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Frequency of I148M Polymorphism of the *PNPLA3* Gene Associated with a Risk of Steatosis and Liver Fibrosis in Residents of the Republic of Sakha (Yakutia)

Snezhana S. Sleptsova [1¶], Aleksandr E. Efimov [1¶*], Nikolai M. Gogolev [2], Palmira G. Petrova [3,] Sergey I. Semenov [5], Polina I. Golikova [6], Anastasiya L. Danilova [6], Filipp F. Vasilev [6], Alexandra E. Yakovleva [6], Aitalina L. Sukhomyasova [6], Tatiana E. Burtseva [4], Jon O. Odland[7,8]

[1] Department of Infectious Diseases, Phthisiology and Dermatovenerology of the North-Eastern Federal University, Institute of Medicine, Yakutsk, Russia

[2] - Department of Surgery of the North-Eastern Federal University, Institute of Medicine, Yakutsk, Russia

[3] Department of Normal and Pathologycal Physiology of the North-Eastern Federal University, Institute of Medicine, Yakutsk, Russia

[4] Department of Pediatrics and Pediatric Surgery of the of the North-Eastern Federal University, Institute of Medicine, Yakutsk, Russia

[5] Research Center of the North-Eastern Federal University, Institute of Medicine, Yakutsk, Russia.

[6] Research Laboratory "Molecular Medicine and Human Genetics" of the North-Eastern Federal University, Institute of Medicine, Yakutsk, Russia.

[7] Department of Public Health and Nursing Norwegian Norwegian university of science and technology, Norway

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[8] Department of General Hygiene I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

E-mail: bourtsevat@yandex.ru

Abstract

Background

Single nucleotide polymorphism (SNP) are the most common type of genetic polymorphism. SNP can significantly affect the expression activity of genes and the level of protein production. Researching the role of SNP in the occurrence of diseases is an important and urgent task, as it allows to predict the risk of pathology, its severity and outcome. Purpose of the study: study of the frequency of I148M polymorphism of the PNPLA3 gene in residents of the Republic of Sakha (Yakutia), associated with a high risk of steatosis and liver fibrosis.

Methods

A total of 3132 peripheral venous blood samples were used for population studies, studies patients with chronic hepatitis B and C, studies patients with NAFLD. Genotyping of DNA samples was carried out by real time-PCR. Reagent kits were used for genotyping I148M polymorphism of the PNPLA3 gene.

Results

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In the present study, it was found that in the Yakut population the carriage of the GG genotype (49%) of the *PNPLA3* gene I148M polymorphism predominates. When conducting a comparative frequency analysis, there were no statistically significant differences between the control group and the group with NAFLD patients(p=0,82). A comparative frequency analysis of the distribution of genotypes and alleles of I148M polymorphism of the PNPLA3 gene in the control group and the group of patients with chronic hepatitis B and C showed that we did not reveal significantly significant differences (p = 0.45).

Conclusions

The frequency of homozygotes for the mutant G allele of the I148M polymorphism of the PNPLA3 gene in the Yakut population significantly exceeds the frequency indicator of the G allele in other world populations.

Keywords: steatosis; fibrosis; gene; Yakutia

1. Introduction

Hereditary diseases and congenital malformations make a significant contribution to the morbidity, disability and mortality of people, being not only a medical, but also a social problem.

The successes of modern genetics are associated with the study of multifactorial diseases. The study of genetic polymorphism was crucial in

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determining the causes of hereditary changes. Genetic polymorphism is a change in the genome of a population in two or more variants (alleles) with a frequency of at least 1%. Single nucleotide polymorphism (SNP) are the most common type of genetic polymorphism. SNP can significantly affect the expression activity of genes and the level of protein production (mRNA stability, transcription rate, changes in the structure of transcription factor binding sites). Researching the role of SNP in the occurrence of diseases is an important and urgent task, as it allows to predict the risk of pathology, its severity and outcome.

Purpose of the study: study of the frequency of I148M polymorphism of the *PNPLA3* gene in residents of the Republic of Sakha (Yakutia), associated with a high risk of steatosis and liver fibrosis. The study showed that the frequency of the mutant allele of functional polymorphism I148M of the PNPLA3 gene in the Yakut population was higher than in other known world populations.

