A.A. Nikanorova, N.A. Barashkov, E.E. Diakonov, S.S. Nakhodkin, V.G. Pshennikova, A.V. Solovyev, S.S. Kuzmina, M.I. Tomsky, T.E. Burtseva, S.A. Fedorova

ANALYSIS OF THE POLYMORPHISM OF SNP-MARKERS OF NON-SHIVERING THERMOGENESIS GENES *UCP1* (RS1800592), *UCP2* (RS659366) AND *UCP3* (RS2075577) IN THE YAKUTS AND CHUKCHI’S

ABSTRACT

For the first time an analysis of the frequencies of alleles polymorphismof the gene *UCP1*-rs1800592, *UCP2*-rs659366 and*UCP3*-rs2075577were studiedthe Yakuts (n=281) and the Chukchi’s (n=39) populations, living in the extreme climate of Eastern Siberia.The Yakut population was divided into three groups: northern (N.YAK), viluysk (V.YAK) and central Yakuts groups (C.YAK).From project of «1000 Genomes», information was received on the frequencies of the studied polymorphisms for Chinese – CHB (n=103), CHS (n=108), CDX (n=99), Japanese – JPT (n=104), Vietnamese populations– KHV (n=101).In general, the frequencies of the studied polymorphisms were analyzed in nine populations of Asia (n=835), living in different climatic zones. Populations living in the subarctic (CHU, N.YAK) and on the border of the temperate and subarctic climate (V.YAK, C.YAK) were merged into the group «Northern Asia». Populations living in the temperate (CHB), subtropical (JPT; CHS; CDX) and subequatorial climate (KHV) were joined into the «Southern Asia» group. Comparative analysis showed that the frequency of the allele A rs1800592 (*UCP1*) in the group «Northern Asia» (61.8%, CI: 56.8-66.7%), did not statistically differ (p>0.01) from the «Southern Asia» group (53.4%, CI: 49.4-57.4%). The frequencies of allele T rs659366 (*UCP2*) in the group «Northern Asia» (49.5%, CI: 44.5-54.6%), as compared with the group «Southern Asia» (41.5%, CI: 37.7-45.5%), also statistically differences not found (p>0.01). It was found that the frequency of allele A rs2075577 (*UCP3*) in the group «Northern Asia» (66.7%, CI: 61.8-71.4%) was much higher in comparison with the group «Southern Asia» (42.3%, CI: 38.4-46.3%) (p<0.01). The increased frequency of allele A rs2075577 of the *UCP3* gene in populations of Yakuts and Chukchi’s living in low temperature conditions, in comparison with other populations of Asia, can be associated with random population effects, or indicate the presence of adaptation mechanisms associated with thermoregulation.

Keywords: brown adipose tissue, nonshivering thermogenesis, uncoupling proteins, *UCP1* gene, *UCP2* gene, *UCP3* gene, adaptation, cold climate, Yakut population, Chukchi population.

Introduction

Recently, in 2015, the first case of finding brown adipose tissue(BAT) in samples from the paraaortic, perirenal, subclavian and perityroid areasof the postmortal body of the adult resident of Yakutia (54 years), who spent most of his time outside and was exposed to cold [1]. It is considered that BAT is one of two types of fatty tissue at the person and mammals which is well developed only at newborns and at the animals falling into hibernation[8]. The main function of the tissue is to participate in the mechanism of thermoregulation, by means of incontinent thermogenesis and the release of energy in the form of heat [16]. Unlike white adipocytes (cells of white adipose tissue) having one large fat drop, in adipocytes of BAT there are several small fat drops and a lot of mitochondria containing more iron (in cytochromes), which causes a brown color of the tissue [9]. It is believed that BAT has evolved in mammals during evolution to protect the body from hypothermia [16] and is optional, that is, it is activated only with prolonged cold exposure [6, 7, 10].

