ISSN 0026-8933, Molecular Biology, 2023, Vol. 57, No. 2, pp. 329–337. © Pleiades Publishing, Inc., 2023.
Russian Text © The Author(s), 2023, published in Molekulyarnaya Biologiya, 2023, Vol. 57, No. 2, pp. 350–359.

EVOLUTIONARY, POPULATION, AND MEDICAL GENOMICS, TRANSCRIPTOMICS

UDC 575.174.015.3:616-00

Increased Frequencies of the −174G and −572C *IL6* Alleles in Populations of Indigenous Peoples of Siberia Compared to Russians

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Received July 27, 2022; revised September 16, 2022; accepted September 29, 2022

Abstract—The study of immune response and inflammation gene polymorphisms in a genogeographic context is relevant in the study of human populations. Here, in the indigenous populations of Siberia the frequencies of polymorphic variants −174G/C (rs1800795) and −572C/G (rs1800796) of the *IL6* gene encoding the proinflammatory cytokine IL-6 were determined. For the first time, it was shown that the frequencies of the −174G and −572C alleles, which determine increased inflammatory response and are also associated with several diseases were statistically significantly higher in ethnic groups of Buryats, Teleuts, Yakuts, Dolgans and Tuvinians than in Russians living in Siberia. These values were in the intermediate position between those in the European and East-Asian groups. We hypothesize an adaptive role of these *IL6* genetic variants in human settlement from Africa to the Eurasian continent. However, due to the departure from the traditional way of life and the increasing anthropogenic environmental pollution, the risk of diseases whose pathogenesis is based on inflammation in indigenous Siberian populations is likely increased.

keywords: cytokines, *IL6*, genetic polymorphism, rs1800795, rs1800796, real-time PCR, Siberian indigenous peoples, Buryats, Teleuts, Yakuts, Dolgans, Tuvinians, Russians

DOI: 10.1134/S002689332302019X

Inflammation is characterized as a protective and adaptive homeostatic reaction of the body to damage or the action of an irritant of a physical, chemical, or biological, including allergic, nature [1]. The inflammatory response is aimed at eliminating the products and agents of damage and maximizing recovery. However, inflammation can play an important role in the induction of various diseases including oncological diseases, cardiovascular diseases, autoimmune diseases, and others [2–8].

The inflammation process is regulated by pro- and anti-inflammatory cytokines—small protein molecules that provide intercellular interaction, determine cell survival, stimulate or suppress cell growth, differentiation, functional activity and apoptosis, and also ensure the coordination of the immune, endocrine and nervous systems under normal conditions and in response to pathological influences. Interleukin-6 (IL-6) is a pro-inflammatory cytokine and functions as a regulator of the immune response and mediator of inflammation [9, 10].

Another important role of IL-6 was identified in connection with the COVID-19 pandemic. The level of IL-6 in the blood of patients began to be considered as a significant prognostic marker of the severity of the disease with the development of the so-called "cytokine storm" [11, 12].

The severity of inflammation, its nature, course and outcome depend not only on the pathogenic potential of the stimulus, but also on the reactivity of the organism [1], which is largely determined by genetic factors. Gene *IL6* is localized on the short arm of chromosome 7 (7p15.3) and contains 5 exons and 4 introns, with a total length of 1183 bp. The most studied polymorphic loci are −174G/C (rs1800795) and −572C/G (rs1800796) in the promoter region of the *IL6* gene.

Allele −174G (rs1800795) *IL6* leads to a significant increase in promoter activity compared to the −174C variant and, as a consequence, increased gene expression [13]. *IL6* allele −572C (rs1800796) is also associated with increased levels of *IL6* expression compared to allele −572G [14, 15].

Variants −174G and −572C, which provide increased production of IL-6, are associated with a number of diseases whose pathogenesis is based on inflammation. It has been shown that their carriers are more likely to suffer from liver diseases [16] and have an increased risk of tuberculosis [15, 17]. Allele −174G is considered a risk factor for squamous cell lung cancer and chronic obstructive pulmonary disease [18], cancer and fundic atrophy of the stomach [19], ovarian cancer [20], intrauterine infection of the fetus [21], development of cerebral arteriovenous malformation [22] and is associated with the risk of developing type 2 diabetes [23, 24]. Allele −572C has also been associated with ischemic stroke in indigenous West African men [25].

However, data on the association of the −174G/C polymorphism of the *IL6* gene with the risk of developing malignant neoplasms remain controversial [26], and interpopulation differences in allele frequencies may be one of the reasons for the existing contradictions [27]. It has been shown that for people of Tatar ethnicity of postmenopausal age, the homozygous −174G/−174G genotype serves as a marker of a reduced risk of developing ovarian cancer [28], while in Caucasians with non-alcoholic steatohepatitis and hepatocarcinoma, the frequency of *IL6* −174G is significantly lower than in healthy people [5, 29, 30]. This variant may be protective against undifferentiated connective tissue dysplasia [31]. The protective role of the *IL6*–572C allele has been established for the development of endocarditis [32]. It is possible that there are interethnic differences in the effects of polymorphic *IL6* gene variants on the development of diseases associated with features of the distribution of allele frequencies of other genes, the products of which mediate the action of IL-6, for example, the gene for the IL-6 transmembrane receptor - *IL6R* [16, 33].

