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Polymorphic Variants of Cytokine Genes in Populations of the Arctic Zone of Russia: Predisposition to Diseases [*]

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Abstract. The strategy for the development of the Arctic zone of Russia is primarily aimed at improving the quality of life of the Arctic population, health saving and reducing morbidity. The climatic and geographical conditions of the Arctic zone are extremely uncomfortable for living and cause the development of a number of diseases, as well as the polysyndrome of "northern stress". Moreover, the Arctic population is affected by persistent organic pollutants that enter the body through a traditional diet and contribute to the development of oncological diseases by suppressing the functions of the immune system. Cytokines — proteins encoded by genes with a high degree of polymorphism, responsible for the nature of inflammatory processes, for the effectiveness of defense functions of the body in response to infections and the oncological process development — are one of the main mediators of the immune system. The distribution of polymorphisms in the cytokine genes produced by different types of cells of immune system (rs2069762 *IL2*, rs2243250 *IL4*, rs2069812 *IL5*, rs1800872 *IL10*, rs1800925 *IL13*, rs2275913 *IL17A*, rs7044343 *IL33*) in the populations of Nenets, Dolgan-Nganasans and Slavs was studied. Analysis of the results showed that the frequency of TG and GG genotypes rs2069762 *IL2*, CT genotype rs2243250 *IL4*, CT genotype rs2069812 *IL5*, TG genotype rs1800872 *IL10*, CC genotype rs1800925 *IL13*, GA genotype rs2275913 *IL17A*, CC rs7044343 *IL33* genotype is significantly higher in Arctic populations compared to Slavs, and may be a potential genetic marker of disease development. The studied mutations are associated with the expression level of the corresponding cytokines and their production, which entails changes in the functioning of the cytokine network. It can be concluded that the indigenous inhabitants of the Russian Arctic have genetically determined rapid development of immune reactions, protection to the development of allergic diseases and resistance to the formation of malignant tumours in comparison with Slavs, i.e. the immigrant population.
Keywords: *Arctic, Nenets, Dolgans, inflammation, oncology, cytokines, gene polymorphism*

Introduction

According to the Arctic Council, an interstate organization created to ensure cooperation in environmental protection and sustainable development of circumpolar regions, the Arctic is the territory of eight member countries: Russia, Denmark, Iceland, Canada, Norway, the United States, Finland, and Sweden. The population of the Arctic is about 4 million people, of which indigenous

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peoples make up only about 10% of the total Arctic population. The indigenous peoples include the Saami of the Sápmi region (the circumpolar territories of Finland, Sweden, Norway, and Russia), the Aleut, Inupiat (Inuit), and Yupik in Alaska, the Inuvialuit (Inuit) in Canada, the Kalaalit (Inuit) in Greenland, and many others [1].

The Arctic zone of the Russian Federation (AZRF) includes all districts of Murmansk Oblast, Nenets, Yamalo-Nenets and Chukotka Autonomous okrugs, 6 municipalities of the Republic of Karelia, 4 districts of the Komi Republic and Krasnoyarsk Krai, 9 municipalities of Arkhangelsk Oblast and 13 districts of the Republic of Sakha (Yakutia). The Russian Arctic is home to 2.5 million inhabitants, including 82.5 thousand representatives of indigenous peoples: Nenets, Chukchi, Khanty, Evens, Evenki, Selkups, Sami, Eskimos, Dolgans, Chuvans, Kets, Nganasans, Yukaghirs, Enets, Mansi, Veps, Koryaks, Itelmens, Kereks [2]. Indigenous communities of the Russian Arctic make up a minority of the population of Murmansk Oblast, Nenets Autonomous Okrug and Yamalo-Nenets Autonomous Okrug, while the overwhelming majority of the inhabitants of these areas are Slavic migrants who came to work in various sectors of the extractive industry.

The topic of environmental change has become extremely relevant today due to its direct and indirect impact on living organisms, including humans. The population of the Arctic is in dire need of increased adaptation and preservation of mental and physical health. Due to the high level of potential for successful economic development of the Arctic zones of the Russian Federation, it is necessary to study the characteristics of disease susceptibility of the Arctic communities in order to protect their health and increase the potential of the AZRF.

Climatic and geographic conditions of living in the Arctic and specific features of disease development among Arctic residents

The Arctic zone is characterized by extremely uncomfortable living conditions. The combination of unfavorable climatic and geographic factors of the Arctic regions is the cause of development of the polysyndrome of “northern stress”, the pathogenesis of which includes immune deficiency, blood hypercoagulation, homeostasis disorders and much more [1, Reis Zh., Zaitseva N.V., Spencer P., pp. 21–38; 2, Khasnulin V.I., Khasnulin P.V., pp. 3–11]. In addition, there is a “latitude syndrome”, first described in 1991 by Gundarov and Zilbert, which means an increase in morbidity and mortality rates as countries are distanced from the equator [3, Solonin Yu. G., pp. 228–239].

Human body in the Arctic is affected by low temperature, geomagnetic field fluctuations, and photoperiodic changes [4, Tereshchenko P. S., Petrov V. N., pp. 145–150]. The population of the Arctic regions faces accelerated ageing processes and increased morbidity of infectious and chronic diseases [5, Nikanov A. N., Dorofeev V. M., Talykova L. V., Sturlis N. V., Gushchin I. V., pp.

[1] Arctic Review. Indigenous Peoples in the Arctic. URL: https://arctic.review/people/indigenous-peoples/ (accessed 23 June 2023).

[2] Tishkov V. Korennye narody rossiyskoy Arktiki: istoriya, sovremennyy status, perspektivy [Indigenous peoples of the Russian Arctic: history, current status, prospects]. URL: https://russiancouncil.ru/analytics-and-comments/comments/korennye-narody-rossiyskoy-arktiki-istoriya-sovremennyy-stat/ (accessed 23 June 2023).

