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Genetic Determinants of Hepatocellular Carcinoma: Role of *PNPLA3*, *FABP2, FADS1/FADS2* Genes in Yakuts

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ABSTRACT

***BACKGROUND*:** Hepatocellular carcinoma is an aggressive primary liver cancer. Major risk factors include cirrhosis, hepatitis B and C infections, nonalcoholic fatty liver disease, and type 2 diabetes mellitus. According to state medical statistics of the Russian Federation for 2021, the highest incidence of malignant neoplasms of the liver and intrahepatic bile ducts was reported in the Republic of Sakha (Yakutia). This may be related to dietary changes that have increased the prevalence of obesity, type 2 diabetes mellitus, and nonalcoholic fatty liver disease.

***AIM*:** The work aimed to investigate the variability of the *PNPLA3*, *FABP2*, *FADS1*, and *FADS2* genes, which are involved in lipid metabolism and associated with nonalcoholic fatty liver disease—a risk factor for hepatocellular carcinoma—in the Yakut population.

***METHODS*:** A total of 498 volunteers participated in the study, of whom 126 were diagnosed with nonalcoholic fatty liver disease with concomitant type 2 diabetes mellitus. Single-nucleotide polymorphisms were determined using polymerase chain reaction followed by restriction fragment length polymorphism analysis.

***RESULTS*:** In the examined polymorphisms of the *PNPLA3*, *FADS1*, and *FADS2* genes, a predominance of alleles pathogenic with respect to nonalcoholic fatty liver disease was found in both groups. For the rs1799883 polymorphism of the *FABP2* gene, a significant association of the Ala allele with nonalcoholic fatty liver disease and concomitant type 2 diabetes mellitus was identified ($p = 0.02$). Compared with other populations from the *1000 Genomes* project database, a high frequency of alleles pathogenic with respect to nonalcoholic fatty liver disease was observed in the Yakut population.

***CONCLUSION*:** The high prevalence of *PNPLA3*, *FABP2*, *FADS1*, and *FADS2* gene variants associated with increased body mass index and nonalcoholic fatty liver disease is likely related to an adaptive mechanism for fat accumulation in the liver. With the dietary shift from lipid-protein to predominantly carbohydrate intake, these previously advantageous allelic variants now contribute to metabolic disorders that influence the incidence of liver diseases, including hepatocellular carcinoma.

Keywords: *PNPLA3*; *FABP2*; *FADS1*; *FADS2*; polymorphism; nonalcoholic fatty liver disease; yakuts.

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Генетические детерминанты гепатоцеллюлярной карциномы: роль генов *PNPLA3*, *FABP2*, *FADS1/FADS2* у якутов

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АННОТАЦИЯ

Обоснование. Гепатоцеллюлярная карцинома представляет собой агрессивный первичный рак печени, факторами развития которого являются цирроз печени, инфекции гепатита B и C, неалкогольная жировая болезнь печени (НАЖБП) и, в частности, сахарный диабет 2 типа (СД2). По данным Государственной медицинской статистики Российской Федерации за 2021 г., самая высокая заболеваемость злокачественными новообразованиями печени и внутрипечёночных жёлчных протоков была отмечена в Республике Саха (Якутия), что, возможно, связано с изменением в привычках питания, которое привело к увеличению числа лиц с ожирением, СД2 и НАЖБП.

Цель. Изучение вариабельности генов *PNPLA3*, *FABP2*, *FADS1* и *FADS2*, участвующих в липидном обмене и ассоциированных с неалкогольной жировой болезнью печени, фактором риска гепатоцеллюлярной карциномы, в якутской популяции.

Методы. Всего в исследовании приняло участие 498 добровольцев, из которых 126 имели диагноз НАЖБП с сопутствующим СД 2 типа. Однонуклеотидные полиморфизмы определяли методом полимеразной цепной реакции с последующим анализом полиморфизма длин рестрикционных фрагментов.

Результаты. В исследованных полиморфизмах генов *PNPLA3*, *FADS1* и *FADS2* выявлено преобладание патологических в отношении к НАЖБП аллелей в обеих группах испытуемых. В отношении полиморфизма rs1799883 гена *FABP2* выявлена значимая (p=0,02) связь аллели Ala с НАЖБП с сопутствующим СД2. При сравнении с другими популяциями из базы данных проекта «1000 Genomes» в популяции якутов установлена высокая частота патологических в отношении к НАЖБП аллелей исследованных полиморфизмов.

