12. Li H [et al.]. Regulation of endothelial-type NO synthase expression in pathophysiology and in response to drugs. *Nitric Oxide*. 2002; (7): 149–164

13. Jin L [et al.]. Role and regulation of autophagy and apoptosis by nitric oxide in hepatic stellate cells during acute liver failure. *Liver International: Official Journal of the International Association for the Study of the Liver*. 2017; 37(11): 1651–1659. DOI: 10.1111/liv.13476

14. Tamemoto H, Ishikawa S-E, Kawakami M. Association of the Glu298Asp polymorphism of the eNOS Gene with ischemic heart disease in Japanese diabetic subjects. *Diabetes Research and Clinical Practice*. 2008; 80(2): 275–279. DOI: 10.1016/j.diabres.2007.12.019

15. Сайт «1000 геномов» [Электронный ресурс]: http://www.internationalgenome.org/

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ETHNIC DIFFERENCES IN DISTRIBUTIONS OF ALLELIC AND GENOTYPIC FREQUENCIES OF *NAT2* POLYMORPHIC VARIANTS IN PATIENTS WITH PULMONARY TUBERCULOSIS

Ethnic differences in allele frequencies and genotype distribution for polymorphic variants of *NAT2* gene (NAT2*5, NAT2*6, NAT2*7) were studied among ethnic Yakuts and Russians with newly diagnosed pulmonary tuberculosis.

This is the first study to establish allele and genotype frequencies for polymorphic variants of *NAT2* gene (NAT2*5, *6, *7) among ethnic Yakuts and Russians, who permanently reside in the Sakha Republic (Yakutia). Prevalence of NAT2*5, *6, *7 polymorphisms among Yakuts and Russians was determined, and ethnic differences were shown in allele frequencies and genotype distribution of NAT2 polymorphic variants: rs1801280 (341T>C), rs1799930 (590G>A), and rs1799931 (857G>A).

Keywords: *NAT2* gene polymorphism, Yakuts, Russians, tuberculosis, adverse drug effects

Introduction. Treatment success indicators are remaining at low levels in Russia. Based on official statistical data, in 2016, effective chemotherapy outcomes were registered in 74.3% out of all new pulmonary TB cases treated with regimens I–III (irrespective of microscopy results at case notification), or in 64.3% of cases with positive sputum microscope results [4]. Clinically, low treatment effectiveness in new TB cases resulted from nonadherence to chemotherapy duration, treatment interruptions, temporary cancellation of drugs due to adverse drug effects (ADE) (up to 61% cases [3] treated for drug-sensitive TB). Development of ADE is associated with variations in drug kinetics, and can be stemming from both transient (inhibition of biotransformation enzymes, as a result of drug interactions, eating habits) and constant causes (sex, concomitant diseases, genetic mutations in genes encoding enzymes involved in drug metabolism) [15, 24].

Genetic polymorphisms have been established and thoroughly researched for N-acetyltransferase (NAT) 2. NAT2 is an enzyme participating in biotransformation phase II, and is responsible for acetylation of more than 70% of xenobiotics, including therapeutic agents [21]. Single-nucleotide substitutions in the structural region of NAT2 gene determine genetic variations in enzyme activity [1,12], and have been linked to decreased or increased rates of xenobiotic metabolism [2]. NAT2 polymorphisms considered the most clinically important in terms of effective and safe TB chemotherapy are: *4, *5, *6, *7, *12, *13, *14. Patients with slow acetylation alleles (NAT2*5, *6, *7, *14) have been shown to be at risk for

developing liver injury [7, 23]. Presence of NAT2 slow metabolism alleles induces damage to hepatocyte cell structures due to significantly reduced amount of N-acetyltransferase in liver, slowdown in metabolic rate, and delayed elimination of antituberculosis drugs from the body. Distribution of NAT2 polymorphic alleles is widely variable between different populations and ethnic groups [19]. Only scarce data are available in current scientific literature regarding genotype prevalence of NAT2 polymorphic variants (NAT2*5, *6, *7) among Yakut and Russian patients with newly identified pulmonary TB permanently residing in the Sakha Republic (Yakutia).

