REVIEWS
AND THEORETICAL ARTICLES

Search for Genetic Markers of Climatic Adaptation in Populations of North Eurasia

V. A. Stepanov[a, b, *], **V. N. Kharkov**[a, b], **K. V. Vagaitseva**[a, b], **A. V. Bocharova**[a],
A. Yu. Kazantsev[c], **A. A. Popovich**[a], and **I. Yu. Khitrinskaya**[a]

[a] *Institute of Medical Genetics, Tomsk National Medical Research Center, Tomsk, 634050 Russia*
[b] *Tomsk State University, Tomsk, 634050 Russia*
[c] *Tomsk Polytechnic University, Tomsk, 634050 Russia*
*e-mail vadim.stepanov@medgenetics.ru
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Abstract—Genetic diversity of native populations of North Eurasia is investigated using a panel of genetic markers of candidate genes for cold climate adaptation. A high level of within- and between-population variability is detected. Comparative analysis of data on North Eurasian populations combined with data on worldwide populations from the 1000 Genomes and HDGP projects reveals correlations of genetic diversity in candidate genes for cold climate adaptation with key climate parameters, as well as the increase of genetic diversity in markers of this group of genes with the increase of latitude, that is, as modern humans migrated out of Africa. Using the method of searching for extreme empirical values of the coefficient of genetic diversity, signals of directional selection for markers of six genes adaptive to cold (*MYOF*, *LONP2*, *IFNL4*, *MKL1*, *SLC2A12*, and *CPT1A*) are found. The data are discussed in framework of the hypothesis of decanalization of genome–phenome relationships under the pressure of natural selection during human settlement throughout the world.

INTRODUCTION

Modern humans are a unique biological species in terms of the range of habitat occupied and the speed of settlement. Ancestors of modern humans for at least several million years evolved in Africa and adapted to the conditions of a hot tropical climate. The settlement of humans from the place of origin of *Homo sapiens* in East Africa across the globe was rapid in evolutionary terms, taking the last 50000–100000 years, and was associated with the change of climatic zones from a tropical climate to temperate and Arctic ones and the environmental parameters associated with these changes, such as temperature, humidity, insolation, and infectious load. Modern humans penetrated into the subarctic and Arctic zones of Eurasia relatively recently, 30000–40000 years ago. Human survival in a cold climate probably involved processes of different scale and different nature, such as short-term acclimatization, long-term adaptation, and sociocultural changes. The relationship and the role of these mechanisms in survival in an extreme climate remain unclear, but the phenotypic features of the present indigenous populations of Northern Eurasia and the features of their gene pool indicate the possible role of directed natural selection in the adaptation of indigenous populations to extreme climatic conditions. We assume that natural selection-mediated adaptation of populations inhabiting Siberia, North Asia, and the north of the European part of Russia to conditions of a cold climate led to the formation of adaptation signals: specific characteristics of the gene pool and genetic diversity for genes involved in the formation of adaptively significant phenotypes. Identification of such signals using modern genomic and bioinformational approaches is an important and urgent fundamental problem of human genetics.

Recently, data on the role of individual genes in adaptation to cold and their markers that reflect specific features of the gene pool of the indigenous population of Siberia and North Asia have been accumulated [1–3]. Several modern studies aimed at searching for signals of natural selection in the human genome and in the gene pools of individual populations revealed a large number of polymorphic positions in the genome which were under selection during human population [3–6]. Some of these markers are probably related to indirect selection by adaptation of the genetic structure of the populations of Northern Eurasia to a cold climate.

Previously, we created a panel of 28 genetic markers potentially associated with adaptation to a cold climate (low temperature) according to the data of genome-wide population studies and involved in biological processes potentially adaptive to cold resistance [7].

The objectives of this study were to characterize the allele frequencies of the markers of this panel in populations of Northern Eurasia, to analyze the relationship between the genetic diversity of this group of markers to climatic and geographical parameters, and to search for natural selection signals for the genes and markers being studied.

MATERIALS AND METHODS

Population Samples

This work was carried out using the population samples from the biological collection of the Institute of Medical Genetics of the Tomsk National Research Medical Center of the Russian Academy of Sciences Biobank of the Population of Northern Eurasia, as well as collections of biological samples from the Research Institute of Therapy (Novosibirsk), representing 12 indigenous groups of Siberia, North Asia, Northeastern Europe, and Central Asia, totaling 870 samples. Siberian populations are represented in the work by samples of Yakuts ($N = 102$), Buryats ($N = 95$), Khanty ($N = 95$), and Kets ($N = 48$). Yakuts speak the language of the Turkic group of the Altaic language family. The language of Buryats belongs to the Mongolian group of the Altai family. Khanty speak the language of the Ugric group of the Finno-Ugric language family. The language of Kets is isolated. The Yakuts and Buryats belong to the Central Asian subtype of the Mongoloid race type, and Khanty and Kets are representatives of the Uralic anthropological type.

The indigenous population of North Asia is represented in the work by Nivkhs ($N = 95$), Koryaks ($N = 89$), Chukchi ($N = 95$), and Eskimos ($N = 8$). Nivkhs belong to the Sakhalin-Amur subtype of the Mongoloid racial type and speak the language of the Nivkh group of the Paleo-Asiatic language family. Koryaks, Chukchi, and Eskimos belong to the Arctic subtype of the Mongoloid race type. The language of Koryaks and Chukchi belongs to the Chukchi-Kamchatka language family, and the language of the Eskimos belongs to the Eskimo-Aleut family.