20–27]. Changes in ambient temperature cause changes in human body temperature as a result of fluctuations in heat exchange processes. Strong winds can act as a factor provoking the development of hypertensive crises and cerebrovascular disorders, while high humidity can cause exacerbations of respiratory diseases [1, Reis J., Zaitseva N.V., Spencer P., pp. 21–38]. Fluctuations in the geomagnetic field and atmospheric pressure cause changes in blood pressure and, as a consequence, disorders of the cardiovascular system [1, Reis J., Zaitseva N.V., Spencer P., pp. 21–38].

In addition, due to the polar night in the North, the human body is subject to disruption of circadian rhythms, which leads to disruption of the sleep-wake cycle. This is due to the lack of natural production of melatonin, the main hormone of the pineal gland (epiphysis), which performs antioxidant activity and regulates circadian rhythms. The pathogenesis of many diseases affecting Arctic residents (for example, bronchial asthma, chronic obstructive pulmonary disease (COPD), etc.) includes the production of reactive oxygen intermediates (ROI) and, accordingly, the development of oxidative stress. There are reasons to assume that melatonin is one of the pathogenetic components of a wide range of diseases (arterial hypertension, coronary pathology, etc.) [4, Tereshchenko P.S., Petrov V.N., pp. 145–150].

Melatonin treatment of animals that were infected with respiratory syncytial virus (RSV), leading to the development of bronchiolitis, contributed to the reduction of ROI generation and normalization of superoxide dismutase and glutathione levels in the lungs [6, Carrillo-Vico A., Lardone P.J., Alvarez-Sánchez N., Rodríguez-Rodríguez A., Guerrero J.M., pp. 8638–8683]. Studies devoted to the relationship between melatonin and immunity show that increased doses of this hormone cause resistance of living organisms to the development of infectious and viral diseases [7, Bonilla E., Valero-Fuenmayor N., Pons H., Chacín-Bonilla L., pp. 430–434]. Thus, residents of the Arctic territories have a greater susceptibility to a number of diseases due to the short daylight hours.

In addition, the role of melatonin in modulating the immune response and its ability to influence cytokine production has been shown [8, Lin G.J., Huang S.H., Chen S. J., Wang C.H., Chang D.M., Sytwu H.K., pp. 11742–11766]. Melatonin treatment of patients infected with the highly pathogenic influenza A virus leads to a decrease in the population of CD4+ Th1 lymphocytes, an increased expression of the anti-inflammatory cytokine IL-10, and suppression of TNF-α production by CD8+ T cells [9, Silvestri M., Rossi G.A., p. 61]. In addition, melatonin has been shown to weaken the development of cytokine storm in COVID-19 and to promote an adaptive immune response.

Depending on the region, people living in the North suffer from metabolic disorders, expressed in increased concentrations of creatinine, malondialdehyde (MD) and lactate in blood [3]. Elevated blood creatinine level indicates decreased renal function or chronic kidney damage [10, Tremblay R., pp. 735–740]. Endogenous MD acts as a marker of oxidative stress; its increased lev-

[3] Federation Council. Problems of the North and Arctic of the Russian Federation. URL: http://council.gov.ru/media/files/41d44f243cef107baf4f.pdf (accessed 09 June 2023).

els are observed in lung cancer and chronic kidney pathologies [11, Moreto F., de Oliveira E.P., Manda R.M., Burini R.C., pp. 505–368]. The increased level of lactate in the blood of people living in the Arctic zone leads to the development of lactacidosis, which contributes to a decrease in tissue oxygen supply, which, in turn, adversely affects the saturation of cells with oxygen and leads to a decrease in their functional activity. Disorders of metabolic processes lead to the development of diseases such as hypertension, dementia, oncology, polycystic ovaries, type 2 diabetes, non-alcoholic fatty liver disease, etc., which in turn leads to a reduction in working age and increased mortality [12, Guerrero R.B., Salazar D., Tanpaiboon P., p. 470].

The Arctic Monitoring and Assessment Program (AMAP) reports summarize the results of studies of persistent organic pollutants (POPs) in circumpolar regions. The impact of POPs on the human body is studied in different areas of the Russian Arctic (Murmansk and Kamchatka oblasts, Chukotka, Nenets, and Taimyr Autonomous okrugs), northern regions of Norway, Finland, Sweden, Canada, Greenland, and the Faroe Islands [3, Solonin Yu.G., pp. 228–239]. In addition to the uncomfortable climatic and geographical parameters, the population of the Arctic is exposed to persistent organic pollutants and metals. Some sources of pollution are local (e.g., mining), but most of the contaminating substances enter the Arctic zone through the transfer of air and ocean currents. POPs, compounds resistant to degradation by photolytic, biological, and chemical processes, include industrial chemicals, some solvents, pharmaceutical products, pesticides, and insecticides [4].

Due to the behavioral characteristics of indigenous peoples, there are several routes for pollutants to enter the body. First, the indigenous population of the Arctic eats marine mammals as a component of traditional and national diets and is therefore exposed to contaminants that, as a result of bio-magnification, accumulate and concentrate in the tissues of organisms as they move through food webs [5] [13, Dudarev A.A., Odland J.O., p. 11951]. Second, the consumption of raw water, which can be a source of chemical and biological pollution, is widespread in the Arctic regions. Thus, the food preferences and traditional way of life of Arctic peoples contribute to the penetration of pollutants of various types into the body, including POPs. It has been proven that POPs have a negative effect on the organs of living organisms, contributing, among other things, to suppression of the immune system, development of neuroendocrine disorders and reduction of bone density [6] [6, Carrillo-Vico A., Lardone P.J., Alvarez-Sánchez N., Rodríguez-Rodríguez A., Guerrero J.M., p. 8638–8683]. In the traditional diet of residents of the Arctic regions, the proportion of fats is up to 85% of the total caloric content, which causes a high level of ketogenesis, at which there is no need for high activity of enzymes that catalyze the oxidation of fatty acids. The indige-

[4] Secretariat of the Stockholm Convention. Stockholm Convention. URL: https://www.pops.int/default.aspx (accessed 14 June 2023).
[5] Arctic Monitoring and Assessment Programme. AMAP and the Arctic Council. URL: https://www.amap.no/ (accessed 09 June 2023).
[6] Permafrost thaw: it's complicated.
URL: https://www.esa.int/Applications/Observing_the_Earth/FutureEO/Permafrost_thaw_it_s_complicated (accessed 15 June 2023).