Knowledge of the nature of the geographical distribution of alleles *IL6* −174G and *IL6* −572C is important for understanding the process of formation of population gene pools and the influence of the adaptive value of alleles on it in various living conditions [34]. Environmental changes associated with the departure from the traditional way of life, as well as the anthropogenic impact on nature, can modulate the adaptive significance of alleles, in connection with which population studies in this area become especially relevant. Currently, a large amount of knowledge has been accumulated on the distribution of polymorphic variants of the *IL6* gene in different countries and among different ethnic groups, including Russia [34–38]. However, for the indigenous populations of Siberia, this issue is poorly understood.

This work presents the results of the study of *IL6* −174G and *IL6* −572C allele frequencies in Siberian samples in comparison with Russians, as well as with some other populations.

EXPERIMENTAL

Samples of study participants. The genetic material for this study was collected during the expeditions of the Laboratory of Population Ethnogenetics in 2000–2019. The study involved volunteers, healthy at the time of the study, who gave informed consent. Blood was taken from the subjects in compliance with the WHO International Rules (https://apps.who.int/iris/bitstream/handle/10665/44298/9789241599252_eng.pdf?sequence=1). Before donating blood, each subject filled out a specially designed demographic questionnaire, in which they specified the nationality of their ancestors up to 3–4 generations. Based on the collected information, 8 samples of the population of Southern and Eastern Siberia were formed. Persons of Buryat nationality who do not have any other ethnic ancestors, living in the villages of Alkhanai and Orlovsky, Aginsky Buryat Okrug (ABO) of the Zabaykalsky Krai, were included in the group of Eastern Buryats (N = 133). Ethnic Buryats of the Ekhirit-Bulagatsky District of the Ust-Ordynsky Buryatsky Okrug (UOBO) of the Irkutsk Region (N = 273) made up the Western Buryat group. The study included the Teleuts of the Belovsky District of the Kemerovo Region (N = 117). Two ethnic groups of Yakuts were also formed: Nyurbinskaya (from those living in the villages of Nyurbachan and Syultsy of the Nyurbinsky Ulus; N = 109) and Ust-Aldanskaya (from the inhabitants of the village of Dyupsya, Ust-Aldan Ulus; N = 99). Residents of the city of Dudinka, the settlements of Volochanka and Ust-Avam of the Taimyr Dolgano-Nenetsky District of the Krasnoyarsky Krai, identifying themselves as the Dolgan ethnos, made up the Dolgan group (N = 179). The seventh sample of the indigenous inhabitants of Siberia included ethnic Tuvinians from the city of Kyzyl (N = 301). Finally, the eighth group included persons who call themselves Russians and live in the Zabaykalsky Krai (N = 65), Irkutsk Region (N = 67) and Tuva (N = 24). Most of the sample consisted of representatives of the Russian old-timer population, who have lived in Siberia for more than one generation. It should be noted that some people, who make up 5% of the sample, indicated among their ancestors, in addition to Russians, also representatives of other European nationalities: Ukrainians, Belarusians, Poles, Germans, etc. The described group did not include the descendants of mixed marriages of Russians with representatives of the peoples of the Caucasus or indigenous Siberian ethnic groups.

Genotyping of single nucleotide polymorphisms: real time PCR. Total DNA was isolated from the leukocyte fraction of venous blood by the standard method of phenol–chloroform extraction [39] using a kit for DNA isolation from whole blood (LLC BioSilica, Russia). Genotyping of single nucleotide substitutions −174G/C (rs1800795) and −572C/G (rs1800796) was performed by real-time PCR using competing TaqMan

Table 1. Structures of primers and probes used for genotyping single nucleotide substitutions in the *IL6* gene

Locus	Primers	Probes[a]
−174G/C, rs1800795	5'-AGGAAGAGTGGTTCTGCTTCT-3'	5'-Fam-CTTTAGCATGGCAAGACACA-BHQ2-3'
	5'-TGGGGCTGATTGGAAACCT-3'	5'-Hex-CTTTAGCATCGCAAGACACA-BHQ2-3'
−572C/G, rs1800796	5'-CATCTGAGTTCTTGTGTGTTCTG-3'	5'-Hex-CAACAGCCCCTCACAGG-BHQ2-3'
	5''-CGAGACGCCTTGAAGTAACTG-3'	5'-Fam-CAACAGCCGCTCACAGG-BHQ2-3'

[a]Fam (phosphoramidite) and Hex (hexachlorofluorescein) are fluorescent dyes (fluorophores); BHQ2 (Black Hole Quencher 2) is a fluorescence quencher for real-time PCR.