Aim: study ethnic differences in allele frequencies and genotype distribution of NAT2 polymorphic variants (NAT2*5, NAT2*6, NAT2*7) among ethnic Yakuts and Russians with newly diagnosed pulmonary TB.

Material and methods: The study comprised 197 patients newly diagnosed with pulmonary TB. Of the patients examined, all of them permanently residing in Yakutia, 132 (67%) were referred to ethnic Yakuts (77 women, 55 men), and 65 (33%) to Russians (35 women, 30 men). Ethnicity was determined by a self-definition method comparable to SSR analysis [10]. Mean patient age was 43.3 with a standard deviation of 14.4 years. All patients completed informed consent to participate in the study. Sequencing of a particular NAT2 region was performed in several steps, using Sanger method with dideoxynucleotide tripshosphates (ddNTP): 1) DNA fragment under study was hybridized with primer; 2) molecule was enzymatically synthetized; 3) substance was further subjected to electrophoresis; 4) radioautographic analysis of results. Sequencing chromatograms were estimated visually, analyzed using Finch TV 1.4 software, and matched with reference NAT2 sequence for determination of individual single-nucleotide polymorphisms (SNP) https://www.ncbi.nlm.nih.gov/nuccore/NM_000015.2. Sequencing was performed for 3 polymorphic variants: rs1801280 (341T>C), rs1799930 (590G>A), rs1799931 (857G>A).

Concordance of genotype frequency distributions with Hardy-Weinberg law was checked using Pearson's chi-squared test. Threshold statistical significance level was 0.05. Statistical analysis was performed in IBM SPSS Statistics 23 software (licensed to North-Eastern Federal University), utilizing classical Pearson χ^2 test, and a modified version with likelihood adjustment applied in case expected frequencies took value of less than 5 in 15 or more cells in contingency table.

Results and discussion. All sought-for polymorphic variants of NAT2 were detected during the study. Distributions of allelic and genotypic frequencies for NAT2 polymorphic markers rs1801280 (T341C) and rs1799931 (G857A) among Yakuts and Russians were concordant with Hardy-Weinberg distribution ($p>0.05$). Significant differences between Yakuts and Russians ($p<0.05$) were observed in allelic and genotypic frequencies of polymorphisms NAT2*5 and NAT2*7 (Table 1).

The T allele of polymorphism NAT2*5(T341C) occurred reliably higher among Yakuts (0.82) than in Russians (0.58). Mutant C allele had the highest observed frequency in Russians (0.42), and was much less frequent in Yakuts (0.18) ($p<0.05$). Estimated frequencies of C allele are 0.45 for European population, 0.35 for South Asia, and 0.04 for East Asia [20]. It is noteworthy, that frequency of C allele of NAT2*5 (T341C) in Yakuts was considerably higher, compared to the population of East Asia. T/T genotype of NAT2*5 (T341C) was prevalent in 68.9% of individuals of Yakut origin. Meanwhile, Russian patients were 2 and 3 times more often carriers of T/C and C/C genotypes, respectively (55.4% and 13.8%, correspondingly) ($p<0.05$) (Table 1).

Meaningful ethnic differences in frequencies of polymorphism NAT2*5 (T341C) among Yakuts and Russians were established (31.1% vs. 69.2%, respectfully) ($p<0.05$). The highest prevalence rates of polymorphism NAT2*5 have been observed among Europeans (35% to 55%) [5,11,13], and among people originating from West Asia (up to 40%) [13], according to Gra O. et al. (2010); frequency among Russians varies between 38% and 45% [16].