The sample of Udmurts ($N = 95$) geographically represents Northeastern Europe. Udmurts belong to the sublapanoid racial type and speak a language included in the Perm subgroup of the Finno-Ugric language family.

The population of Central Asia is represented by samples from populations of Uzbeks ($N = 53$), northern Kyrgyz from Bishkek ($N = 48$), and southern Kyrgyz from Osh ($N = 47$). The languages of Uzbeks and Kyrgyz belong to the Turkic group of the Altaic language family. Anthropologically, Kyrgyz belong to the South Siberian subtype of the Mongoloid racial type, and Uzbeks are a metis group that combines features of the Caucasoid and Mongoloid anthropological types.

The samples included unrelated individuals not meticised in three generations who signed an informed consent for the study. Detailed characteristics of the samples are given in previous papers [7–9]. The study was approved by the ethics committee of the Research Institute of Medical Genetics.

To analyze the relationship of the genetic diversity to climatic and geographical parameters and to search for natural selection signals for the genes and markers studied, an array of allele frequencies was used, consisting of 12 populations of Northern Eurasia and 42 populations not meticised from the 1000 Genomes [10, 11] and Human Genome Diversity (HGDP) projects [12], representing the population of different regions of the world.

From the 1000 Genomes Project, we extracted data for the following 19 populations (ethnic group names and places of residence are indicated):

• Africa: Ishans (Nigeria), Gambians (Gamiya), Luhya (Kenya), Mende (Sierra Leone), and Yoruba (Ibadan, Nigeria);

• Europe: Finns (Finland), British (England and Scotland), Iberians (Spain), and Tuscans (Italy);

• Hindustan: Bengali (Bangladesh), Indians (Gujarat, India), Telugu (India), Punjabis (Lahore, Pakistan), and Sri Lanka Tamil of Tamil (Sri Lanka);

• Southeast Asia: Chinese (Xishuangbanna-Dai Autonomous Region, China); Chinese (Beijing), southern Chinese (China), Japanese (Tokyo, Japan); Vietnamese (Ho Chi Minh City, Vietnam).

From the HGDP project, data were taken for 23 populations:

• Africa: Mandenka (Sierra Leone), Bayaka pygmies (Republic of Congo), and Mozabits (Algeria);

• Europe: Basques (Spain), French (France), and Sardinians (Sardinia, Italy);

• Middle East: Bedouins (Jordan), Druze (Israel), and Palestinians (Israel);

• Central and South Asia: Baloch, Brahui, Burushas, Hazaras, Kalashis, Pashtuns, Makran, and Sindhi (all Pakistan);

• America: Maya Indians (Mexico); Pima Indians (Mexico), Caritian Indians (Brazil), Surui Indians (Brazil).

• Oceania: Papuans (Papua New Guinea) and Melanesians (Solomon Islands).

The frequencies of alleles and genotypes for the studied loci in the populations from the 1000 Genomes and HGDP projects are available on request from the authors.

The correlation of allele frequencies and genetic diversity (expected heterozygosity) with climate parameters for all the populations were analyzed by obtaining their geographic coordinates as well as key climate characteristics (mean annual temperature, minimum and average winter temperatures, maximum and average summer temperatures, spread of mean and extreme temperatures, average annual humidity, and precipitation level). The climatic characteristics of the habitats of the studied populations were obtained from the Weatherbase database (http://www.weatherbase.com).

Choice of Genetic Markers and Genotyping

The list of 28 single nucleotide genetic markers (SNP) used in the work and their belonging to genes and regions of the genome are given in Table 1. The principles of the choice of genetic markers for the search for genetic signals of adaptation to climate in the population of Northern Eurasia were described by us earlier [13]. The study included markers located in the genome regions under the possible action of natural selection, according to complete genomic and genome-wide studies [3–6], as well as markers belonging to genes involved in biological processes potentially adaptive to cold resistance. Such processes include thermoregulation, response to temperature stress, energy metabolism, lipid metabolism, regulation of muscle contractions, regulation of blood pressure, signaling, and intercellular interactions.

Genotyping was carried out by the method of multilocus PCR and matrix-activated laser desorption/ionization with flight time measurement (MALDI-TOF mass spectrometry) using a Sequenom MassARRAY 4 mass spectrometer as described earlier [13, 14].

Statistical Processing of Results

For statistical processing of the results, standard population-genetic approaches implemented in the Arlequin package [15] and described earlier [16] were used. The correspondence of the distribution of the genotypes to the Hardy–Weinberg equilibrium was estimated using an accurate test of Guo and Thomson. Intra- and interpopulation genetic diversity was estimated by molecular dispersion (AMOVA).

Correlations of allele frequencies and genetic diversity with geographic and climatic parameters were estimated using the Spearman rank correlation coefficient (R) in the Statistica software package.

The search for loci under the possible effect of directional natural selection during human settlement was carried out by analyzing the distribution of the observed F_{ST} values as compared to the expected distribution (FDIST test) obtained in simulations (20000 simulations) based on the hierarchical island model of

the population structure [17–20]. Values ($1-F_{ST}$ quantile) <0.01 were considered as a nonrandom entry of empirical F_{ST} values into the number of outliers (analog of significance level $p < 0.01$).