2. Materials and methods

2.1 Blood samples

Whole blood samples (N = 1561) were obtained during scientific research expedition of the Medical Institute of North-Eastern Federal University (NEFU, Yakutsk, Russia) to the districts of Republic of Sakha (Yakutia, Russia) in 2016. Republic of Sakha (Yakutia) is located in the northeastern part of Siberia.

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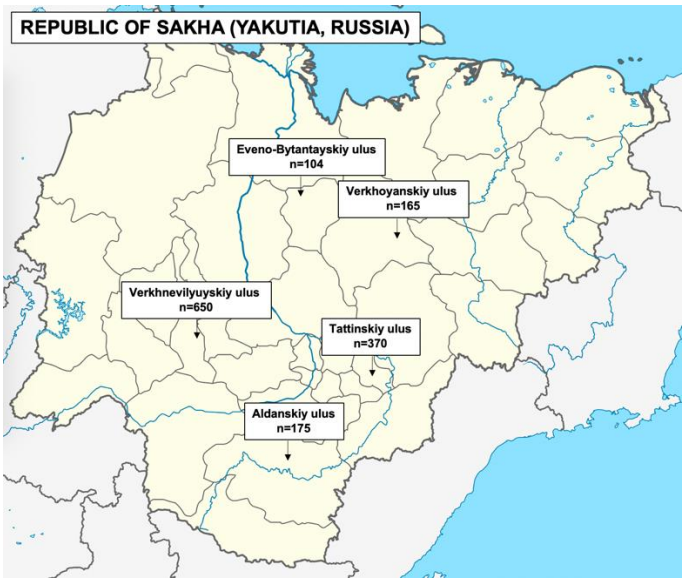

Figure 1. Distribution of study samples. Whole blood samples were collected from four districts (ulus) of Republic of Sakha (Yakutia): Central Economic Zone (Tattinskiy and Aldanskiy ulus); Western economic zone: Verkhnevilyuyskiy ulus; Arctic economic zone (Verkhoyanskiy and Eveno-Bytantayskiy ulus).

Inclusion in the study control group (n=1425) required that all individuals belong to the Yakut, Even or Russian ethnic group, were healthy and unrelated. Patients with non-alcoholic fatty liver disease (NAFLD) (n = 97), chronic hepatitis B and chronic hepatitis C (n = 39) were included in the study. All of them are living in the above areas. Verification of NAFLD, chronic hepatitis B and chronic hepatitis C was carried out using clinical data, laboratory studies, ultrasound studies and serological blood tests (ELISA).

Population studies of the prevalence of NAFLD among the population of the republic have not been previously conducted. A total of 1006 people were examined from 4 regions of the republic - Verkhnevilyuysky (Western Economic Zone), Tattinsky (Central Economic Zone), Eveno-Bytantaysky and Verkhoyansk (Arctic Economic Zone) regions. The population aged 18 and over was examined.

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Among the men examined, there were only 283 (28.1%) people, women - 723 (71.9%). The average age of the examined men was 46.7 ± 15.1 years, women - 47.8 ± 14.4 years. In order to identify various liver pathologies in 994 (98.8%) of the examined, an ultrasound examination (ultrasound) was performed. At the same time, the criteria for steatosis were diffuse hyperechoogenicity of the liver parenchyma, vague vascular pattern. Distribution of patients with signs of NAFLD and changes in the liver and pancreas parenchyma presented in table 1.

Table 1. Distribution of patients with signs of hepatosis / steatosis of the liver and changes in the liver and pancreas parenchyma (n = 629)

Indicators	NAFLD (n=120)				Diffuse changes in the liver parenchyma without NAFLD (n=114)				Diffuse changes in the pancreatic parenchyma (n=395)			
	n	%	χ^2	*p*	n	%	χ^2	*p*	n	%	χ^2	*P*
men	30	10,6	*0,8*	*0,37*	33	11,7	*0,04*	*0,8*	112	39,6	*0,06*	*0,8*
18-59 years, men	26	11,4			27	11,8			91	39,9		
60 years and older, men	4	7,4			6	10,9			21	38,2		
women	90	12,4	*0,1*	*0,7*	87	12,0	*0,3*	*0,6*	283	39,1	*0,03*	*0,9*
18-59 лет, women	68	12,2			65	11,7			217	39,0		
60 years and older, women	22	13,3			22	13,3			66	39,8		
Average age men	45,4±14,8				44,4±16,0				46,7±14,6			
Average age women	47,8±14,4				49,2±14,1				47,9±14,6			

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Note: Group 1–1 - patients with signs of NAFLD (n = 120); Group 2–2 - patients with signs of diffuse changes in the liver parenchyma without NAFLD (n = 120); Group 3–3 - patients with signs of diffuse changes in the pancreatic parenchyma (n = 395).

