Studying polymorphic variants of the NAT2 gene (NAT2*5 and NAT2*7) in Nenets populations of Northern Siberia

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Abstract

Background: N-acetyltransferase 2 plays a crucial role in the metabolism of a wide range of xenobiotics, including many drugs, carcinogens, and other chemicals in the human environment. The article presents for the first time data on the frequency of two important “slow” variants of NAT2 gene (NAT2*5, rs1801280 and NAT2*7, rs1799931), which significantly affect the rate of xenobiotics acetylation, among representatives of indigenous populations of Forest and Tundra Nenets in Northern Siberia. The aim of this study was to identify the frequencies of these variants and compare them with frequencies in other ethnic populations.

Results: NAT2*5 (T341C) genotyping revealed frequencies of 28.0% and 38.6% for Tundra and Forest Nenets, respectively. The frequencies of NAT2*7 (G857A) variant were 9.8% and 8.2% for Tundra and Forest Nenets, respectively. Polymorphic variants frequencies for Nenets are intermediate between those in populations of Europeans and Asians. These results can probably be explained by the presence of both European and Asian components in Nenets gene pools.

Conclusions: The results of this study expand the knowledge of NAT2 polymorphism in world populations. These data may also help assess the genetic predisposition of Nenets to multifactorial diseases associated with polymorphism in the NAT2 gene and, in general, contribute to the development of personalized medicine in reference to native people of Siberia.

Keywords: Xenobiotics, NAT2 gene, NAT2*5, rs1801280, NAT2*7, rs1799931, Forest and Tundra Nenets, Northern Siberia

Background

A person’s life expectancy and quality of life are determined by many factors, including heredity, lifestyle, physical activity, nutrition, stress, and the exposure to foreign substances (xenobiotics). These include exotoxins, mutagens and carcinogens in tobacco smoke, food, air, medicines, industrial and agricultural products [1–3].

Foreign substances entering the body are metabolized by the enzymes of the xenobiotic biotransformation system (XBS). XBS genes are highly polymorphic. Numerous studies have shown that the combination of adverse environmental factors with the inheritance of unfavorable polymorphic variants of genes, which include XBS genes, determines individual sensitivity to various toxins. Such sensitivity may contribute to the development of socially significant diseases in both adults and children. Similarly, resistance or hypersensitivity of an individual to a particular drug may lead to lack of therapeutic effect.
or development of adverse reactions in response to treatment [4–14].

The process of xenobiotic metabolism in the body occurs in three stages or phases. The first phase, the activation phase, is carried out by a large family of cytochrome P450 enzymes (CYPs). The second phase involves various transferases and hydrolases that neutralize hydrophilic and often toxic phase I products. During the third phase, the xenobiotic compounds may be removed from cells by energy-dependent transporters to the extracellular medium, where they may be further metabolized or excreted [15, 16].

For the most effective neutralization of many foreign substances, it is necessary to have the combined action of enzymes from phases I and II. It has been revealed that the desynchronization of the biotransformation phases leads to the accumulation of peroxidation products, carcinogens and mutagens in the organism, leading to its rapid poisoning. Especially unfavorable is the combination of high activity of phase I enzymes and low activity of phase II enzymes [17–19]. Among the phase II enzymes, the families of glutathione-S-transferases (GSTs) and N-acetyltransferases (NATs) display the widest and most diverse activity [20].

There are two functional isoenzymes in NAT family, which metabolize a wide range of xenobiotics. These include carcinogens such as aromatic amines (4-aminobiphenyl), heterocyclic amines (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridines) contained in cigarette smoke and food [21]. The enzyme NAT1 is involved in the metabolism of folate, para-aminosalicylic and para-aminobenzoic acids. NAT2 is considered the main enzyme of xenobiotic acetylation. It is responsible for the biotransformation of a wide range of clinically important drugs (antihypertensive, hydrazine, hydralazine, phenelzine; arylamine drugs, including antiarthritis and antianginal) as well as the sensitivity of individuals to drugs, such as isoniazid, that are used to treat tuberculosis [1, 37].

