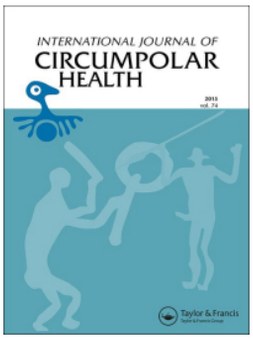

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Prevalence of genetically determined trehalase deficiency in populations of Siberia and Russian Far East

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ABSTRACT

In order to be digested, the disaccharide trehalose needs to be cleaved by the trehalase enzyme. There were reports suggesting that trehalase deficiency was more common in high-latitude than in the temperate climate populations. New horizons were opened for the epidemiologic research of trehalase enzymopathy when it became clear that reduced trehalase activity is determined by the A allele of t*TREH* gene (rs2276064). The aim of this study was to analyze the frequencies of the trehalase gene alleles and genotypes among the indigenous peoples of Siberia and the Russian Far East. We genotyped 567 samples representing the indigenous peoples of Siberia and the Russian Far East and 146 samples representing Eastern Slavs as the reference dataset. We found that the frequencies of the A*TREH alleles increased to the east. The A*TREH allele frequency was 0.03 in the reference group, 0.13-0.26 in the North-West Siberian indigenous populations, 0.29-0.30 in the South Siberia, 0.43 in West Siberia, and 0.46 in the low Amur populations. The highest frequency of the A allele (0.63) was observed in the Chukchi and Koryak populations. From 1 to 5% of European origin individuals are at risk of trehalase enzymopathy. In the indigenous populations, the frequency of the A*TREH allele varies 13% to 63%, whereas the frequency of the *AA*TREH* genotype from 3% to 39%. Thus, the total risk of trehalase enzymopathy among the homo- and heterozygous carriers of the A*TREH allele in the studied indigenous populations may be as high as 24% to 86%.

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Introduction

Growing carbohydrate consumption is a vivid example of "modernization" in the diet of the indigenous peoples of the Russian North. Until the 1930s, sugar was rarely used in their traditional cuisines. Today, the diet of Arctic populations is dominated by purchased foods and is high in refined carbohydrates [1,2]. There is an association between the abrupt transition to a high-carbohydrate diet and an increase in body weight and obesity [3–7], which are now common among the populations of the Russian North [8,9]. Due to some characteristic features of their gene pool, the populations of the Russian Arctic and North are at additional risk for metabolic disorders [10].

The relatively poor availability of sugars to reindeer herders and fishermen who live a traditional lifestyle in boreal woodlands and tundra may have weakened the selection pressure directed towards maintaining the high level of saccharidase production [1]. This hypothesis was confirmed by the increased rates of enzymopathies among the aboriginal populations manifesting as malabsorption of di- and polysaccharides, such as lactose, saccharose, trehalose, and starch [10]. This article focuses on the analysis of the metabolic disorder specific to the indigenous populations of the Russian North and associated with trehalose deficiency.

Known as "mushroom sugar" or mycose, trehalose is found in insect hemolymph, lichens, algae, yeast and higher fungi. The primary natural sources of trehalose for humans are yeast and mushrooms. In the past two decades, trehalose has been widely used in the food industry [11], leading to the increased exposure of humans to "mushroom sugar".

In order to be absorbed into the intestinal wall, the disaccharide trehalose needs to be cleaved into two glucose molecules. Cleavage is performed by the

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enzyme from the β-galactosidase family known as trehalase [12]. Trehalase deficiency (ICD-11 code H02090) belongs to a group of disorders of carbohydrate absorption and transport.

Trehalase deficiency is difficult to diagnose. Its clinical symptoms are very similar to other saccharidase-associated enzymopathies. The severity of symptoms varies depending on the activity of the enzyme and the composition and activity of the patient's microbiota. The main approach to diagnosing trehalase deficiency involves analysis of enzymatic activity in the intestinal villi; villi samples can be obtained only through biopsy [13,14]. Due to the invasive nature of the method, its use is limited in clinical practice and absolutely impossible in population studies. Less aggressive diagnostic methods like trehalose tests to measure blood glucose and breath hydrogen [15,16] are sensitive but not widespread.

