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Association of the Genenetic Polymorphism of Cytokines and Their Receptors with Climate and Geographic Factors in Human Populations

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Abstract—The variability of eight polymorphic variants of the *IL4*, *IL4R*, *IL10*, *IL13*, *IL12A*, and *IL12RB2* genes encoding key cytokines and their receptors in 57 world populations has been assessed. A correlation between the allele frequency distribution of the examined genes and climatic and geographic factors was observed.

The analysis of the genetic structure of human populations with respect to immune response genes is an important issue [1, 2]. Immune response genes include a wide variety of genes, including cytokine genes, the products of which represent immunomodulating proteins. Some studies previously revealed an adaptive role of gene polymorphisms in several cytokines in human populations and demonstrated decanalisation of the immune response under natural selection conditions in the course of the settling of modern humans [3, 4]. The aim of this study was to assess the interpopulation variability of allele frequencies in anti-inflammatory cytokine genes *IL4*, *IL10*, *IL13*, pro-inflammatory cytokine *IL12A*, and their receptors *IL4R* and *IL12RB2*, as well as the associations of cytokine genetic variability with climatic and geographical factors.

Eight polymorphic variants of genes associated with disturbances of normal functioning of the immune system were genotyped in the study. Polymorphic marker rs20541 of the *IL13* gene, located in exon four, was associated with asthma and an increased concentration of IgE [5−7]. Promoter polymorphism rs1800896 affected the expression of the *IL10* gene and was associated with allergy. The association of allele *G* with asthma was also revealed [8, 9]. Alleles *T* and *G* of polymorphic markers rs485499 and rs6441286 of *IL12A* were associated with primary biliary liver cirrhosis [10, 11] as well as intron-located polymorphism rs3790567 (*IL12RB2*) [11, 12]. Polymorphic variant rs2070874 of *IL4* was associated with the risk of development of asthma and allergy [13−15]. Exon polymorphisms of the *IL4R* gene, rs1801275 and rs1805015, were associated with IgE concentration [16].

In this study, the allele and genotype frequencies of the examined SNPs in 26 populations representing the native population of Eastern Europe (Russians, Komi, Mari, Tsezi, Gagauz, Aguls, Bezhtin, Ukrainians, and Moldavians), the Middle East (Kazakhs, Uzbeks, and Kyrgyz), and Siberia and the Far East (Yakuts, Kets, Northern Altaians, Southern Altaians, Evenks, Buryats, Khants, Tuvinians, Khakass, Shors, Chukchi, Nivkhs, Koryaks, and Udeghe) were determined. The total sample volume was 1228 unrelated and nonmetis subjects.

Genotyping was conducted using MALDI-TOF mass-spectrometry described previously [17, 18]. The allele frequencies in the examined populations are presented in Table 1; genotypes are available on request from authors. For statistical analysis, the data for 26 personal populations were combined with data on 31 ethnic groups from the HapMap/1000 Genomes project (Yoruba, Luhya, Toscani, British, Finnish, Japanese, Chinese, Masai, and Indians) and the "Human Genome Diversity Project" (HGDP; Biaka Pygmies, Mandenka, Karitiana, Maya, Pima, Surui, Basque, French, Sardinian, Bedouin, Druze, Mozabite, Palestinian, Melanesian, Papuan, Balochi, Brahui, Burusho, Hazara, Kalash, Pathan, and Sindhi) [19−21]. From these projects, only nonmetis native populations were selected.