A characteristic of BAT is the high expression of the *UCP1* gene (uncoupling protein1), which encodes a protein of thermogenin, which in turn reduces the proton gradient in oxidative phosphorylation and weakens the work of mitochondrial ATP synthase, thereby stimulating nonshivering thermogenesis [2]. In 1997, the homologues of the uncoupling protein 1 — *UCP2* and *UCP3* [19, 20]. The *UCP2* gene is widely expressed in adipocytes of white adipose tissue and in pancreatic beta-cell, whereas the *UCP3* gene is expressed mainly in skeletal muscles and, to a lesser extent, in BAT [21]. It is now known that the uncoupling proteins *UCP2* and *UCP3* are involved in the regulation of the metabolism of the adipocytes of BAT [17] and transport fatty acids through the mitochondrial membrane during nonshivering thermogenesis [5, 12, 15]. Thus, it is believed that one of the most likely candidate genes associated with adaptation to a cold climate is the genes involved in nonshivering thermogenesis, such as the genes *UCP1*, *UCP2* and *UCP3* [13]. In turn, adaptation to various environmental factors can occur both due to the emergence and spread of novel mutations, and by changing the frequencies of the alleles of genes that were present in the gene pool of the population [11]. It is possible that in populations living in a cold climate, the frequency distribution of gene alleles potentially associated with nonshivering thermogenesis will differ from populations living in a warmer climate.

Thereby, the purpose of this work is to analyze the polymorphism of genes*UCP1*, *UCP2* and *UCP3*,involved in nonshivering thermogenesis,in populations of the Yakuts and Chukchi, living in low temperatures in comparison with southern populations of Asia.

Materials and methods

The sample of Yakuts(YAK) was 281 people, women (n=186) and men (n=95), the average age of which was 19.84±1.97 years. The sample of the Yakuts was divided into three groups according to ethno-territorial affiliation: northern (N.YAK, n=16), vilyuysk (V.YAK, n=67) and central Yakuts (C.YAK, n=198). The sample of Chukchi’s (CHU) was 39 people, women (n=18) and men (n=21), the average age of which was – 14.23±2.62 years. From the open sources of the project «1000 Genomes» [18], information was received on the frequencies of the polymorphisms studied for Chinese populations – CHB (n=103), CHS (n=108), CDX (n=99), Japanese - JPT (n=104), Vietnamese – KHV (n=101). Thus, the final sample was 835 people.Populations living in the subarctic (CHU; N.YAK) and on the border of the temperate and subarctic climate (V.YAK; C.YAK) were grouped into the group «Northern Asia». Populations living in the temperate (CHB), subtropical (JPT, CHS, CDX) and subequatorial (KHV) climates were combined into the group «Southern Asia» (Fig.1).

This work was approved by the local ethics committee on biomedical ethics at the YSC CMP. Blood samples were taken with informed written consent of the examined individuals or their parents (Yakutsk, protocol #16 of December 13, 2014).

Genotyping was performed by PCR-RFLP analysis. The original oligonucleotide primers were selected using the FastPCR program (http://primerdigital.com/) (Table 1). For the polymorphisms rs1800592 (*UCP1*) and rs659366 (*UCP2*) for the restriction endonuclease Ksp22I and BspFNI, respectively, natural restriction sites were used (Fig.2-A,B). For the polymorphism rs2075577 (*UCP3*), an artificial restriction site created for the RsaNIendonuclease was used with a mismatch reverse primer differing from the template sequence by one nucleotide, where guanine (G) is replaced by cytosine (C) (Fig.2-C).

The detection was carried out using standard PCR, followed by hydrolysis of the amplification products with restriction endonucleases and electrophoresis in a 3% agarosegel at a voltage of 120V (Fig.3-A, B, C).

Statistical analysis of the frequencies of identified major alleles of the polymorphisms rs1800592 of the *UCP1* gene, rs659366 of the *UCP2*gene and rs2075577 of the *UCP3* gene was performed using the Sampling program, kindly provided by M. Macaulay and M. Metspalu (Tartu, Estonia). Differences at the 99% significance level were considered statistically significant.

