ISSN 0026-8933, Molecular Biology, 2015, Vol. 49, No. 6, pp. 881–889. © Pleiades Publishing, Inc., 2015.
Original Russian Text © A.A. Cherednichenko, E.A. Trifonova, K.V. Vagaitseva, A.V. Bocharova, A.M. Varzari, M.O. Radzhabov, V.A. Stepanov, 2015, published in Molekulyarnaya Biologiya, 2015, Vol. 49, No. 6, pp. 984–992.

GENOMICS.
TRANSCRIPTOMICS

UDC 575.174:599.9

Prevalence of Gene Polymorphisms Associated with Immune Disorders in Populations of Northern Eurasia

A. A. Cherednichenko[a, b], E. A. Trifonova[a, b], K. V. Vagaitseva[a, b], A. V. Bocharova[b], A. M. Varzari[c], M. O. Radzhabov[d, e], and V. A. Stepanov[a, b]

[a] *National Research Tomsk State University, Tomsk, 634050 Russia;*
e-mail: anastasia.cherednichenko@medgenetics.ru
[b] *Research Institute for Medical Genetics, Tomsk, 634050 Russia*
[c] *Chiril Draganiuc Institute of Phthisiopulmonology, Chisinau, MD 2025, Republic of Moldova*
[d] *Analytical Center for Collective Use, Dagestan Scientific Center, Russian Academy of Sciences, Makhachkala, 367001 Russia*
[e] *Dagestan Medical Dental Institute, Makhachkala, 367015 Russia*

Received March 11, 2015; in final form, May 15, 2015

Abstract—Allele-frequency distributions for gene polymorphisms associated with autoimmune and allergic diseases, as well as the regulation of immunoglobulin E and cytokines levels, were studied in 26 populations of Northern Eurasia. There was no significant correlation between the values of average expected heterozygosity by 44 gene polymorphisms and climate or geographic factors. Population groups exhibited clustering according to their geographic location. The degree of genetic differentiation among populations and the selective neutrality of gene polymorphisms were also assessed. The results demonstrate substantial genetic diversity and differentiation of human populations by the genes studied.

DOI: 10.1134/S0026893315060047

Keywords: single nucleotide polymorphisms, populations of Northern Eurasia, genetic diversity, immune disorders, climate and geographic factors

INTRODUCTION

Immune reactions to environmental challenges are determined by a combination of different types of immune activity. The imbalanced regulation of the immune response can promote allergic and autoimmune diseases. Manifestations of immune response and predisposition to immune disorders are controlled genetically and involve the products of many genes. For instance, polymorphisms of different genes were shown to be associated with asthma, multiple sclerosis, Crohn's disease, psoriasis, and rheumatoid arthritis [1–10]. Populations of different ethnicities exhibit significant variations in frequencies of marker alleles [11–15]. The variations by immunity-regulating gene polymorphisms may underlie the differences in the prevalence of these diseases observed among ethnic groups [16]. For instance, it was shown that African Americans are more sensitive to allergen challenges than Americans of European origin [17–20].

In this work, we investigated the genetic structure of populations of Northern Eurasia by genes associated with autoimmune and allergic diseases, as well as with the regulation of immunoglobulin E (IgE) and cytokine levels. To analyze the adaptive significance of markers associated with immunity phenotypes, as assumed by the hypothesis postulating decanalization of immune response during the dispersal of modern humans [17, 21], we assessed the relationships between allele frequencies and genetic diversity by selected single nucleotide polymorphisms (SNPs), as well as climate and geographic factors.

EXPERIMENTAL

Population samples represented 26 ethnic groups and comprised altogether 1228 individuals residing in Eastern Europe (Aghuls, Bezhta, Gagauz, Komi, Maris, Moldavians, Russians, Ukrainians, Tsez), Central Asia (Uzbeks, Kazakhs, Kyrgyz), Siberia (Northern Altaians, Southern Altaians, Buryats, Kets, Tyvans, Khakas, Khanty, Shors, Evenks), and Far East (Koryaks, Nivkhs, Udegei, Chukchi, Yakuts) (Table 1).

Genotyping was performed by real-time PCR and MALDI-TOF mass spectrometry, as described previously in [22, 23]. Polymorphisms of genes selected based on their association with immune disorders or with the regulation of IgE and cytokine secretion levels were used as markers (Table 2).

Statistical analysis was performed with STATISTICA 7.0 and ARLEQUIN 3.11 software. The agreement of genotype distributions with the Hardy–Weinberg equilibrium was assessed using the χ^2 test. Genetic differentiation of populations was described

Table 1. Anthropological and linguistic characterization of the ethnic groups studied