As a result, there were very few reports of clinically confirmed trehalase deficiency until recently and data about its prevalence was accumulated at a very slow pace.

Trehalase deficiency was not detected in healthy Caucasian Americans and Danes [15,17]. In another publication, trehalose malabsorption occurred in 0.3% of the UK population [18]. This suggests that trehalose malabsorption is rare among the populations of European descent.

Reports about the significantly higher frequency of trehalase deficiency among the indigenous peoples of Greenland suggested ethnic differences. According to the study by N.G.Asp et al. [19], trehalase activity was low in 2 of 19 Inuit participants. In another study, low trehalase activity was observed in 8% of 97 Greenlanders [15]. In other words, trehalase deficiency is more common among the Greenlandic Inuit than among Europeans by an order of magnitude: 8–10% vs 0.3%, respectively [14,15]. The high prevalence of trehalase deficiency among Greenlanders was initially regarded as a manifestation of some endemic disorder probably caused by the Inuit diet.

Evidence to support this hypothesis was insufficient, but there were arguments favoring the idea about the hereditary nature of trehalase deficiency [17,20–22]. In 2013, the trehalase gene *TREH* was localized to chromosome 11q23 [14]. The G→A substitution in the rs2276064 locus was shown to affect trehalase activity, which is the highest (29.3 IU/g protein) in the carriers of the *GG*TREH* genotype, the lowest (10.2 IU/g) in the AA homozygotes, and moderate in the AG heterozygotes (20.5 IU/g).

Preliminary estimates based on small samples suggest that the frequency of the risk allele rs2276064-A*TREH varies among populations [23–25]. Our earlier studies conducted on sufficiently large samples of Siberian Shors and Komi inhabiting Northwest Russia confirmed that the frequency of the allele differed between these two populations and was higher than in the populations of Western Europe [26].

This gives rise to the hypothesis that trehalose malabsorption is genetically determined and may be widespread among the populations of the indigenous peoples of the Russian North.

The aim of this study was to analyze the frequency of *TREH* alleles and genotypes (rs2276064 *TREH*) in the northern populations of the indigenous peoples of Siberia and the Russian Far East.

Materials and methods

The analysis was conducted using 567 specimens collected from small-numbered indigenous populations of Siberia and the Russian Far East: the Ob Ugrians (Khanty and Mansi; $n = 149$), West Siberian Nenets from the Yamal Peninsula ($n = 120$), Shors ($n = 92$), Tofalars and Tozhu Tuvinians of South Siberia ($n = 53$), Amur Nanai ($n = 48$), East Siberian taiga hunters (Evens and Evenks; $n = 54$), Chukchi and Koryaks of Northern Kamchatka ($n = 51$). The reference dataset was represented by 146 specimens collected from the Eastern Slavic populations of Belarus, European Russia and South Siberia (Russians, Ukrainians and Belarusians) that did not differ in the frequency of A*TREH. In total, 713 samples were included in the analysis. The geography of the included populations and their language families are provided in Figure 1.

The majority of the specimens were provided by the Biobank of North Eurasia and had been initially collected from unrelated individuals whose ancestors from 2 generations, including grandparents, self-identified as a member of the studied indigenous group and descended from the same population. Informed consent had been obtained from every donor. The study was approved by the Ethics Committee of Bochkov Research Center of Medical Genetics (Moscow, Russia).

Genotyping was conducted using an Infinium iSelect HD Custom BeadChip (Illumina, USA) and the iScan platform (Illumina, USA). The microarray was customized to include the marker of trehalase activity and a few other genetic markers associated with certain phenotypes.

The fraction of the successfully called genotypes (CallRate) estimated in Genome Studio was 0.99, suggesting the high quality of genotyping (according to the manufacturer, it should be ≥0.97). The obtained genotyping data were converted into the PLINK format; based on the information about the beadchip design, the data were processed so that substitutions for each marker were described in the 5'->3' direction and the alleles matched those available in genetic databases, such as dbSNP. Then,