Table 2. Distribution of genotypes *IL6* in samples of indigenous peoples of Siberia and Russians

Polymorphism[a]			Buryats		Teleuts	Yakuts		Dolgans	Tuvinians	Russians
			Eastern	Western		Nyurbinsky Ulus	Ust-Aldansky Ulus			
−174G/C, rs1800795	Distribution of genotypes, *n* (%)	G/G	113 (85.6)	241 (88.3)	87 (75.0)	91 (93.8)	88 (94.6)	143 (82.6)	266 (89.9)	54 (34.8)
		G/C	18 (13.6)	30 (11.0)	28 (24.1)	5 (5.1)	5 (5.4)	29 (16.8)	28 (9.4)	70 (45.2)
		C/C	1 (0.8)	2 (0.7)	1 (0.9)	1 (1.1)	0	1 (0.6)	2 (0.7)	31 (20.0)
	N, ppl		132	273	116	97	93	173	296	155
	p (H–W)		0.952	0.861	0.839	0.729	0.975	0.937	0.830	0.621
−572C/G, rs1800796	Distribution of genotypes, *n* (%)	G/G	35 (26.3)	86 (32.3)	46 (39.3)	23 (21.1)	17 (17.2)	65 (36.3)	90 (29.9)	120 (76.9)
		G/C	65 (48.9)	119 (44.8)	57 (48.7)	62 (56.9)	56 (56.6)	92 (51.4)	159 (52.8)	34 (21.8)
		C/C	33 (24.8)	61 (22.9)	14 (12.0)	24 (22.0)	26 (26.2)	22 (12.3)	52 (17.3)	2 (1.3)
	N, ppl		133	266	117	109	99	179	301	156
	p (H–W)		0.883	0.391	0.787	0.404	0.391	0.556	0.499	0.952

[a]*N*, ppl —sample size, number of people; *n*—number; *p* (H–W) is the value of the probability of deviation from the equilibrium Hardy–Weinberg distribution.

probes complementary to polymorphic DNA regions. The structure of primers and probes was selected according to the sequences available in the NCBI database (http://www.ncbi.nlm.nih.gov/) using the programs UGENE (version 1.14, http://ugene.unipro.ru/) and Oligo Analyzer (version 1.0.3, https://eu.idtdna.com/pages/tools/oligoanalyzer) (Table 1).

Amplification was carried out in a volume of 25 μL, the PCR mixture included: 300 nM of each primer, 100 nM TaqMan probes, 65 mM Tris-HCl (pH 8.9), 16 mM $(NH_4)_2SO_4$, 2.5 mM $MgCl_2$, 0.05% Tween-20, 0.2 mM dNTPs, 0.5–10 ng DNA, and 0.5 U Taq-DNA polymerase (hot-start, Biosan, Latvia). PCR was performed under the following conditions: initial denaturation 3 min at 96°C; then 46 cycles, including denaturation at 96°C for 5 s, primer annealing and subsequent elongation at 61°C for 30 s (each step was accompanied by the registration of a fluorescent signal at the emission wavelength of the fluorophores Fam (517 nm) and Hex (549 nm).

Statistical processing of results. The population frequencies of allelic variants were determined based on the observed genotype frequencies. The correspondence of the empirically observed distribution of genotype frequencies to the theoretically expected distribution, which is equilibrium according to the Hardy–Weinberg law, was checked using the Pearson test (χ^2; at p (H–W) > 0.05 equilibrium is satisfied, where p (H–W) is the value of the probability of deviation from the equilibrium Hardy–Weinberg distribution). Assessing the significance of differences in allele frequencies between the studied samples was carried out according to the criterion χ^2 using the Yates correction for continuity; at $p < 0.025$ (corrected for multiplicity comparison: 0.025 = 0.05/2) the results were considered statistically significant.

RESEARCH RESULTS

Genotyping results *IL6* −174G/C (rs1800795) and *IL6* −572C/G (rs1800796) in samples of Buryats, Teleuts, Yakuts, Dolgans, Tuvinians, and Russians are given in Table 2.

The observed distribution of genotype frequencies of both polymorphic loci in the studied samples corresponded to the expected distribution under the Hardy–Weinberg equilibrium. Allele frequencies −174G and −572C in the studied samples, as well as in some ethnic groups described in the literature [35], and comparison of populations (p-value) are presented in Tables 3 and 4.

It has been shown that the *IL6*–174G allele frequency in a sample of Russians corresponds to its frequency in European groups [35]. The indigenous peo-

Table 3. Allele frequency −174G *IL6* in some populations (ethnic groups) and comparison of populations