Ethnic group (*N**)	Population (settlement)	Linguistic family/group	Race (anthropological type)
Eastern Europe			
Aghuls (50)	Aghul region, Republic of Daghestan	Northeastern Caucasian/ Eastern Lezgic	Caucasian (Caucasus)
Bezhta (45)	Bezhta region, Republic of Daghestan	Nakho-Daghestanian/ Eastern Tsezic	Caucasian (Caucasus)
Gagauz (45)	Etulia, Kongaz; Moldova	Altaian/Turkic	Caucasian (lower Danube)
Komis (45)	Republic of Komi	Uralic/Finno-Ugric	Caucasian (sublaponoid)
Maris (50)	Mari El Republic	Uralic/Finno-Ugric	Caucasian (sublaponoid)
Moldavians (40)	Karagasani, Moldova	Indo-European/Roman	Caucasian (lower Danube)
Russians (50)	Tomsk, Russia	Indo-European/Slavic	Caucasian (East European)
Ukrainians (50)	Ukraine	Indo-European/Slavic	Caucasian (East European)
Tsez (45)	Tsuntinskii region, Republic of Daghestan	Nakho-Daghestanian/ Western Tsezic	Caucasian (Caucasus)
Central Asia			
Uzbeks (44)	Osh, Dzhalalabad; Kyrgyzstan	Altaian/Turkic	Caucasian (Pamir-Iranian)
Kazakh (50)	Kazakhstan	Altaian/Turkic	Mongoloid (Central Asian and South Siberian)
Kyrgyz (50)	Osh, Bishkek, Kegety; Kyrgyzstan	Altaian/Turkic	Mongoloid (South Siberian)
Siberia			
Northern Altaians (50)	Turochak, Gorno-Altaisk; Republic of Altai	Altaian/Turkic	Mongoloid (South Siberian)
Southern Altaians (50)	Kulada, Republic of Altai	Altaian/Turkic	Mongoloid (Central Asian)
Buryats (50)	Kurumkanskii region, Republic of Buryatia	Altaian/Mongolian	Mongoloid (Central Asian)
Kets (44)	Kellog; Krasnoyarsk krai	Yenisean	Uralic (Yenisean)
Tyvans (50)	Kyzyl, Republic of Tyva	Altaian/Turkic	Mongoloid (Central Asian)
Khakas (50)	Askiz region, Republic of Khakassia	Altaian/Turkic	Uralic, Mongoloid (South Siberian)

Table 1. (Contd.)

Ethnic group (*N**)	Population (settlement)	Linguistic family/group	Race (anthropological type)
Khanty (45)	Kazym, Khanty–Mansi autonomous okrug	Uralic/Finno-Ugric	Uralic
Shors (45)	Kemerovo oblast	Altaian/Turkic	Mongoloid (Uralic)
Evenks (45)	Chara, Tungokochen; Zabaikalskii krai	Altaian/Tungusic	Mongoloid (Baikalic)
Far East			
Koryaks (50)	Kamchatka krai	Chukotko-Kamchatkan	Mongoloid (Arctic)
Nivkh (45)	Moskal'vo, Nekrasovka; Sakhalin oblast	Paleoasian/Nivkh	Mongoloid (Sakhalin-Amur)
Udegei (45)	Krasnyi Yar, Agzu; Primorskii krai	Altaian/Tungusic	Mongoloid (Baikalic)
Chukchi (50)	Lorino, Novoe Chaplino, Sireniki; Chukotka autonomous okrug	Chukotko-Kamchatkan	Mongoloid (Arctic)
Yakuts (45)	Dyupsya, Byadi; Republic of Sakha (Yakutia)	Altaian/Turkic	Mongoloid (Central Asian)

* *N*, sample size.

using analysis of molecular variance (AMOVA); the association of polymorphic gene variants with climate and geographic factors was assessed using the Spearman's correlation coefficient, and selective neutrality of gene markers was analyzed using the Ewens–Watterson test [70]. Genetic relationships among the populations were analyzed using the principal components approach. The climate data (average annual temperature, average temperatures of the warmest and the coldest month, temperature range, average annual precipitation, average relative humidity) were obtained from the Weatherbase database (http://www.weatherbase.com).

RESULTS

Genetic Diversity in Population Samples

The data on allele and genotype frequency distributions, as well as on the heterozygosity of the polymorphisms analyzed are provided in Appendix (for supplementary materials, see www.molecbio.com/downloads/2015/6/supp_cherednichenko_en.pdf) and are available from the authors on request. Genotype frequency distributions disagreed with the Hardy–Weinberg equilibrium in 51 cases out of 1144, which, however, does not exceed the expected number of random deviations from the equilibrium ($p < 0.05$). Deviations from the equilibrium did not seem to accumulate for any individual locus or in population groups. After the Bonferroni correction for multiple comparisons was applied, the deviation from the equilibrium remained significant for only four distributions. Genetic variations by the markers used differed considerably among the populations studied. The lowest and the highest values of average expected heterozygosity by 44 gene markers were observed in Koryaks (0.34) and in Uzbeks (0.41), respectively. An analysis of correlations between the allele frequencies and climate and geographic factors revealed significant correlations (Spearman's coefficient, $p < 0.05$) with absolute latitude (for 12 markers), absolute longitude (33 markers), average annual temperature (17 markers), the coldest month temperature (27 markers), temperature range (27 markers), and average annual precipitation (26 markers) (Fig. 1). None of the 44 markers studied showed a significant correlation with the warmest month temperature, nor did the average expected heterozygosity by 44 markers correlate with any climate or geographic factor.