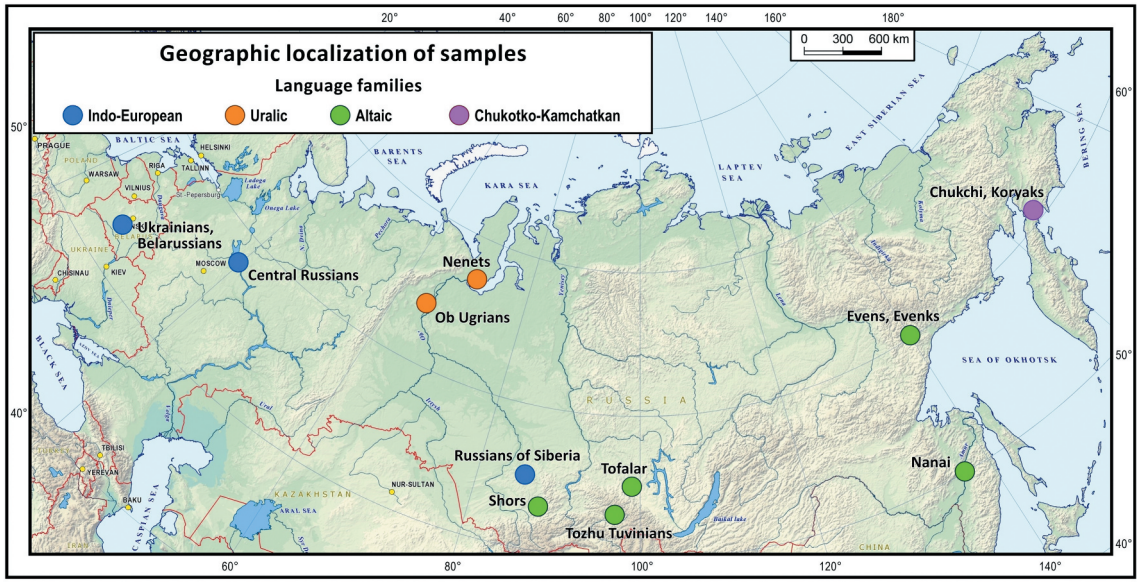

Figure 1. The geographic origin and language families of the studied populations

frequencies of the rs2276064*A allele were calculated for each population using PLINK.

In addition to the samples provided by the Biobank of North Eurasia, we used the specimens representing the Ob Ugrian (Khanty and Mansi) and Nenets populations obtained as part of collaboration research between the Institute and Museum of Anthropology (Moscow State University, MSU) and Kemerovo State Medical University (KemSMU). Informed consent had been obtained from every donor. DNA was extracted from the biological specimens by means of phenol-chloroform extraction. DNA concentration was checked using a NanoDrop 2000C spectrophotometer. Genotyping for rs2276064 was carried out using real-time PCR and a Bio-Rad CFX96 Touch detection system.

Methodological differences between the analysis of Biobank and MSU-KemSMU datasets were insignificant because both real-time PCR and microarray-based genotyping are highly reliable technologies, which was confirmed by good agreement of the obtained allele frequencies.

Computations and data processing were performed in Statistica 8.0 and PLINK 1.9. The maximum likelihood chi-square estimates were used to perform pair-wise comparison of allele frequencies. The *p*-values were adjusted using the Bonferroni method.

Results

Frequencies of the *TREH* alleles and genotypes (rs2276064) in the dataset of small-numbered indigenous peoples of Siberia and the Russian Far East and in the reference dataset represented by Eastern Slavic populations are provided in Table 1.

Intergroup differences in the frequencies of the studied *TREH* alleles are shown in Table 2.

All the analyzed groups, including geographically close Northwest Siberian populations (Ob Ugrians represented by Khanty, Mansi and Nenets), differed significantly in the frequency of the A*TREH allele ($p < 0.001$) from the reference group of Eastern Slavs. No differences in the frequency of the A*TREH allele were observed between the Nenets population and the indigenous peoples of South Siberia (Shors, Tofalars, Tozhu Tuvinians) and between Nenets and the populations of East Siberian taiga (Evens and Evenks). The frequency of the A*TREH allele was higher in the lower Amur populations of Nanai than in Nenets. The highest frequency of the A allele coupled with the low frequency of the G*TREH allele was observed in Chukchi and Koryaks.