Population/ethnic group	*N*, ppl	Frequency −174G, %	Population Comparison (*p*-value)[a]							
			Buryats		Teleuts	Yakuts		Dolgans	Tuvinians	Russians
			Eastern	Western		Nyurbinsky Ulus	Ust-Aldansky Ulus			
Eastern Buryats	132	92.4		0.549	0.071	0.111	0.043	0.638	0.276	**<0.001**
Western Buryats	273	93.8	0.549		**0.003**	0.238	0.099	0.151	0.652	**<0.001**
Teleuts	116	87.1	0.071	**0.003**		**0.001**	**<0.001**	0.175	**<0.001**	**<0.001**
Yakuts (Nyurbinsky Ulus)	97	96.4	0.111	0.238	**0.001**		0.835	0.030	0.417	**<0.001**
Yakuts (Ust-Aldansky Ulus)	93	97.3	0.043	0.099	**<0.001**	0.835		**0.010**	0.189	**<0.001**
Dolgans	173	91	0.638	0.151	0.175	0.030	**0.010**		0.047	**<0.001**
Tuvinians	296	94.6	0.276	0.652	**<0.001**	0.417	0.189	0.047		**<0.001**
Russians of Eastern Siberia	155	57.4	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	
Dai Chinese (Xishuangbanna, China)[b]	93	100	**<0.001**	**0.001**	**<0.001**	0.026	0.071	**<0.001**	**0.002**	**<0.001**
Han Chinese (Beijing, China)[b]	103	100	**<0.001**	**<0.001**	**<0.001**	**0.018**	0.054	**<0.001**	**0.001**	**<0.001**
Southern Han Chinese (China)[b]	105	100	**<0.001**	**<0.001**	**<0.001**	**0.017**	0.051	**<0.001**	**0.001**	**<0.001**
Japanese (Tokyo, Japan)[b]	104	100	**<0.001**	**<0.001**	**<0.001**	**0.017**	0.053	**<0.001**	**0.001**	**<0.001**
Kinh (Viets) (Ho Chi Minh City, Vietnam)[b]	99	99.5	**<0.001**	**0.002**	**<0.001**	0.069	0.185	**<0.001**	**0.005**	**<0.001**
Finns (Finland)[b]	99	54.5	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.740
English and Scottish[b]	91	58.8	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.701
Iberians (Spain)[b]	107	65.0	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.074
Toscani (Italy)[b]	107	64.5	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.094

[a]Values in bold $p < 0.025$, at which the differences were considered statistically significant.
[b]The data of the consortium "The 1000 Genomes Project Consortium" [35] are presented.

Table 4. Allele frequency –572C *IL6* in some populations (ethnic groups) and comparison of populations

Population/ethnic group	*N*, ppl	Frequency –572C, %	Population Comparison (p-value)[a]							
			Buryats		Teleuts	Yakuts		Dolgans	Tuvinians	Russians
			Eastern	Western		Nyurbinsky Ulus	Ust-Aldansky Ulus			
Eastern Buryats	133	49.2		0.334	**0.005**	0.847	0.300	**0.007**	0.154	**<0.001**
Western Buryats	266	45.3	0.334		0.025	0.224	0.033	0.036	0.630	**<0.001**
Teleuts	117	36.3	**0.005**	0.025		**0.003**	**<0.001**	0.740	0.061	**<0.001**
Yakuts (Nyurbinsky Ulus)	109	50.5	0.847	0.224	**0.003**		0.473	**0.004**	0.099	**<0.001**
Yakuts (Ust-Aldansky Ulus)	99	54.5	0.300	0.033	**<0.001**	0.473		**<0.001**	**0.010**	**<0.001**
Dolgans	179	38.0	**0.007**	0.036	0.740	**0.004**	**<0.001**		0.099	**<0.001**
Tuvinians	301	43.7	0.154	0.630	0.061	0.099	**0.010**	0.099		**<0.001**
Russians of Eastern Siberia	156	12.2	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	
Dai Chinese (Xishuangbanna, China)[b]	93	82.3	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Han Chinese (Beijing, China)[b]	103	71.8	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Southern Han Chinese, (China)[b]	105	78.6	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Japanese (Tokyo, Japan)[b]	104	82.2	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Kinh (Viets) (Ho Chi Minh City, Vietnam)[b]	99	80.8	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Finns (Finland) [b]	99	5.1	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.012**
English and Scottish[b]	91	3.8	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.003**
Iberians (Spain)[b]	107	5.1	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.009**
Toscani (Italy)[b]	107	5.1	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.009**

[a]Values in bold $p < 0.025$, at which the differences were considered statistically significant.
[b]Data from The 1000 Genomes Project Consortium [35] are presented.

ples of Siberia are statistically significantly different in the higher frequency of occurrence of this polymorphism compared to the Russians and European populations described in the literature and lower in comparison with a number of East Asian populations: the Chinese, Japanese and Vietnamese, in which this figure is close to 100%.

In the samples of Siberian ethnic groups studied by us, the *IL6*-572C allele frequency is statistically significantly higher than in the groups of Russians and Europeans. Statistically significant differences between Siberian samples and East Asian populations, in which this indicator is even higher, were demonstrated.

Thus, according to the frequency of occurrence of Alleles *IL6*–174G and *IL6*–572C in Siberian indigenous populations are located between Europeans and samples from East Asia. The same trend was revealed by us earlier in studies of polymorphisms in other functionally important genes [40, 41].