Заключение. Высокая распространённость вариантов генов *PNPLA3*, *FABP2*, *FADS1* и *FADS2*, ассоциированных с повышенным индексом массы тела и НАЖБП, вероятно, связана с адаптивным механизмом к накоплению жира в печени. С изменением липидно-белковой диеты на преимущественно углеводную благоприятные ранее аллельные варианты этих генов сегодня приводят к метаболическим нарушениям, что влияет на заболеваемость патологиями печени, в том числе к гепатоцеллюлярной карциноме.

Ключевые слова: *PNPLA3*; *FABP2*; *FADS1*; *FADS2;* полиморфизм; неалкогольная жировая болезнь печени; якуты.

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INTRODUCTION

For ten consecutive years, the incidence rate of hepatocellular carcinoma (HCC) in the Republic of Sakha (Yakutia) has been 2.0–3.9 times higher than the national average in the Russian Federation. The primary risk factor for HCC in Yakutia is infection with hepatitis C, B, and D viruses. Additional contributing factors include alcohol abuse, type 2 diabetes mellitus (T2DM), overweight (obesity), and tobacco smoking [1]. In recent years, dietary changes among the Yakut population have led to an increased prevalence of obesity and other metabolic disorders, such as T2DM and nonalcoholic fatty liver disease (NAFLD).* Studies have demonstrated a frequent overlap of T2DM and NAFLD, the latter being characterized by lipid accumulation both within hepatocytes and in the intercellular space [2, 3]. Particularly concerning is the global increase in NAFLD prevalence, which rose from 25% in 1990–2006 to 38% in 2016–2019 [4]. Data on NAFLD prevalence in Russia remain limited. According to the DIREG-2 epidemiological study, which included more than 50,000 patients from 16 Russian cities, the prevalence of NAFLD among outpatients increased from 27% to 37% over the period from 2007 to 2015 [5]. No statistical data on NAFLD prevalence are available for the Republic of Sakha (Yakutia), but the region is considered unfavorable in terms of chronic diffuse liver diseases [6]. Furthermore, according to state medical statistics of the Russian Federation for 2021, the highest incidence of malignant neoplasms of the liver and intrahepatic bile ducts was reported in the Republic of Sakha (Yakutia) [7]. Inflammation of liver tissue leads to an increase in the proportion of connective tissue elements relative to functional hepatocytes, resulting in fibrosis and cirrhosis. In addition, the presence of NAFLD substantially predisposes to the development of HCC, liver cancer. For example, a recent study by Liu et al. (2023) established that NAFLD is associated with an increased risk of cancer and that there is a correlation with the age of disease onset [8]. Hepatocellular carcinoma is an aggressive primary liver cancer, the risk factors for which include liver cirrhosis, hepatitis B and C virus infections, NAFLD, and, in particular, type 2 diabetes mellitus [9].

Dietary polyunsaturated fatty acids (PUFAs) are metabolized primarily in the liver and may have a direct impact on the development of NAFLD [10, 11]. Genome-wide association studies (GWAS) are providing increasing evidence of genetic variants associated with NAFLD susceptibility and progression [12]. These include variants of the *PNPLA3*, *FADS1*, *FADS2*, and *FABP2* genes, which affect hepatic lipid metabolism. Numerous studies have attempted to elucidate the genetic basis of human adaptation to different environmental conditions and diets [13–15]. For example, in their studies, Matteo Fumagalli of the University of California, Berkeley, and colleagues demonstrated that genes involved in the regulation of long-chain fatty acids show strong positive selection driven by adaptation to cold climates or high-fat diets [16]. According to Panin (2010), under extreme conditions a polar metabolic type is formed, characterized by lipid-based rather than carbohydrate-based energy metabolism, which in turn influences human dietary patterns [17].