Discussion

It would be reasonable to start the discussion by characterizing the reference dataset of ethnic groups that dominate the Russian population. The frequency of the A*TREH allele in this dataset was 0.03 (Table 1). The ratio of the studied homo- to heterozygous genotypes demonstrates that there is 1 *AA*TREH* homozygote (severe trehalose malabsorption) per 3–4 *GA*TREH* heterozygotes (moderately reduced trehalase activity; see Table 1). From the standpoint of

Table 1. The frequencies of the *TREH* alleles and genotypes (rs2276064) in the dataset of small-numbered indigenous peoples of Siberia and the Russian Far East and in the reference dataset represented by Eastern Slavic populations

		Frequencies				
		Alleles		Genotypes		
Group	NN	G	A	GG	GA	AA
Eastern Slavs (reference group)	146	0.97	0.03	0.95	0.04	0.01
Ob Ugrians (Khanty and Mansi)	149	0.87	0.13	0.77	0.21	0.03
Nenets	120	0.74	0.26	0.53	0.43	0.04
Shors	92	0.71	0.29	0.49	0.43	0.08
Tofalars and Tozhu Tuvinians	53	0.70	0.30	0.49	0.42	0.09
Nanai	48	0.54	0.46	0.29	0.50	0.21
Evens and Evenks	54	0.57	0.43	0.28	0.59	0.13
Chukchi and Koryaks	51	0.37	0.63	0.14	0.47	0.39

Table 2. The significance of intergroup differences in the frequency of the A*TREH allele

	Eastern Slavs (reference group)	Ob Ugrians (Khanty and Mansi)	Nenets	Shors	Tofalars and Tozhu Tuvinians	Nanay	Evens and Evenks
Ob Ugrians	0.0001						
Nenets	0.0000	0.0048					
Shors	0.0000	0.0007	NS				
Tofalars and Tozhu Tuvin	0.0000	0.0039	NS	NS			
Nanay	0.0000	0.0000	0.0128	NS	NS		
Evens and Evenks	0.0000	0.0000	NS	NS	NS	NS	
Chukchi and Koryaks	0.0000	0.0000	0.0000	0.0000	0.0001	NS	NS

a gastroenterologist or a nutritionist, this would mean that up to 5% of Russians, Ukrainians and Belarusians are genetically predisposed to trehalose malabsorption. These estimates give insight into the actual prevalence of trehalase deficiency in major Slavic populations of Russia. They are consistent with the results of clinical [15,17] and genetic [23–25] studies conducted in the populations of Caucasian origin from other world's regions.

The frequency of the A*TREH allele increases to the east: from the speakers of Indo-European languages (Russian, Ukrainian, Belarussian) to the speakers of Uralic languages (Khanty, Mansi, Nenets) to the speakers of the Altaic language family (Shors, Tofalars, Nanai, Evens, Evenks) to Chukotko-Kamchatkan populations in the easternmost part of North Eurasia (Koryaks, Chukchi). This pattern agrees with the distribution of the A*TREH allele previously reported for very small samples of 2 to 18 individuals. B.A. Malyarchuk and M.V. Derenko [25] summarized the results of their earlier studies and some published whole-exome sequencing data for various world's populations [23,24]. They found that the A*TREH allele occurred in 0.6% of African populations, in 1.9% of European populations and in 4.4% of South Asian populations. It is reported that the frequency of this allele reaches 31–32% in the populations of Central Asia (Tuvinians, Shors, Yakuts, Buryats) and 58.9% in the populations of the Far North-East (Eskimos, Chukchi, Koryaks) [25]. Clinical data suggest that the prevalence of trehalase deficiency is also high among Greenland Inuit [15]. This adds to the picture of A*TREH geographic distribution.

The populations included in our analysis, except for the reference dataset, were represented by small indigenous peoples living their traditional lifestyle until the first third of the 20th century. Noticeable changes in their lifestyle and diet started in the 1960s; at the turn of the 21st century the diet underwent profound modernization [27]. Specifically, there was a surge in the consumption of carbohydrates, including table sugar and sweets. Using the data accumulated during the Decade of Indigenous Peoples, we were able to estimate disaccharide consumption by the Nenets, Sami and Chukchi in the first decade of the 21st century: 40 kg/year/person vs 36.2 kg/year/person in Russia and Europe in that period [2,28]. Extremely high consumption of sugar and sweets by native Northerners was lately reported in other regions [29].

