presents a study of the frequencies of *PNPLA3* and *GCKR* gene variants in samples of Yakuts, Evenks, and Russians. A total of 728 people living in the Sakha Republic (Yakutia) participated (331 Yakuts, 147 Evenks, and 250 Russians). Single nucleotide polymorphisms were determined by polymerase chain reaction followed by restriction fragment length polymorphism analysis. The study revealed significant differences between the studied samples. For the rs738409 polymorphism of the *PNPLA3* gene, the G allele was 72-75% in Yakuts and Evenks versus 53% in Russians. For the rs2294918 polymorphism, the protective allele A is virtually absent in Yakuts (6.7%) and very rare in Evenks (17%), the Russian population has a significantly higher proportion of A (43%). For rs1260326 of the *GCKR* gene, the risk allele T was more common in Russians than in Yakuts and Evenks. For the associated SNP rs780094, Russians have a higher percentage of the risk allele A, approximately 48% versus 40% in Yakuts and 44% in Evenks. Linkage disequilibrium (LD) analysis between the pair of polymorphisms rs738409 and rs2294918 in the *PNPLA3* gene showed an extremely weak association between these SNPs. Polymorphisms rs780094 and rs1260326 *GCKR* demonstrated strong linkage in all three studied samples. In the Russian sample, an association was noted between the genotype of the rs738409 *PNPLA3* polymorphism and the concentration of triglycerides, and polymorphisms of the *GCKR* gene showed a significant effect on ALT activity. The obtained data are consistent with the hypothesis that some pathological alleles became established in northern populations due to previous adaptive advantages, but in modern conditions, they have transformed from beneficial to harmful.

Keywords: *PNPLA3, GCKR, NAFLD,* Yakuts, Evenks, Russians

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Introduction. The populations of the Republic of Sakha (Yakutia) represent a unique model for studying genetic and ecological interactions. Russians, Evenks, and Yakuts living in this region differ in their genetic background, history, and traditional diets formed under harsh climates and extreme environmental factors. Until the middle of the 17th century, there was no agriculture in Yakutia, and the nutrition of the indigenous peoples was based on products of animal and plant origin [1]. With the development of industrialization, the historically established way of life and nutrition of the population have changed, so the traditional protein-lipid diet has been replaced by a modern Western one with a predominance of carbohydrates. The main organ of food metabolism is the liver. Consumption of high-calorie foods with high fructose content leads to an increase in circulating triglycerides and very low-density lipoproteins (VLDL), increased ALT levels, which in turn leads to insulin resistance and accumulation of visceral and liver fat [5, 17].

Yakutia is one of the most disadvantaged regions in terms of liver diseases, while the indigenous population is more susceptible to chronic diffuse liver diseases than newcomers [3]. Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases in developed and developing countries, its prevalence varies from 2.8% to 24.0% in different populations. It accounts for 60% of all chronic liver diseases [15]. Also, up to 15% of all liver cancer cases are detected in patients with NAFLD [2]. The main causes of NAFLD are sedentary lifestyle, poor nutrition, and genetic polymorphism of various genes 11]. Thus, the genetic variants involved in lipid and glucose metabolism, rs738409 (C/G) in gene 3 containing the domain of patatin-like phospholipase *(PNPLA3*), rs780094 (G/A) and rs1260326 (C/T) in the glucokinase regulatory protein (*GCKR*) gene, are consistently associated with the risk of NAFLD and liver complications of NAFLD.

The rs738409 polymorphism of the *PNPLA3* gene, which leads to the substitution of isoleucine for methionine at position 148 of the protein (I148M), is the most well-known genetic determinant of NAFLD [7]. Thus, the I148M variant disrupts the function of the enzyme adiponutrin (a product of the *PNPLA3* gene), which leads to the accumulation of lipids in hepatocytes and accelerates the progression of the disease. The association of this allele with NAFLD has been confirmed in various populations of the world, including the Chinese, Indians, and Malays [6] and the peoples of Central Asia [7]. In addition to rs738409, the rs2294918 polymorphism is described in the *PNPLA3* gene, which itself is not directly related to the disease, but modifies the effect of the I148M variant. This SNP is localized in the same gene and is associated with reduced expression of the PNPLA3 protein [18]. The carriage of the rs2294918 A allele leads to a decrease in the amount of the active enzyme, which to some extent weakens the negative effect of the rs738409 allele.:G affects the accumulation of fat in the liver [10].