Numerous studies have shown a reliable link between polymorphisms in the NAT2 gene and the risk of cancer, including cancer of the head and neck, lungs, mammary glands, larynx, bladder, digestive tract [38–45]. The presence of a “slow” NAT2 genotype in combination with a “zero” GSTM1 (0/0) genotype is a risk factor for the development of lymphatic leukemia in children [46]. CYP1A1 Val, NAT2*6 (G590A) variants and GSTM1 (0/0) genotype are associated with a predisposition to bronchial asthma development in children [47]. A study conducted in the Krasnodar Region of Russia showed that the presence of the NAT2*6 (G590A/A) genotype increases by a factor of 3.5 the risk of developing congenital malformations such as cleft lip and/or palate in females compared to males [48].

Certain NAT2 genotypes and some lifestyle features can be considered as combined risk factors for the development of psoriasis in a sample of Muscovites [49]. It has been shown that polymorphic variants of the GSTT1,
GSTM1, and NAT2 genes can potentially modulate the risk of tuberculosis development in ethnic Russians [50]. Certain polymorphic variants of GSTT1, GSTM1, NAT2, and MTRR genes can modulate the risk of acute leukemia in children living in the European part of Russia [51]. In Yakuts, the allele NAT2*7 (857A) and the genotype NAT2*7 (857G/A) are markers of increased risk of lung cancer [52].

Since the 1960s, in the northern areas of Western Siberia, the development of industry has been growing. This has led to changes in the traditional way of life for indigenous ethnic groups and the introduction of new chemicals, drugs and toxic pollutants into their habitats. Therefore, it is necessary to determine whether these indigenous ethnic groups are resistant to these xenobi-otics and whether there is a high risk of exposure of the population that leads to serious health issues, such as respiratory diseases, cancer and allergies. For this purpose, it is necessary to study the genetic profile of indigenous populations and their ability to metabolize xenobiotics.

Ethnography, anthropology, demographic history of indigenous Nenets populations and genetic markers such as polymorphism in genes GSTM1, GSTT1, CYP2C9, and CYP2D6 associated with xenobiotics metabolism have been studied previously [53–61].

In this study, we analyzed the occurrence of NAT2*5 (rs1801280, T341C) and NAT2*7 (rs1799931, G857A) variants of the NAT2 gene in the populations of Tundra and Forest Nenets of the Yamalo-Nenets Autonomous Okrug (YaNAO).

Results

The frequencies of the studied polymorphic variants of the NAT2 gene in Nenets and other world populations are shown in Table 1. The data were collected according to the established protocols [67] and the results were confirmed by the statistical estimates [68, 69].

**Table 1** NAT2*5 and NAT2*7 variant frequencies of the NAT2 gene in some human populations, %

| Population                      | NAT2*5 (341C) | NAT2*7 (857A) |
|---------------------------------|--------------|--------------|
| Tundra Nenets*, YaNAO, Russia   | 28.0 (n = 182) | 9.8 (n = 194) |
| Forest Nenets*, YaNAO, Russia   | 38.6 (n = 290) | 8.2 (n = 330) |
| Tatars, Bashkiria region, Russia | No data      | 9.5 (n = 136) |
| Europeans, Moscov, Russia       | 42.0 (n = 198) | 3.0 (n = 198) |
| Russians, Voronezh region, Russia | 42.0 (n = 580) | 3.0 (n = 580) |
| Germans, Germany [31]          | 46.5 (n = 1688) | 1.3 (n = 1688) |
| Romanians, Central Europe [64]  | 43.5 (n = 280) | 3.2 (n = 280) |
| Egyptians [65]                 | 49.7 (n = 400) | 2.8 (n = 400) |
| Kyrgyz, Central Asia [64]      | 19.3 (n = 580) | 12.1 (n = 580) |
| Han Chinese, China [66]        | 1.8 (n = 224) | 17.0 (n = 224) |
| Bantu, Africa [34]             | 38.3 (n = 204) | 6.1 (n = 204) |

n number of alleles examined; *own study

**NAT2** T341C (Ile114Thr)

Genotype counts in Forest and Tundra Nenets were as follows: TT – 55 and 45; TC – 68 and 41; CC – 22 and 5 respectively. In each sample, the distribution of NAT2*5 (T341C) frequencies reflected Hardy-Weinberg equilibrium (\( \chi^2 = 0.017, p = 0.896 \) and \( \chi^2 = 1.244, p = 0.265 \) for Forest and Tundra Nenets).

The frequency of the “slow” NAT2*5 (T341C) variant in the Tundra Nenets was statistically significantly lower (28.0%) than in the Forest Nenets (38.6%), \( p = 0.024 \).