The strongest genome-wide association study (GWAS) signal ever reported for genetic susceptibility to NAFLD is the single nucleotide polymorphism (SNP) rs738409 in the adiponutrin (*PNPLA3*) gene. This variant is significantly associated not only with hepatic fat accumulation but also with histological severity and progression of NAFLD [18]. Another polymorphism in the same gene, rs2294918, reduces PNPLA3 protein expression, thereby mitigating the effect of rs738409 on susceptibility to steatosis and liver injury [19]. In our previous study of the *PNPLA3* polymorphisms rs738409 and rs2294918 in the Yakut population, we found a high frequency of the pathogenic G allele (rs738409) and a low frequency of the protective A allele (rs2294918) [20]. Susceptibility to NAFLD has also been demonstrated in carriers of the loss-of-function variant rs58542926 in the transmembrane 6 superfamily member 2 (*TM6SF2*) gene [21, 22]. Fatty acid desaturase genes 1 and 2 (*FADS1* and *FADS2*) play a key role in PUFA metabolism. In the *FADS* gene cluster, two linkage disequilibrium blocks can be distinguished: haploblock 1, defined by polymorphic variants in *FADS1* and the first part of *FADS2*, and haploblock 2, defined by polymorphisms in the remaining part of *FADS2*. Within haploblock 1, two main haplotypes have been identified: A and D. Haplotype D is associated with higher gene expression, leading to increased synthesis of fatty acids such as arachidonic acid and docosahexaenoic acid. By contrast, haplotype A is characterized by lower expression, which may result in reduced levels of these essential fatty acids in the body. Thus, carriers of haplotype D are better able to utilize plant-based sources of these fatty acids, whereas individuals with haplotype A may require greater intake of fish and seafood to achieve optimal levels [23]. Fatty acid–binding protein 2 (FABP2) is secreted by intestinal epithelial cells and participates in all aspects of long-chain fatty acid metabolism.

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* State Budgetary Institution of the Republic of Sakha (Yakutia). Yakut Republican Medical Information-Analytical Center [Internet]. Available at: https://yakmed.ru

The threonine-containing variant of the protein has a much higher affinity for long-chain fatty acids than the alanine-containing variant, which in turn leading to enhanced triglyceride transport into intestinal cells, increased lipid oxidation, and insulin resistance [24].

Studies on the genetic basis of human adaptation to a lipid-rich diet are rather limited, which in turn highlights the problem of dietary changes. The shift from a traditional lipid-based diet to a modern Western diet dominated by vegetable oils has a considerable impact on human health [25].

AIM

Given the high incidence of hepatocellular carcinoma in the Republic of Sakha (Yakutia), for which NAFLD is a known risk factor, this study aimed to investigate the variability of the *PNPLA3*, *FABP2*, *FADS1*, and *FADS2* genes involved in lipid metabolism and associated with nonalcoholic fatty liver disease—a risk factor for hepatocellular carcinoma—in the Yakut population.

METHODS

Study Design

A single-center, retrospective, comparative study was conducted.

Eligibility Criteria

Inclusion criteria for the study group comprised male and female patients, unrelated by blood, residing in the Republic of Sakha (Yakutia), with a diagnosis of NAFLD confirmed by abdominal ultrasound and concomitant T2DM. *Non-inlusion criteria* were liver disease of other etiologies, acute or chronic viral hepatitis, psychoactive substance abuse, and alcoholism. *Inclusion criteria for the control group* were the absence of diabetes mellitus and liver disease.

Study Setting and Duration

The study was conducted from January 2018 to December 2023. Examination, diagnosis, and treatment of patients with NAFLD confirmed by abdominal ultrasound and concomitant T2DM were carried out in the Endocrinology Department of the Republican Hospital No. 2 of the State Budgetary Institution “Center for Emergency Medical Care” and in the Endocrinology Department of the Clinic of the Yakut Scientific Center for Complex Medical Problems (YSCCMP) from January 2018 to December 2019. The second comparison group consisted of DNA samples from volunteers without chronic diseases, collected by YSCCMP during field expeditions between January 2018 and December 2023.