All individuals provided informed consent before the study was performed. Blood samples were collected in sterile VACUETTE ethylenediaminetetraacetic acid tubes (Greiner Bio-One, Austria).

2.2 Genotyping methods

Genomic DNA was isolated from peripheral blood by phenol-chloroform extraction, ExtractDNA commercial kit (Evrogen, Russia) and kits for isolating genomic DNA from blood using magnetic particles “NucleoMag 96 Blood” (Macherey-Nagel, Germany). The purified DNA was eluted in Milli-Q™ water. The concentration and purity of extracted DNA was determined by measuring the optical density using Nanodrop ND-1000 spectrophotometer (Thermo Fisher Scientific, USA).

Allele frequencies of single nucleotide polymorphisms were obtained from the SNP database at the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/snp). Specific SNP (*PNPLA3* p.I148M, rs738409) was chosen for study due to association with pathological states.

Genotyping of p.I148M polymorphism of the *PNPLA3* gene was performed by real time-PCR. Real-time PCR was performed using a CFX96 Touch Real-Time PCR Detection System (Bio-Rad, USA) and iCycler iQ5 Real-Time PCR Detection System (Bio-Rad, USA). All reagents (except *Taq* polymerase) were thawed at room temperature before use. After thawing, the contents of the tubes are thoroughly mixed. The 20 uL reaction volume contained 1–2 units *Taq* DNA polymerase, PCR mixture, Milli-Q™ water and 100 ng of genomic DNA. All components (except DNA samples) were mixed in a separate sterile tube based on the calculation: PCR mixture volume = (component volume for 1 sample) * (number of samples + 2 (negative control). The reaction mixture was mixed by

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pipetting followed by vortexing. PCR thermal cycling conditions were as follows: 95°C - 2 min, 94°C - 10 sec, 58°C - 20 sec, 40 cycles.

2.3 Statistics

Statistical analysis was performed using the software STATISTICA 7.0 (StatSoft Inc.). Compliance of genotype frequency distributions with the Hardy-Weinberg equilibrium was established by online calculator provided by Tufts University, Boston, MA, USA (http://www.tufts.edu/mcourt01/Documents/Court%200llab%20%20HW%20calculator.xls). Hardy-Weinberg equation: $p2 + 2pq + q2 = 1$ (p - frequency of the dominant allele, q - frequency of the recessive allele. The significance of differences in the frequencies of genotypes was evaluated using the χ^2 criteria (df=1) with Yates correction and Fisher's exact test. All differences were considered significant at $P<0.05$.

3. Results and discussion

Several authors have identified the association of NAFLD with the *PNPLA3* gene and confirmed in different ethnic groups as the cause of the disease [1, 2, 3]. So, in a study by Romeo et al. (2008) [5] identified the association of the *PNPLA3* gene with the development of NAFLD among Americans.

The most significant polymorphism in the *PNPLA3* gene is I148M (rs738409). The I148M polymorphism is the replacement of the cytosine nucleotide with guanine, which leads to a change in the amino acid isoleucine to methionine at position 148. This replacement leads to a disruption of the mechanism of lipid metabolism in the liver. This polymorphism is associated with susceptibility to NAFLD and affects the histological picture and the development of fibrosis in

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children and adolescents with obesity [3]. The frequency of the studied polymorphism in various world populations is presented in Table 2.

Table 2. Frequencies of genotypes and alleles of the polymorphic variant I148M of the *PNPLA3* gene (rs738409) in various populations from the database of the US NCBI (National Center for Biotechnological Information).