Evaluation of Selective Neutrality of Gene Polymorphisms

Using the Ewens–Watterson test, we identified 35 loci under selection ($p < 0.05$) and 9 selectively neutral loci (rs144651842, rs1800925, rs1801275, rs1805015,

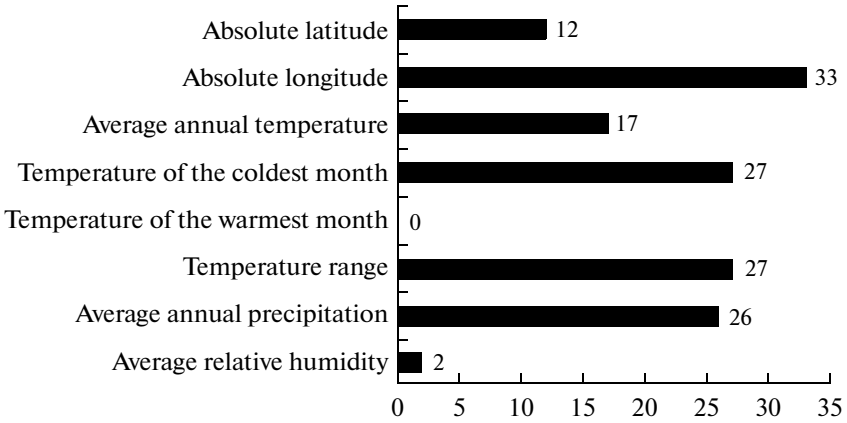

Fig. 1. Correlations between the allele frequencies of the polymorphic loci studied and climate and geographic factors. Bars correspond to the number of loci for which the p value for the Spearman's correlation coefficient was lower than 0.05.

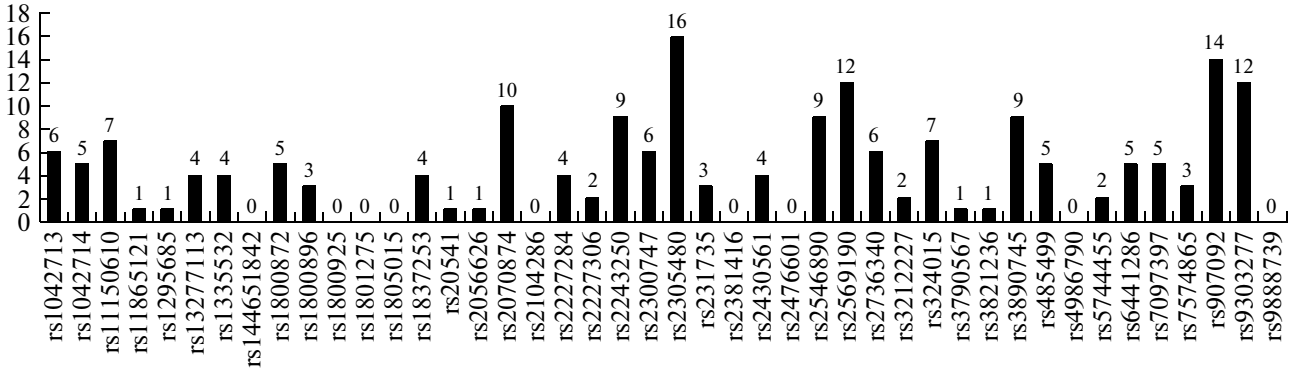

Fig. 2. Deviations from the hypothesis of selective neutrality of genetic markers associated with immune disorders in different populations studied. Bars correspond to the number of populations for which P values for the Ewens–Watterson test are lower than 0.05.

rs2104286, rs2381416, rs2476601, rs4986790, rs9888739) ($p > 0.05$) (Fig. 2).

The loci rs2305480, rs2569190, rs907092, and rs9303277 deviated most from the predictions based on the selective neutrality hypothesis; deviations were observed in 16, 12, 14, and 12 population samples out of 26, respectively.

Genetic Differentiation and Genetic Relationships among Populations

The extent of genetic differentiation was evaluated by calculating the Fst coefficient in the total sample by each marker studied (Fig. 3). Significant differentiation ($p < 0.05$) was observed for all loci except rs2305480. High levels of genetic differentiation were observed for rs1335532 (0.1732), rs2070874 (0.1605), rs2243250 (0.1675), rs2300747 (0.1846), and rs6441286 (0.2307). The lowest Fst value was obtained for rs2305480 (0.0029), and the highest, for rs6441286 (0.2307). The total genetic differentiation level by the 44 loci was 0.0749 (7.5%).

Genetic relationships among populations were studied using the principal component analysis. The first two principal components of allele frequencies were responsible for 53.45% of the total variation in the populations studied (Fig. 4). On the whole, the populations' positions in the principal component space reflected their geographic location, with the first component corresponding to longitude. This relationship was also confirmed by the correlation between the first factor and the longitude of the population-sampling site (Spearman's coefficient, $p = 0.0000$). The second principal component cannot be interpreted as straightforwardly, since its values did not show significant correlation with any climate parameter, but only a slight trend to correlation with latitude ($p = 0.0897$).