The *GCKR* gene encoding the glucokinase regulator was first identified among the NAFLD-associated loci in 2011 [13]. Two related SNPs have been most studied: rs780094 and rs1260326 in the exon of the *GCKR* gene. The A alleles in rs780094 [4] and T alleles in rs1260326 are considered unfavorable. These variants are associated with a decrease in the function of the glucokinase regulator, which leads to increased glucokinase activity and enhanced lipogenesis in the liver [16]. A decrease in the function of the GCKR protein leads to a redistribution of metabolic fluxes: fatty acid synthesis in the liver increases, which promotes steatosis, although paradoxically the same alleles are associated with low blood glucose and elevated triglycerides in population studies [9].

The purpose of this study is to compare the frequencies of polymorphisms rs738409, rs2294918 of the *PNPLA3* gene and rs780094, rs1260326 of the *GCKR* gene in samples of Yakuts, Evenks and Russians.

Materials and methods. The study protocol was approved by the local Committee on Biomedical Ethics at the Yakut Scientific Center for Complex Medical Problems (YSC CMP). Informed written consent was obtained from all the volunteers. Clinical information about patients was collected in a special database, and DNA samples were stored in the collection of biomaterial of the YSC CMP using the USU "Genome of Yakutia" (reg. no. USU_507512). The study included 728 healthy volunteers, including 331 Yakuts (244 men average age 46.5±0.78, 87 women average age 51.8±1.18), 147 Evenks (54 men average age 49.9±2.68, 93 women average age 51.1±2.1) and 250 Russians (90 men average age 44.7±1.78, 160 the average age of women was 43.6±1.22). Ethnicity was taken into account up to the third generation, all subjects live in the Republic of Sakha (Yakutia). SNP genotyping was performed using classical polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) in the Laboratory of Hereditary Pathology of the Department of Molecular Genetics of the YSC CMP. The conditions for amplification of the gene region containing polymorphic variants, indicating the sequence of oligonucleotide primers, the restrictase used, and the lengths of the extraction fragments, are presented in Table 1.

The correspondence of the genotype distributions to the expected values at Hardy-Weinberg equilibrium and the comparison of the frequencies of allelic variants/genotypes were carried out using the χ2 (chi-squared) criterion with the Yates correction. SNP linkage disequilibrium analysis was studied by pairwise comparing r2 and D using Haploview software (version 4.2; Broad Institute, Cambridge, Massachusetts, USA) [14].

Results and discussions. A comparative analysis of the frequency distribution of the genotypes and alleles of the *PNPLA3* and *GCKR* gene polymorphisms revealed significant differences between the studied samples (Table 2).

According to the rs738409 polymorphism of the *PNPLA3* gene, Yakuts and Evenks have an extremely high proportion of the G allele (with impaired adiponutrin function): 72-75% against 53% for Russians. More than half of the Yakuts (57.9%) and Evenks (51.5%) had the GG genotype, while only 40.5% of Russians have GG. Statistically, the differences in *PNPLA3:* G frequencies between Yakuts and Russians are significant (χ2≈38.6; p<0.001), while there is no significant difference between Yakuts and Evenks (p=0.42). This confirms that both northern peoples carry a sharply increased proportion of the *PNPLA3* 148M variant, whereas it is significantly less common among Europeans (Russians). At the second *PNPLA3* locus (rs2294918), the A allele, characterized by reduced protein expression, is practically absent in Yakuts (6.7%) and very rare in Evenks (17%); the Russian population has a significantly higher proportion of A (43%). Thus, the protective effect of the rs2294918 variant is practically absent in the Yakut and Evenk groups, while it is much more pronounced in Russians.

In contrast to the above, according to variant rs1260326 of the *GCKR* gene, on the contrary, the T allele (which weakens the function of glucokinase and increases the risk of steatosis) was more common in Russians than in Yakuts and Evenks. The difference between Yakuts and Russians for this allele was statistically significant (p=0.02). Similarly, according to the related SNP rs780094, Russians have a higher percentage of the A allele, about

Table 1

Primers and restriction enzymes used to detect *PNPLA3* and *GCKR* gene polymorphisms

Gene / SNP	Primers	Annealing Temperature (˚C)	Restriction Endonuclease	Restriction fragments
PNPLA3 rs2294918	F: CCTCTAAGCCAACTTCCTCC R: CCTCAAGTGACTCACAGACTC	66	Ama87 I	AA - 271 b.p. GG – 160, 111 b.p.
PNPLA3 rs738409	F: TGGGCCTGAAGTCCGAGGGT R: CCGACACCAGTGCCCTGCAG	66	BstF5 I	CC – 200, 133 b.p. GG – 333 b.p.
GCKR rs780094	F: CATGTTGGCTAGGCTTGTTGAG R: AGCTCACGCTGGAACTTCTG	62	Pci I	GG - 126, 176, 258 b.p. AA - 302, 258 b.p.
GCKR rs1260326	F: TGCAGACTATAGTGGAGCCG	63	MspI	TT - 231 b.p. CC - 81, 150 b.p.