Intervention

To confirm the diagnosis of NAFLD, all patients with T2DM (n = 126) underwent abdominal ultrasound. For subsequent DNA extraction, a total of 498 blood samples were collected and prepared by venipuncture using vacuum tubes containing ethylenediaminetetraacetic acid. DNA was extracted from whole frozen blood using a commercial Newteryx kit (Yakutsk, Russia). For analysis, the following SNPs were selected: rs738409 in *PNPLA3*, rs1799883 in *FABP2*, rs174537 in the *FADS1*/*FADS2* enhancer, rs174547 in *FADS1*, and an insertion/deletion (indel) polymorphism in *FADS2* rs3834458. Genotyping of SNPs was performed at the Laboratory of Hereditary Pathology, Department of Molecular Genetics, YSCCMP, using conventional polymerase chain reaction (PCR) according to the manufacturer’s protocol (Biolabmix, Russia). Restriction fragment length polymorphism analysis was carried out using restriction endonucleases produced by Sibenzyme LLC. The conditions for amplification of gene regions containing polymorphic variants, with specification of oligonucleotide primer sequences, the restriction enzymes employed, and the lengths of restriction fragments, are presented in Table 1.

Genotypes were determined by analyzing the sizes of resulting fragments via gel electrophoresis on 4% agarose gel with ethidium bromide in a standard tris-acetate buffer at 120 V for one hour. Restriction products were visualized using a gel documentation system under ultraviolet light (Vilber Lourmat, France).

Group Analysis

The cohort comprised 126 patients from the Endocrinology Department of Republican Hospital No. 2 of the State Budgetary Institution “Center for Emergency Medical Care” and the Endocrinology Department of the YSCCMP, diagnosed with NAFLD, confirmed by abdominal ultrasound, and concomitant T2DM. The control group included 372 volunteers without chronic diseases. All participants were of Yakut ethnicity, verified up to the third generation.

To contextualize the results, allele frequencies of rs738409 *PNPLA3*, rs1799883 *FABP2*, rs174537 *FADS1* enhancer, *FADS2*, rs174547 *FADS1*, and the insertion/deletion (indel) variant *FADS2* rs3834458 were compared with global population data from the 1000 Genomes database using descriptive analysis.

Outcomes Registration

Clinical information was collected through questionnaires and medical records. All patient

Table 1. Conditions for conducting polymerase chain reaction

Gene / SNP	Group	*n*	Primers	Annealing temperature, °C	Restriction enzyme	Restriction fragments
FABP2 / rs1799883	NAFLD+T2DM	126	F: ACA GGT GTT AAT ATA GTG AAA AG	58	AspLEI	Ala/Ala — 99, 81 bp Thr/Thr — 180 bp
	Control	153	R: GAC GGA ACT GAA CTC AGG GTA			
FADS1, *FADS2* / rs174537	NAFLD+T2DM	67	F: CAG GGG AGA GAG GTG GAG TA	64	AvaII	G — 149, 158 bp T — 307 bp
	Control	160	R: AGG TCT GTC TGG CTG TCT CC			
FADS1 / rs174547	NAFLD+T2DM	67	F: AGG CTT TAT GTC CCC AAA CC	62	BssECI	G — 75, 186 bp T — 261 bp
	Control	160	R: GCC TTA ACC TCA CTG CTC CA			
FADS2 / rs3834458	NAFLD+T2DM	67	F: GGC AGT CTT TAT TTG CTG GAG T	64	DdeI	T — 9, 76, 127, 257 bp deletion — 9, 76, 384 bp
	Control	160	R: ACC TGA TGC CGA CAC AAA G			
PNPLA3 / rs738409	NAFLD+T2DM	126	F: TGG GCC TGA AGT CCG AGG GT	66	BstF5I	CC — 200, 133 bp GG — 333 bp
	Control	212	R: CCG ACA CCA GTG CCC TGC AG			

Note: SNP, single nucleotide polymorphism; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; bp, base pairs.

information was collected in a specialized database, and DNA samples were stored in the biomaterial collection of the YSCCMP using the unique scientific facility Yakutia Genome (reg. no. USU_507512). DNA quality and quantity were assessed with a NanoPhotometer N50-Touch UV/Vis spectrophotometer (Implen, Germany). PCR analysis was performed on a GeneExplorer GE-96G thermal cycler for conventional PCR (Bioer, China). Restriction fragment length polymorphism analysis was conducted using a BD023-230V thermostat (Binder, Germany). Restriction products were visualized using a gel documentation system under ultraviolet light (Vilber Lourmat, France).