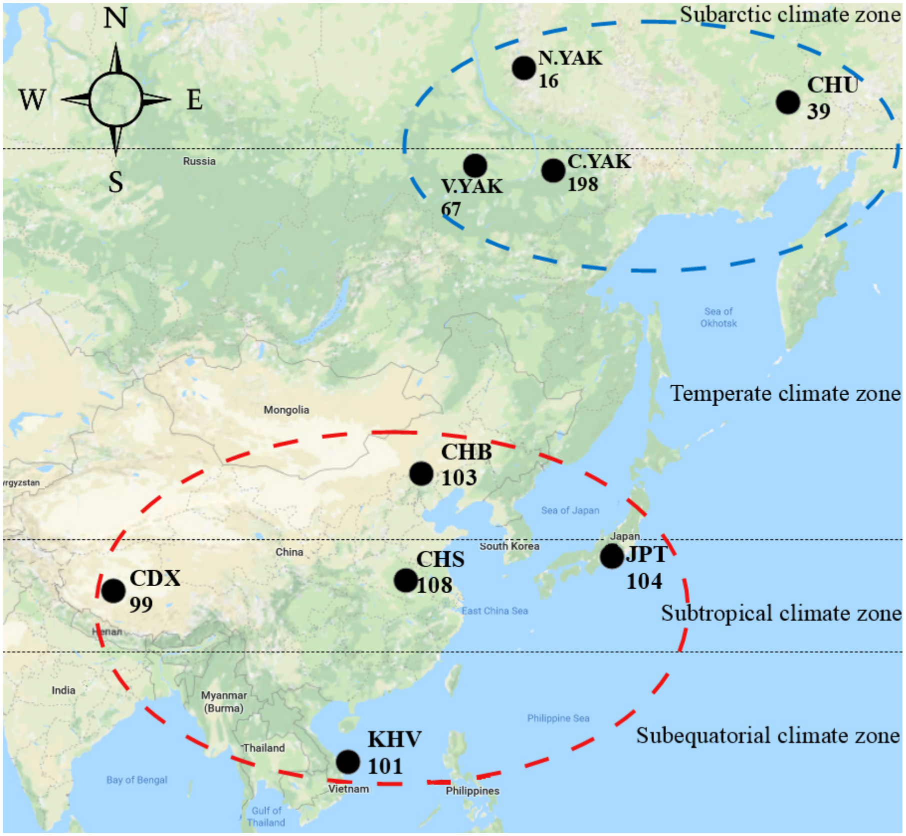

Fig. 1. Regions of residence of the studied populations «North Asia»: N.YAK – the northern Yakuts, V.YAK –vilyuyskYakuts, C.YAK –centralYakuts; CHU – Chukchi's; «South Asia»: CHB, CHS, CDX – Chinese; JPT – Japanese; KHV – Vietnamese

Results

At the first stapes of the study, the frequencies of the polymorphisms rs1800592 of the *UCP1* gene, rs659366 of the *UCP2* gene and rs2075577 of the *UCP3* gene in the Yakuts and Chukchi'spopulations were determined using the detection method developed by

Table 1

Oligonucleotide primers and detection methods for rs1800592 of the gene *UCP1*, rs659366 of the *UCP2* gene and rs2075577 of the *UCP3* gene

Gene	SNP	Majorallele	Minorallele	The primer sequence from the 5'®3' end	The size of the fragment to be amplified	Restrictionenzymes	Results of electrophoretic separation
UCP1	rs1800592	A	G	F: 5'–ACATTTTGTGC AGCGATTTCTG-3' R: 5'–TTCACCACTT CTGACAGGCT–3'		*Ksp22I*/ T↑GATCA	Normally, one restriction site, fragment sizes of 36 bp and 265 bp.If there is a mutation, the restriction site is absent, the fragment size is 301 bp.
UCP2	rs659366	T	C	F: 5'–AGCGTGACCT CACGCTCCTA–3' R: 5'–GACTGAACGT CTTTGGGACTCCGT–3'	299 п.н.	*BspFNI*/ CG↑CG	Normally, one restriction site, fragment sizes 178 bp and 121 bp.If there is a mutation, the restriction site is absent, the fragment size is 299 bp.
UCP3	rs2075577	A	G	F: 5'-GGGACTGGAA CCCAAGTCT-3' R: 5'-ACGACATCCT CAAGGAGAAGCTGCTGGAGTA-3'	249 п.н.	*RsaNI*/ G↑TAC(G)	Normally, one restriction site, fragment sizes of 218 bp and 32 bp.If there is a mutation, the restriction site is absent, the fragment size is 249 bp.

us. The frequencies of the major alleles of the SNP-markers we studied in the northern, vilyuysk, central Yakuts and Chukchi’s, as well as the frequencies of the polymorphisms studied for the populations of the Chinese – CHB (n=103), CHS (n=108), CDX (n=99), Japanese – JPT (n=104), Vietnamese – KHV (n=101) are presented in Table 2.