DISCUSSION

The geographic structure of genetic diversity probably constitutes the most general pattern in the organization of human gene pools and can be observed in any data set that is sufficiently representative of the num-

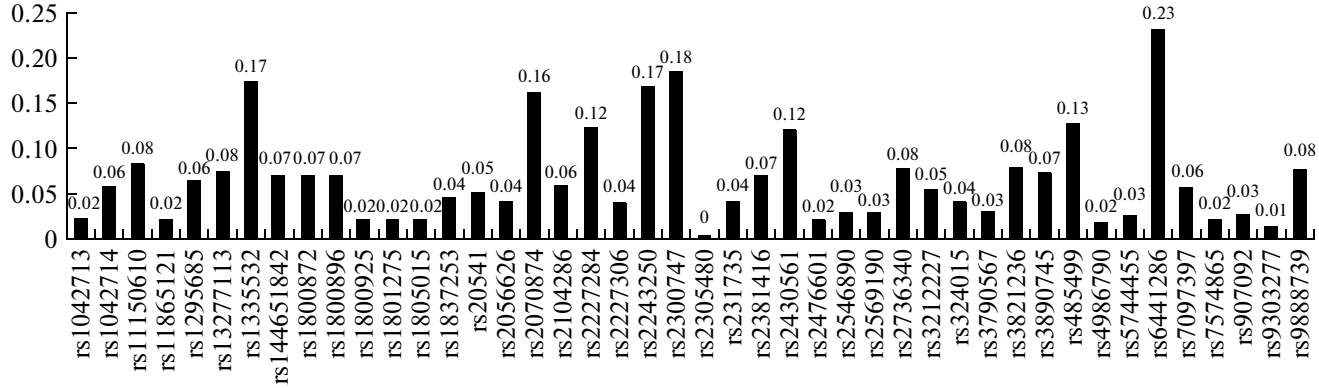

Fig. 3. Total genetic differentiation by polymorphisms associated with immunity-dependent diseases.

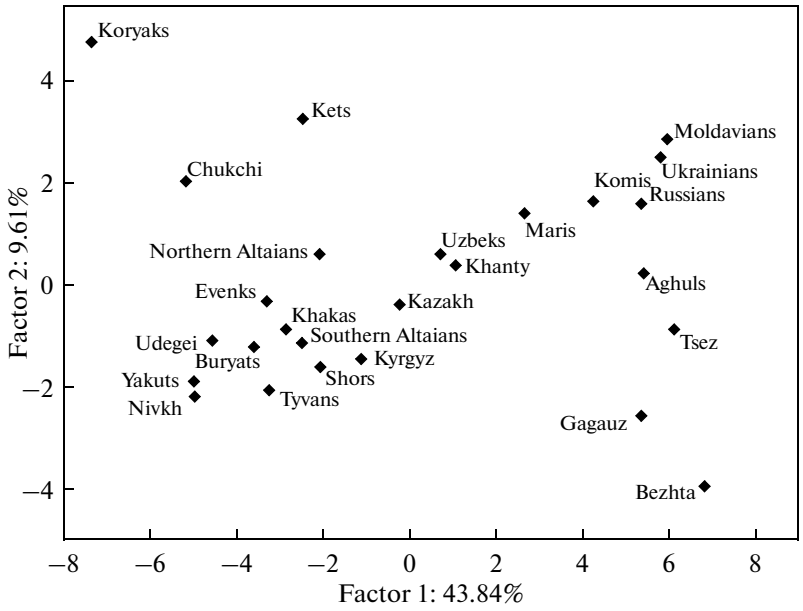

Fig. 4. Positions of population groups in the principal component space by allele frequencies of gene polymorphisms.

ber of markers and populations studied [16]. These patterns can be established in both the analysis of conventionally neutral genetic marker systems [15] or large sets of polymorphic genomic loci [16, 71], and in genotyping genes and markers related to a common biological function, e.g., genes associated with multifactorial diseases [11, 16]. The correlation between the genetic differentiation of human populations with geographic distances is probably explained by the evolutionary history of gene pools of modern populations formed in the course human dispersal mainly due to migrations, genetic drift, and isolation by distance [16]. At the same time, individual genome fragments or groups of functionally related genes may exhibit deviations from the conventionally neutral geographic pattern because of the adaptive significance of the corresponding phenotypes. For instance, it has been shown in some of the world's populations that the frequencies of polymorphic gene variants involved in sodium homeostasis, energy metabolism, and several other biological functions correlated with the climate parameters [72–75]. Immunity-related phenotypes are among the most obvious selection targets, and several studies determined that the genetic diversity of immune-system genes is related to potential selection factors. For example, allele frequencies by *IL6* polymorphism showed a positive correlation with the pathogenic load in populations from Russia and from other parts of the world [76], while the prevalence of filariasis was related to the frequencies of alcohol dehydrogenase gene (*ADH1B*) alleles [77]. In one of our previous works, it was shown that genetic diversity by gene markers most closely associated with immune disorders can be explained based on the assumption of immune response decanalization under the pressure of natural selection in the course of dispersal of modern