RESULTS AND DISCUSSION

Understanding the features of the frequency distribution of the polymorphic variants –174G/C (rs1800795) and –572C/G (rs1800796) of the *IL6* gene, encoding the pro-inflammatory cytokine IL-6 in the indigenous population of various regions of the world is important both for fundamental population genetic studies and in the medical aspect. As a result of our screening in the ethnic groups of Buryats, Teleuts, Yakuts, Dolgans and Tuvinians, the allele frequencies of *IL6* –174G and *IL6* –572C associated with an increase in the production of IL-6, an enhanced inflammatory response, and a number of diseases were determined for the first time. It is shown that in samples of indigenous Siberian ethnic groups, the frequencies of both studied variants are statistically significantly higher than among Russians, and lower than among East Asian peoples, that is, they occupy an intermediate position.

Interestingly, in the indigenous population of Africa, the frequency of the *IL6*–174G variant is 100%, it is close to this value in Asian countries. In the populations of Europe, it is lower - up to the predominance of the allelic variant -174C of the gene *IL6*, which is "responsible" for the reduced production of the pro-inflammatory cytokine [35]. S.A. Borinskaya et al. [34] suggested that in European populations, a decrease in the frequency of the *IL6*–174G allele was the result of adaptation to new living conditions: a temperate climate with a reduced load of pathogens, that is, with a decrease in selection pressure. There is a similar geographic distribution of the *IL6*–572C allele, determining the high level of transcription of the gene. In African countries, the frequency of this allele is about 10%, it is even lower in the indigenous populations of Europe—up to 5%, but significantly increased in the peoples of Asia—80% and higher [35].

Based on the publication of summary pathogen load indices calculated from historical data for nine infectious diseases (leishmaniasis, trypanosomiasis, malaria, schistosomiasis, filariasis, leprosy, dengue, typhoid, and tuberculosis) [42], S.A. Borinskaya et al. [34] found that the frequency of the *IL6*–174G, which determines high-level protein expression and a strong inflammatory response, positively correlates with the pathogen load index. Probably, in the process of human settlement from the African continent to Asia, both options *IL6*: –174G and –572C—had adaptive advantages.

It is known that in some cases, especially after the "exit" of a person from reproductive age, an increased response of the body to a pathogenic stimulus can also have negative effects, triggering pathological processes (including carcinogenesis), maintaining chronic inflammation underlying metabolic, cardiovascular vascular, neurodegenerative and neoplastic diseases in the elderly [43]. It can be assumed that due to the increase in anthropogenic environmental pollution, which provokes inflammatory reactions, the risk of inflammation-associated diseases will also increase in ethnic groups with increased *IL6*–174G and –572C allele frequencies gene. However, to test this hypothesis, additional medical genetic studies are needed in various populations with a large sample size, as well as the study of the frequencies of allelic variants, not only of *IL6*, but also of other functionally significant inflammatory genes.

ACKNOWLEDGMENTS

The authors are grateful to PhD Karafet T.M., PhD Lichman D.V., Vavilova N.A., Moletotova N.A., Voronkova M.R., PhD Sangaev S.S. and Likhacheva A.O. for participation in expeditions. For active assistance in collecting the biomaterial of Tuvinians, the authors are grateful to Dr. Kawai-ool U.N. and employees of the State Budgetary Institution of Health of the Republic of Tyva "Republican Center for Medical Prevention," Kyzyl.

FUNDING

The study was carried out within the state task of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences (No. FWNR-2022-0021).

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare no conflict of interest.

Statement of compliance with standards of research involving humans as subjects. All procedures for human research comply with the ethical standards of the institutional and national research ethics committee and the 1964 Declaration of Helsinki and its subsequent amendments. Informed consent was obtained from each of the participants included in the study.