Next, we conducted a comparative analysis of polymorphisms’frequenciesin studied by us nine populations of Asia, living in different climatic (subarctic and temperate to subtropical and subequatorial).

Comparative analysis showed: that the frequency of the allele A rs1800592 of the *UCP1* gene in the group «Northern Asia» (61.8%, CI: 56.8-66.7%) was not statistically different from the group «Southern Asia» (53.4%, CI: 49.4-57.4%) (p >0.01) (Fig. 4, A); the frequency of the allele T rs659366 of the *UCP2* gene in the group «Northern Asia» (49.5%, CI: 44.5-54.6%), as compared with the «Southern Asia» group (41.5%, CI: 37.7-45.5%), also statistically did not differ (p>0.01) (Fig. 4, B);the frequency of the allele A rs2075577 of the *UCP3* gene in the «Northern Asia» group (66.7%, CI: 61.8-71.4%) was significantly higher than the «South Asia» group (42.3%, CI: 38.4-46.3%) (p<0.01) (Fig. 4, C).

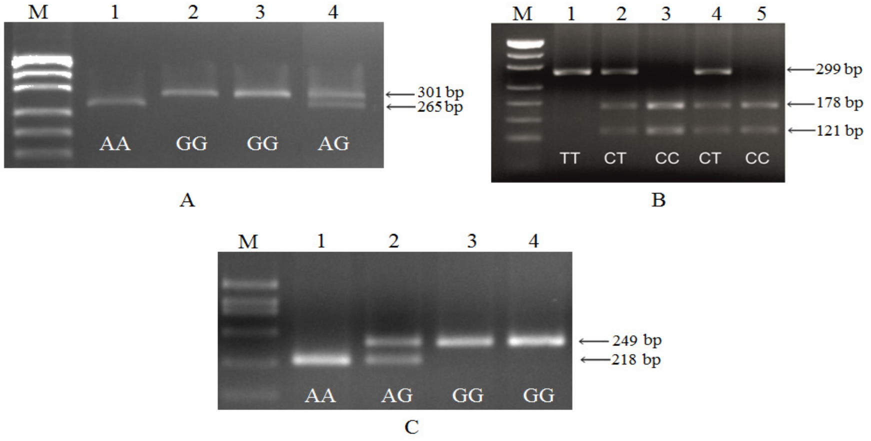

Fig.2. Design of PCR-RFLP analysis of rs1800592 gene of UCP1 (A), rs659366 of UCP2 gene (B) and rs2075577 of UCP3 gene (C)