Table 2. Characteristics of genetic markers

Clinical phenotype	Gene (SNP)
Asthma	*ADRB2* (rs1042713) [24, 25], *IL13* (rs1800925) [26, 27], *IL4R* (rs1801275, rs1805015) [28, 29], *LOC105379121, TSLP* (rs1837253) [30, 31], *IL4* (rs2227284) [32], *IL8* (rs2227306) [33], *GSDMB* (rs2305480) [34], *RANBP6, GTF3AP1* (rs2381416) [31], *IL12B* (rs3212227) [35], *STAT6* (rs324015) [36]
IgE levels	*ADRB2* (rs1042714) [37, 38], *IL13* (rs1295685, rs20541) [39–42], *CD14* (rs2569190) [43]
Systemic lupus erythematosus	*ITGAM* (rs11150610, rs9888739) [44, 45], *FAM167A, BLK* (rs13277113, rs2736340) [45–47], *IFNG* (rs2430561) [48], *WDFY4* (rs7097397) [49]
Multiple sclerosis	*CLEC16A* (rs11865121) [50], *CD58* (rs1335532, rs2300747) [50–52], *LOC285626* (rs2546890) [51], *IL2RA* (rs2104286) [50, 53]
Rheumatoid arthritis	*IL10* (rs1800872, rs1800896) [54–56], *NPM1P33, LOC105373844* (rs231735) [57], *PTPN22* (rs2476601) [58, 59], *MMEL1* (rs3890745) [58, 59], *STAT4* (rs7574865) [58, 60]
Interleukin levels	*TLR4* (rs4986790) [61]
Allergy	*IL10* (rs1800896) [62]
Allergic rhinitis	*IL4* (rs2070874) [63]
Systemic sclerosis	*CD247*(rs2056626) [64, 65], *STAT4* (rs3821236) [64, 65]
Primary biliary cirrhosis	*IL12RB2* (rs3790567) [66, 67], *IL12A-AS1* (rs485499, rs6441286) [66–68], *IKZF3* (rs907092, rs9303277) [66, 67, 69]

humans [21]. Data obtained in this work contribute to the understanding of the structure and possible mechanisms of genetic differentiation affecting the hereditary component of immunity-related phenotypes.

To sum up, in this work, we have characterized the gene pools of Northern Eurasian populations based on a set of markers associated with immune-dependent phenotypes. Some loci were found to deviate from selective neutrality, and allele frequencies were related to key climate and geographic parameters, whereas on the whole, the genetic diversity of the populations studied reflected their geographic relationships.

ACKNOWLEDGMENTS

This work was supported by the Russian Foundation for Basic Research (project no. 5-04-02442) and the Program "Mendeleev Science Foundation of the Tomsk State University."

REFERENCES

1. Ramasamy A., Kuokkanen M., Vedantam S., et al. 2012. Genome-wide association studies of asthma in population-based cohorts confirm known and suggested loci and identify an additional association near HLA. *PLOS ONE*. **7**, e44008.
2. Wan Y.I., Shrine N.R., Soler Artigas M., et al. 2012. Genome-wide association study to identify genetic determinants of severe asthma. *Thorax*. **67**, 762–768.
3. Hirota T., Takahashi A., Kubo M., et al. 2011. Genome-wide association study identifies three new susceptibility loci for adult asthma in the Japanese population. *Nat. Genet*. **43**, 893–896.
4. Ferreira M.A., Matheson M.C., Duffy D.L., et al. 2011. Identification of IL6R and chromosome 11q13.5 as risk loci for asthma. *Lancet*. **378**, 1006–1014.
5. International Multiple Sclerosis Genetics Consortium, Hafler D.A., Compston A., Sawcer S., et al. 2007. Risk alleles for multiple sclerosis identified by a genomewide study. *N. Engl. J. Med*. **357**, 851–862.
6. Gourraud P.A., Sdika M., Khankhanian P., et al. 2013. A genome-wide association study of brain lesion distribution in multiple sclerosis. *Brain*. **136**, 1012–1024.
7. Raelson J.V., Little R.D., Ruether A., et al. 2007. Genome-wide association study for Crohn's disease in the Quebec Founder Population identifies multiple validated disease loci. *Proc. Natl. Acad. Sci. U. S. A*. **104**, 14747–14752.
8. Franke A., McGovern D.P., Barrett J.C., et al. 2010. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat. Genet*. **42**, 1118–1125.
9. Nair R.P., Duffin K.C., Helms C., et al. 2009. Genome-wide scan reveals association of psoriasis with

IL-23 and *NF-kappaB* pathways. *Nat. Genet.* **41**, 199–204.