RESULTS AND DISCUSSION

Allele Frequencies and Genetic Diversity in Indigenous Populations of Northern Eurasia

Allele frequencies of 28 markers in 12 populations of Northern Eurasia and mean values of the expected heterozygosity are presented in Table 2. The distribution of genotypes in populations in most cases corresponded to the Hardy–Weinberg equilibrium (HWE). An exact test for the Hardy–Weinberg equilibrium with the Bonferroni correction revealed three deviations from the HWE in a small sample of Eskimos and one deviation in Yakuts and Nivkhs each.

The maximum values of the average expected heterozygosity were found in the populations of Uzbeks and Kyrgyz (0.42–0.39); the minimum values were observed in Buryats, Yakuts, and Khanty (0.31–0.33). In general, the populations under study revealed a downward tendency of genetic diversity from the southwest to the northeast. In the most northern populations, the diversity is reduced owing to a higher frequency of the derived (non-ancestral, the most frequent in African populations) allele.

The overall level of genetic differentiation of the investigated populations for 28 markers was 7.6% ($F_{ST} = 0.0764$).

The change in the genetic structure of human populations in the course of adaptation to habitat conditions, mediated by natural selection, is a long-term process implemented over many generations. Attempts to capture the signals of this process in modern populations require a comparative analysis of the characteristics of genetic diversity in populations of different geographic and climatic regions. In particular, in order to detect the peculiarities of the genetic structure of populations living in the Arctic and continental temperate climates associated with adaptation to cold, it is necessary to compare this structure (allele frequencies and genetic diversity) with populations of other climatic and geographic zones of the globe. For this analysis, we combined our above data on allele frequencies in 12 populations of Northern Eurasia with published data on 42 world populations living in tropical, subtropical, and temperate climates.

To identify the relationship of the genetic structure to the characteristics of the habitat and to search for possible mechanisms that mediate such a relationship, we used two approaches: (1) analysis of the correlation of allele frequencies and genetic diversity with climatic and geographic parameters; (2) search for loci under the possible directional selection during human settlement by analyzing the distribution of observed F_{ST} values over the expected distribution (FDIST).

Table 1. Genes and genetic markers

No.	Marker (SNP)	Alleles	Chromosome	Position on chromosome	Gene	Name of gene or its product
1	rs10509653	C/T	10	93366834	*MYOF*	Myoferlin
2	rs10887778	C/T	10	88093685	*LOC105378415*	RNA-encoding gene *LOC105378415*
3	rs12446160	A/G	16	48324457	*LONP2*	Lon-protease 2, peroxisomal
4	rs12946049	C/T	17	80620869	*RPTOR*	Regulatory protein associated with rapamycin target in mammals, complex 1
5	rs12979860	C/T	19	39248147	*IFNL4*	Interferon, lambda 4
6	rs133036	C/T	22	40616434	*MKL1*	Gene of acute megakaryoblastic leukemia (translocation) 1
7	rs1513687	C/T	18	39724791	*LINC00669*	Extended intergenic protein noncoding RNA 669
8	rs16984239	A/C	2	18053180	*KCNS3/RDH14*	Potential-dependent potassium channel modifier, subfamily S, member 3/retinol dehydrogenase 14
9	rs1800592	A/G	4	140572807	*UCP1*	Thermogenin, uncoupling protein 1, RB-1
10	rs1800849	C/T	11	74009120	*UCP3*	Thermogenin, uncoupling protein 3
11	rs1805490	A/G	12	13588137	*GRIN2B*	Ionotropic glutamate receptor, N-methyl-D-aspartate 2B
12	rs2015865	A/C	22	43393211	*LOC105373053/ LOC105373054*	RNA-encoding gene *LOC105373053*/RNA-encoding gene *LOC105373054* (RNA gene)
13	rs2193045	A/G	12	68140740	*HNRNPA1P70/ LOC100509370*	Heterogeneous nuclear ribonucleoprotein A1, pseudogene 70/ribosomal protein L21, mitochondrial pseudogene
14	rs2216163	C/T	12	68137176	*HNRNPA1P70/ LOC100509370*	The same
15	rs2273428	C/T	6	69933126	*COL19A1*	Collagen, type XIX, α1
16	rs2283792	G/T	22	21776836	*MAPK1*	Mitogen-activated protein kinase 1
17	rs2298432	A/C	22	21768900	*MAPK1*	The same
18	rs2301727	C/T	7	20381596	*ITGB8*	β-subunit of integrin αvβ8
19	rs2305508	A/G	11	68782078	*CPT1A*	Hepatic carnitine-palmitoyltransferase 1A
20	rs3741135	C/T	11	74002915	*UCP3*	Thermogenin, uncoupling protein 3
21	rs4507607	A/G	6	134088661	*SLC2A12*	Family 2 of glucose transport proteins, isoform 12

Table 1. (Contd.)