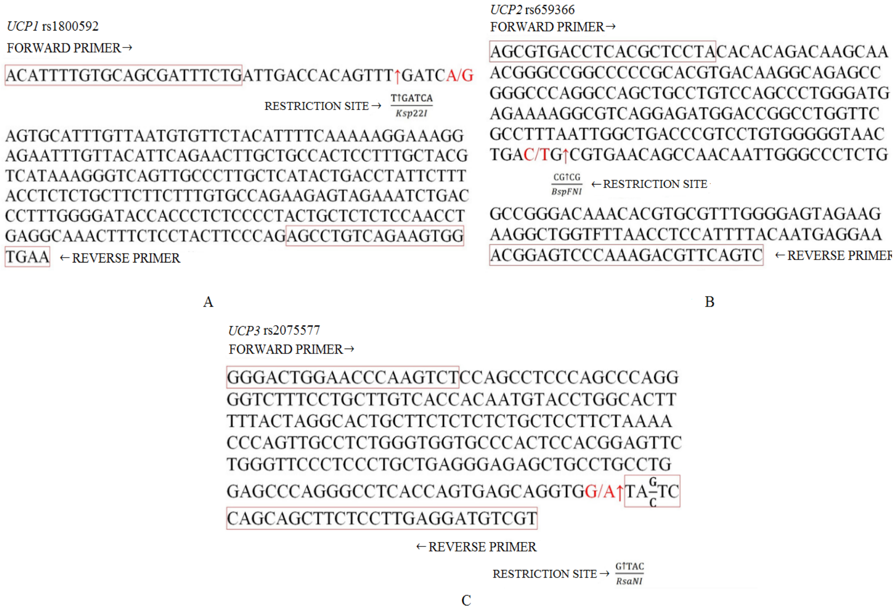

Fig.3. Detection of polymorphismrs1800592 gene of UCP1 (A), rs659366 of UCP2 gene (B) and rs2075577 of UCP3 gene (C)

Discussion

In the present work, for the first time, the frequencies alleles of the polymorphism of the genes *UCP1* (rs1800592), *UCP2* (rs659366) and *UCP3* (rs2075577) in the Yakuts and Chukchi’spopulations living in the extreme climatic conditions of Eastern Siberia were detected, where the lowest temperatures of air were recorded (-71°C). For the detection of adaptation to cold signals, an analysis was made of allele frequencies between populations living in a relatively cold climate (subarctic and temperate climatic zone), compared to populations living in a relatively warm climate (subtropical and subequatorial climatic zone). Populations living in the subarctic (CHU; N.YAK) and on the border of the temperate and subarctic climate (V.YAK; C.YAK) were merged into the «Northern Asia» group. Populations living in the temperate (CHB), subtropical (JPT; CHS; CDX) and subequatorial (KHV) climates were combined into the «Southern Asia» group (Fig. 3). As a result of the comparative analysis, statistically significant increased frequencies were found for the A allele of polymorphism rs2075577 of the *UCP3* gene in the group «Northern Asia» compared to the «Southern Asia» group. The obtained results on the increased frequency of the allele A polymorphism rs2075577 of the *UCP3* gene in the population of the Yakuts and Chukchi’s living in conditions of low temperatures in comparison with other populations of Asia can be associated with random population effects (for the Yakut population, the pronounced founder effect on the paternal lines of the Y-chromosome) [4], or may indicate the existence of adaptation mechanisms aimed at increasing cold resistance. In general, the data obtained by us agree with the previously obtained results on the involvement of the genes *UCP1* (rs1800592), *UCP2* (rs659366) and *UCP3* (rs1800849, rs2075577) to nonshivering thermogenesis in human populations [3; 14].

Thus, a group of Russians researchers investigated the frequencies of alleles of 28 genes potentially associated with adaptation to cold climate (to low temperatures) in populations of Northern Eurasia, including Yakuts (n=102) and Chukchi’s (n=95). As a result of these studies, a significant relationship was established between the polymorphisms rs1800592 of the gene *UCP1* and rs1800849 of the *UCP3* gene with climatic (temperature) and with geographical (latitude and longitude) variables. However, during the additional FDIST-test, The authors did not record directional selection signals for the polymorphisms rs1800592 of the *UCP1* gene and rs1800849 of the *UCP3* gene [3]. Another research team from the University of Chicago, using an evolutionary approach, tested the hypothesis that high expression of the genes of uncoupling proteins (*UCP1*-rs1800592, *UCP2*-rs659366 and *UCP3*-rs1800849) may indicate adaptation to a cold climate [14]. To do this, they calculated the correlation of allele frequencies with the winter climate variables for these polymorphisms with genotyping of 52 world populations.

Table 2

The frequency of polymorphisms of the genes *UCP1, UCP2* and *UCP3* in nine populations of Asia living in different climatic zones

	Populations	n	Climaticzones	*UCP1* rs1800592	*UCP2* rs659366	*UCP3* rs2075577
				AlleleA	Allele T	Allele A
«North Asia»	Chukchi (CHU)	39	subarctic	0,62	0,52	0,71
	NorthernYakuts(N.YAK)	16	subarctic	0,62	0,46	0,62
	VilyuyskYakuts(V.YAK)	67	temperate	0,60	0,50	0,69
	CentralYakuts(C.YAK)	198	temperate	0,62	0,51	0,65
«South Asia»	Chinese(CHB)	103	temperate	0,49	0,47	0,47
	Japanese(JPT)	104	subtropical	0,53	0,53	0,54
	Chinese (CHS)	108	subtropical	0,56	0,35	0,36
	Chinese (CDX)	99	subtropical	0,53	0,38	0,37
	Vietnamese (KHV)	101	subequatorial	0,54	0,34	0,35
	Total	n=835				