Ethics Approval

The study protocol was approved by the Local Biomedical Ethics Committee of the YSCCMP (protocol no. 60, April 10, 2024; decision 2). Written informed consent was obtained from all participants.

Statistical Analysis

Sample Size Calculation

The sample size was not pre-calculated.

Methods of Statistical Data Analysis

Analysis was performed using Microsoft Windows tools, including Excel (Microsoft Office 2010, USA). The significance of differences in allele and genotype frequencies between groups was assessed using the chi-square test with Yates' correction. Odds ratios (ORs) were calculated to evaluate the strength of association for SNP rs738409 *PNPLA3*, rs1799883 *FABP2*, rs174537 *FADS1* enhancer, *FADS2*, rs174547 *FADS1*, and the *FADS2* rs3834458 insertion/deletion (indel). To determine the significance of the odds ratios, 95% confidence interval (95% CI) limits were calculated. Results were considered significant at $p < 0.05$.

RESULTS

Participants

The cohort of patients diagnosed with NAFLD and concomitant T2DM included 126 individuals: 86 women with a mean age of 61 ± 0.08 years and 40 men with a mean age of 58.2 ± 0.17 years. The control sample comprised 372 volunteers with normal body mass index (BMI), including 211 women with a mean age of 33.8 ± 0.08 years and 154 men with a mean age of 45.3 ± 0.10 years. All participants were of Yakut ethnicity, verified up to the third generation.

Primary results

The analysis of allele frequency distribution for the studied polymorphisms is presented in Table 2.

In the examined polymorphisms of the *PNPLA3*, *FADS1*, and *FADS2* genes, a predominance of alleles pathogenic with respect to NAFLD was identified in both groups of participants. Among these, the alleles of the *FADS* gene polymorphisms belonged to the ancestral haplotype A [26]. Odds ratio analysis of the *FABP2* rs1799883 polymorphism demonstrated a significant association (p = 0.02) of the Ala allele with NAFLD concomitant with T2DM (OR = 1.51, 95% CI: 1.08–2.12). No statistically significant differences were observed for the other polymorphisms.

The frequency of alleles pathogenic with respect to NAFLD for all polymorphisms analyzed in this study differed substantially from that observed in other populations from the 1000 Genomes project (see Fig. 1).

DISCUSSION

In the Yakut population, the *PNPLA3* gene polymorphism rs738409 demonstrates a high frequency of the G allele, reaching 72%. Comparison with data from other populations in the 1000 Genomes project shows that the highest frequency of the G allele is observed in Central and South American populations: 71.8% in Peruvians, 55.5% in Mexicans, and 41% in Colombians. By contrast, the mean frequency of the G allele among Europeans is 22.6%. Among East Asian populations, a relatively high frequency of the G allele is reported in Japanese (41.8%). The lowest frequency of the G allele is found in Africans, averaging 11.8%.* These findings highlight the unique genetic characteristics of the Yakut population, which may reflect adaptation to specific environmental conditions and lifestyle. The high frequency of the *PNPLA3* G allele may indicate the presence of selective pressure in this group, potentially driven by historical, ecological, or metabolic factors. The diagram also shows that the frequency of the Thr allele of the *FABP2* rs1799883 polymorphism is the highest in the Yakut population (59%). The *FADS* locus haplotype A is characterized by a high frequency (78%) and shows correlation with the frequency of the rs738409 G allele in American populations (81% in Peruvians, 70% in Mexicans, and 43% in Colombians). At the same time, haplotype A occurs with high frequency in East Asian populations (82% in Vietnamese and 78% in Han Chinese).