No.	Marker (SNP)	Alleles	Chromosome	Position on chromosome	Gene	Name of gene or its product
22	rs4930248	C/T	11	68798436	*CPT1A*	Hepatic carnitine-palmitoyl-transferase 1A
23	rs4944925	A/G	11	74648484	*POLD3*	Auxiliary subunit of DNA polymerase, Delta 3
24	rs608343	A/G	11	68429362	*LRP5*	Protein 5 associated with low density lipoprotein receptor
25	rs6724627	A/G	2	170651752	*MYO3B*	Myosin IIIB
26	rs809812	A/G	10	93448022	*MYOF*	Myoferlin
27	rs892878	C/T	2	137114290	*THSD7B*	Thrombospondin, type I, containing a 7B region
28	rs908394	A/G	12	59119000	*LOC105369791*	RNA-encoding gene *LOC105369791*

Correlations of Allele Frequencies and Genetic Diversity with Geographical and Climatic Parameters

For an absolute majority of polymorphic markers in the genes of adaptation to cold climate and for the general characteristics of the genetic diversity of the selected marker system, a significant correlation with the absolute latitude (27 markers), average annual temperature (27 markers), temperature of the coldest month (27 markers), and temperature spread (28 markers) was revealed (Table 3).

The Figure 1 illustrates the correlation of the most common parameter characterizing the genetic variability of the studied group of markers—the average expected heterozygosity—with the absolute latitude ($r = 0.65$, $p = 0.0000$). The points in the lower left part of the graph represent populations of tropical regions (Africa, South and Central America, and Oceania). The populations of Eurasia are concentrated on the right side of the graph, where samples of the studied populations of the north of the continent occupy a place in the upper right corner of the graph, that is, they are characterized by the maximum distance from the equator and high values of genetic diversity. The growth of the genetic diversity of populations as we move from the equator to the poles completely contradicts the picture observed for conditionally neutral markers or for genomic diversity in general, but repeats the trend we recorded earlier for genes of immune-dependent phenotypes [9, 21].

It is noteworthy that the allele frequencies and genetic diversity of the populations are highly correlated with the parameters that primarily reflect the "severity" of the climate—geographical latitude and temperature values forming the first principal component of climatic variables (see [22]). At the same time, genetic parameters (allele frequencies and heterozygosity) are much less closely related to longitude and variables characterizing the climate humidity and forming the second principal component of climate characteristics. So, the longitude and average annual precipitation correlates with only 20 markers out of 28, and the average relative humidity correlates with only two markers. The average expected heterozygosity of populations is related, from these variables, only to the average annual precipitation ($r = -0.43$, $p = 0.0003$).

Thus, almost all genetic markers in the candidate genes of adaptation to cold show a significant correlation of allele frequencies with the temperature indices of the climate and with the geographic latitude of localization of populations. The only exception to this pattern is the *ITGB8* gene marker, which encodes the beta subunit of αVβ8 integrin (rs2301727). This gene is involved in the processes of cell adhesion and in signaling in intercellular interactions [23], and its possible role in adaptation to cold was documented in the previous complete genomic study [24].

Search for Directional Selection Signals

The search for loci under the possible effect of directional natural selection during human settlement was carried out by analyzing the distribution of the observed F_{ST} values over the expected distribution (FDIST test) obtained in simulations (20 000 simulations) on the basis of the hierarchical island model of the population structure [17–20]. The test is based on a comparison of the empirical F_{ST} values with the 99% quantile of the F_{ST} simulation distribution for different indices of the intrapopulation variety. The entry of the empirical value into 1% of extreme indications (sharply deviating from neutral values, outliers) implies possible differentiation of the populations under the action of selection.