nous peoples of the Arctic are characterized by the presence of the P479L mutation in the carnitine palmitoyltransferase 1A (PT1A) gene, which is a protective factor against excessively high levels of fatty acid oxidation under conditions of excess fat intake. However, in modern conditions, when the diet of the indigenous peoples of the Arctic has changed in the direction of increasing carbohydrates and decreasing fats, the described protective mechanism in combination with infections can lead to hypoketonemic hypoglycemia with a high risk of infant mortality [14, Tereshchenko S.Y., Smolnikova M.V., pp. 145–149]. In addition, the authors of several studies have found that carriers of this mutation are characterized by a severe course of various infections, obesity, type 2 diabetes, and complicated course of pregnancy [15, Gessner B.D., Wood T., Johnson M.A., Richards C.S., Koeller D.M., pp. 933–939].

It is obvious from the above that there are differences in the level of morbidity between the inhabitants of the Arctic zone of the Russian Federation and the population of the middle zone. For example, it has been found that residents of Apatity and Kirovsk, Murmansk Oblast, located above the Arctic Circle, have a 2.4–2.6 times higher incidence of diseases of the genitourinary system than residents of Serpukhov, Moscow Oblast, which belongs to the middle zone of Russia [4, Tereshchenko P.S., Petrov V.N., pp. 145–150]. This group of diseases mainly includes inflammatory processes of the reproductive system and kidneys.

Factors influencing inflammation and immune system of the Arctic population

Inflammation is a genetically programmed response of the body to various injuries. The development of inflammation is localized, but many organ systems are involved, mainly the immune and neuroendocrine systems.

The course of inflammatory processes has specific features in the Arctic population. For example, the destructive processes (necrotic changes, cell death) predominate, resulting in an increase in the duration of diseases and a more frequent transition to the chronic stage. Respiratory diseases (functional changes in the respiratory system, bronchial asthma) common among residents of the North are characterized by more frequent exacerbations, high risk of developing respiratory insufficiency (RI) and “pulmonary heart disease” than the average in the Russian Federation [5, Nikanov A.N., Dorofeev V.M., Talykova L.V., pp. 20–27].

Unfavorable environmental factors, to which Arctic residents are exposed, contribute to a decrease in the functions of the organism, leading to an increased risk of diseases, which, among other things, are caused by the state of the immune system. Photoperiodicity characteristic of the Arctic regions causes significant changes in the parameters of the immune system. During the polar day, there is a sharp increase in phagocytic activity and antibody formation, which causes abnormally high levels of serum immunoglobulins and their complexes, which, in turn, increases the risk of developing pathologies of the cardiovascular and bronchopulmonary systems. On the contrary, during the polar night, there is a sharp decrease in the level of T-lymphocytes, phagocytic defense and erythropoiesis. In addition, during the polar night, residents of the Arctic regions have high concentrations of autoantibodies and circulating immune complexes compared to normal. The most significant increase in autoantibodies is in relation to DNA, cardiolipin, phospholipids and autohemagglutinins [16, Potutkin D.S., Tipisova E.V., Devyatova E.N., Popkova V.A., Lobanov A.A., Andronov S.V., Popov A.I., pp. 179–184].

Due to human habitation in high-latitude conditions, deviations from normal values are observed in the blood system, such as anemia due to iron deficiency and a decrease in the number of leukocytes, resulting in increased susceptibility to infectious diseases (viral hepatitis, chlamydia, tuberculosis, etc.). This disruption of the immune system in the population of the North causes the development of functional immunodeficiency, in which there is a decrease in the number of T-helpers and T-suppressors by 10–15% [7].

According to research by the Arctic Council Working Group, various pollutants — metals, POPs, perfluoroalkyl and polyfluoroalkyl compounds (PFAC) — can have immunosuppressive effects on the immune system, including an increased risk of developing pathological conditions such as allergies, bronchial asthma and other chronic diseases associated with inflammation. In addition, exposure to PFAC can reduce the effectiveness of tetanus and diphtheria vaccines, indicating a general weakening of the immune system.

It has been shown that ultradisperse particles in the air have an effect on inflammatory processes in the body. In particular, they have the ability to produce reactive oxygen species when interacting with cells of living organisms, which leads to the formation of pro-inflammatory cytokines (IL-1, IL-6, IL-12, IL-8, interferons, chemokines, etc.), which effectively destroy pathogens as a result of the development of an inflammatory response [8].

Significant fluctuations in cellular content and, consequently, in the functioning of the immune system lead to an increase in the incidence of infectious, oncological and autoimmune profiles. In particular, an imbalance in the level of cytokines — proteins secreted by cells of the immune system that ensure intercellular interactions — leads to the failure of inflammatory reactions and a prolonged course of diseases.

Cytokines play one of the main roles in the immune system and the development of the inflammatory process, the level of these proteins and the patterns of their functioning are genetically determined.

Cytokine genes are characterized by polymorphism associated with a change in the level of expression, and, accordingly, the level of protein production, reflecting, among other things, the presence of inflammatory processes in the body. Single nucleotide polymorphisms (SNP) in the

[7] Ovechkina E., Ovechkin F. Human Pathophysiology in the Conditions of North Russia. URL: https://papers.ssrn.com/abstract=3930766 (accessed 09 June 2023).

[8] Dyadik V.V., Masloboev V.A., Nikanov A.N. Otsenka vliyaniya promyshlennogo zagryazneniya atmosfernogo vozdukha mikrochastitsami na zdorov'e naseleniya Arkticheskogo regiona (na primere Murmanskoy oblasti) [Assessment of the impact of industrial air pollution by microparticles on the health of the population of the Arctic region (on the example of the Murmansk Oblast)]. URL: https://rio.ksc.ru/data/documents/dyadik-2022.pdf (accessed 09 June 2023).

regulatory regions of cytokine genes are widely distributed, affecting the production and functioning of the protein.