The analysis of genetic diversity, the matching of genotype distribution to the Hardy−Weinberg equilibrium, and the Ewens−Watterson test revealing selective neutrality of gene polymorphisms was conducted using ARLEQUIN 3.11 software (http://cmpg.unibe.ch/software/arlequi3) [22]. The association of ancestor allele frequencies and average expected heterozygosis with climate and geographical indices was

Table 1. Frequencies of ancestral alleles of cytokine genes and their receptors in the examined populations

Population	Gene, SNP, ancestral allele							
	IL10 rs1800896 Allele *A*	*IL4R* rs1801275 Allele *G*	*IL4R* rs1805015 Allele *T*	*IL13* rs20541 Allele *C*	*IL4* rs2070874 Allele *T*	*IL12RB2* rs3790567 Allele *A*	*IL12A* rs485499 Allele *T*	*IL12A* rs6441286 Allele *T*
Russians	0.51	0.17	0.87	0.67	0.32	0.24	0.48	0.65
Komi	0.55	0.14	0.89	0.69	0.22	0.22	0.64	0.63
Mari	0.77	0.15	0.91	0.68	0.39	0.38	0.49	0.50
Yakuts	0.93	0.20	0.92	0.73	0.59	0.19	0.96	0.39
Kets	0.75	0.18	0.89	0.52	0.55	0.34	0.63	0.06
Kazakhs	0.74	0.21	0.88	0.78	0.49	0.16	0.69	0.00
Uzbeks	0.70	0.17	0.92	0.64	0.39	0.19	0.74	0.48
Southern Altaians	0.71	0.23	0.87	0.73	0.51	0.20	0.88	0.38
Buryats	0.85	0.22	0.92	0.73	0.52	0.32	0.93	0.48
Khants	0.68	0.09	0.96	0.69	0.27	0.16	0.68	0.62
Kyrgyz	0.75	0.18	0.93	0.76	0.45	0.17	0.89	0.25
Tsezi	0.47	0.06	0.95	0.82	0.04	0.41	0.56	0.41
Tuvinians	0.81	0.19	0.92	0.74	0.55	0.25	0.80	0.00
Gagauz	0.71	0.16	0.87	0.88	0.17	0.26	0.69	0.01
Khakass	0.84	0.09	0.98	0.79	0.53	0.15	0.79	0.38
Shors	0.85	0.09	0.94	0.72	0.47	0.19	0.86	0.21
Chukchi	0.84	0.15	0.91	0.40	0.78	0.18	0.87	0.03
Nivkhs	0.89	0.41	1.00	0.60	0.52	0.21	0.92	0.00
Koryaks	0.78	0.22	1.00	0.39	0.85	0.19	0.89	0.44
Udeghe	0.84	0.14	0.91	0.62	0.70	0.47	0.86	0.49
Aguls	0.58	0.17	0.86	0.77	0.14	0.15	0.51	0.39
Bezhtin	0.57	0.24	0.77	0.80	0.10	0.15	0.40	0.08
Ukrainians	0.63	0.13	0.92	0.66	0.21	0.31	0.52	0.62
Moldavians	0.63	0.11	0.90	0.72	0.21	0.29	0.64	0.51
Northern Altaians	0.90	0.15	0.95	0.67	0.47	0.21	0.84	0.10
Evenks	0.76	0.08	0.95	0.72	0.57	0.22	0.82	0.07

assessed using the Spearman's correlation coefficient. Climate changes were acquired from the Weatherbase Database (http://www.weatherbase.com).

We revealed deviation from Hardy–Weinberg equilibrium ($p < 0.05$) in 12 cases from 208 distributions. No accumulation of deviations from the equilibrium in individual populations and polymorphic variants of cytokine genes and their receptors was observed. In ethnically dissimilar populations, significant variability in the ancestral allele frequencies and the average expected heterozygosis (*He*) was revealed. The *He* of proinflammatory cytokine and the receptor *IL12RB2* (*He*-pro) gene varied from 0.20 in the Chukchi to 0.49 in the Mari; the *He* of the anti-inflammatory *IL4R*

(*He*-anti) gene and receptor varied from 0.21 in the French to 0.42 in the Masai. The total average expected heterozygosis (*He*-total) varied from 0.26 in the Chukchi to 0.42 in Pima Indians. For polymorphic variants rs1805015, rs3790567, and rs6441286, a correlation of allele frequencies and heterozygosis with latitude (in equator degrees), longitude (in Greenwich degrees), average annual temperature, temperatures of the coldest and warmest months, and temperature variability was demonstrated (Table 2). No significant association of average expected heterozygosis in all of the marker systems of pro- and anti-inflammatory cytokines and their receptor markers (*He*-total, *He*-pro, *He*-anti) with climatic and geographical parameters