**Table 2.** Allele frequencies and genetic diversity in the populations studied

Marker (SNP)	Ancestral allele	Uzbeks	Kets	Udmurts	Chukchi	Eskimos	Yakuts	Koryaks	Buryats	Northern Kyrgyz	Southern Kyrgyz	Nivkhs	Khanty
rs10509653	T	0.4423	0.3617	0.6344	0.2000	0.2857	0.2245	0.2528	0.3118	0.3864	0.3023	0.1649	0.4421
rs10887778	C	0.6923	0.5000	0.6667	0.9286	0.7857	0.5153	0.9326	0.5591	0.5814	0.6163	0.3736	0.4632
rs12446160	G	0.1923	0.0326	0.2340	0.0769	0.0714	0.0459	0.0449	0.0215	0.1250	0.1977	0.0319	0.0526
rs12946049	T	0.6739	0.5682	0.7713	0.7640	0.7857	0.6237	0.8512	0.5966	0.7558	0.7907	0.5769	0.7000
rs12979860	T	0.2453	0.2021	0.1755	0.1395	0.2857	0.0918	0.0730	0.0460	0.0930	0.1744	0.1452	0.3032
rs133036	T	0.6163	0.4651	0.5000	0.6429	0.4286	0.8093	0.7471	0.8333	0.6905	0.6310	0.8295	0.3511
rs1513687	C	0.6569	0.4468	0.5000	0.3846	0.4286	0.5567	0.3352	0.5753	0.5341	0.5233	0.4149	0.4789
rs1984239	C	0.6442	0.7174	0.8500	0.4835	0.5000	0.5266	0.4709	0.5298	0.6364	0.6279	0.5053	0.6789
rs1800592	A	0.6226	0.7234	0.8032	0.5222	0.5714	0.5714	0.6180	0.5538	0.5227	0.5814	0.3817	0.8579
rs1800849	C	0.7453	0.6522	0.6543	0.6685	0.5714	0.3939	0.4659	0.5195	0.6429	0.6463	0.7802	0.4842
rs1805490	G	0.6275	0.5652	0.5220	0.7472	0.7143	0.6134	0.6292	0.5707	0.6047	0.7093	0.7957	0.5585
rs2015865	C	0.8396	0.6848	0.7554	0.7474	0.5714	0.7350	0.9157	0.7419	0.8636	0.8023	0.7234	0.6263
rs2193045	A	0.3750	0.6196	0.3404	0.6319	0.2143	0.5306	0.6685	0.6344	0.3750	0.4186	0.5638	0.4521
rs2216163	C	0.6250	0.3804	0.6720	0.3667	0.7857	0.4643	0.3315	0.3736	0.6477	0.5814	0.4362	0.5474
rs2273428	T	0.5769	0.5745	0.5532	0.6374	0.2143	0.5206	0.6193	0.4892	0.6477	0.7326	0.7011	0.5000
rs2283792	G	0.5094	0.4111	0.3333	0.2750	0.0714	0.2418	0.1477	0.3900	0.3125	0.4342	0.3556	0.4000
rs2298432	C	0.5769	0.5543	0.5815	0.4611	0.5714	0.4439	0.2753	0.4620	0.4432	0.4651	0.3883	0.6579
rs2301727	C	0.7830	0.9130	0.9362	0.7692	0.4286	0.8061	0.8427	0.7688	0.7841	0.7326	0.7128	0.9521
rs2305508	A	0.5800	0.5213	0.4130	0.7926	0.7857	0.7474	0.8621	0.6193	0.6786	0.6512	0.9138	0.4000
rs3741135	C	0.7547	0.6522	0.7021	0.6474	0.5714	0.4750	0.5730	0.6290	0.6818	0.6744	0.7287	0.5851
rs4507607	A	0.1038	0.0638	0.0638	0.0632	0.0714	0.0859	0.0920	0.0272	0.0465	0.0581	0.0053	0.0842
rs4930248	C	0.3654	0.1170	0.2021	0.0914	0.0714	0.3300	0.0899	0.2283	0.3523	0.3837	0.0684	0.2234
rs4944925	G	0.7075	0.9239	0.8830	0.7637	0.7857	0.9175	0.8483	0.8187	0.7558	0.8140	0.7581	0.8351
rs608343	G	0.2451	0.1413	0.1044	0.0611	0.0000	0.2263	0.0562	0.2965	0.2955	0.2442	0.0860	0.1383
rs6724627	A	0.2404	0.1889	0.2394	0.2500	0.3571	0.0765	0.1067	0.0806	0.1932	0.1512	0.0815	0.2000
rs809812	G	0.2596	0.1087	0.2074	0.1813	0.2857	0.1378	0.2191	0.1183	0.2273	0.2907	0.1330	0.1684
rs892878	C	0.5755	0.6596	0.7181	0.6552	0.3571	0.8163	0.8034	0.7312	0.6818	0.6744	0.4840	0.6809
rs908394	A	0.2642	0.1304	0.3351	0.4444	0.4286	0.0408	0.2191	0.1559	0.1591	0.2209	0.0266	0.2000
H_e		0.4212	0.3762	0.3777	0.3638	0.3979	0.3375	0.3627	0.3152	0.3836	0.3969	0.4077	0.3318

H_e is the average expected heterozygosity.

Table 3. Correlation of allele frequencies and mean expected heterozygosity with climatic and geographic variables