Population	Genotype frequency, %			Allele frequency, %	
	GG	GC	CC	G	C
Caucasoid population AFD_EUR_PANEL ss24098326 (n=44)	0	40,9	59,1	20,5	79,5
Caucasoid population HapMap-CEU ss76896972 (n=120)	3,3	40	56,7	23,3	76,7
Asian population AFD_CHN_PANEL ss24098326 (n=46)	0	47,8	52,2	24	76
Asian population HapMap-HCB ss76896972 (n=90)	13,3	42,2	44,5	34,4	65,6
Asian population HapMap-JPT ss76896972 (n=88)	22,7	40,9	36,4	43,2	56,8
African population	4,3	30,4	65,3	19,6	80,4

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AFD_AFR_PANEL ss24098326 (n=46)					

Note: C– cytosine (cytosine), G - guanine (guanine)

In this study, we genotyping of the polymorphic variant I148M of the *PNPLA3* gene (rs738409). The frequencies of alleles and genotypes of the studied polymorphic variant of the *PNPLA3* gene in residents of the Republic of Sakha (Yakutia) are show in Table 3.

Table 3. Frequencies of genotypes and alleles of the polymorphic variant I148M of the *PNPLA3* gene in residents of the Republic of Sakha (Yakutia), n = 1464

SNP	Genotype	Genotype frequency				Genotype
		observed		expected		
		%	n	n		
PNPLA3 I148M (G/C), n=175, russian (newcomers)	GG	9,8	18	15,9	0,5388	0,4629
	GC	39,3	72	76,1		
	CC	50,9	93	90,9		
	G	30,0	–	–		
	C	70,0	–	–		
PNPLA3 I148M (G/C),	GG	52,0	338	346,4	2,784	0,095
	GC	42,0	273	256,2		
	CC	6,0	39	47,4		

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n=650, yakuts (Verkhnevilyuysky region)	G	73,0	–	–		
	C	26,0	–	–		
PNPLA3 I148M (G/C), n=22, evens (Eveno-Bytantaysky region)	GG	45,5	10	10,9	0,8887	0,3458
	GC	50,0	11	9,2		
	CC	4,5	1	1,9		
	G	70,0	–	–		
	C	30,0	–	–		
PNPLA3 I148M (G/C), n=82, yakuts (Eveno-Bytantaysky region)	GG	53,7	44	44,6	0,1323	0,7160
	GC	40,2	33	31,7		
	CC	6,1	5	5,6		
	G	74,0	–	–		
	C	26,0	–	–		
PNPLA3 I148M	GG	51,4	76	75,2	0,1020	0,7493
	GC	39,9	59	60,6		

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(G/C), n=148, yakuts (Verkhoyansk region)	CC	8,8	13	12,2		
	G	71	–	–		
	C	29	–	–		
PNPLA3 I148M (G/C), n=17, evens (Verkhoyansk region)	GG	58,8	10	10,7	1,1426	0,2850
	GC	41,2	7	5,6		
	CC	0	0	0,7		
	G	79,0	–	–		
	C	21,0	–	–		
PNPLA3 I148M (G/C), n=370, yakuts (Tatta region)	GG	41,6	154	148,6	1,4508	0,2283
	GC	43,5	161	171,8		
	CC	14,9	55	49,6		
	G	63,0	–	–		
	C	37,0	–	–		

Notes: [1] G - guanine (guanine), C - cytosine (cytosine); [2] χ^2 - “chi” square Hardy-Weinberg equilibrium

Determination of the frequency of alleles and genotypes of the polymorphic variant I148M of the *PNPLA3* gene in the studied groups showed

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that this indicator corresponded to Hardy-Weinberg equilibrium, which indicates the representativeness of the sample.

A comparative analysis of the frequencies of the I148M genotypes of the *PNPLA3* gene showed no statistically significant differences between groups with individuals of Yakut nationality in the Verkhnevilyuysky, Eveno-Bytantaysky, Verkhoyansk and Tatta regions (Table 4).

Table 4. Frequencies of genotypes and alleles of the polymorphic variant I148M of the *PNPLA3* gene in the Yakut population, N = 1250

Genotyp *PNPLA3* I148M (G/C)	Genotype frequency, %							
	Verkhnevilyuysky region (n=650)		Eveno-Bytantaysky region (n=82)		Verkhoyansk region (n=148)		Tatta region (n=370)	
	%	n	%	n	%	n	%	n
GG	52,0	338	53,7	44	51,4	76	41,6	154
GC	42,0	273	40,2	33	39,9	59	43,5	161
CC	6,0	39	6,1	5	8,8	13	14,9	55

Notes: G - guanine (guanine), C - cytosine (cytosine)

An analysis of the frequency distribution of alleles and genotypes of the I148M polymorphic point of the *PNPLA3* gene (rs738409) established similar frequencies in the studied groups of individuals of Yakut and Even nationality

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($\chi 2$ = 2.07, p = 0.35). Statistically significant differences were found between the group with individuals of Russian nationality and the group with individuals of Yakut nationality (p <0.0001) (Table 5).