Importantly, the diversity of consumed sugars also increased. In the 1920s, table sugar (saccharose) was the prevalent disaccharide in the Sami diet; by the end of the 21st century its contribution to the total energy value of consumed foods was almost the same as that of other sweets, including chocolate, soda, desserts, etc [30].. Today, sweets make up one-third of dietary sugars consumed by adolescent and young Nenets: 50 g of 170 g/

day/person of mono- and disaccharides [10]. This means that in times of traditional diet sugars could be properly digested by saccharase alone (or lactose in the case of children), but today the whole complex of enzymes is needed to metabolize one-third to one half of consumed sugars.

Changes in trehalose consumption can be estimated only indirectly from the consumption of mushrooms, the primary source of this disaccharide. According to anthropological reports, the traditional diets of Siberian Yupik, Chukchi and Nenets were free of mushrooms [1]. Reports made by physicians in the first third of the 21st century emphasized that the Kola Sami ate mushrooms on rare occasions and did so reluctantly. Then mushrooms became the object of trade. In 2005, we studied the diet of the indigenous peoples of Kola Peninsula in the Arctic zone and found that the majority of Sami women cooked mushrooms for their families on a regular basis [30]. The same is true for Chukotka. In the 1960s, Chukchi and Siberian Yupik, who had always thought of mushrooms as poisonous devil sticks, started selling them to Russian settlers and later, in the 1970–1980s, added mushrooms to their diet [31].

Ethnographic data suggest that trehalose was introduced to the diet of the Russian North before the 20th century. It is yet to be elucidated to what extent cross-cultural contacts and the increased frequency of the G*TREH allele among the descendants of interethnic marriages between the indigenous peoples of the Russian North and Eastern Slavs contributed to the transformation of the Northern diet.

Before the 21st century, exposure to trehalose was limited because its primary source was mushrooms. As the diversity of sugars in the Western diet was expanding, trehalose consumption was growing. In 1995, trehalose was approved in Japan as a food additive. Since 2000, its use in the American and European food industries has been increasing. Today, mushroom sugar serves as a sweetener to substitute saccharose and has cryoprotective, stabilizing and water-binding properties exploited in meat production [11,12,32].

Such use of trehalose in the food industry is determined by the needs of European consumers. Our study shows that high-latitude populations of indigenous peoples carry the A*TREH allele predisposing to trehalose malabsorption at high frequencies. Trehalose-containing foods can cause abdominal disorders among the carriers of the *GA*TREH* (and especially *AA*TREH*) genotypes. Besides, carriership of the A allele in the rs2276064 locus of the *TREH* gene increases the risk of type 2 diabetes [14].

Conclusion

Clinical research has identified trehalase deficiency as a separate disorder. Until recently the prevalence of trehalose malabsorption in different populations was difficult to estimate due to diagnostic challenges.

The analysis of the population genetics data shows that the risk of abdominal disorders caused by trehalase deficiency is quite high even in the groups of European origin, where this enzymopathy is observed in 1–5% of the population. The frequency of the A*TREH allele responsible for reduced trehalase activity varies from 13% to 63% among the indigenous peoples of Siberia and the Russian Far East, whereas the frequency of the *AA*TREH* genotype varies from 3% to 39%. Thus, the total risk of trehalase enzymopathy among the homo- and heterozygous carriers of the A*TREH allele in indigenous populations may be as high as 24% to 86%.

Our findings suggest that trehalose malabsorption is an underestimated problem that requires attention from gastroenterologists, public health specialists and medical geneticists delivering care to high-latitude populations.

Limitations

The authors recognize the following limitation of this study. Two genotyping procedures that were used in different populations were not cross verified on our material. The question on to what degree the genotype-determined trehalase deficiency comes out clinically needs further elaboration.

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Disclosure statement

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Appendix. The geography of samples

Group	Long (°E)	Lat (°N)
Ob Ugrians (Khanty, Mansi)	65	64
Nenets	71	67
Shors	88	53
Tofalar	99	55
Tozhu Tuvinians	97	53
Nanai	137	50
Evens, Evenks	140	60
Chukchi, Koryaks	165	60
Eastern Slavs (reference group)	55	37