The distribution of cytokine polymorphisms differs in different populations of the world; therefore, studying the prevalence of polymorphic variants of cytokine genes is relevant in order to be able to predict the development and course of diseases in a certain population.

In this regard, the aim of this work was to study the distribution of allelic variants and genotypes of cytokine genes produced by various cells of the immune system (*IL2, IL4, IL5, IL10, IL13, IL17A, IL33*) in populations of the Russian Arctic (Nenets, Dolgan-Nganasans).

Materials and methods

The sample of representatives of populations of the Arctic territories of Krasnoyarsk Krai and the city of Krasnoyarsk consisted of 454 specimens, of which 171 specimens were obtained from residents of villages with a predominantly Nenets population; 112 — from residents of villages with a predominantly Dolgan-Nganasan population; 171 — from newborns of the city of Krasnoyarsk, Slavic origin. DNA was isolated from dry blood spots using the sorbent method. Genotyping of single nucleotide polymorphisms in the promoter regions of cytokine genes (rs2069762 of the *IL2* gene, rs2243250 of the *IL4* gene, rs2069812 of the *IL5* gene, rs1800872 of the *IL10* gene, rs1800925 of the *IL13* gene, rs2275913 of the *IL17A* gene) and in intron 5 (rs7044343 of the *IL33* gene) was performed using the real-time PCR method on a Rotor-Gene 6000 device (Qiagen, Germany) and fluorescent probes (DNA-Synthesis LLC, Russia).

The study was approved by the Ethics Committee of the Research Institute of Medical Problems of the North (No. 9 dated September 8, 2014). Informed consent for participation in the study was obtained from the parents or legal representatives of all participants.

Comparison of the frequencies of alleles and genotypes between the groups was performed using an online calculator (https://medstatistic.ru/). Conformity of genotype frequencies to Hardy-Weinberg equilibrium was tested using $\chi 2$. Differences were considered statistically significant at $p < 0.05$.

Results

The analysis of genotype and allele frequencies of the rs2069762 polymorphism of the *IL2* gene showed that the heterozygous genotype TG is more frequent in the Nenets population relative to the Slavs (59.1% versus 43.3%). The homozygous genotype GG of the studied polymorphism is most common in the Dolgan-Nganasan and Nenets populations compared to the Slavs (26.8% and 19.9% versus 11.1%). The frequency of the minor allele G of the studied polymorphism in the Nenets and Dolgan-Nganasans is consistent with the frequency of prevalence in the population of South Asians according to the ensemble.org resource (49.4%, 51.8% and 50.0%, respectively), and in the Krasnoyarsk population — with the world population of Caucasians (32.7% and 29.0%, respectively) (Table 1).

It was found that the frequency of occurrence of the CT genotype of the rs2243250 polymorphism of the *IL4* gene is lower in Slavs than in Nenets and Dolgan-Nganasans (36.3% versus 54.4% and 55.4%, respectively). It was revealed that the homozygous TT genotype of the studied polymorphism is less common in Slavs than in Nenets and Dolgan-Nganasans (7.0% versus 25.7% and 23.2%).

Table 1

Frequency of genotypes and allelic variants of the studied polymorphisms for different populations [9]

Genotype/ allele	Nenets *n* = 171 (1)	Dolgan-Nganasans *n* = 112 (2)	Slavs *n* = 171 (3)	Caucasians *n* = 503 (a)	East Asia *n* =504 (b)	South Asia *n* =489 (c)	*p*	χ^2
rs2069762 (*IL2*)								
TT**	21.0 (36)	23.2 (26)	45.6 (78)	49.0 (245)	46.0 (231)	23.9 (117)	1.3<0.001; 2.3<0.001; 1a<0.001; 2a<0.001; 1b<0.001; 2b<0.001; 3c<0.001;	1.2=0.18; 1.3=23.21; 2.3=14.60;
TG	59.1 (101)	50.0 (56)	43.3 (74)	44.0 (222)	44.0 (221)	52.2 (255)	1.3=0.004; 1a<0.001; 1b<0.001; 3c=0.046;	1.2=2.25; 1.3=8.53; 2.3=1.23;
GG	19.9 (34)	26.8 (30)	11.1 (19)	7.0 (36)	10.0 (52)	23.9 (117)	1.3=0.026; 2.3<0.001; 1a<0.001; 2a<0.001; 1b=0.002; 2b<0.001; 3c<0.001;	1.2=1.84; 1.3=5.02; 2.3=11.61;
T	50.6 (173)	48.2 (108)	67.3 (230)	71.0 (712)	68.0 (683)	50.0 (489)	1.3<0.001; 2.3<0.001; 1a<0.001; 2a<0.001; 1b<0.001; 2b<0.001; 3c<0.001;	1.2=0.30; 1.3=19.62; 2.3=20.39;
G*	49.4 (169)	51.8 (116)	32.7 (112)	29.0 (294)	32.0 (325)	50.0 (489)		
rs2243250 (*IL4*)								
CC	19.9 (34)	21.4 (24)	56.7 (97)	70.0 (353)	4.0 (21)	68.1 (333)	1.3<0.001; 2.3<0.001; 1a<0.001; 2a<0.001; 3a=0.002; 1b<0.001; 2b<0.001; 3b<0.001; 1c<0.001; 2c<0.001; 3c=0.008;	1.2=0.09; 1.3=49.11; 2.3=34.45;
CT	54.4 (93)	55.4 (62)	36.3 (62)	26.0 (131)	36.0 (181)	27.0 (132)	1.3<0.001; 2.3=0.002; 1a<0.001; 2a<0.001; 3a=0.011; 1b<0.001; 2b<0.001; 2c<0.001; 3c=0.023;	1.2=0.03; 1.3=11.34; 2.3=10.03;

[9] Note: The sign "*" denotes a rare allele. Only results with p<0.05 are shown. The sign "**" denotes genotypes, carriers of which, according to literature data, have increased cytokine production.