10. Okada Y., Terao C., Ikari K., et al. 2012. Meta-analysis identifies nine new loci associated with rheumatoid arthritis in the Japanese population. *Nat. Genet.* **44**, 511–516.
11. Adeyemo A., Rotimi C. 2010. Genetic variants associated with complex human diseases show wide variation across multiple populations. *Public Health Genomics.* **13**, 72–79.
12. Akey J.M., Eberle M.A., Rieder M.J., Carlson C.S., Shriver M.D., Nickerson D.A., Kruglyak L. 2004. Population history and natural selection shape patterns of genetic variation in 132 genes. *PLoS Biol.* **2**, e286.
13. Akey J.M., Zhang G., Zhang K., Jin L., Shriver M.D. 2002. Interrogating a high-density SNP map for signatures of natural selection. *Genome Res.* **12**, 1805–1814.
14. Hoffmann S.C., Stanley E.M., Cox E.D., et al. 2002. Ethnicity greatly influences cytokine gene polymorphism distribution. *Am. J. Transplant.* **2**, 560–567.
15. Stepanov V.A. 2002. *Etnogenomika naseleniya Severnoi Evrazii* (Ethnogenomics of the Population of Northern Eurasia). Tomsk: Pechatnaya Manufaktura.
16. Stepanov V.A. 2010. Genomes, populations and diseases: Ethnic genomics and personalized medicine. *Acta Naturae.* **2**, 15–30.
17. Le Souëf P.N., Candelaria P., Goldblatt J. 2006. Evolution and respiratory genetics. *Eur. Respir. J.* **28**, 1258–1263.
18. Gold D.R., Rotnitzky A., Damokosh A.I., Ware J.H., Speizer F.E., Ferris B.G., Jr., Dockery D.W. 1993. Race and gender differences in respiratory illness prevalence and their relationship to environmental exposures in children 7 to 14 years of age. *Am. Rev. Respir. Dis.* **148**, 10–18.
19. Nelson D.A., Johnson C.C., Divine G.W., Strauchman C., Joseph C.L., Ownby D.R. 1997. Ethnic differences in the prevalence of asthma in middle class children. *Ann. Allergy Asthma Immunol.* **78**, 21–26.
20. Akinbami L.J., Moorman J.E., Bailey C., Zahran H.S., King M., Johnson C.A., Liu X. 2012. Trends in asthma prevalence, health care use, and mortality in the United States, 2001–2010. *NCHS Data Brief.* **94**, 1–8.
21. Stepanov V.A., Candelaria P., Khoo S., Zhang G., Trifonova E.A., Simonova K.V., Bocharova A.V., Laing I.A., Hayden C., Backer V., Bjerregaard P., Lynch N., Hagel I., Musk A.W., Bittles A., et al., 2013. Decanalization of immune response during the dispersion of modern humans: The relationships of genetic diversity in immune system genes and climatic and geographic factors. *Med. Genet.* **12**, 8–18.
22. Stepanov V.A., Trifonova E.A. 2013. Multiplex SNP genotyping by MALDI-TOF mass spectrometry: Frequencies of 56 immune response gene SNPs in human populations. *Mol. Biol.* (Moscow). **47**, 852–862.
23. Stepanov V.A., Trifonova E.A., Simonova K.V., Cherednichenko A.A. 2013. Variability of interleukin 4 and its receptor genes in native populations of Siberia. *Med. Genet.* **12**, 38–40.
24. Contopoulos-Ioannidis D.G., Manoli E.N., Ioannidis J.P. 2005. Meta-analysis of the association of beta2-adrenergic receptor polymorphisms with asthma phenotypes. *J. Allergy Clin. Immunol.* **115**, 963–972.
25. Karam R.A., Sabbah N.A., Zidan H.E., Rahman H.M. 2013. Association between genetic polymorphisms of beta2 adrenergic receptors and nocturnal asthma in Egyptian children. *J. Investig. Allergol. Clin. Immunol.* **23**, 262–266.
26. Black S., Teixeira A.S., Loh A.X., Vinall L., Holloway J.W., Hardy R., Swallow D.M. 2009. Contribution of functional variation in the *IL13* gene to allergy, hay fever and asthma in the NSHD longitudinal 1946 birth cohort. *Allergy.* **64**, 1172–1178.
27. Cui L., Jia J., Ma C.F., et al. 2012. *IL-13* polymorphisms contribute to the risk of asthma: A meta-analysis. *Clin. Biochem.* **45**, 285–288.
28. Al-Muhsen S., Vazquez-Tello A., Alzaabi A., Al-Hajjaj M.S., Al-Jahdali H.H., Halwani R. 2014. *IL-4* receptor alpha single-nucleotide polymorphisms rs1805010 and rs1801275 are associated with increased risk of asthma in a Saudi Arabian population. *Ann. Thorac. Med.* **9**, 81–86.
29. Pino-Yanes M., Corrales A., Cumplido J., et al. 2013. Assessing the validity of asthma associations for eight candidate genes and age at diagnosis effects. *PLOS ONE.* **8**, e73157.
30. He J.Q., Hallstrand T.S., Knight D., et al. 2009. A thymic stromal lymphopoietin gene variant is associated with asthma and airway hyperresponsiveness. *J. Allergy Clin. Immunol.* **124**, 222–229.
31. Torgerson D.G., Ampleford E.J., Chiu G.Y., et al. 2011. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. *Nat. Genet.* **43**, 887–892.
32. Baye T.M., Butsch Kovacic M., Biagini Myers J.M., et al. 2011. Differences in candidate gene association between European ancestry and African American asthmatic children. *PLOS ONE.* **6**, e16522.
33. Puthothu B., Krueger M., Heinze J., Forster J., Heinzmann A. 2006. Impact of *IL8* and *IL8-receptor alpha* polymorphisms on the genetics of bronchial asthma and severe RSV infections. *Clin. Mol. Allergy.* **4**, 2.
34. Moffatt M.F., Gut I.G., Demenais F., et al. 2010. A large-scale, consortium-based genomewide association study of asthma. *N. Engl. J. Med.* **363**, 1211–1221.
35. Chen T., Liang W., Gao L., Wang Y., Liu Y., Zhang L., Zhang L. 2011. Association of single nucleotide polymorphisms in interleukin 12 (*IL-12A* and *-B*) with asthma in a Chinese population. *Hum. Immunol.* **72**, 603–606.
36. Gao P., Mao X., Roberts M., et al. 2000. Variants of *STAT6* (signal transducer and activator of transcription 6) in atopic asthma. *J. Med. Genet.* **37**, 380–382.
37. Qiu Y.Y., Zhang X.L., Yin K.S. 2006. Association between beta2-adrenergic receptor genetic polymorphisms and total serum IgE in asthmatic patients of Chinese Han nationality. *Respiration.* **73**, 180–184.
38. Dewar J.C., Wilkinson J., Wheatley A., et al. 1997. The glutamine 27 beta2-adrenoceptor polymorphism is associated with elevated IgE levels in asthmatic families. *J. Allergy Clin. Immunol.* **100**, 261–265.
39. Bottema R.W., Reijmerink N.E., Kerkhof M., et al. 2008. Interleukin 13, *CD14*, pet and tobacco smoke