Table 5. Distribution of alleles and genotypes of I148M polymorphism of the *PNPLA3* gene (rs738409) among residents of the Republic of Sakha (Yakutia), n = 1425

SNP	Genotyp	Genotype frequency, %				χ^2	*p*	OR	
		russian (n=175)		yakuts (n=1250)				Знач.	95% CI
		n	%	n	%				
PNPLA3 I148M (G/C)	GG	18	9,8	612	49	251,39	<0,0001	8,79	5,34 – 14,48
	GC	72	39,3	526	42			1,12	0,82 – 1,54
	CC	93	50,9	112	9			0,10	0,07 – 0,13

Notes: [1] G - guanine (guanine), C - cytosine (cytosine); [2] χ^2 - “chi” square Hardy-Weinberg equilibrium; [3] OR (odds ratio) - odds ratio; [4] CI (confidence interval) - confidence interval.

It is known that the frequency of allelic variants in a population may vary depending on ethnicity. In the present study, it was found that in the Yakut

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population the carriage of the GG genotype (49%) of the *PNPLA3* gene I148M polymorphism predominates.

We analyzed the frequency distribution of genotypes and alleles of the studied polymorphic variant of the *PNPLA3* gene according to the available scientific literature. It was found that the frequency of homozygotes for the mutant G allele of the I148M polymorphism of the *PNPLA3* gene in the Yakut population significantly exceeds the rate of the G allele in other world populations. More similar indicators of frequency to the Yakut population according to the GG genotype were established in a study by Romeo et al. (2008) [4]. The rate of GG carriage in the Hispanic population was 49.8%. The frequency distribution of the alleles and genotypes of the I148M *PNPLA3* polymorphism in the studied Russian population corresponded to the values found in the world European ethnic populations (Table 6).

Table 6. Distribution of alleles and genotypes of I148M polymorphism of the *PNPLA3* gene (rs738409) in various ethnic populations

Population	N	Genotype frequency, %			A source
		GG	GC	CC	
Yakutian	1250	49	42	9	Real study
Russian	175	9,8	39,3	50,9	Real study
Latin american	30	30	40	30	F. Stickel [5]
Uzbekistan	50	22	28	50	Y.Rotman [6]

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Korean	184	20	50	30	S.S. Lee[7]
Japanese	578	18	52	30	K. Hotta[8]
Chinese (Han)	553	11	47	42	X.E. Peng[9]
Caucasoid	328	9	36	55	W. Dunn[10]
Chinese	202	8	45	47	Y. Li [11]
Caucasoid	326	6	36	58	F. Stickel [5]
Italian	179	3	31	66	Valenti [1]
German	162	2	34	64	M.O. Baclig [12]
African	38	0	26	74	F. Stickel [5]

Notes: G - guanine (guanine), C - cytosine (cytosine).

For the first time, the association of the polymorphic variant I148M of the *PNPLA3* gene with fatty liver infiltration was established in 2008 [4]. Since then, many studies have been conducted to establish the association of this polymorphism with NAFLD [1, 3, 13, 14, 15, 16]. The association remained significant even despite adjustments for body mass index, diabetic status, alcohol use, and the absence of dyslipidemia [17, 18, 19]. In addition, it was found that this polymorphism is associated with increased serum levels of aminotransferase [4]. In a study by Seko et al. [19] it was found that the GG genotype is a predictor of the development of hepatocellular carcinoma in the Japanese population. In a previous study, it was shown that homozygous carriers

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of the GG genotype were characterized by an increased risk of steatohepatitis (3.8 times, CI 95%: 3.03-4.79) and liver fibrosis (2.3 times, CI 95%: 1.77-3.23) [20].

It is known that the prevalence of NAFLD varies significantly in different regions of the world. In a study by Wagenknecht et al. (2011) [21] it has been suggested that I148M polymorphism may influence the prevalence of NAFLD in different ethnic groups.