TT**	25.7 (44)	23.2 (26)	7.0 (12)	4.0 (19)	60.0 (302)	4.9 (24)	1.3<0.001; 2.3<0.001; 1a<0.001; 2a<0.001; 3a=0.081; 1b<0.001; 2b<0.001; 3b<0.001; 1c<0.001; 2c<0.001;	1.2=0.23; 1.3=21.87; 2.3=15.27;
C	47.1 (161)	49.1 (110)	74.9 (256)	83.0 (837)	22.0 (223)	82.0 (798)	1.3<0.001; 2.3<0.001; 1a<0.001; 2a<0.001; 2a<0.001; 1b<0.001; 2b<0.001; 3b<0.001; 1c<0.001; 2c<0.001; 3c=0.008;	1.2=0.22; 1.3=55.44; 2.3=39.27;
T*	52.9 (181)	50.9 (114)	25.1 (86)	17.0 (169)	78.0 (785)	18.0 (180)		
rs2069812 (*IL5*)								
CC**	36.8 (63)	22.3 (25)	56.2 (96)	47.9 (241)	9.7 (49)	48.9 (239)	1.3<0.001; 2.3<0.001; 1a=0.012; 2a<0.001; 1b=0.001; 2b<0.001; 3b<0.001; 1c=0.007; 2c<0.001;	1.2=6.66; 1.3=12.80; 2.3=31.62;
CT	46.8 (80)	52.7 (59)	33.9 (58)	41.4 (208)	44.5 (224)	41.1 (201)	1.3=0.016; 2.3=0.003; 2a=0.029; 3b=0.016; 2c=0.026;	1.2=0.94; 1.3=5.88; 2.3=8.87;
TT	16.4 (28)	25.0 (28)	9.9 (17)	10.7 (54)	45.8 (231)	10.0 (49)	2.3<0.001; 2a<0.001; 3a=0.771; 1b<0.001; 2b<0.001; 3b<0.001; 1c=0.026; 2c<0.001;	1.2=3.17; 1.3=3.09; 2.3=11.48;
C	60.2 (206)	48.7 (109)	73.1 (250)	69.0 (690)	32.0 (322)	69.0 (679)	1.2=0.007; 1.3<0.001; 2.3<0.001; 1a=0.005; 2a<0.001; 1b<0.001; 2b<0.001; 3b<0.001; 1c=0.002; 2c<0.001; 3c=0.201;	1.2=7.34; 1.3=12.74; 2.3=34.85;
T*	39.8 (136)	51.3 (115)	26.9 (92)	31.0 (316)	68.0 (686)	31.0 (299)		
rs1800872 (*IL10*)								
GG**	42.7 (73)	25.9 (29)	57.3 (98)	57.9 (291)	10.0 (50)	30.6 (149)	1.2=0.005; 1.3=0.007; 2.3<0.001; 1a<0.001; 2a<0.001; 3a=0.902; 1b<0.001; 2b<0.001; 3b<0.001; 1c=0.004; 3c<0.001;	1.2=8.28; 1.3=7.31; 2.3=27.00;
TG	44.4 (76)	47.3 (53)	35.1 (60)	36.4 (183)	45.0 (227)	42.2 (232)	2.3=0.040; 2a=0.032; 3b=0.023; 3c=0.006;	1.2=0.23; 1.3=3.12; 2.3=4.22;

TT	12.9 (22)	26.8 (30)	7.6 (13)	5.7 (29)	45.0 (227)	22.2 (108)	1.2=0.004; 2.3<0.001; 1a=0.003; 2a<0.001; 1b<0.001; 2b<0.001; 3b<0.001; 1c=0.010; 3c<0.001;	1.2=8.74; 1.3=2.58; 2.3=19.33;
G	64.9 (222)	49.6 (111)	74.9 (256)	76.0 (765)	32.0 (327)	54.0 (530)	1.2<0.001; 1.3=0.005; 2.3<0.001; 1a<0.001; 2a<0.001; 1b<0.001; 2b<0.001; 3b<0.001; 1c<0.001; 3c<0.001;	1.2=13.18; 1.3=8.03; 2.3=38.00;
T*	35.1 (120)	50.4 (113)	25.1 (86)	24.0 (241)	68.0 (681)	46.0 (448)		
rs1800925 (*IL13*)								
CC	67.2 (115)	67.8 (76)	50.3 (86)	68.4 (344)	66.3 (334)	63.8 (312)	1.3=0.002; 2.3=0.004; 3a<0.001; 3b<0.001; 3c=0.002;	1.2=0.01; 1.3=10.15; 2.3=8.53;
CT	32.2 (55)	25.9 (29)	42.7 (73)	27.6 (139)	31.9 (161)	32.3 (158)	1.3=0.045; 2.3=0.005; 3a<0.001; 3b=0.011; 3c=0.015;	1.2=1.27; 1.3=4.04; 2.3=8.28;
TT	0.6 (1)	6.3 (7)	7.0 (12)	4.0 (20)	1.8 (9)	3.9 (19)	1.2=0.005; 1.3=0.002; 1a=0.028; 2b=0.008; 3b<0.001; 1c=0.031; 3c=0.096;	1.2=7.91; 1.3=9.67; 2.3=0.06;
C	83.3 (285)	80.8 (181)	71.6 (245)	82.2 (827)	82.2 (829)	80.0 (782)	1.3<0.001; 2.3=0.014; 3a<0.001; 3b<0.001; 3c=0.002;	1.2=0.59; 1.3=13.41; 2.3=6.11;
T*	16.7 (57)	19.2 (43)	28.4 (97)	17.8 (179)	17.8 (179)	20.0 (196)		
rs2275913 (*IL17A*)								
GG	43.3 (74)	48.2 (54)	49.7 (85)	38.8 (195)	25.6 (129)	40.7 (199)	3a=0.013; 1b<0.001; 2b<0.001; 3b<0.001; 3c=0.041;	1.2=1.09; 1.3=1.42; 2.3=0.06;
GA	48.5 (83)	45.5 (51)	36.8 (63)	46.5 (234)	50.2 (253)	42.5 (208)	1.3=0.029; 3a=0.028; 3b=0.003;	1.2=0.24; 1.3=4.78; 2.3=2.12;
AA**	8.2 (14)	6.3 (7)	13.5 (23)	14.7 (74)	24.2 (122)	16.8 (82)	1a=0.029; 2a=0.017; 1b<0.001; 2b<0.001; 3b=0.004; 1c=0.007; 2c=0.005;	1.2=0.37; 1.3=2.45; 2.3=3.70;
G	67.5 (231)	71.0 (159)	68.1 (233)	62.0 (624)	50.7 (511)	62.0 (606)	2a=0.012; 3a=0.043; 1b<0.001; 2b<0.001; 3b<0.001; 2c=0.012; 3c=0.042;	1.2=0.75; 1.3=0.03; 2.3=0.52;
A*	32.5 (111)	29.0 (65)	31.9 (109)	38.0 (382)	49.3 (497)	38.0 (372)		
rs7044343 (*IL33*)								