**NAT2** G857A (Gly286Gln)

Genotype counts in samples of Forest and Tundra Nenets were as follows: GG – 139 and 78; GA – 25 and 19; AA – 1 and 0, respectively. An additional file contains more detailed information on individual genotyping results (See Additional File 1). In both samples, the distribution of frequencies NAT2*7 (G857A) reflected Hardy-Weinberg equilibrium (\( \chi^2 = 0.012, p = 0.914 \) and \( \chi^2 = 1.143, p = 0.285 \) for Forest and Tundra Nenets, respectively).

The frequencies of the “slow” NAT2*7 (857A) variant in the study populations did not statistically differ from each other, with Forest and Tundra Nenets having essentially the same values (8.2 and 9.8%, \( \chi^2 = 0.22; p = 0.64 \)).

**Discussion**

As described above, the polymorphic variant NAT2*5 (341C) is found in the world populations with an average frequency of 30–50% among Europeans, 33–42% among Africans, and quite rarely among Asians (up to 5%). The results of our study showed that the frequencies of the NAT2*5 (341C) variant in Forest Nenets and Europeans did not statistically significantly differ. Tundra Nenets, by contrast, have a statistically significantly lower frequency of NAT2*5 compared to the comparative populations (Russians, Romanians, Germans, Egyptians, Bantu Africans), as well as Forest Nenets (in all cases of pairwise comparison \( p < 0.05 \)). In addition, there are statistically significant differences between the Nenets and Kyrgyz, as well as with Han Chinese, for whom the frequency of NAT2*5 (341C) is low enough, as in other Asian populations (\( p < 0.05 \)).

We have mentioned above that the frequency of NAT2*7 (857A) is low for Europeans (less than 2%) and Africans (3–6%), and among Asians it reaches 10–12%. Our study showed that with respect to the frequency of the NAT2*7 (857A) variant, both Forest and Tundra Nenets are statistically significantly different from Russians, Romanians, Germans, and Egyptians (\( p < 0.05 \)), although there are no statistically significant differences with Africans, Kyrgyz, and Tatars.
In Forest and Tundra Nenets, the frequencies of “slow” polymorphic variants \textit{NAT2*5} and \textit{NAT2*7} of one of the key genes of the xenobiotics biotransformation system, including carcinogens and the main clinically important drugs, occupy an intermediate value between the frequencies among the considered populations of Europeans and Asians. Such results can probably be explained by the presence in the gene pools of the Nenets, both European and Asian components, which were determined according to anthropological and genetic data [53–60].

Based on our data on lower frequencies of the “slow” \textit{NAT2*5} variant in Nenets, compared with Europeans, we can assume that at the population level these northern peoples, unlike the studied European populations, are at a lower risk of developing cancer and other multifactorial diseases with which a polymorphic variant of \textit{NAT2*5} is associated. Especially since the standardized mortality rate from cancer in the Yamalo-Nenets okrug in 2017 fell below the level in the Russian Federation [61]. However, to confirm our assumption, it is necessary in the future to use additional population genetic parameters and the necessary statistical methods of data processing.

**Conclusion**

Currently, changes in the habitual way of life of indigenous ethnic groups are taking place due to the cross-breeding of the population and the rapid development of industry in the Yamalo-Nenets Autonomous Okrug. New chemical substances and carcinogens penetrate into the Nenets’ habitat. The development of medicine, in turn, contributes to the active penetration of drugs. Changing standards of treatment require the use of more and more new medicines, which indigenous peoples have never encountered before.

Therefore, having an idea about polymorphic variants frequencies of the genes of the xenobiotic biotransformation system, which include medicinal products, and hence the peculiarity of their metabolism in indigenous Samoyedic ethnic groups, it is possible to plan the safest and most effective therapy with medicines. Knowledge about the distribution of polymorphic variants of genes in the xenobiotic biotransformation system allows us to identify genotypes associated with socially significant, multifactorial diseases, which makes it possible to identify predisposition to them and to take preventive measures to avoid the development of pathological conditions.

**Methods**

**Study populations**

To conduct the study, samples of representatives of Tundra and Forest Nenets living in the Purovsky region of the YaNAO were obtained. These samples did not include descendants of intermarriages with Russians and other ethnic groups. The material for the study was collected during the 1988–2009 expeditions to the YaNAO under the guidance of L. P. Osipova. Peripheral blood collection was carried out according to international rules [67] with the use of genealogical information and “Informed consent” from volunteers who were healthy at the time of the study.