influence atopy in three Dutch cohorts: The allergenic study. *Eur. Respir. J.* **32**, 593–602.

40. Bottema R.W., Nolte I.M., Howard T.D., et al. 2010. Interleukin 13 and interleukin 4 receptor-α polymorphisms in rhinitis and asthma. *Int. Arch. Allergy Immunol.* **153**, 259–267.
41. Sadeghnejad A., Karmaus W., Hasan Arshad S., Ewart S. 2007. *IL13* gene polymorphism association with cord serum immunoglobulin E. *Pediatr. Allergy Immunol.* **18**, 288–292.
42. Granada M., Wilk J.B., Tuzova M., et al. 2012. A genome-wide association study of plasma total IgE concentrations in the Framingham Heart Study. *J. Allergy Clin. Immunol.* **129**, 840–845.
43. Choi W.A., Kang M.J., Kim Y.J., et al. 2012. Gene-gene interactions between candidate gene polymorphisms are associated with total IgE levels in Korean children with asthma. *J. Asthma.* **49**, 243–252.
44. Graham R.R., Cotsapas C., Davies L., et al. 2008. Genetic variants near *TNFAIP3* on 6q23 are associated with systemic lupus erythematosus. *Nat. Genet.* **40**, 1059–1061.
45. Chung S.A., Taylor K.E., Graham R.R., et al. 2011. Differential genetic associations for systemic lupus erythematosus based on anti-dsDNA autoantibody production. *PLoS Genet.* **7**, e1001323.
46. Ito I., Kawasaki A., Ito S., et al. 2009. Replication of the association between the *C8orf13–BLK* region and systemic lupus erythematosus in a Japanese population. *Arthritis Rheum.* **60**, 553–558.
47. Hom G., Graham R.R., Modrek B., et al. 2008. Association of systemic lupus erythematosus with *C8orf13–BLK* and *ITGAM–ITGAX. N. Engl. J. Med.* **358**, 900–909.
48. Kim K., Cho S.K., Sestak A., Namjou B., Kang C., Bae S.C. 2010. Interferon-gamma gene polymorphisms associated with susceptibility to systemic lupus erythematosus. *Ann. Rheum. Dis.* **69**, 1247–1250.
49. Yang W., Shen N., Ye D.Q., et al. 2010. Genome-wide association study in Asian populations identifies variants in *ETS1* and *WDFY4* associated with systemic lupus erythematosus. *PLoS Genet.* **6**, e1000841.
50. De Jager P.L., Jia X., Wang J., et al. 2009. Meta-analysis of genome scans and replication identify *CD6, IRF8*, and *TNFRSF1A* as new multiple sclerosis susceptibility loci. *Nat. Genet.* **41**, 776–782.
51. International Multiple Sclerosis Genetics Consortium, Wellcome Trust Case Control Consortium, Sawcer S., Hellenthal G., Pirinen M., Spencer C.C., et al. 2011. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature.* **476**, 214–219.
52. Patsopoulos N.A., Bayer Pharma MS Genetics Working Group, Steering Committees of Studies Evaluating IFNβ-1b and a CCR1-Antagonist, ANZgene Consortium, et al. 2011. Genome-wide meta-analysis identifies novel multiple sclerosis susceptibility loci. *Ann. Neurol.* **70**, 897–912.
53. Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene), Bahlo M., Booth D.R., Broadley S.A., et al. 2009. Genome-wide association study identifies new multiple sclerosis susceptibility loci on chromosomes 12 and 20. *Nat. Genet.* **41**, 824–828.
54. Ying B., Shi Y., Pan X., Song X., Huang Z., Niu Q., Cai B., Wang L. 2011. Association of polymorphisms in the human *IL-10* and *IL-18* genes with rheumatoid arthritis. *Mol. Biol. Rep.* **38**, 379–385.
55. Hee C.S., Gun S.C., Naidu R., Gupta E., Somnath S.D., Radhakrishnan A.K. 2007. Comparison of single nucleotide polymorphisms in the human interleukin-10 gene promoter between rheumatoid arthritis patients and normal subjects in Malaysia. *Mod. Rheumatol.* **17**, 429–435.
56. Ates O., Hatemi G., Hamuryudan V., Topal-Sarikaya A. 2008. Tumor necrosis factor-alpha and interleukin-10 gene promoter polymorphisms in Turkish rheumatoid arthritis patients. *Clin. Rheumatol.* **27**, 1243–1248.