The association of SNP I148M with NAFLD was established in various ethnic groups: Chinese (OR = 1.94, 95% CI: 1.12-3.37), Indian (OR = 3.51, 95% CI: 1.69-7,26), Malay (OR = 2.05, 95% CI: 1.25-3.35), Uyghur (OR = 2.25, 95% CI: 1.23-4.09) [22]. In a study by Lee et al. (2014) [7] it was shown that the frequency of the G allele (31.6%) in the group of patients with NAFLD was significantly higher than in the control group (20.1%). It was also found that the frequency of GC + GG genotypes among NAFLD patients was significantly higher in patients with advanced fibrosis.

In this study, we performed genotyping of patients with NAFLD of Yakut nationality. The results of the comparison of the I148M polymorphism of the *PNPLA3* gene in a group of relatively healthy individuals and patients with NAFLD of Yakut nationality are presented in Table 7.

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Table 7. Distribution of alleles and genotypes of I148M polymorphism of the *PNPLA3* gene (rs738409) in a group of conditionally healthy individuals and patients with NAFLD of Yakut nationality, n = 1347

SNP	Genotype	Genotype frequency, %				χ^2	*p*	OR	
		Control group (n=1250)		Patients with NAFLD (n=97)				Value	95% CI
		n	%	n	%				
PNPLA3 I148M (G/C)	GG	612	49	49	50,5	0,41	0,82	0,94	0,62 – 1,42
	GC	526	42	38	39,2			1,13	0,74 – 1,72
	CC	112	9	10	10,3			0,86	0,43 – 1,69

Notes: [1] G - guanine (guanine), C - cytosine (cytosine); [2] χ2 - "chi" – square; [3] OR (odds ratio) - odds ratio; [4] CI (confidence interval) - confidence interval

When conducting a comparative frequency analysis, there were no statistically significant differences between the control group and the group with NAFLD patients (p = 0.82).

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In a study by Jiang et al. (2014) [23] it was found that the frequency of the G allele in the Chinese population (Qingdao, China) has significant differences between the group with patients with chronic hepatitis B (31.9%) and the group with conditionally healthy individuals (21.9%). Carriers of the GG genotype of *PNPLA3* gene polymorphism had a higher risk of hepatitis B in comparison with carriers of alternative genotypes (OR = 1.67, 95% CI: 1.18-2.34). Carriage of the G allele among patients with chronic hepatitis B was a predisposing factor for the development of steatosis, steatohepatitis, lobular inflammation, and accumulation of iron in the liver [24].

The results of a previous meta-analysis showed the effect of the *PNPLA3* gene I148M polymorphism on the risk of hepatitis C (OR = 2.20, 95% CI: 1.56-3.11). The frequency of the mutant variant in the group of patients with hepatitis C was 20.4%, the frequency in the control group was 10.23% [25]. A comparative table on the frequency of genotypes of I148M polymorphism in patients with hepatitis C according to the available literature is presented in Table 8.

Table 8. Distribution of alleles and genotypes of the I148M polymorphism of the PNPLA3 gene (rs738409) in a group of relatively healthy individuals and patients with chronic hepatitis C.

SNP	**N**	Chronic hepatitis C patients	Control group	A source

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		CC	CG	GG	CC	CG	GG	
PNPLA3 I148M (G/C)	352	85	64	13	112	69	9	H.D. Nischalke [26]
	998	424	310	85	118	56	5	L. Valenti [27]
	305	68	104	48	23	51	11	M. Miyashita[28]
	518	133	103	25	146	95	16	L. Valenti [29]
	362	90	106	34	66	54	12	S. Ezzikouri[30]

Notes: G - guanine (guanine), C - cytosine (cytosine)

In this study, we performed a comparative frequency analysis of the distribution of genotypes and alleles of the I148M polymorphism of the *PNPLA3* gene in the control group and the group of patients with chronic hepatitis B and C. In this analysis, we did not reveal significantly significant differences ($p = 0.45$) (Table 9).