Table 2. Association of ancestor allele frequencies of cytokine genes and their receptors and the average expected heterozygosis with climatic and geographic parameters

SNP	Latitude from equator	Longitude from Greenwich	Average annual temperature	Temperature of the coldest month	Temperature of the warmest month	Temperature variation
rs1800896	0.7091	**0.0000**	0.7656	0.2842	0.3420	**0.0215**
rs1801275	**0.0004**	0.3301	**0.0011**	**0.0007**	**0.0314**	**0.0025**
rs1805015	**0.0030**	**0.0000**	**0.0002**	**0.0001**	**0.0142**	**0.0002**
rs20541	0.1480	**0.0000**	0.0929	0.0592	0.3866	**0.0079**
rs2070874	0.2199	**0.0000**	**0.0279**	**0.0213**	0.3876	**0.0006**
rs3790567	**0.0001**	**0.0228**	**0.0004**	**0.0003**	**0.0136**	**0.0024**
rs485499	**0.0221**	**0.0000**	0.1752	0.2005	0.0753	0.9160
rs6441286	**0.0000**	**0.0021**	**0.0000**	**0.0000**	**0.0064**	**0.0000**
He-total	0.5995	**0.0197**	0.1193	0.2061	0.4410	0.3452
He-pro	0.6343	**0.0037**	0.3794	0.6001	0.3503	0.5131
He-anti	0.0989	0.4156	0.1125	0.0887	0.9226	0.1379

The Table shows values of Spearman's correlation coefficient. Significant correlations ($p < 0.05$) with climatic and geographic parameters are presented in bold. *He*-total, total expected heterozygosis. *He*-pro, average expected heterozygosis of proinflammatory cytokine and receptor *IL2RB2*. *He*-anti, average expected heterozygosis of anti-inflammatory cytokine and receptor *IL4R*.

**Table 3.** Deviation from marker selective neutrality in populations

Marker	Populations
rs1800896	Russians (0.0117); Komi (0.0385); Tsezi (0.0261); British (0.0067); French (0.0237); Sindhi (0.0442)
rs1801275	–
rs1805015	Luhya (0.0202); Yoruba (0.0192); Masai (0.0031)
rs20541	Kets (0.0242)
rs2070874	Kets (0.0454); Kazakhs (0.0128); Buryats (0.0193); Kyrgyz (0.0396); Tuvinians (0.0429); Khakass (0.0284); Shors (0.0320); Nivkhs (0.0234); Southern Altaians (0.0131); Northern Altaians (0.0275); Yoruba (0.0055); Mandenka (0.0290); Pima (0.0290); Melanesian (0.0099)
rs3790567	Udeghe (0.0317)
rs485499	Russians (0.0190); Mari (0.0132); Tsezi (0.0437); Aguls (0.0111); Ukrainians (0.0238)
rs6441286	Mari (0.0037); Uzbeks (0.0241); Buryats (0.0218); Udeghe (0.0165); Moldavians (0.0144); Basque (0.0302); Hazara (0.0089); Maya (0.0097); Chinese (0.0151); Japanese (0.0177); Brahui (0.0451)

The significance of the population declination from the hypothesis of neutrality, where $p < 0.05$ are presented in brackets.

was revealed. Among environmental variables, a higher number of correlations with allele frequencies was observed with Greenwich longitude (Table 2). In total, four out of the eight examined markers demonstrated stable associations of allele frequencies with the distance from equator and climate parameters, which was expected in accordance with the concept of decanalization of immune response [4]. At the same time, no differentiation in correlation specificity between pro- and anti-inflammatory cytokines was noted.