Frequency of G allele of NAT2*7 was 0.84 in Yakuts, and 0.93 in Russians. Mutant A allele occurred in 0.16 of Yakuts, and 0.07 of Russians ($p<0.05$). Global frequencies of A allele of NAT2*7 are 0.02 in Europeans, 0.18 in East Asia, and 0.07 in South Asia [20]. Our findings suggest the highest prevalence of A allele of NAT2*7 among ethnic Russians of Yakutia, exceeding that in residents of Europe by 3.5 times. Individuals of Yakut origin were 1.9 times more often carriers of G/A genotype of NAT2*7 (G857A), compared to Russians (26.5% vs. 13.8%, respectively) ($p<0.05$). Genotype A/A was detected in none of Russian patients, while 2.3% of Yakuts carried it (Table 1). Existing evidence on link between hepatotoxicity and NAT2*7 genotypes is scarce and contradictory. Increased risk of hepatotoxicity was suggested in carriers of G/A genotype receiving chemotherapy with anti-tuberculosis first line drugs, compared to carriers of G/G genotype [14,18], although this association was never detected in other studies [6, 9].

Polymorphic variant NAT2*7 (G857A) was more frequent in Yakuts (28.8%), than in Russian patients (13.8%) ($p<0.05$). This finding is coherent with reported data, and is in agreement with average 20% frequency observed in Asian population of Central, East, and South-East Asia. Compared to Europeans, Russian population of Yakutia, showed notably higher prevalence of this polymorphism (5%) [5, 11, 13].

Frequencies of rs1799930 (G590A) NAT2 genotypes had no statistically significant differences between Yakuts and Russians, which is consistent with reported data. Frequencies of G and A alleles of NAT2*6 (G590A) were 0.78 and 0.22

Distribution analysis of polymorphic variants of *NAT2* gene in Yakut and Russian patients with pulmonary tuberculosis

Genotype	Yakuts, n (%)	Russians, n (%)	χ^2	p
NAT2*5 (T341C)				
T/T	91 (68.9)	20(30.8)	26.54	0.000*
T/C	35 (26.5)	36(55.4)		
C/C	6(4.5)	9(13.8)		
NAT2*6 (G590A)				
G/G	78(59.1)	29(44.6)	5.57	0.062
G/A	49(37.1)	29(44.6)		
A/A	5(3.8)	7(10.8)		
NAT2*7 (G857A)				
G/G	94(71.2)	56(86.2)	7.06	0.029*
G/A	35(26.5)	9(13.8)		
A/A	3(2.3)	0		

Note: χ^2 – Pearson chi-squared value. *- statistically significant differences are bold-typed. ($p<0.05$)

in Yakuts, and 0.67 and 0.33 in Russians, respectively. Reported frequencies of G and A alleles of NAT2*6 are 0.74 and 0.26 in East Asia, and 0.72 and 0.28 in Europe, respectively [20]. Compared to Russians, and residents of East Asia and Europe, while Yakuts had the lowest frequency of A allele.

Genotype G/G of NAT2*6 was prevalent in predominating 59.1% of Yakuts, while Russians had genotypes G/G and G/A, with the same frequencies of 29.0%. Genotype A/A was common in patients of Russian origin, and occurred 2.8 times more frequent, than in Yakut patients (Table 1). A allele of NAT2*6 (G590A) has been linked with increased risk of ADE [9]. Studies have found the highest hepatotoxicity risk during chemotherapy in residents of Turkey, China, and Tunisia with confirmed TB diagnosis, who had A/A genotype of rs1799930 (G590A) NAT2 gene, compared to patients with the same diagnosis, who were carriers of genotypes G/G and G/A [8,18,22]. Residents of Korea with AA or GA genotype receiving treatment for TB were found to have slower drug acetylation, than patients with GG genotype [9].

Polymorphism NAT2*6 is reportedly prevalent all over the world with approximately the same frequency (10%-35%) [5,11]. In our study, the frequencies of this polymorphism among Yakuts and Russians with pulmonary TB were higher than the rates reported in literature: 55.4% in Russians, and 40.9% in Yakuts, without notable ethnic differences.