CC**	33.3 (57)	21.4 (24)	11.1 (19)	12.7 (64)	19.0 (97)	18.8 (92)	1.2=0.031; 2.3=0.019; 1a<0.001; 2a=0.002; 1b<0.001; 3b=0.015; 1c<0.001; 3c=0.021;	1.2=4.69; 1.3=1.42; 2.3=5.59;
CT	52.6 (90)	57.2 (64)	55.6 (95)	47.9 (241)	49.0 (248)	47.3 (231)	1a=0.004; 3a<0.001; 3a<0.001;	1.2=0.55; 1.3=0.29; 2.3=0.07;
TT	14.1 (24)	21.4 (24)	33.3 (57)	39.4 (298)	32.0 (159)	33.9 (166)	1.2=0.041; 1.3<0.001; 2.3<0.001; 1a<0.001; 2a<0.001; 3a<0.001; 1b<0.001; 2b=0.035; 1c<0.001; 2c=0.011;	1.2=4.20; 1.3=17.62; 2.3=28.36;
C	59.6 (204)	50.0 (112)	38.9 (133)	36.7 (369)	43.8 (442)	42.0 (415)	1.2=0.024; 1.3<0.001; 2.3=0.010; 1a<0.001; 2a<0.001; 1b<0.001; 1c<0.001; 2c=0.040;	1.2=5.11; 1.3=29.48; 2.3=6.81;
T*	40.4 (138)	50.0 (112)	61.1 (209)	63.3 (637)	56.2 (566)	58.0 (563)		

It was shown that the frequency of occurrence of the heterozygous genotype CT of the polymorphic variant rs2069812 of the *IL5* gene is lower in Slavs than in Nenets and Dolgan-Nganasans (33.9% versus 46.8%, p=0.016 and 52.7%, p=0.003). The frequency of homozygous genotype TT in Dolgan-Nganasans is higher compared to Slavs (25.0% versus 9.9%, p>0.001). It was shown that the rare T allele of the studied polymorphism in Krasnoyarsk Slavs is comparable with the world population of Caucasians (26.9% and 31.0%, respectively).

In our study it was revealed that the heterozygous TG genotype of the rs1800872 polymorphism of the *IL10* gene is more common in the Dolgan-Nganasan population compared to the Slavs (47.3% versus 35.1%, p=0.040). It was found that the homozygous TT genotype of the studied polymorphism is more common in the Dolgan-Nganasan compared to the other populations studied (26.8%, p>0.005). It was shown that the frequency of the minor T allele of the studied polymorphism in the Slavs is consistent with the world population of Caucasians (25.1% and 24.0%, respectively).

The CT genotype of the rs1800925 polymorphic locus of the *IL13* gene is more common among the Slavs compared to the Nenets and Dolgan-Nganasans (42.7% versus 32.2%, p=0.045 and 25.9%, p=0.005, respectively). It was revealed that the homozygous TT genotype is less common among the Nenets compared to the Dolgan-Nganasans and Slavs (0.6% versus 6.3%, p=0.005 and 7.0%, p=0.002, respectively). The frequency of the rare T allele of the studied polymorphism among the Nenets and Dolgan-Nganasans is consistent with the frequency of prevalence in the population of East Asians according to the ensemble.org resource (16.7%, 19.2% and 17.8%, respectively).

Differences in the frequency of heterozygous genotype GA of the rs2275913 polymorphism of the *IL17A* gene were revealed: this genotype is more common among the Nenets than among the Slavs (48.5% versus 36.8%, p=0.029). It was shown that the frequency of the rare G allele of the studied polymorphism in the Nenets correlates with the frequency of prevalence in the population of South Asians according to the ensemble.org resource (32.5% and 38.0%, respectively), and in the Krasnoyarsk population — with the world population of Caucasians (31.9% and 38.0%, respectively).

It was found that the TT genotype of the rs7044343 polymorphism of the *IL33* gene is more common among the Slavs than among the other populations studied in the work (33.3%, p=0.005). The frequency of the rare T allele of the studied polymorphism in the Dolgan-Nganasans is consistent with the frequency of prevalence in the population of East Asians according to the ensemble.org resource (50.0% and 56.2%, respectively), and in the Slavs of Krasnoyarsk — with the world population of Caucasians (61.1% and 63.3%, respectively).

Discussion

Residents of the Arctic regions are exposed daily to various climatic and photoperiodic changes, geomagnetic storms and accompanying phenomena. As a result of risk factors specific to the Arctic regions, including POPs, their inhabitants experience impaired immune control of the internal environment, increased risk of tumour development and accelerated chronicity of certain inflammatory processes. It is noted that the native inhabitants of Alaska and the circumpolar region of Nunavik are more susceptible to infection (with subsequent hospitalization) with the respiratory syncytial virus compared to other populations of the USA and Canada. This virus causes acute damage to the lower respiratory tract in the form of rapidly developing broncholithiasis and pneumonia [17, Gilca R., Billard M.N., Zafack J., pp. 101–180].