Marker (SNP)	Latitude		Longitude		Average annual temperature		Temperature of the coldest month		Temperature of the warmest month		Temperature spread		Average amount of precipitation		Average relative humidity	
	R	p	R	p	R	p	R	p	R	p	R	p	R	p	R	p
rs10509653	−0.4184	0.0005	−0.7315	0.0000	0.3564	0.0038	0.4531	0.0001	0.1830	0.1475	−0.5210	0.0000	0.1971	0.1184	0.0133	0.9165
rs10887778	−0.4696	0.0000	−0.2282	0.0696	0.3580	0.0036	0.4838	0.0000	0.1846	0.1442	−0.5499	0.0000	0.2892	0.0204	0.2007	0.1117
rs12446160	−0.7042	0.0000	−0.4803	0.0000	0.6286	0.0000	0.7300	0.0000	0.4151	0.0006	−0.7578	0.0000	0.3657	0.0029	0.0186	0.8836
rs12946049	−0.5817	0.0000	−0.5312	0.0003	0.6070	0.0000	0.6695	0.0000	0.3868	0.0124	−0.7174	0.0000	0.5127	0.0006	0.1740	0.2764
rs12979860	−0.3433	0.0279	−0.7849	0.0000	0.3903	0.0116	0.4885	0.0011	0.1461	0.3617	−0.5906	0.0000	0.3209	0.0407	0.2135	0.1799
rs133036	0.5096	0.0000	0.2123	0.0921	−0.5316	0.0000	−0.6087	0.0000	−0.3057	0.0140	0.6272	0.0000	−0.3376	0.0063	−0.1176	0.3545
rs1513687	−0.8283	0.0000	−0.1730	0.1713	0.6852	0.0000	0.7755	0.0000	0.5017	0.0000	−0.7852	0.0000	0.4948	0.0000	0.0206	0.8711
rs1698239	−0.7916	0.0000	−0.3129	0.0118	0.7248	0.0000	0.7871	0.0000	0.5489	0.0000	−0.7758	0.0000	0.4093	0.0007	−0.0427	0.7371
rs1800592	0.5415	0.0002	−0.0978	0.5427	−0.3686	0.0177	−0.4197	0.0062	−0.3245	0.0384	0.4243	0.0056	−0.3548	0.0227	−0.0322	0.8415
rs1800849	−0.5998	0.0000	−0.3257	0.0086	0.5519	0.0000	0.6113	0.0000	0.4275	0.0004	−0.5947	0.0000	0.2707	0.0304	−0.0312	0.8063
rs1805490	−0.6110	0.0000	−0.2685	0.0319	0.4395	0.0002	0.5610	0.0000	0.2773	0.0265	−0.6180	0.0000	0.2694	0.0313	0.0765	0.5476
rs2015865	−0.7774	0.0000	−0.1916	0.1292	0.6895	0.0000	0.7663	0.0000	0.5503	0.0000	−0.7217	0.0000	0.4320	0.0003	−0.0332	0.7944
rs2193045	0.7446	0.0000	0.2562	0.0409	−0.6703	0.0000	−0.7186	0.0000	−0.5712	0.0000	0.7056	0.0000	−0.3433	0.0054	0.1337	0.2919
rs2216163	−0.7836	0.0000	−0.3321	0.0073	0.7047	0.0000	0.7631	0.0000	0.5792	0.0000	−0.7428	0.0000	0.3866	0.0015	−0.1243	0.3275
rs2273428	−0.7739	0.0000	−0.1414	0.2648	0.6181	0.0000	0.7193	0.0000	0.4461	0.0002	−0.6876	0.0000	0.5507	0.0000	0.0863	0.4975
rs2283792	−0.5033	0.0000	−0.5194	0.0000	0.4470	0.0002	0.4945	0.0000	0.4036	0.0009	−0.4886	0.0000	0.0430	0.7355	−0.1524	0.2290
rs2298432	−0.5951	0.0000	−0.5501	0.0000	0.5288	0.0000	0.6181	0.0000	0.3273	0.0082	−0.6583	0.0000	0.1976	0.1173	−0.0541	0.6706
rs2301727	−0.1379	0.2771	−0.3211	0.0096	0.1864	0.1401	0.2314	0.0657	0.1096	0.3886	−0.2891	0.0204	−0.1370	0.2803	−0.0448	0.7246
rs2305508	−0.4907	0.0000	0.0858	0.5000	0.3529	0.0042	0.4322	0.0003	0.2237	0.0755	−0.4082	0.0008	0.4017	0.0010	0.0049	0.9689
rs3741135	−0.4594	0.0001	−0.2629	0.0357	0.5002	0.0000	0.5240	0.0000	0.4447	0.0002	−0.4868	0.0000	0.1228	0.3333	−0.0985	0.4385
rs4507607	−0.7984	0.0000	−0.3431	0.0055	0.6908	0.0000	0.8033	0.0000	0.4510	0.0001	−0.8506	0.0000	0.4814	0.0000	0.0417	0.7435
rs4930248	−0.5478	0.0000	−0.4597	0.0001	0.4846	0.0000	0.5583	0.0000	0.4070	0.0008	−0.5285	0.0000	0.2196	0.0811	−0.0975	0.4432
rs4944925	0.6557	0.0000	−0.2083	0.0984	−0.6254	0.0000	−0.6558	0.0000	−0.5373	0.0000	0.6079	0.0000	−0.3194	0.0100	0.0248	0.8455
rs608343	−0.4156	0.0006	−0.6219	0.0000	0.3811	0.0018	0.4133	0.0006	0.3184	0.0103	−0.4016	0.0010	0.1741	0.1686	−0.3171	0.0106
rs6724627	−0.5292	0.0000	−0.3119	0.0120	0.4006	0.0010	0.5521	0.0000	0.1327	0.2957	−0.6414	0.0000	0.5266	0.0000	0.2499	0.0464
rs809812	−0.7654	0.0000	−0.3269	0.0083	0.6871	0.0000	0.7696	0.0000	0.5010	0.0000	−0.7780	0.0000	0.3940	0.0012	−0.0750	0.5556
rs892878	−0.7696	0.0000	−0.0478	0.7073	0.6305	0.0000	0.6839	0.0000	0.4402	0.0002	−0.6962	0.0000	0.4945	0.0000	0.0019	0.9875
rs908394	−0.6318	0.0000	−0.1122	0.3771	0.5429	0.0000	0.6466	0.0000	0.3158	0.0109	−0.6915	0.0000	0.3538	0.0041	0.2045	0.1049
H_e	0.6531	0.0000	0.1520	0.2303	−0.5033	0.0000	−0.6331	0.0000	−0.2764	0.0270	0.6867	0.0000	−0.4371	0.0003	−0.2122	0.0921