Notes:A: M – molecular weight marker pUC19/MspI, line 1 – DNA sample with AA genotype (265 bp), lines 2, 3 – DNA samples with genotypes of GG (301 bp), line 4 – DNA sample with genotype AG (301 and 265 bp); B: M – molecular weight marker pUC19/MspI, line 1 – DNA sample with genotype TT (299 bp), lines 2, 4 –DNA samples with genotypes of CT (299, 178 and 121 bp), lines 3, 5 – DNA samples with CC genotypes (178 and 121 bp); C: M - molecular weight marker pUC19/MspI, line 1 - DNA sample with AA genotype (218 bp), line 2 – DNA sample with genotype AG (249 and 218 bp), line 2 – DNA samples with genotypes of GG (249 bp).

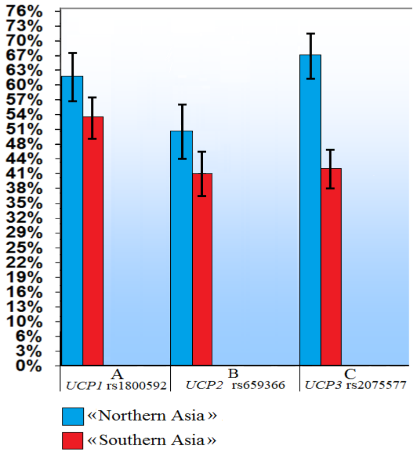

Fig.4. Comparative analysis of frequencies of major alleles of polymorphism of UCP1 (A), UCP2 (B), UCP3 (C) genes by populations of «Northern Asia» in comparison with «Southern Asia» populations

It was found that the high frequency of allele A rs1800592 of the *UCP1* gene is found in populations living in high geographical latitudes, where the least amount of solar radiation is observed. It was also found that the frequencies of the major alleles of several polymorphisms (rs1800849, rs2075577) of the *UCP3* gene have strong correlations with temperature, are associated with cold resistance and, apparently, represent several independent signals of directional selection. However, for polymorphism rs2075577 of the *UCP3* gene, allele frequencies presented in the HapMap project were available only for eleven human populations [14].

In general, further studies are needed to study the mechanisms of nonshiveringthermogenesis associated with BAT in humans, especially the need to clarify the role of the genes of uncoupling proteins *UCP1*, *UCP2*, *UCP3*, as the most promising candidate genes involved in the mechanisms of thermogenesis and human adaptation to cold climates.

Conclusion

Thus, the obtained results on the increased frequency of the allele A polymorphism rs2075577 of the *UCP3* gene in the population of the Yakuts and Chukchi's living at low temperatures, compared with other more southern populations of Asia, may be associated with random population effects, or evidence of the existence of adaptive mechanisms, associated with the genes of nonshivering thermogenesis, and aimed at increasing cold resistance.

Acknowledgements

This study was supported by the Ministry of Education and Science of the Russian Federation №6.1766.2017, the project NEFU M.K. Ammosov: «Genetic features of the population of Yakutia: the structure of the gene pool, adaptation to cold, psychogenetic characteristics, the prevalence of some hereditary and infectious diseases» and the program of bioresource collections of the FASO of Russia «The Genome of Yakutia» YSC CMP (BRK: 0556-2017-0003).

References

1. Tomskiy M.I. [et al.] Buraja zhirovaja tkan i jekstremalno holodnyj klimat [Brown fat tissue and extremely cold climate] Yakutskij medicinskij zhurnal [Yakut medical journal], 2015, № 1, P.44-45.

2. Nelson D., Koks M. Osnovy biohimii Lenindzhera [Basics of Biogeochemistry of Lenin] Moscow: Binom [Binom], 2014, V. 2, P.586.