REFERENCES

1. Vismont F.I. 2006. *Vospalenie (patofiziologicheskie aspekty). Uchebno-metodicheskoe posobie* (Inflammation (Pathophysiological Aspects). Teaching Aid). Minsk: BGMU.
2. Kidane D., Chae W.J., Czochor J., Eckert K.A., Glazer P.M., Bothwell A.L., Sweasy J.B. 2014. Interplay between DNA repair and inflammation, and the link to cancer. *Crit. Rev. Biochem. Mol. Biol.* **49**, 116–139. https://doi.org/10.3109/10409238.2013.875514
3. Becker C., Fantini M. C., Schramm C., A Lehr H.A., Wirtz S., Nikolaev A., Burg J., Strand S., Kiesslich R., Huber S., Ito H., Nishimoto N., Yoshizaki K., Kishimoto T., Galle P.R., Blessing M., Rose-John S., Neurath M.F. 2004. TGF-β suppresses tumor progression in colon cancer by inhibition of IL-6 *trans*-signaling. *Immunity.* **21**, 491–501. https://doi.org/10.1016/j.immuni.2004.07.020
4. Stephens O.W., Zhang Q., Qu P., Zhou Y., Chavan Sh., Tian E., Williams D.R., Epstein J., Barlogie B., Shaughnessy J.D. 2012. An intermediaterisk multiple myeloma subgroup is defined by sIL-6r: levels synergistically increase with incidence of SNP rs2228145 and 1q21 amplification. *Blood.* **119**, 503–512. https://doi.org/10.1182/blood-2011-07-367052
5. Giannitrapani L., Soresi M., Giacalone A., Campagna M.E., Marasà M., Cervello M., Marasà S., Montalto G. 2011. IL-6 −174G/C polymorphism and IL-6 serum levels in patients with liver cirrhosis and hepatocellular carcinoma. *OMICS.* **15**, 183–186. https://doi.org/10.1089/omi.2010.0093
6. Aukrust P., Ueland T., Lien E., Bendtzen K., Müller F., Andreassen A.K., Nordøy I., Aass H., Espevik T., Simonsen S., Frøland S.S., Gullestad L. 1999. Cytokine network in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am. J. Cardiol.* **83**, 376–382. https://doi.org/10.1016/s0002-9149(98)00872-8
7. Muscaritoli M., Molfino A., Bollea M.R., Fanelli F.R. 2009. Malnutrition and wasting in renal disease, *Curr. Opin. Clin. Nutr. Metab. Care*. **12**, 378–383. https://doi.org/10.1097/MCO.0b013e32832c7ae1
8. Tys R.P., Osipova L.P. 2022. Interleukin-6: its role in the body, genetic polymorphism and significance in some diseases (literature review). *Med. Genet.* **21** (1), 14–27. https://doi.org/10.25557/2073-7998.2022.01.14-27
9. Fernández-Real J.M., Broch M., Vendrell J., Richart C., Ricart W. 2000. Interleukin-6 gene polymorphism and lipid abnormalities in healthy subjects. *J. Clin. Endocrinol. Metab.* **85**, 1334–1339. https://doi.org/10.1210/jcem.85.3.6555
10. Braunersreuther V., Viviani G.L., Mach F., Montecucco F. 2012. Role of cytokines and chemokines in non-alcoholic fatty liver disease. *World J. Gastroenterol.* **18** (8), 727–735.
11. Coomes E.A., Haghbayan H. 2020. Interleukin-6 in COVID-19: a systematic review and meta-analysis. *Rev. Med. Virol.* **30**, 1–9. https://doi.org/10.1002/rmv.2141
12. Rodríguez-Hernández M.A., Carneros D., Núñez-Núñez M., Coca R., Baena R., López-Ruiz G.M., Cano-Serrano M.E., Martínez-Tellería A., Fuentes-López A., Praena-Fernandez J.M., Garbers C., Hernández-Quero J., García F., Rose-John S., Bustos M. 2022. Identification of IL-6 signalling components as predictors of severity and outcome in COVID-19. *Front. Immunol.* **13**, 891456. https://doi.org/10.3389/fimmu.2022.891456
13. Fishman D., Faulds G., Jeffery R., Mohamed-Ali M., Yudkin J.S., Humphries S., Woo P. 1998. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *J. Clin. Invest.* **102**, 1369–1376. https://doi.org/10.1172/JCI2629
14. Brull D.J., Montgomery H.E., Sanders J., Dhamrait S., Luong L., Rumley A., Lowe G.D., Humphries S.E. 2001. Interleukin-6 gene −174G>C and −572G>C promoter polymorphisms are strong predictors of plasma interleukin-6 levels after coronary artery bypass surgery. *Arterioscler. Thromb. Vasc. Biol.* **21**, 1458–1463. https://doi.org/10.1161/hq0901.094280
15. Zhang G., Zhou B., Wang W., Zhang M., Zhao Y., Wang Z., Yang L., Zhai J., Feng C.G., Wang J., Chen X. 2012. A functional single-nucleotide polymorphism in the promoter of the gene encoding interleukin 6 is associated with susceptibility to tuberculosis. *J. Infect. Dis.* **205**, 1697–1704. https://doi.org/10.1093/infdis/jis266
16. Wang X., Zhenghui Yan Zh., Ye Q. 2019. Interleukin-6 gene polymorphisms and susceptibility to liver diseases. *Medicine* (Baltimore). **98**, e18408. https://doi.org/10.1097/MD.0000000000018408
17. Wang H., Caishuang Pang C., Zeng N., Wan Ch., Shen Y., Wen F. 2017. Association between the IL-6 gene polymorphism and tuberculosis risk: a meta-analysis. *Infect. Drug Resist.* **10**, 445–454. https://doi.org/10.2147/IDR.S144296
18. Gordeeva L.A., Mun S.A., Voronina E.N., Polenok E.G., Magatina A.D., Titov V.A., Ragozhina S.E., Vafin I.A., Romanova E.L., Glushkov A.N. 2018. Associations of polymorphisms in cytokine genes with the risk of squamous cell lung cancer in men depending on the duration of smoking. *Ekol. Genet.* **16**, 60–69. https://doi.org/10.17816/ecogen16160-69
19. Belkovets A.V., Kurilovich S.A., Maksimov V.N., Ragino Yu.I., Scherbakova L.V., Cheremisina O.V., Cherdyntseva N.V., Andryushina N.A., Voevoda M.I. 2018. Polymorphism of genes of inflammatory cytokines IL6 and IL1b in patients with gastric cancer in a clinical case–control study. *Eksp. Klin. Gastroenterol.* **4** (152), 9–17.
20. Hefler L.A., Grimm C., Ackermann S., Malur S., Radjabi-Rahat A.R., Leodolter S., Beckmann M.W., Zeillinger R., Koelbl H., Tempfer C.B. 2003. An interleukin-6 gene promoter polymorphism influences the biological phenotype of ovarian cancer. *Cancer Res.* **63**, 3066–3068.
21. Kan N.E., Sirotkina E.A., Tyutyunnik V.L., Donnikov A.E., Bystritskii A.A., Kadochnikova V.V.,

Markelova E.G., Kurchakova T.A., Veresova A.A. 2015. Diagnostic role of clinical and molecular genetic predictors of intrauterine infection. *Akush. Ginekol.* **4**, 44–49.