48% versus 40% for Yakuts and 44% for Evenks.

The analysis of linkage disequilibrium (LD) between a pair of rs738409 and rs2294918 polymorphisms in the *PNPLA3* gene showed an extremely weak association of these SNPs in the representatives of the studied populations. Low LD was observed in the samples of Yakuts, Evenks, and even Russians: the values of D' were only 0.032, 0.131, and 0.045, respectively, with virtually zero coefficient of determination (r2 ≈ 0.0). For comparison, in global populations, according to data from 1000 Genomes [12], these SNPs in *PNPLA3* are in almost complete linkage. So, for Africans, D' ≈ 1 with r2 ≈ 0.015; for Americans, D' ≈ 0.98, r2 ≈ 0.242; in East Asians, D' ≈ 1, r2 ≈ 0.12; in Europeans, D' ≈ 1, r2 ≈ 0.172; in South Asian populations, D' ≈ 1, r2 ≈ 0.097. Thus, in the studied samples of populations of Yakuts, Evenks and Russians, two *PNPLA3* variants are inherited almost independently, whereas in large global populations There is a strong cohesion between them (Fig.).

The polymorphisms rs780094 and rs1260326 *GCKR* demonstrated strong coupling in all three samples studied, so for Yakuts and Evenks, D' was 1.0 with r2 ~ 0.8–0.99, and for Russians, D' = 0.898, r2 = 0.769. Thus, in the studied populations, the alleles of these two *GCKR* SNPs are transmitted almost as a single block. The combination of alleles of two *PNPLA3* variants (rs738409 and rs2294918) forms four possible haplotypes. The frequency distribution of these haplotypes demonstrates noticeable differences between Yakuts, Evenks, Russians, and the reference populations of the world (Table 3).

As can be seen from Table 3, the G–G haplotype is most common in the populations of Yakutia. Among Russians, there is a more uniform distribution across several haplotypes: in addition to G–G, hap-

Table 2

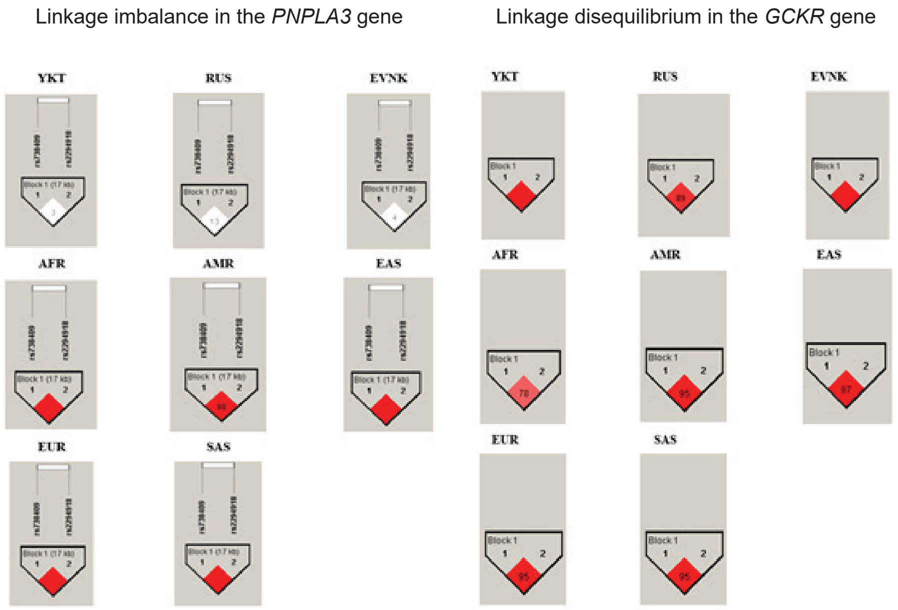
Comparison of the frequency distribution of genotypes and alleles of *PNPLA3* and *GCKR* gene polymorphisms in the studied populations