3. Stepanov V.A. [et al.] Poisk geneticheskih markerov adaptacii k klimatu u naselenija severnoj Evrazii [The search for genetic markers of adaptation to climate in the population of northern Eurasia] Genetika [Russian Journal of Genetics], 2017, V. 53, № 11, P.1254-1266.

4. Autosomal and uniparental portraits of the native populations of Sakha (Yakutia): implications for the peopling of Northeast Eurasia / S.A. Fedorova[et al.] // BMC Evol Biol. –2013. –.V. 13. – №. 1. – P.127.

5. Brand M.D. Physiological functions of the mitochondrial uncoupling proteins *UCP2* and *UCP3* / M.D. Brand, T.C. Esteves // Cell metabolism. – 2005. – V. 2. – №. 2. – P.85-93.

6. Cannon B. Brown adipose tissue: function and physiological significance / B. Cannon, J.A.N. Nedergaard // Physiological reviews. – 2004. – V. 84. – №. 1. – P.277-359.

7. Cold-activated brown adipose tissue in healthy men / W.D. van MarkenLichtenbelt [et al.] // New England Journal of Medicine. – 2009. – V. 360. – №. 15. – P.1500-1508.

8. Developmental origin of fat: tracking obesity to its source / S. Gesta, Y.H. Tseng, C.R. Kahn // Cell. – 2007. – V. 131. – №. 2. – P.242-256.

9. Enerbäck S. The origins of brown adipose tissue / S. Enerbäck // New England Journal of Medicine. – 2009. – V. 360. – №.19. – P.2021-2023.

10. High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity / M. Saito[et al.] // Diabetes. – 2009. – V. 58. – №. 7. – P.1526-1531.

11. Identification of a variant associated with adult-type hypolactasia / N.S. Enarrah[et al.] // Nature Genet. – 2002. –30. –P.233-237.

12. Loss of *UCP2* impairs cold-induced non-shivering thermogenesis by promoting a shift toward glucose utilization in brown adipose tissue / A. Caron[et al.] // Biochimie. – 2017. – V.

134. – P.118-126.

13. Nedergaard J. Uncoupling proteins: current status and therapeutic prospects: Meeting on Uncoupling Proteins / J. Nedergaard, D. Ricquier, L.P. Kozak //EMBO reports. – 2005. – V. 6. – №. 10. – C. 917-921.

14. Population genetic analysis of the uncoupling proteins supports a role for *UCP3* in human cold resistance / A.M. Hancock[et al.] // MolBiolEvol. –2011. –№1. –P.601-614.

15. Schrauwen P. Putative function and physiological relevance of the mitochondrial uncoupling protein-3: involvement in fatty acid metabolism? / P. Schrauwen, J. Hoeks, M.K.C. Hesselink // Progress in lipid research. – 2006. – V. 45. – №. 1. – P.17-41.

16. Tam C.S. Brown adipose tissue: mechanisms and potential therapeutic targets / C.S. Tam, V. Lecoultre, E. Ravussin // Circulation. – 2012. – V. 125. – №. 22. – P.2782-2791.

17. The expression of *UCP3* directly correlates to *UCP1* abundance in brown adipose tissue / K.E. Hilse[et al.] // BiochimicaetBiophysicaActa (BBA)-Bioenergetics. – 2016. – V. 1857. – №. 1. – P.72-78.

18. The 1000 Genomes Project Consortium. A global reference for human genetic variation // Nature. 2015. V. 526. P. 68–74. doi 10.1038/nature15393

19. Uncoupling protein-2: a novel gene linked to obesity and hyperinsulinemia / C. Fleury [et al.] // Nature genetics. – 1997. – V. 15. – №. 3. – P.269.

20. Uncoupling protein-3: a new member of the mitochondrial carrier family with tissue-specific expression / O. Boss[et al.] // FEBS letters. – 1997. – V. 408. – №. 1. – P.39-42.

21. *UCP3* and its putative function: consistencies and controversies / M.E. Harper [et al.] // BiochemSoc Trans. – 2001. – №6. – P.768-73.