22. Erkinova S.A., Kiselev V.S., Strel'nikov N.V., Orlov K.Yu., Dubovoi A.V., Voronina E.N., Filipenko M.L. 2016. Study of the association of polymorphic variants of cytokine genes with the development of arteriovenous malformations. *Tekhnol. Zhivykh Sist.* **13** (6), 62–66.
23. Huth C., Heid I.M., Vollmert C., Gieger C., Grallert H., Wolford J. K., Langer B., Thorand B., Klopp N., Hamid Y.H., Pedersen O., Hansen T., Lyssenko V., Groop L., Meisinger C., Döring A., Löwel H., Lieb W., Hengstenberg C., Rathmann W., Martin S., Stephens J.W., Ireland H., Mather H., Miller G.J., Stringham H.M., Boehnke M., Tuomilehto J., Boeing H., Möhlig M., Spranger J., Pfeiffer A., Wernstedt I., Niklason A., López-Bermejo A., Fernández-Real J.M., Hanson R.L., Gallart L., Vendrell J., Tsiavou A., Hatziagelaki E., Humphries S.E., Wichmann H.E., Herder C., Illig T. 2006. *IL6* gene promoter polymorphisms and type 2 diabetes: joint analysis of individual participants' data from 21 studies. *Diabetes*. **55** (10), 2915–2921. https://doi.org/10.2337/db06-0600
24. Svechnikova E.V., Spitsyna A.V., Nemchaninova O.B., Lykova S.G., Maksimova Yu.V., Maksimov V.N. 2018. General genetic aspects of psoriasis and type 2 diabetes mellitus. *Med. Al'm.* **3**, 124–127.
25. Akinyemi R., Arnett D.K., Tiwari H.K., Ovbiagele B., Sarfo F., Srinivasasainagendra V., Irvin M.R., Adeoye A., Perry R.T., Akpalu A., Jenkins C., Owolabi L., Obiako R., Wahab K., Sanya E., Komolafe M., Fawale M., Adebayo P., Osaigbovo G., Sunmonu T., Olowoyo P., Chukwuonye I., Obiabo Y., Akpa O., Melikam S., Saulson R., Kalaria R., Ogunniyi A., Owolabi M., SIREN Investigators. 2017. Interleukin-6 (*IL-6*) rs1800796 and cyclin dependent kinase inhibitor (*CDKN2A/CDKN2B*) rs2383207 are associated with ischemic stroke in indigenous West African men. *J. Neurol. Sci.* **15** (379), 229–235. https://doi.org/10.1016/j.jns.2017.05.046
26. Peng X., Shi J., Sun W., Ruan X., Guo Y., Zhao L., Wang J., Li B. 2018. Genetic polymorphisms of IL-6 promoter in cancer susceptibility and prognosis: a meta-analysis. *Oncotarget.* **5**, 12351–12364. https://doi.org/10.18632/oncotarget.24033
27. Capurso C., Solfrizzi V., D'Introno A., Colacicco A.M., Capurso S.A., Capurso A., Panza F. 2004. Interleukin 6 –174G/C promoter gene polymorphism and sporadic Alzheimer's disease: geographic allele and genotype variations in Europe. *Exp. Gerontol.* **39**, 1567–1573. https://doi.org/10.1016/j.exger.2004.07.006
28. Mingazheva E.T., Prokof'eva D.S., Valova Ya.V., Nurgalieva A.Kh., Valiev R.R., Romanova A.R., Faiskhanova R.R., Sakaeva D.D., Khusnutdinova E.K. 2019. The role of polymorphic variants of immune response and inflammation genes in the pathogenesis of ovarian cancer in women of different ethnic origins. *Med. Genet.* **18** (10), 10–20. https://doi.org/10.25557/2073-7998.2019.10.10-20
29. Carulli L., Canedi I., Rondinella S., Lombardini S., Ganazzi D., Fargion S., De Palma M., Lonardo A., Ricchi M., Bertolotti M., Carulli N., Loria P. 2009. Genetic polymorphisms in non-alcoholicfatty liver disease: interleukin-6 –174G/C polymorphismis associated with nonalcoholic steatohepatitis. *Dig. Liver Dis.* **41**, 823–828. https://doi.org/10.1016/j.dld.2009.03.005
30. Kurbatova I.V., Topchieva L.V., Dudanova O.P. 2017. Caspase 3, 6, 8, and 9 gene expression in peripheral blood leukocytes and plasma concentrations of IL-6 and TNF-α in carriers of different polymorphic marker –174G>C genotypes of IL6 gene associated with the risk of nonalcoholic steatohepatitis. *Bull. Exp. Biol. Med.* **162** (9), 356–361.
31. Ben Salkha M., Repina N.B., Dmitrieva M.N. 2018. Methods for diagnosing postoperative adhesions in the small pelvis in women with chronic pelvic pain against the background of undifferentiated connective tissue dysplasia. *Vestn. Avitsenny*. **20** (1), 13–19. https://doi.org/10.25005/2074-0581-2018-20-1-13-19
32. Bakhareva Yu.S., Maksimov V.N., Ivanova A.A., Chapaeva N.N., Aidagulova C.V., Voevoda M.I. 2022. Candidate gene polymorphisms associated with clinical and hemostasiological characteristics of endocarditis of various etiologies. *Byull. Sib. Med.* **21** (1), 6–13. https://doi.org/10.20538/1682-0363-2022-1-6-13
33. Topchieva L.V., Kurbatova I.V., Dudanova O.P., Sokolovskaya A.A., Shipovskaya A.A. 2017. Polymorphism of proinflammatory cytokine genes (*TNF*, *IL6*) and their receptors (*TNFRSF1A*, *TNFRSF1B*, and *IL6R*) and non-alcoholic fatty liver disease. *Tr. Karel. Nauchn. Tsentra Ross. Akad. Nauk.* **5**, 3–22. https://doi.org/10.17076/eb568
34. Borinskaya S.A., Gureev A.S., Orlova A.A., Sanina E.D., Kim A.A., Gasemianrodsari F., Shirmanov V.I., Balanovsky O.P., Rebrikov D.V., Koshechkin A.V., Yankovsky N.K. 2013. Allele frequency distributions of –174G/C polymorphism in regulatory region of interleukin 6 gene (*IL6*) in Russian and worldwide populations. *Russ. J. Genet.* **49** (1), 98–109. https://doi.org/10.1038/nature11632
35. The 1000 Genomes Project Consortium. 2012. An integrated map of genetic variation from 1092 human genomes. *Nature*. **491**, 56–65. https://doi.org/10.17076/eb568
36. Samgina T.A., Zhivotova G.A., Nazarenko P.M., Polonikov A.V. 2017. The role of cytokine gene polymorphisms in the development of acute pancreatitis: analysis of intergenic and gene–environmental interactions. *Ross. Zh. Gastroenterol. Gepatol. Koloproktol.* **27** (3), 27–33. https://doi.org/10.22416/1382-4376-2017-27-3-27-33
37. Minushkina L.O., Aseycheva O.Yu., Kochkina M.S., Nikitin A.G., Zateyschikov D.A. 2017. Genetic polymorphism of cytokine genes of the inflammatory system and the state of the vascular wall in patients with arterial hypertension. *Arterial'naya Gipertenziya*. **23** (2), 103–111. https://doi.org/10.18705/1607-419X-2017-23-2-103-111
38. Zotova I.V., Brovkina A.N., Fattakhova E.N., Nikitina A.N., Nosikov V.V., Brazhnik V.A., Zateishchikov D.A. 2015. Genetic polymorphism of inflammato-