R is the Spearman rank correlation coefficient; p is the level of correlation significance. H_e is the average expected heterozygosity.
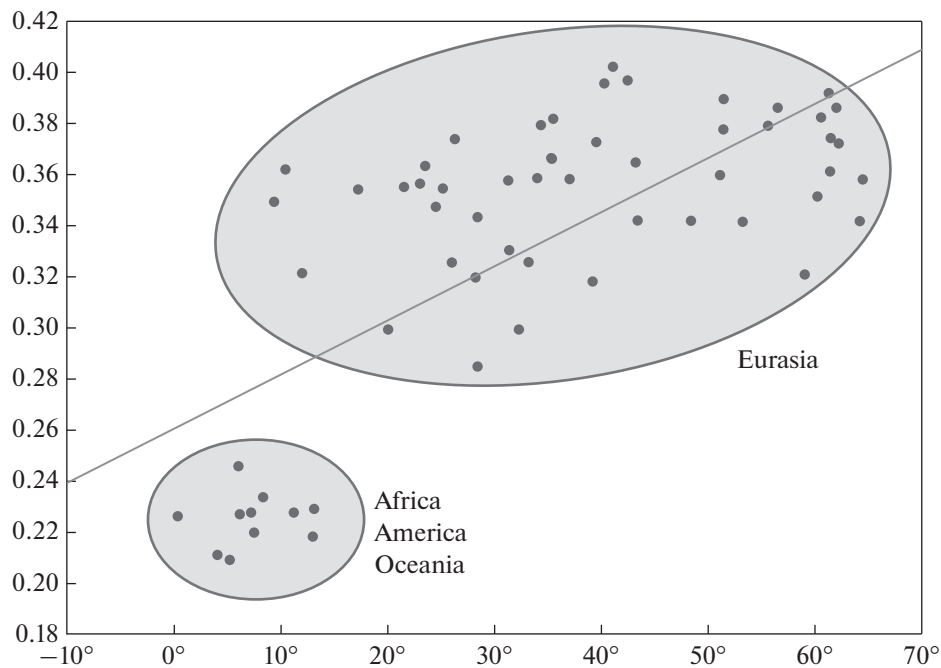
Fig. 1. Correlation of the average expected heterozygosity with absolute latitude ($r = 0.65$, $p = 0.0000$). Points represent the position of the investigated populations in the space formed by the values of the average expected heterozygosity (Y axis) and the absolute distance from the equator in degrees (X axis).

For each marker, Table 4 presents empirical F_{ST} values calculated on the basis of allele frequencies of 28 markers of the candidate cold adaptation genes in 54 populations (12 populations from the present work and 42 world populations from the 1000 Genomes and HGDP projects), as well as values ($1 - F_{ST}$ quantile) reflecting the nonrandomness of the entry of the empirical value of the indicator of genetic differentiation into the number of values sharply deviating from neutral expectations.

The coefficient of genetic differentiation of the world populations for individual markers varies from 4.21% (for rs3741135 of gene *UCP3*) to 50.4% (for rs4507607 of locus *LOC107986645*). The overall level of genetic differentiation of the world populations by candidate genes for adaptation to cold is 16.2%, which significantly exceeds the level of genetic differentiation in populations of Northern Eurasia (7.6%).

Six of the 28 markers demonstrate empirical F_{ST} values falling within 1% of the upper values of the simulated distribution of the genetic differentiation coefficient. The average F_{ST} value for these markers was 31.3%, which is almost two times higher than the level of genetic differences in the world populations across the entire SNP panel.

As implied by the FDIST test, significantly higher differentiation of the populations for these markers may be the result of directed selection of rare alleles in certain populations, which leads to higher interpopulation differences compared with neutral expectations

[20]. Of course, other explanations of the observed phenomenon are theoretically possible, for example, the genetic subdivision within the studied populations, the heterogeneity of the gene flow between populations, and certain scenarios of change in the effective population size. Nevertheless, a large range of studied populations and consideration of the hierarchical model of the population structure by the FDIST test minimize the probability of false positive results and allow interpretation of the extreme values of the observed levels of genetic differentiation as a possible result of directional selection [20].

We recorded directional selection signals for the markers of six candidate cold adaptation genes, *MYOF*, *LONP2*, *IFNL4*, *MKL1*, *SLC2A12*, and *CPT1A*. The *MYOF* gene encodes a myoferlin protein, which is involved in the repair of endothelial cell plasmalemma and the differentiation and growth of the striated musculature. The possible role of the *MYOF* gene in adaptation to cold is associated with the participation of myoferlin in the regeneration and repair of muscle fibers, including in response to low-temperature stress [25, 26].

The *LONP2* gene encodes the enzyme Lon protease 2, which relates to ATP-dependent serine proteases of mitochondria and is involved in processes of beta-oxidation of fatty acids in peroxisomes and may play a role in the response to heat shock, participating in the degradation of damaged or improperly assembled protein molecules in the mitochondrial matrix [27, 28].

Table 4. Analysis of the distribution of the observed F_{ST} values in comparison with the expected distribution obtained in simulation calculations (10 000 simulations) on the basis of the hierarchical island model of the population structure