The Ewens–Watterson test has shown that a deviation from neutrality in 14 examined populations for polymorphic variant rs2070874 and in 11 populations for marker rs6441286 for other loci deviation was observed in rare instances (Table 3).

The method of principle components (PC) was applied for the analysis of genetic relations between populations. PC1 and PC2 account for 71.13% of allele frequency variability. African populations form a separate cluster in the PC1–PC2 space. Overall, the
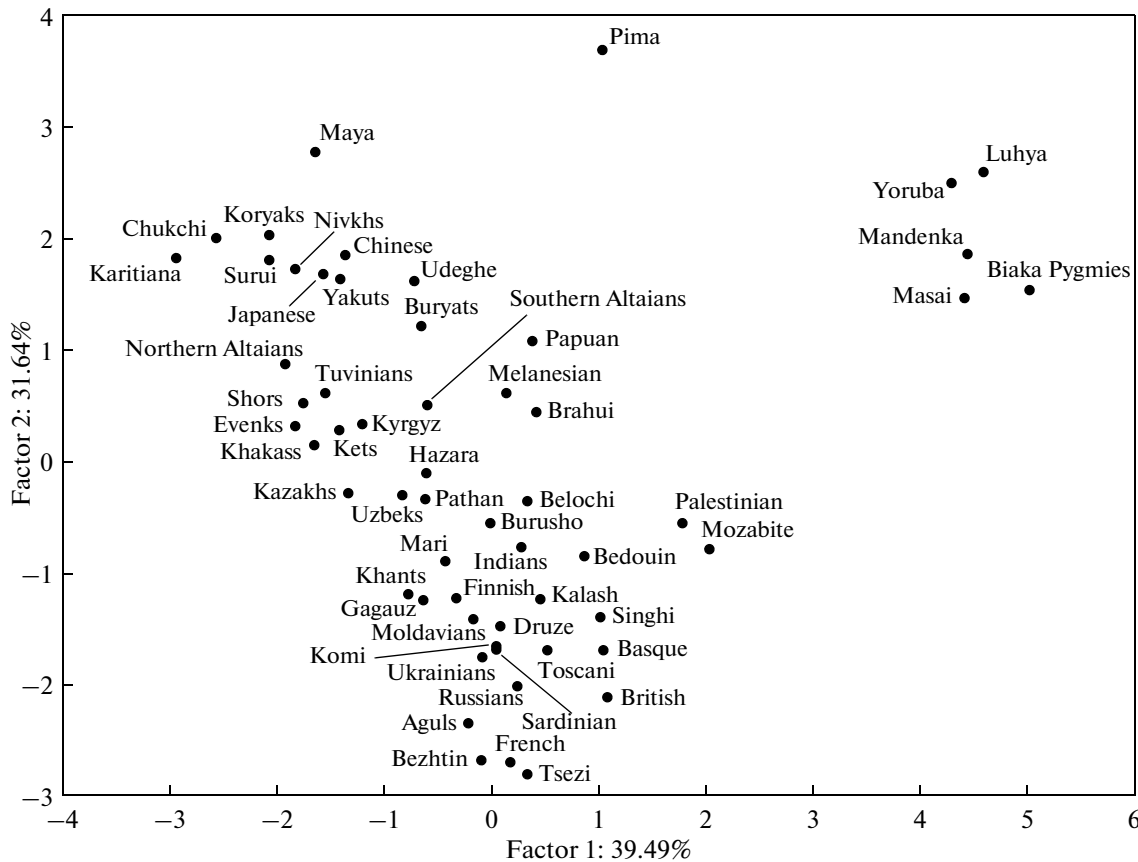
Spatial location of populations of major components according to ancestral allele frequencies of the examined cytokine genes and their receptors.

expected trend toward clusterization of populations in accordance with their affiliation to geographic regions was observed (figure).

Our results show significant interpopulation genetic variability of pro- and anti-inflammatory cytokines and their receptor genes and the association of this variability with climatic and geographic parameters. Our data support the existing hypothesis of decanalization of genetic variability of immune response genes in the course of human settlement [4].

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