Population	Genotype frequency (%)			Allele frequency (%)		Chi-square	p
rs738409 PNPLA3	CC	CG	GG	C	G		
Yakuts	7.9	34.2	57.9	25.0	75.0	38.62	0.00
Russian	33.5	25.9	40.5	46.5	53.5		
Yakuts	7.9	34.2	57.9	25.0	75.0	0.66	0.42
Evenks	7.6	40.9	51.5	28.0	72.0		
Evenks	7.6	40.9	51.5	28.0	72.0	20.07	0.00
Russian	33.5	25.9	40.5	46.5	53.5		
PNPLA3 rs2294918	AA	AG	GG	A	G		
Yakuts	0.4	12.5	87.1	6.7	93.3	151.18	0.00
Russian	11.4	63.9	24.7	43.4	56.6		
Yakuts	0.4	12.5	87.1	6.7	93.3	18.67	0.00
Evenks	0.0	34.1	65.9	17.0	83.0		
Evenks	0.0	34.1	65.9	17.0	83.0	45.02	0.00
Russian	11.4	63.9	24.7	43.4	56.6		
GCKR rs780094	AA	AG	GG	A	G		
Yakuts	17.1	45.4	37.5	39.8	60.2	5.43	0.02
Russian	27.8	41.1	31.0	48.4	51.6		
Yakuts	17.1	45.4	37.5	39.8	60.2	1.04	0.31
Evenks	18.9	50.0	31.1	43.9	56.1		
Evenks	18.9	50.0	31.1	43.9	56.1	0.99	0.32
Russian	27.8	41.1	31.0	48.4	51.6		
GCKR rs1260326	TT	CT	CC	T	C		
Yakuts	17.1	45.4	37.5	39.8	60.2	5.43	0.02
Russian	25.3	46.2	28.5	48.4	51.6		
Yakuts	17.1	45.4	37.5	39.8	60.2	0.19	0.67
Evenks	11.4	53.0	35.6	37.9	62.1		
Evenks	11.4	53.0	35.6	37.9	62.1	6.07	0.01
Russian	25.3	46.2	28.5	48.4	51.6		

lotypes C–G (30.9%) and G–A (23.9%) have significant proportions. The G–A haplotype is practically absent in the main world populations, but, on the contrary, it is present in Yakuts and Evenks (5.2% and 12.2%, respectively). The European sample (EUR) has a remarkably high proportion of the C–A haplotype (37.1%), which is also quite common in South Asians (22.8%). The frequency of C–A in Russians is 17.1%, which is noticeably higher than in Yakuts (1.9%), but lower than in the European population. Thus, the Yakuts and Evenks are characterized by the predominance of the G–G haplotype and the presence of the G–A haplotype, which is unique to them, whereas the distribution of *PNPLA3* haplotypes in Russians is closer to the European type. For the *GCKR* gene, the combination of alleles of polymorphisms rs780094 and rs1260326 also forms four haplotypes. However, unlike *PNPLA3*, only two main haplotypes are observed in all populations, while the remaining two are extremely rare (Table 4).

According to Table 4, in each population considered, the main share (>90%) is accounted for by the G–C and A–T haplotypes, whereas combinations of G–T and A–C are rare minor haplotypes. These data confirm that the two substitutions under consideration in *GCKR* are closely related: in fact, only two main haplotype lines can be traced in all groups, whereas recombination variants (G–T, A–C) have evolved rarely and therefore persist with low frequency.

To assess the functional effect of genes, the average value of biochemical parameters in the studied samples of Russians and Evenks was stratified depending on the genotype according to a number of polymorphisms. The effect of the *PNPLA3* variant on the biochemical parameters manifested itself as expected. In the Russian sample, the rs738409 *PNPLA3* polymorphism genotype was associated with triglyceride concentration, so carriers of the unfavorable GG genotype had a lower TG level (on average 1.6±0.9 mmol/l), and carriers of the favorable CC genotype had a higher TG (2.5±1.6 mmol/l, p=0.01). This reverse effect is consistent with the known data on *PNPLA3* [6]. variant 148M promotes fat accumulation in the liver by reducing TG secretion into the blood, therefore, GG carriers often exhibit reduced levels of circulating triglycerides against the background of severe liver steatosis. In Evenks, *PNPLA3* genotypes also influenced the indicators, although not so significantly. For example, the average AST activity in Evenks with the GG gen-


Linkage imbalance in the *PNPLA3* gene

Linkage disequilibrium in the *GCKR* gene

Linkage disequilibrium in the *PNPLA3* and *GCKR* genes. Note. The color of the cell indicates the strength of the bond between the SNPs: red is a strong bond (D'= 1, LOD> 2), white is a weak bond (D' <1, LOD <2). Abbreviations: YKT – Yakuts; RUS – Russians; EVNK - Evenks; AFR - Africans; AMR - Americans; EAS – East Asians; EUR - Europeans; SAS – South Asians.