The authors:

Yakutsk, Republic Sakha (Yakutia), Russia:

1. Nikanorova Alena Afanasyevna – junior researcher of the Yakut Scientific Center of Complex Medical Problems, the Master's Student, Institute of Natural Science, NEFU M.K. Ammosov. E-mail: nikanorova.alena@mail.ru, 89244611585;
2. Barashkov Nikolay Alekseyevich – Candidate of Biological Sciences, Leading Researcher - the Head of Laboratory of the Yakut Scientific Center of Complex Medical Problems. E-mail: barashkov2004@mail.ru;
3. Diakonov Egor Egorovich – student, Institute of Natural Sciences NEFU. M.K. Ammosov. E-mail: diakonov2007@mail.ru;
4. Pshennikova Vera Gennadiyevna – Candidate of Biological Sciences, Research Associate of the Yakut Scientific Center of Complex Medical Problems. E-mail: pshennikovavera@mail.ru;
5. Nakhodkin Sergey Sergeyevich – Engineer-researcher of the Laboratory of Molecular Biology, The Institute of Natural Sciences NEFU M.K. Ammosov. E-mail: sergnahod@mail.ru
6. Solovyev Aisen Vasilyevich – Postgraduate Student, Institute of Natural Science, NEFU M.K. Ammosov. E-mail: nelloann@mail.ru;
7. Kuzmina Sargylana Semenovna – Candidate of Biological Sciences, Associate Professor, Department of Biology, The Institute of Natural Sciences NEFU M.K. Ammosov. E-mail: sskuzmina@bk.ru;
8. Tomsky Mikhail Innokentyevich – Doctor of Medical Sciences, Acting as Director of the Yakut Scientific Center of Complex Medical Problems. E-mail: ogus@list.ru;
9. Burtseva Tatiana Egorovna – Doctor of Medical Sciences, Professor of the Medical Institute of NEFU M.K. Ammosov. E-mail: bourtsevat@rambler.ru;
10. Fedorova Sardana Arkadyevna – Doctor of Biological Sciences, Head of the Laboratory of Molecular Biology, Institute of Natural Sciences NEFU M.K. Ammosov. E-mail: sardaanafedorova@mail.ru.

A.T.Dyakonova, N.I.Pavlova, N.A.Solovyova, N.P.Filippova, V.V.Dodokhov, L.M.Neustroeva, M.A.Varlamova, Kh.A.Kurtanov

POLYMORPHISM RS738409 OF THE ADIPONUTRIN GENE (*PNPLA3*) AMONG THE INDIGENOUS RESIDENTS OF THE NORTH

ABSTRACT

In this paper, we analyzed the polymorphism rs738409 of the adiponuclein gene *(PNPLA3)* among the indigenous inhabitants of the North of the Republic of Sakha (Yakutia). Under the constant influence of low temperatures, the human body needs a high level of energy metabolism, which in turn is accompanied by a significant consumption of lipids. Epidemiological data indicate the frequent combination of type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) characterized by accumulation of lipids both in the hepatocytes themselves and in the intercellular space. Recently, great importance is attached to the genetic conditionality of NAFLD.

Keywords: diabetes mellitus type 2, insulin resistance, adiponutrin gene, polymorphism.

Introduction

The problem of adaptation to the conditions of the North is being actively studied in the world. The achievements of Russian science are related to the identification of physiological, mental, biochemical features of the organism, the fundamental differences in the state of the organism of the northerners and inhabitants of the middle latitudes. By the present time it is an established fact that when a person adapts to the extreme natural conditions of the North, all kinds of metabolism of proteins, fats, carbohydrates, vitamins, macro- and microelements are restructured. Under the constant influence of low temperatures, the human body needs a high level of energy metabolism, which in turn is accompanied by a significant consumption of lipids.

Metabolism of the organism passes to a qualitatively new level of homeostasis, characterized by greater use of fats and proteins for energy needs and less use of carbohydrates.

High-calorie nutrition, excessive intake of (saturated) fats correlate with increased body weight and obesity, and recently their relationship with NAFLD has been revealed. Non-alcoholic fatty liver disease (NAFLD) is usually associated with obesity, metabolic syndrome and type 2 diabetes mellitus (DM 2), is one of the most common chronic liver diseases [1]. Epidemiological data indicate a fre-