A high prevalence of Helicobacter pylori infection was found among the northern aborigines of Canada compared to populations in the non-Arctic regions of Canada, the United States, and Russia. The authors note that these populations should be included in the list of ethnic groups with an increased risk of H.pylori infection. Besides, northern aborigines have high resistance to a number of antibiotics, which prevents effective therapy and leads to the development of gastric and duodenal ulcers, and subsequently to cancer [18, Goodman K.J., Jacobson K., Veldhuyzen van Zanten S., pp. 289–295].

The life expectancy of some Arctic peoples is much lower than of other peoples of the world. For example, residents of the Inuit Nunangat (Canada) live 11 years less than other Canadians, and half of deaths are due to cancer. The incidence of some types of cancer is critically high among all circumpolar Inuit living in Canada, Alaska and Greenland [19, Circumpolar Inuit Cancer Review Working Group, Kelly J., Lanier A., Santos M., pp. 408–420]. In addition, the highest incidence of lung and bronchial cancer occurs among the indigenous peoples of the Arctic in the eight Arctic Council member states [20, Young T.K., Kelly J.J., Friborg J., Soininen L., Wong K.O., pp. 297–87]. Nasopharyngeal cancer (NPC) among women in Inuit Nunangat is 4 times higher than the incidence among women in the rest of Canada.

Nevertheless, according to scientists in Norway and Sweden, the Saami population has a low incidence of cancer, regardless of ethnicity, compared to other populations in Norway, Sweden, Denmark, and Russia [21, Hassler S., Sjölander P., Grönberg H., Johansson R., Damber L., pp. 273–280]. Finnish scientists came to the same conclusion, having identified a low incidence of cancer among the Sami compared to the Skolts, whose data were close to the national average [22, Soininen L., Järvinen S., Pukka-la E., pp. 342–346]. It is important to note that in the northern regions of Russia, cancer incidence is less pronounced than in other regions of the Russian Federation. According to the data for 2020, provided by the Ministry of Health of Russia, none of the regions of the Russian Arctic was included in the list of territories with a high level of cancer, and Yamalo-Nenets Autonomous Okrug was included in the list of regions with the lowest level of cancer incidence [10]. However, the detection rates of oncological diseases at stages I and II remain low. Nevertheless, the FSBI "Centre for Strategic Planning" of the Federal Medical and Biological Agency of Russia, according to 2016–2019 data, notes a high incidence of oncological diseases of the digestive system among residents of the northern territories of the Russian Federation, the largest number is in the Chukotka Autonomous Okrug [23, German S.V., Bobrovnitskiy I.P., Balakaeva A.V., pp. 525–530].

Most human diseases are associated with the development of an inflammatory process. Cytokines as immune factors implement their effector function at the site of inflammation. They activate platelets, stimulate the migration of neutrophils, eosinophils and other cells involved in inflammation. Due to the presence of so-called "functional" polymorphisms in cytokine genes, the concentration of produced proteins changes and their functional activity is disturbed.

This paper examines the prevalence of cytokine gene polymorphisms located on chromosomes 1, 4, 5 and 9 in Arctic populations (Nenets and Dolgan-Nganasans) in comparison with the Slavic population.

IL-2 producers are activated Th0 and Th1 cells, as well as cytotoxic T-lymphocytes, which have a proliferative and activating effect on T-killers and B-cells. There are differences in serum IL-2 concentration levels between carriers of different rs2069762 *IL2* genotypes: it has been shown that the TT genotype of this polymorphism is associated with a high concentration of IL-2 [24, Martins M.B., Marcello M.A., de Assis Batista F., Peres K.C., Meneghetti M., de Camargo Etchebehere E.C.S., da Assumpção L.V.M., Ward L.S., p. 10021]. Our study revealed that the homozygous TT genotype is significantly less frequent in Nenets and Dolgan-Nganasans compared to the population of Slavs of Krasnoyarsk. Recent studies show that increased IL-2 expression promotes dendritic cell proliferation and their subsequent infiltration of malignant tumours, which improves antigen presentation and makes the tumour more sensitive to immune checkpoint inhibition [25, Raeber M.E., Rosalia R.A., Schmid D., Karakus U., Boyman O., c. eaba5464]. This may indicate that

[10] Rakovaya karta Rossii. Gde chashche vsego zabolevayut onkologiey i izmenilas' li kartina za god [Cancer map of Russia. Where oncology most often occurs and has the picture changed over the year]. URL: https://life.ru/p/1332562 (accessed 02 August 2023).

the indigenous people of the Arctic, carriers of the TT rs2069762 *IL2* genotype, are potentially more vulnerable to the development of cancer tumours compared to representatives of the Slavic population.

IL-4 is a factor regulating the immune response of Th2 cells, as well as inhibiting the functions of Th1 cells. IL-4 activity is associated with the rs2243250 polymorphism in the promoter region of the *IL4* gene [26, Završnik M., Letonja J., Makuc J., Šeruga M., Cilenšek I., Petrovič D., pp. 347–351]: carriers of the TT genotype of rs2243250 *IL4* have a higher level of the IL-4 cytokine in the blood serum than those with the CC genotype. We have found that Nenets and Dolgan-Nganasans have a significantly higher frequency of the TT genotype of the rs2243250 polymorphism of the *IL4* gene compared to the Slavs. This cytokine limits the synthesis of proinflammatory cytokines, the formation of reactive nitrogen and oxygen species, and induces the synthesis of IgE and IgG4. Increased production of this cytokine may contribute to a more rapid development of the immune response and less active processes of lipid peroxidation and aging of the body in the population of the Arctic.

The anti-inflammatory cytokine IL-5 in the human body functions as an activator of humoral immunity, stimulates the maturation of eosinophils, and participates in allergic reactions, activating mast cells to synthesize histamine [27, Biały S., Iwaszko M., Świerkot J., Bugaj B., Kolossa K., Jeka S., Bogunia-Kubik K., p. 13177]. It has been shown that the CC genotype of the rs2069812 polymorphism of the *IL5* gene is associated with a high level of IL-5 production, and the TT genotype is associated with a low level [28, Inoue N., Watanabe M., Morita M., Tatusmi K., Hidaka Y., Akamizu T., Iwatani Y., pp. 318–323]. The TT genotype of the rs2069812 polymorphism of the *IL5* gene is more common among Nenets and Dolgan-Nganasans than among the Slavs of Krasnoyarsk. This may indicate that these populations are characterized by a reduced ability to grow and proliferate eosinophils, as well as secrete IgA and IgM, which may be associated with a lower incidence of allergopathologies [11].