**DNA isolation and SNP genotyping**

DNA samples were isolated from the leukocyte fractions of venous blood by the standard method of phenol-chloroform extraction using proteinase K. Genotyping of \textit{NAT2*5 (T341C)} and \textit{NAT2*7 (G857A)} SNPs of \textit{NAT2} gene was performed using real-time PCR with competing TaqMan-probes carrying a quencher at the 3′-end and different fluorescent dyes (FAM or R6G) at the 5′-end. Probe sequences for \textit{NAT2*5 (T341C)} were as follows: 5′-FAM-CAGGTTGACATTGACGGCAG-BHQ-3′ and 5′-R6G-CAGGTGACCATGACGGCAG-BHQ-3′. The primer sequences for \textit{NAT2*7 (T341C)} were as follows:

\textit{NAT2-RT-R3} GTTTTCTTCTTTGGCAGGAGATGAG
\textit{NAT2-RT-U3} AGCTGGTGATGAATC-BHQ-3

The total volume of the reaction mixture was 8 μl, the mixture contained DNA with a concentration of 15 ng/μl, 300 nM of each primer; 100–200 nM each of Taqman probes conjugated with FAM or R6G; 200 μM dNTPs, amplification buffer (650 mM Tris-HCl, 240 mM (NH₄)₂SO₄, 0.5% Tween 20, 35 mM MgCl₂), thermostable Taq polymerase - 0.5 units/μl/μl. PCR was performed under the following conditions: initial denaturation 5 min at 95 °C; then 48 cycles including denaturation at 95 °C for 10 s, annealing of primers and subsequent elongation at 60 °C for 40 s (each step was accompanied by registration of the fluorescence signal in the ranges corresponding to the fluorescence intervals of FAM and R6G fluorophores). The work was carried out using the amplifier Bio-Rad CFX manager (USA). The obtained data were processed with the help of “CFX manager” software.

**Statistical analysis**

The population frequencies of polymorphic variants were calculated on the basis of the observed genotype

**Informed consent**

From volunteers who were healthy at the time of the study.
Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s12863-020-00909-4.

Additional file 1. Results of genotyping of point substitutions in NAT2 gene. File containing the results of genotyping (individuals genotypes) of point substitutions NAT2*5 (rs 1801280) and NAT2*7 (G857A) is 1799931) by Real-time PCR. The study involved healthy volunteers, representatives of indigenous peoples, Forest Nenets and Tundra Nenets living in Purovsky district of Yamalo-Nenets Autonomous Okrug, Russian Federation, settlement Samburg for the Tundra Nenets and settlements Khar- ampur, Khalyasavey, Tarko-Sale for the Forest Nenets. All research participants gave a written informed consent to the clinical examination and the publication of their anonymous data.

Abbreviations
DNA: Deoxyribonucleic acid; dNTPs: deoxynucleotide triphosphates; NAT: N-acetyltransferase; PCR: Polymerase chain reaction; YaNAO: Yamalo-Nenets Autonomous Okrug; XBS: Xenobiotic biotransformation system

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Authors’ contributions
LO managed and collected the genetics material for the study during the expeditions to the Yamalo-Nenets Autonomous Okrug, interpreted the results and corrected the manuscript. EV and MF developed a method of genotyping NAT2*5 (T341C) and NAT2*7 (G857A) single nucleotide replacements of NAT2 gene. DL interpreted the results and corrected the manuscript. RT worked out literary data, conducted genetic analysis of samples, statistical analysis of data, interpreted the results and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data obtained and analyzed during this study is included in this published article. Individual genotyping data are available at the Novosibirsk State university site (http://fcg.nsu.ru/erv/links/). The data obtained for each of the studied genetic samples are also provided in an Additional file 1.

Ethics approval and consent to participate
The study was conducted using the genetic material of healthy volunteers. Blood sampling of these individuals was carried out according to international WHO rules, using the “Informed consent” and with the approval of Ethics Committee of the Research Institute of Internal and Preventive Medicine – Branch of the Federal State Budget Scientific Institution “The Federal Research Center Institute of Cytology and Genetics” of Siberian Branch of the Russian Academy of Sciences, 17511 Borisa Bogatkovka Street, Novosibirsk 630089, Russia (Protocol No 37–2001). All research participants gave a written informed consent to the clinical examination and the publication of their anonymous data.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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