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* Ensembl [Internet]. Ensembl genome browser. Available from: https://www.ensembl.org/index.html

Table 2. Frequency distribution (%) and odds ratio of *PNPLA3*, *FABP2*, *FADS1* and *FADS2* gene polymorphisms

Polymorphism, gene	Allele	NAFLD+T2DM	Control	OR	χ^2	p
rs738409, *PNPLA3*	C	32.1	28.0	1.26 (0.89–1.77)	1.53	0.22
	G	67.9	72.0	0.79 (0.57–1.12)		
rs1799883, *FABP2*	Ala	50.8	40.5	1.51 (1.08–2.12)	5.48	0.02
	Thr	49.2	59.5	0.66 (0.47–0.92)		
rs174537, *FADS1, FADS2*	G	25.4	21.9	1.21 (0.76–1.94)	0.47	0.49
	T	74.6	78.1	0.82 (0.51–1.32)		
rs174546, *FADS1*	G	25.4	21.9	1.21 (0.76–1.94)	0.47	0.49
	T	74.6	78.1	0.82 (0.51–1.32)		
rs3834458, *FADS2*	T	25.4	22.5	1.17 (0.73–1.87)	0.29	0.59
	d	74.6	77.5	0.85 (0.53–1.36)		

Note: NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; OR, odds ratio; Ala, alanine; Thr, threonine.

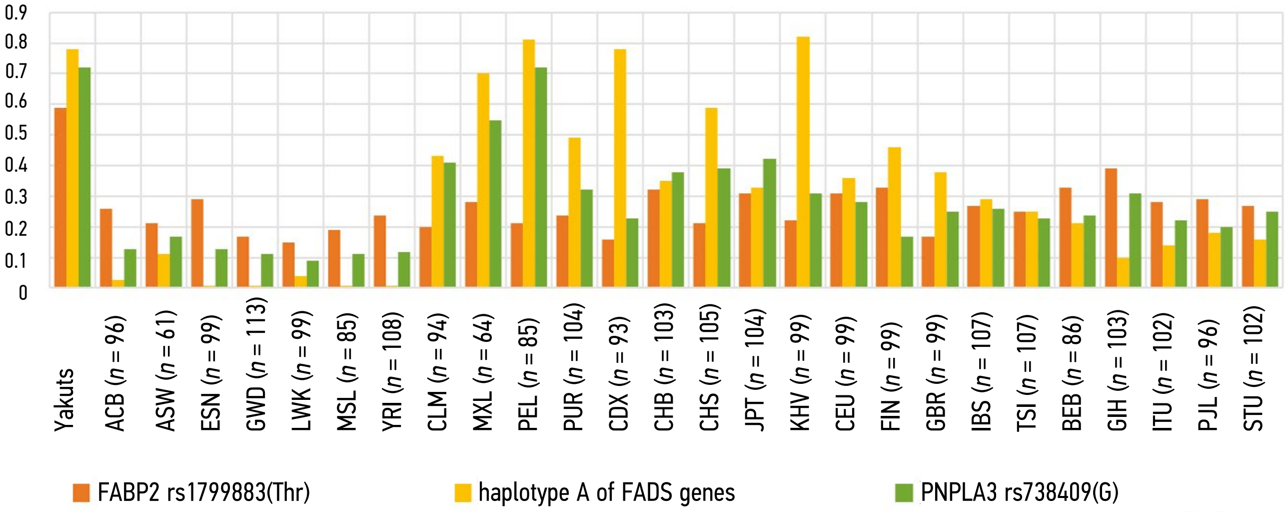

Figure 1. Frequency of occurrence of NAFLD pathological alleles in world populations. OY axis, frequency in the population, Yakuts; present study; ACB, Negroid people from Barbados; ASW, African Americans from the Southwestern United States; ESN, Esan people from Nigeria; GWD, Gambians from western Gambia; LWK, Luhya people from Webue, Kenya; MSL, Mende people from Sierra Leone; YRI, Yoruba people from Ibadan, Nigeria; CLM, Colombians from Medellin, Colombia; MXL, Mexicans from Los Angeles, California; PEL, Peruvians from Lima, Peru; PUR, Puerto Ricans from Puerto Rico; CDX, Dai Chinese from Xishuangbanna, China; CHB, Han Chinese from Beijing, China; CHS, Han Chinese from southern China; JPT, Japanese from Tokyo, Japan; KHV, Vietnamese from Ho Chi Minh City, Vietnam; CEU, Utah residents of Northern and Western European descent; FIN, Finns from Finland; GBR, British from England and Scotland; IBS, Iberian population from Spain; TSI, Tuscans from Italy; BEB, Bengalis from Bangladesh, India; GIH, Gujarati Indians from Houston, Texas; ITU, Telugu Indians from the UK; PJL , Punjabis from Lahore, Pakistan; STU, Sri Lankan Tamils from the UK.