Conclusion. This was the first study to establish allelic and genotypic frequencies of NAT2 polymorphic variants (NAT2*5, *6, *7) among ethnic Yakuts and Russians newly diagnosed with pulmonary TB and permanently residing in the Sakha Republic (Yakutia). Prevalence of polymorphisms NAT2*5, *6, *7 among Yakuts and Russians was determined. Ethnic differences in allele frequencies and genotype distributions of NAT2 polymorphic variants rs1801280 (341T>C), rs1799930 (590G>A), and rs1799931 (857G>A) were analyzed.

References

1. Сатырова Т. В., Михайлова Е. И., Осипенко А. Н., Осипенко Н. Б., Васенда М. Н. Вариабельность фенотипа N-ацетилтрансферазы у жителей г. Гомеля и Гомельской области. *Проблемы здоровья и экологии.* 2010;1(23):73-77. [Satyrova T. V., Mihailova E. I., Osipenko A. N., Osipenko N. B., Vasenda M. N. Variability of N-acetyltransferase phenotype in the citizens of Gomel and Gomel region. *Problemy zdorovia i ekologii.* 2010;1(23):73-77. (In Russ.).]

2. Казаков Р.Е., Бердникова Н.Г., Сычёв Д.А. Фармакогенетика и клинические исследования: точки соприкосновения. *Фармакогенетика и фармакогеномика.* 2016;1:18-23. [Kazakov R.E., Berdnikova N.G., Sychev D.A. Pharmacogenetics and clinical studies: common ground. *Farmakogenetika i farmakogenomika*. 2016;1:18-23. (In Russ.).]

3. Степанова Н.А., Стрельцова Е.Н., Галимзянов Х.М., Кантемирова Б.И. Нежелательные побочные реакции на противотуберкулезные препараты основного ряда. *Туберкулез и болезни легких.* 2016;94(5):42-45. [Stepanova N.A., Streltsova E.N., Galimzyanov K.M., Kantemirova B.I. Unfavorable side effects to first line anti-tuberculosis drugs. *Tuberkulez i bolezni legkih.* 2016; 94(5):42-45. (In Russ.).] DOI: 10.21292/2075-1230-2016-94-5-42-45.

4. Центральный научно-исследовательский институт организации и информатизации здравоохранения Министерства здравоохранения Российской Федерации. Показатели по туберкулезу в Российской Федерации 2008-2017 гг. [Federal Research Institute for Health Organization and Informatics of Ministry of Health of the Russian Federation. Indicators for tuberculosis in Russian Federation 2008-2017. (In Russ.)]. URL: https://mednet.ru/images/materials/CMT/2018_god_tuberkulez_epidsituaciya.pdf. (accessed 8 June 2019).

5. Sabbagh A, Darlu P, Crouau-Roy B, Poloni ES. Arylamine N-acetyltransferase 2 (NAT2) genetic diversity and traditional subsistence: a worldwide population survey. *PLoS One.* 2011;4(6). URL: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0018507 (accessed 20 June 2019). DOI:10.1371/journal.pone.0018507.

6. Chan S.L., Chua APG, Aminkeng F, Chee CBE, et al. Association and clinical utility of NAT2 in the prediction of isoniazid-induced liver injury in Singaporean patients. *PLoS One*. 2017; 12(10). URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5642896/pdf/pone.0186200.pdf (accessed 20 June 2019). DOI:10.1371/journal.pone.0186200.

7. Zabost A, Brzezińska S, Kozińska M, Błachnio M, et al. Correlation of N-acetyltransferase 2 genotype with isoniazid acetylation in Polish tuberculosis patients. *Biomed Res. Int.* 2013. URL: https://www.ncbi.nlm.nih.gov/pubmed/?term=Correlation+of+N-acetyltransferase+2+genotype+with+isoniazid+acetylation+in+Polish+tuberculosis+patients. (accessed 6 June 2019). DOI: 10.1155/2013/853602.

8. Bozok Cetintaş V, Erer OF, Kosova B, Ozdemir I, et al. Determining the relation between N-acetyltransferase-2 acetylator phenotype and antituberculosis drug induced hepatitis by molecular biologic tests. *Tuberk Toraks.* 2008; 56(1):81-86.