The *IL10* gene is located on chromosome 1q31-32, in a locus associated with predisposition to a number of autoimmune diseases. The anti-inflammatory cytokine IL-10 promotes the development of antiparasitic and allergic reactions of the body by suppressing the activity of Th1 cells and macrophages [29, Iyer S.S., Cheng G., pp. 23–63], and plays an important role in suppressing inflammatory reactions. It is known that the GG genotype of the rs1800872 polymorphism of the *IL10* gene causes high serum levels of IL-10, while TT causes low levels. We have found that the frequency of the GG genotype of the rs1800872 polymorphism of the *IL10* gene is lower in Nenets and Dolgan-Nganasans compared to the Slavs. It can be assumed that the Nenets and Dolgan-Nganasans have reduced allergic reactivity of the body, which is due to the presence of a smaller number of allergens due to the harsh climatic conditions in the Arctic regions compared to other regions.

[11] Pelaia C., Paoletti G., Puggioni F. Interleukin-5 in the Pathophysiology of Severe Asthma. URL: https://www.frontiersin.org/articles/10.3389/fphys.2019.01514 (accessed 28 July 2023).

The anti-inflammatory cytokine IL-13, together with IL-10 and IL-4, takes part in the immune reactions of Th2 cells and stimulates the secretion of IgE and IgG (subclass 4), and is capable of causing bronchial hyperreactivity [30, Al Abdulsalam E.A., Al-Hajjaj M.S., Alanazi M.S., Warsy A.S., p. 196]. In addition, along with IL-4, it is a key cytokine in the pathogenesis of allergic diseases. Polymorphism rs1800925 of the *IL13* gene is potentially associated with COPD, while differences in IL-13 concentrations in the blood serum depending on one or another genotype have not been described [31, Choto E.T., Mduluza T., Chimbari M.J., c. e0252220]. It has been shown that the frequency of occurrence of the CT and TT genotypes of rs1800925 of the *IL13* gene in the Nenets and Dolgan-Nganasans is lower than in the Slavs.

The main biological function of cytokines of the interleukin 17 family is the activation of the synthesis of proinflammatory cytokines such as IL-1β, TNFα, IL-6 [32, Prosekova E.V., Turyanskaya A.I., Dolgopolov M.S., pp. 15–20]. IL-17A is the most studied cytokine of the IL-17 family and plays a central role in the development of inflammatory processes. IL-17A, which is a factor in the body's defense against pathogens, is produced by memory cells (Th17). An increased level of IL-17A is observed in the owners of genotype AA of *IL17A* gene rs2275913, while a decreased level is observed in the owners of GG genotype [33, Ghaznavi H., Soltanpour M.S., pp. 35–40]. The Nenets have a higher frequency of the GA rs2275913 genotype of the *IL17A* gene compared to the other populations studied by us. It is known that a high level of this cytokine, when combined with TNFa, stimulates the synthesis of the Shnur-ri 3 (Shn3) protein, which, in the presence of rheumatoid arthritis in humans, promotes rapid bone destruction [34, Lavocat F., Osta B., Miossec P., pp. 89–96].

A member of the IL-1 family, IL-33, is characterized by increased synthesis of Th2 cells and selective stimulation of humoral immunity [35, Pollheimer J., Bodin J., Sundnes O., Edelmann R.J., Skånland S.S., Sponheim J., Brox M.J., Sundlisaeter E., Loos T., Vatn M., Kasprzycka M., Wang J., Küchler A.M., Taskén K., Haraldsen G., Hol J., pp. e47–e55]. It has been shown that the CC genotype of the rs7044343 polymorphism of the *IL33* gene is associated with an increased concentration of this interleukin in the culture of monocytes of healthy people [36, Angeles-Martínez J., Posa-das-Sánchez R., Llorente L., p. e0168828]. The results obtained in this work indicate that the indigenous peoples of the Russian Arctic are more likely to have elevated levels of IL-33 in the body. This can potentially affect the rate of development of inflammatory reactions, since the function of this interleukin is to stimulate the synthesis of Th2 cells. In addition, IL-33 is involved in the development of malignant neoplasms, specifically affecting the stimulation of tumour cell activity and generally promoting carcinogenesis [37, Gorbacheva A.M., Mitkin N.A., pp. 774–789].

In the course of the work, we also showed that the prevalence of polymorphic variants of the studied single nucleotide substitutions in Slavs is consistent with the Caucasoid populations of the world, and in the indigenous populations of the Arctic — with Asian populations. These data confirm the migration of related haplogroups N and O of the human Y chromosome from China and Vietnam towards the North. Haplogroup N spread along the Yenisei and Irtysh river valleys, and representatives of haplogroup O migrated north to Kamchatka.

Conclusion

The uncomfortable climatic conditions of the Arctic regions have a significant impact on the health of the population, increasing the risk of developing many diseases, in the pathogenesis of which cytokines, mediators of the immune system, play an important role. The cytokine network has a high degree of polymorphism and intergenic interactions. The study of the prevalence of functional mutations associated with different levels of production of proteins of the immune system is relevant in the populations of the Arctic territories. Polymorphisms of the *IL2, IL4, IL5, IL10, IL17A and IL33* genes are potential genetic markers, the determination of which in the future can be recommended as a preventive measure for the development of pathologies and the adoption of effective measures to protect the Arctic population from diseases that reduce life expectancy.

The present study shows that due to the presence of certain variants of cytokine gene polymorphisms, the indigenous inhabitants of the Russian Arctic have a genetically determined low level of ROI production, rapid development of immune reactions, protection against the development of allergies and resistance to malignancy compared to the Slavic immigrant population.

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