Marker (SNP)	Gene	F_{ST}	$1 - F_{ST}$ quantile
rs10509653	*MYOF*	0.2878	0.000004446
rs10887778	*LOC105378415*	0.1454	0.463
rs12446160	*LONP2*	0.4135	0.000000000
rs12946049	*RPTOR*	0.0636	0.997
rs12979860	*IFNL4*	0.2167	0.01712
rs133036	*MKL1*	0.2243	0.005823
rs1513687	*MIR924HG*	0.0998	0.939
rs16984239	*KCNS3/LOC105373451*	0.1425	0.0493
rs1800592	*UCP1/RN7SL152P*	0.1355	0.600
rs1800849	*UCP3*	0.0922	0.965
rs1805490	*GRIN2B*	0.0748	0.993
rs2015865	*LOC105373053/LOC105373054*	0.0829	0.9601
rs2193045	*LOC107984526/LOC100509370*	0.1558	0.330
rs2216163	*LOC107984526/LOC100509370*	0.1774	0.134
rs2273428	*COL19A1*	0.1223	0.759
rs2283792	*MAPK1*	0.0658	0.998
rs2298432	*MAPK1*	0.1649	0.228
rs2301727	*ITGB8*	0.1128	0.803
rs2305508	*CPT1A*	0.1624	0.264
rs3741135	*UCP3*	0.0421	1.000
rs4507607	*SLC2A12*	0.5042	0.000000000
rs4930248	*CPT1A*	0.2359	0.00163
rs4944925	*POLD3*	0.0687	0.997
rs608343	*LRP5*	0.1676	0.213
rs6724627	*MYO3B*	0.1666	0.214
rs809812	*MYOF*	0.1504	0.399
rs892878	*THSD7B*	0.1507	0.388
rs908394	*LOC105369791*	0.1237	0.746

Values ($1 - F_{ST}$ quantile) < 0.01 are highlighted.

The *MKL1* gene encodes a protein that interacts with the transcription factor myocardin, a key regulator of smooth muscle cell differentiation. MKL mediates TGF-beta-1-induced expression of smooth muscle actin [29].

The *CPT1A* gene encodes the liver enzyme carnitine palmitoyltransferase 1A, which, as Lon protease-2, plays a role in beta-oxidation of long chain fatty acids in mitochondria; namely, it catalyzes transfer of

an acyl group from conjugates of long chain fatty acids to carnitine [30].

Markers of genes *MYOF, LONP2, MKL1,* and *CPT1A* showed signals of directional election for cold adaptation in one of the preceding genome-wide studies [3] and were also identified as candidate targets of directional selection in Siberian populations in our genome-wide data partially presented in [22]. In addition, for gene *CPT1A*, associations with lipid metabolism rates in Canadian Eskimos were found [31]. The

high frequency of the "Arctic" variant of the gene was previously found in the paleo-Asiatic populations of Northeast Asia: among Koryaks, Chukchi, and Eskimos [1].

The *SLC2A12* gene encodes a membrane protein responsible for the transfer of glucose through the cell membrane. Previously, for various genes of the family of soluble SLC transport proteins, a directional selection effect associated with phenotypes such as skin pigmentation and a response to pathogens was revealed [32−35].

The IFN-λ4 gene encodes interferon IFN-λ4, which belongs to type III interferons, and is a rare example of human orphan genes. The ability to produce IFN-λ4 is controlled by alleles of the dinucleotide genetic variant rs368234815 (*TT/dG*). The ancestral allele *dG* supports and the derived *TT* allele eliminates the open reading frame for the *IFNL4* gene [36]. The *TT* allele specific to humans originated in Africa about 60 000 years ago and, through directional selection, became highly prevalent in non-African populations, primarily in Asia, where the *TT* frequency reaches 90−100% [37]. The reason for the selective advantage of the *TT* allele is unclear, but since it was shown that the absence of the IFN-λ4 protein improves the response to the hepatitis C virus [36], perhaps *TT* carriers are more resistant to other infectious agents. Earlier, in the study of the *IFNL4* allele frequency distribution in the world populations, we showed that frequencies of the derived allele (*TT*) are minimal in Africa (5−30%), low in the indigenous populations of the Indians of South and Central America (35−50%), and maximal in East Asia, Siberia, and North Asia (70−100%) [38].

CONCLUSIONS

As a result of the presented study, we found correlations of the genetic diversity of the candidate genes for adaptation to cold climate with key climatic characteristics; for some of these genes, we revealed possible directional selection action and found an increase in the genetic diversity in this gene system with an increase in the distance from the equator, that is, during the human resettlement from Africa.

One of the potential contradictions in the recorded trends is that we demonstrate directional selection signals in northern populations with the growth of genetic diversity, while directional selection ultimately should lead to a decrease in diversity owing to the gradual elimination of the selected allele from the population. The solution of this contradiction is that, firstly, the selection is not the strongest and not the only microevolutionary factor that determined the genetic structure of the populations of Northern Eurasia. Isolation by distance, genetic drift, and gene flow may be more significant factors of population dynamics at the population gene pool level as a whole. Sec-

ondly, selection in the case of genes for adaptation to cold climate is aimed at maintaining in the northern populations a derived allele that in the ancestral population was either absent at the time of modern human origin (as in the case of the *TT* allele of gene *IFNL4*) or its frequency was minimal (as in modern African populations) owing to selection of a derived allele that is adaptive to the initial conditions of the habitat of ancestral human populations. Thus, directional selection during the process of human settlement outside the tropics changed the frequency of the derived allele derivative from the initial values close to 0 to the current values in the populations of Northern Eurasia (for most markers, around 30−60%, see Table 2). In other words, directional selection of a rare allele led to its transformation into a frequent one and, correspondingly, to an increase in heterozygosity in proportion to moving further away from Africa, in contrast to the variability of the overall level of genetic diversity in world populations.

The data obtained in this work, as well as their interpretation from the point of view of the role of selection in adaptation to the change in climatic and geographical conditions of the habitat, support the hypothesis of decanalization of the genome−phenome relations under the influence of natural selection during human settlement across the globe, which was formulated earlier by Gibson [39, 40] and further developed by us [9, 21, 22].

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SPELL: 1. decanalization