9. Kim SH, Kim SH, Bahn JW, Kim YK, et al. Genetic polymorphisms of drug-metabolizing enzymes and anti-TB drug-induced hepatitis. *Pharmacogenomics*. 2009;10(11):1767-1779. DOI:10.2217/pgs.09.100.

10. Hua Tang, Tom Quertermous, Beatriz Rodriguez, Sharon L. R. Kardia, et al. Genetic structure, self-identified race/ethnicity, and confounding in case-control association studies. *Am J Hum Genet*. 2005;76(2):268-275. DOI: 10.1086/427888.

11. Hein DW. N-acetyltransferase 2 genetic polymorphism: effects of carcinogen and haplotype on urinary bladder cancer risk. *Oncogene.* 2006;25(11):1649-1658. DOI: 10.1038/sj.onc.1209374.

12. Jarrar YB, Balasmeh AA, Jarrar W. Sequence analysis of the N-acetyltransferase 2 gene (NAT2) among Jordanian volunteers. *Libyan J Med.* 2018;13(1). URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5717714/–1408381 (accessed 1 June 2019). DOI: 10.1080/19932820.2017.1408381.

13. Kurose K, Sugiyama E, Saito Y. Population differences in major functional polymorphisms of pharmacokinetics/pharmacodynamics-related genes in Eastern Asians and Europeans: implications in the clinical trials for novel drug development. *Drug Metab Pharmacokinet*. 2012;27(1):9-54.

14. Cramer JP, Lohse AW, Burchard GD, Fischer L, et al. Low N-acetyltransferase 2 activity in isoniazid-associated acute hepatitis requiring liver transplantation. *Transpl Int.* 2010;23(2):231-233. DOI: 10.1111/j.1432-2277.2009.00921.x.

15. Ma Q, Lu AY. Pharmacogenetics, pharmacogenomics, and individualized medicine. *Pharmacol Rev*. 2011; 63(2):437-459. DOI: 10.1124/pr.110.003533.

16. Gra O, Mityaeva O, Berdichevets I, Kozhekbaeva Z, et al. Microarray-based detection of CYP1A1, CYP2C9, CYP2C19, CYP2D6, GSTT1, GSTM1, MTHFR, MTRR, NQO1, NAT2, HLADQA1, and AB0 allele frequencies in native Russians. *Genet Test Mol Biomarkers*. 2010; 14(3):329-342. DOI: 10.1089/gtmb.2009.0158.

18. An HR, Wu XQ, Wang ZY, Zhang JX, Liang Y. NAT2 and CYP2E1 polymorphisms associated with antituberculosis drug-induced hepatotoxicity in Chinese patients. *Clin Exp Pharmacol Physiol*. 2012; 39(6):535-543. DOI: 10.1111/j.1440-1681.2012.05713.x.

19. Dursun R, Dursun HG, Zamani AG, Yıldırım MS, Çınar İ. NAT2 gene polymorphisms in Turkish patients with psoriasis vulgaris. *Biomed Res Int*. 2018. URL: https://www.ncbi.nlm.nih.gov/pubmed/?term=NAT2+Gene+Polymorphisms+in+Turkish+Patients+with+Psoriasis+Vulgaris (accessed 15 June 2019). DOI: 10.1155/2018/3258708.

20. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, et al. Pharmacogenomics knowledge for personalized medicine. *Clinical Pharmacology & Therapeutics*. 2012;92(4):414-417. DOI: 10.1038/clpt.2012.96.

21. Klein DJ, Boukouvala S, McDonagh EM, Shuldiner SR, et al. PharmGKB summary: isoniazid pathway, pharmacokinetics. *Pharmacogenet Genomics*. 2016;26(9):436-444. DOI: 10.1097/FPC.0000000000000232.