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Table 9. Distribution of alleles and genotypes of I148M polymorphism of the *PNPLA3* gene (rs738409) in a group of relatively healthy individuals and patients with chronic hepatitis B and C of Yakut nationality, N = 1289

SNP	Genotype	Genotype frequency, %				χ^2	*p*	OR	
		Control group (n=1250)		Patients with chronic hepatitis B and C (n=39)				Value	95% CI
		n	%	n	%				
PNPLA3 I148M (G/C)	GG	612	49	17	39,1	1,61	0,45	1,24	0,65 – 2,36
	GC	526	42	20	54,3			0,69	0,36 – 1,31
	CC	112	9	2	13,8			1,82	0,43 – 7,65

Notes: [1] G - guanine (guanine), C - cytosine (cytosine); [2] χ^2 - "chi" square; [3] OR (odds ratio) - odds ratio; [4] CI (confidence interval) - confidence interval.

Thus, in the present study, it was found that the frequency of the mutant allele of functional polymorphism I148M of the *PNPLA3* gene is higher than in other known world populations. A normally functioning *PNPLA3* gene protein regulates

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the activity of triglyceride hydrolase and lysophosphatidic acid acyltransferase. I148M polymorphism leads to the replacement of the amino acid isoleucine with methionine at position 148, which does not affect the orientation of the catalytic dyad, but the longer side chain of methionine limits the substrate access to the catalytic serine at position 47 [31]. The size of the access site to the substrate is significantly reduced in the presence of the mutant G allele, which leads to limited access of palmitic acid to the catalytic dyad [32]. In a study by Kumari et al. (2012) [33] it was found that the P *PNPLA3* I148M polymorphism induces an increase in lipogenic activity, which leads to an increase in the synthesis of triglycerides in the liver. Pollorphism I148M of the *PNPLA3* gene has three effects on the metabolism of triglycerides in the liver: increased synthesis of fatty acids and triglycerides; violation of the hydrolysis of triglycerides; a decrease in the level of polyunsaturated fatty acids [34]. Therefore, it can be assumed that the high frequency of the mutant G allele of the I148M polymorphism of the *PNPLA3* gene in the Yakut population may be one of the reasons for the violation of the mechanism of lipid metabolism in the liver.

It is now recognized that the prevalence dynamics of NAFLD is an epidemic. The studies revealed the presence of regional fluctuations in the level of detection of NAFLD. Apparently, this disease has genetic determinism, that is, it depends on ethnic factors. The *PNPLA3* gene I148M polymorphism is associated with susceptibility to NAFLD, chronic hepatitis B, chronic hepatitis C. The presence of a

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mutant allele affects the histological picture, the development of steatosis, and liver fibrosis. It is likely that due to the high frequency of the mutant G allele of the I148M polymorphism of the *PNPLA3* gene, the Yakut population will be more susceptible to the above pathological conditions. However, in this study, we did not establish an association between the control group and groups with sick liver diseases (NAFLD, chronic hepatitis B, chronic hepatitis C).

In view of the fact that the G14 allele of *PNPLA3* gene polymorphism I148M is associated with an increased risk of developing liver diseases and is a marker of the progression of the pathological process, it is necessary to conduct a thorough and detailed scientific study of this association among the indigenous population of the Republic of Sakha (Yakutia). The establishment of this polymorphism as a marker indicating the risk of adverse development of the disease will allow for effective preventive and therapeutic measures.

4. Conclusion

The study showed that the frequency of the mutant allele of functional polymorphism I148M of the PNPLA3 gene in the Yakut population was high, as in other world populations.

Therefore, it can be assumed that the high frequency of the mutant G allele of the I148M polymorphism of the *PNPLA3* gene in the Yakut population may be the cause of the hereditary pathology of lipid metabolism in the liver. It is likely that due to the high frequency of the mutant G allele of the I148M

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polymorphism of the *PNPLA3* gene, the Yakut population has a high predisposition to the development of steatosis, liver fibrosis, especially in combination with chronic viral hepatitis B, C, D.

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Ethics Statement

All written informed consent forms signed by the participants or the guardians of the underage participants involved in our study were obtained before beginning the testing procedures. This study was approved by the local Biomedical Ethics Committee of North-Eastern Federal University, Yakutsk, Russia (Yakutsk, Protocol No 11, September 18, 2017).

Competing interests

The authors have declared that no competing interests exist.

Author Contributions

Conceived and designed the experiments: SS AE NG PP TB. Performed the experiments: SS TB SS ND PG AD FV AY AS. Analyzed the data: SS AE PG AD FV AY AS. Contributed reagents/materials/analysis tools: PG AD FV AY AS. Wrote the paper: SS AE TB AS SS FV JO.

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