Table 3

Frequency of PNPLA3 haplotypes (rs738409–rs2294918) in Yakutia and worldwide populations

haplotypes rs738409-rs2294918	Frequency of *PNPLA3* haplotypes							
	YKT (n=330)	RUS (n=178)	EVNK (n=138)	AFR (n=661)	AMR (n=347)	EAS (n=504)	EUR (n=503)	SAS (n=489)
G-G	0.701	0.281	0.599	0.118	0.482	0.350	0.226	0.246
C-G	0.228	0.309	0.235	0.778	0.306	0.468	0.404	0.526
G-A	0.052	0.239	0.122	0	0	0	0	0
C-A	0.019	0.171	0.044	0.104	0.210	0.182	0.371	0.228

Note: n is the number of people studied; YKT – Yakuts; RUS – Russians; EVNK - Evenks; AFR - Africans; AMR - Americans; EAS – East Asians; EUR - Europeans; SAS – South Asians

Table 4

Frequency of *GCKR* haplotypes (rs780094–rs1260326) in populations of Yakutia and the world

haplotypes rs780094-rs1260326	Frequency of *GCKR* haplotypes							
	YKT (n=331)	RUS (n=250)	EVNK (n=147)	AFR (n=661)	AMR (n=347)	EAS (n=504)	EUR (n=503)	SAS (n=489)
G-C	0.580	0.489	0.568	0.851	0.628	0.512	0.579	0.792
A-T	0.417	0.449	0.378	0.076	0.350	0.469	0.400	0.191
G-T	0	0.025	0	0.018	0.012	0.012	0.010	0.009
A-C	0.003	0.037	0.054	0.055	0.010	0.007	0.010	0.007

Note: n is the number of people studied; YKT – Yakuts; RUS – Russians; EVNK - Evenks; AFR - Africans; AMR - Americans; EAS – East Asians; EUR - Europeans; SAS – South Asians otype was higher (31.1 U/l) compared with CC (24.8 U/l), but this difference was not significantly significant (p=0.06). The *PNPLA3* genotype in Evenks did not significantly affect lipid levels (p>0.3 for TG, cholesterol), although the same trend was observed, GG carriers had a slightly lower average TG than CC carriers.

In the Russian sample, polymorphisms of the *GCKR* gene showed a significant effect on the activity of ALT, a key enzyme that reflects the degree of liver damage in NAFLD. Carriers of risky alleles had significantly higher ALT. For example, among Russians, the average ALT for carriers of the AA genotype (rs780094) was 19.2±11.6 U/L, while for the GG genotype it was only 13.5±5.3 U/l (p<0.001). A similar effect was confirmed for the associated rs1260326 variant: the TT genotype was associated with ALT of 18.3±11.6 U/l versus ~13.5 U/l for CC (p=0.02). In Evenks, the effect of *GCKR* on ALT and other indicators did not reach statistical significance. For example, according to rs780094, the ALT of Evenks was ~19-21 U/l for all genotypes (p=0.90). It can be assumed that with a smaller sample size of Evenks, the associations might not appear, although Evenks with the TT genotype according to rs1260326 had a slightly higher ALT than with CC, but did not achieve a significant difference.

Conclusion. Collectively, the genetic profile of Yakuts and Evenks for polymorphisms rs738409 and rs2294918 of the *PNPLA3* gene is characterized by an increased proportion of alleles associated with the risk of liver obesity, while Russians have significantly lower frequencies of these alleles. However, according to the polymorphisms rs780094 and rs1260326 of the *GCKR* gene, Russians have a higher proportion of alleles with reduced glucokinase function than the northern groups. When comparing the average biochemical parameters depending on the genotype, reliable values were found only in the sample of Russians, which may be due to the low variability of genotypes in Evenks. The results of the study demonstrate how genetic adaptation to extreme environmental conditions can affect the health of a population in new conditions. In Yakuts and Evenks, long-term evolution in conditions of cold and limited nutrition led to the consolidation of alleles optimizing the accumulation and use of energy, which, in an environment of excess calories, became factors of increased vulnerability to non-alcoholic fatty liver disease.

The authors declare that there is no conflict of interest.

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