22. Ben Mahmoud L, Ghozzi H, Kamoun A, Hakim A, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatotoxicity in Tunisian patients with tuberculosis. *Pathol Biol (Paris)*. 2012;60(5):324-330. DOI: 10.1016/j.patbio.2011.07.001.

23. Zhu R, Kiser JJ, Seifart HI, Werely CJ, et al. The pharmacogenetics of NAT2 enzyme maturation in perinatally HIV exposed infants receiving isoniazid. *J Clin Pharmacol*. 2009;6(11):1249-1254. DOI: 10.1177/0091270011402826.

24. Raquel Lima de Figueiredo Teixeira, Márcia Quinhones Pires Lopes, Philip Noel Suffys, Adalberto Rezende Santos. *Tuberculosis pharmacogenetics*: state of the art (March 20th 2013). Tuberculosis – Current Issues in Diagnosis and Management. URL: https://www.intechopen.com/books/tuberculosis-current-issues-in-diagnosis-and-management/tuberculosis-pharmacogenetics-state-of-the-art (accessed 5 June 2019). DOI: 10.5772/54984.

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RESTRUCTURING OF HEART RATE VARIABILITY, GAS EXCHANGE AND MICROCIRCULATION AT CYCLE-ERGOMETRY IN PERSONS WITH DIFFERENT DEGREES OF EXERCISE TOLERANCE

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An objective criterion for assessing the functional state of the human body, as well as the degree of balance of its physiological systems may be the study of physical performance. The **purpose** of this work was to study the specific features of urgent adaptations of a number of functional systems of the body in response to a cycle-ergometric test, and to identify marker criteria for assessing the level of exercise tolerance.

Based on the study of heart rate variability, indirect calorimetry, capillary blood flow and a modified PWC170 test, a comparative study was carried out on 63 young men aged 17-19 who were students from among Caucasians born in the North in the 1st and 2nd generations. Analysis of the data showed that during the stress test, most values of heart rate variability, microcirculation and metabolism increase as compared with the background level or at different stages of cycle-ergometry. At the same time, these changes are different for people with different degrees of tolerance to the load.

The results of the study made it possible to establish that the most important and informative indices reflecting the degree of tolerance to the load are the heart rate, the concentration of carbon dioxide in the exhaled air, the oxygen utilization factor, and the rate of capillary blood flow. During the performance of the stress test, such criteria are heart rate, MxDMn in relation to heart rate, reflecting the degree of decrease in parasympathetic activation, as well as the level of oxygen consumption, whose values in individuals with normal load resistance continue to increase until the end of the test.

Keywords*:* young men, heart rate variability, gas exchange, microcirculation, exercise test.

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Examination of physical working capacity is an important element of the quantitative assessment of the level of health, and an assessment of the degree of exercise tolerance can serve as a prognostic and objective criterion of the functional state and a quantitative indicator of individual human health [6]. A reduced level of motor activity is accompanied by a decrease in the overall working capacity of the organism and an increase in the "physical cost of the load," which is associated with a high tension of functioning systems involved in response to this load [10]. The autonomic nervous system plays an important role in modulating the cardiovascular system in various situations [16], including physical exercise [17]. To maintain cardiovascular homeostasis during exercise, it is necessary to connect mechanisms based on the rapid action of the autonomic nervous system [17]. Heart rate variability (HRV) characteristics are available and fast in use indicators reflecting changes in cardiovascular homeostasis, and also are indirect indicators of vagal nerve activity of the heart. In doing so, they allow us to determine the relative contribution of the parasympathetic and sympathetic link in the regulation of the rhythm of the heart in stress testing, being an accessible measure of the overall function of the ANS [8, 15].

Cardiovascular reactions, in response to physical exertion, are characterized by a direct expressed decrease in the activity of the parasympathetic link of the autonomic nervous system at the beginning of the test, with an increase in heart rate due to the activation of sympathetic activity. Immediately after the end of exercise, the heart rate decreases due to vagal reactivation [19].

It is important to judge the peculiarities of the changes in metabolic processes during the performance of load tests, preferably using indirect calorimetry,