ry system factors associated with thromboembolic complications of atrial fibrillation. *Ross. Kardiol. Zh.* **20** (10), 35–41.
https://doi.org/10.15829/1560-4071-2015-10-35-41201

39. Sambrook J., Fritsch E.F., Maniatis T. 1989. *Molecular Cloning: A Laboratory Manual.* Cold Spring Harbor, N.Y.: Cold Spring Harbor Lab. Press, 2nd ed.
40. Tabikhanova L.E., Osipova L.P., Voronina E.N., Bragin A.O., Filipenko M.L. 2019. Polymorphism of lipid exchange genes in some populations of South and East Siberia. *Vavilov. Zh. Genet. Sel.* **23** (8), 1011–1019.
https://doi.org/10.18699/VJ19.578
41. Tabikhanova L.E., Osipova L.P., Churkina T.V., Voronina E.N., Filipenko M.L. 2022. Polymorphism of the TCF7L2 gene in the populations of five ethnic groups of Siberia. *Vavilov. Zh. Genet. Sel.* **26** (2), 188–195.
https://doi.org/10.18699/VJGB-22-23
42. Murray D.R., Schaller M. 2010. Historical prevalence of infectious diseases within 230 geopolitical regions: a tool for investigating origins of culture. *J. Cross-Cult. Psychol.* **1**, 99–108.
https://doi.org/10.1177/0022022109349510
43. Cole S.W., Arevalo J.M., Manu K., Telzer E.H., Kiang L., Bower J.E., Irwin M.R., Fuligni A.J. 2011. Antagonistic pleiotropy at the human *IL6* promoter confers genetic resilience to the pro-inflammatory effects of adverse social conditions in adolescence. *Dev. Psychol.* **47**, 1173–1180.
https://doi.org/10.1037/a0023871