Pathophysiology of NAFLD suggests that free fatty acids may exert toxicity through enhanced oxidative stress and activation of inflammatory pathways [27]. Numerous studies have reported that carriers of the Thr54 variant of *FABP2* are associated with higher BMI, insulin resistance, metabolic syndrome, and T2DM. However, our study yielded contradictory findings: we identified a significant association (p = 0.02) of the Ala allele with NAFLD and concomitant T2DM. It remains unclear whether the *FABP2* rs1799883 polymorphism is a predictor of NAFLD or T2DM, since patients with NAFLD alone were not included in this study.

The expression of the genes investigated—*PNPLA3*, *FABP2*, *FADS1*, and *FADS2*—is strongly influenced by a hypocaloric diet enriched with polyunsaturated fats. For example, in the study by D. de Luis et al. (2012), Thr54 allele carriers demonstrated a better metabolic response to such a diet than obese individuals with the Ala54Ala genotype [28]. Shun-he Wang et al. (2017) showed that dietary alpha-linolenic acid (ALA) can increase blood levels of ω-3 long-chain polyunsaturated fatty acids (LC-PUFAs) and affect the expression of genes involved in the hepatic conversion of ALA into ω-3 LC-PUFAs [29]. Dysregulation of PUFA desaturation may directly contribute to NAFLD development. It is also known that the effect of the *PNPLA3* rs738409 polymorphism can be modulated by a high dietary n-6/n-3 PUFA ratio and promote NAFLD in obese young individuals carrying the risk allele [30].

Accumulation of pathogenic alleles in the Yakut population may be associated with an adaptive mechanism for storing fat in the liver to generate heat and energy during winter periods with extremely low temperatures (down to −60 °C). In a study by Nasibulina et al. (2013), it was hypothesized that the Thr allele confers endurance [31]. Therefore, it can be assumed that the high frequency of this allele is a consequence of adaptation to the living conditions in Yakutia and to a specific diet rich in polyunsaturated fatty acids.

Understanding the frequency and distribution of the studied polymorphisms in different populations, including the Yakut population, is of great importance for risk assessment and the development of disease prevention strategies. Moreover, such data may contribute to a deeper exploration of genetic factors influencing health and disease in the context of different ethnic groups. This also opens new perspectives for further research in genetics, anthropology, and medicine, providing insights into the mechanisms underlying ethnic predisposition to certain diseases.

Study Limitations

The present study had several limitations. The limited sample size (126 patients with NAFLD and T2DM and 372 volunteers in the control group) may reduce statistical power and increase the likelihood of error. The considerable age difference between the groups may bias the assessment of genetic associations without appropriate adjustment. The absence of data on patients with NAFLD without T2DM constrains the analysis of the role of the *FABP2* rs1799883 polymorphism in the pathogenesis of NAFLD. The cross-sectional design precludes evaluation of disease trends, and the lack of biochemical data narrows the understanding of the mechanisms through which genetic variants exert their effects. These limitations should be considered in future research to improve the accuracy of genetic associations.

CONCLUSION

Our molecular genetic study in the Yakut population demonstrates a high prevalence of *PNPLA3*, *FABP2*, *FADS1*, and *FADS2* gene variants associated with increased BMI and NAFLD. This is likely related to an adaptive mechanism for fat accumulation in the liver. With the shift from a lipid–protein diet to a predominantly carbohydrate-based one, these previously advantageous allelic variants now lead to metabolic disorders, influencing the incidence of liver conditions, including hepatocellular carcinoma, compared with other regions of the Russian Federation.

ADDITIONAL INFORMATION

Author contributions: N.I. Pavlova: conceptualization, investigation, formal analysis, writing—original draft, visualization, methodology; A.V. Krylov: investigation; A.A. Bochurov: investigation; I.P. Troev: resources; Kh.A. Kurtanov: supervision, writing—review & editing, methodology. All the authors approved the version of the manuscript to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval: The study was approved by the local Biomedical Ethics Committee at the Yakut Scientific Center for Complex Medical Problems (protocol No. 60, April 10, 2024, decision 2).

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