57. Gregersen P.K., Amos C.I., Lee A.T., et al. 2009. *REL*, encoding a member of the NF-kappaB family of transcription factors, is a newly defined risk locus for rheumatoid arthritis. *Nat. Genet.* **41**, 820–823.
58. Stahl E.A., Raychaudhuri S., Remmers E.F., et al. 2010. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. *Nat. Genet.* **42**, 508–514.
59. Orozco G., Viatte S., Bowes J., et al. 2014. Novel rheumatoid arthritis susceptibility locus at 22q12 identified in an extended UK genome-wide association study. *Arthritis Rheumatol.* **66**, 24–30.
60. Lee Y.H., Woo J.H., Choi S.J., Ji J.D., Song G.G. 2010. Association between the rs7574865 polymorphism of *STAT4* and rheumatoid arthritis: A meta-analysis. *Rheumatol. Int.* **30**, 661–666.
61. Dhiman N., Ovsyannikova I.G., Vierkant R.A., Ryan J.E., Pankratz V.S., Jacobson R.M., Poland G.A. 2008. Associations between SNPs in toll-like receptors and related intracellular signaling molecules and immune responses to measles vaccine: Preliminary results. *Vaccine.* **26**, 1731–1736.
62. Gaddam S.L., Priya V.H., Babu B.M., Joshi L., Venkatasubramanian S., Valluri V. 2012. Association of interleukin-10 gene promoter polymorphism in allergic patients. *Genet. Test. Mol. Biomarkers.* **16**, 632–635.
63. Movahedi M., Amirzargar A.A., Nasiri R., et al. 2013. Gene polymorphisms of Interleukin-4 in allergic rhinitis and its association with clinical phenotypes. *Am. J. Otolaryngol.* **34**, 676–681.
64. Radstake T.R., Gorlova O., Rueda B., et al. 2010. Genome-wide association study of systemic sclerosis identifies *CD247* as a new susceptibility locus. *Nat. Genet.* **42**, 426–429.
65. Allanore Y., Saad M., Dieudé P., et al. 2011. Genome-wide scan identifies *TNIP1*, *PSORS1C1*, and *RHOB* as novel risk loci for systemic sclerosis. *PLoS Genet.* **7**, e1002091.
66. Hirschfield G.M., Liu X., Xu C., et al. 2009. Primary biliary cirrhosis associated with *HLA*, *IL12A*, and *IL12RB2* variants. *N. Engl. J. Med.* **360**, 2544–2555.
67. Liu X., Invernizzi P., Lu Y., Kosoy R., et al. 2010. Genome-wide meta-analyses identify three loci associated with primary biliary cirrhosis. *Nat. Genet.* **42**, 658–660.

68. Mells G.F., Floyd J.A., Morley K.I., et al. 2011. Genome-wide association study identifies 12 new susceptibility loci for primary biliary cirrhosis. *Nat. Genet.* **43**, 329–332.

69. Nakamura M., Nishida N., Kawashima M., et al. 2012. Genome-wide association study identifies *TNFSF15* and *POU2AF1* as susceptibility loci for primary biliary cirrhosis in the Japanese population. *Am. J. Hum. Genet.* **91**, 721–728.

70. Excoffier L., Laval G., Schneider S. 2007. Arlequin (version 3.0): An integrated software package for population genetics data analysis. *Evol. Bioinform. Online*. **1**, 47–50.

71. HUGO Pan-Asian SNP Consortium, Abdulla M.A., Ahmed I., Assawamakin A., et al. 2009. Mapping human genetic diversity in Asia. *Science*. **326**, 1541–1545.

72. Thompson E.E., Kuttab-Boulos H., Witonsky D., Yang L., Roe B.A., Di Rienzo A. 2004. *CYP3A* variation and the evolution of salt-sensitivity variants. *Am. J. Hum. Genet.* **75**, 1059–1069.

73. Hancock A.M., Clark V.J., Qian Y., Di Rienzo A. 2011. Population genetic analysis of the uncoupling proteins supports a role for *UCP3* in human cold resistance. *Mol. Biol. Evol.* **28**, 601–614.

74. Young J.H., Chang Y.P., Kim J.D., et al. 2005. Differential susceptibility to hypertension is due to selection during the out-of-Africa expansion. *PLoS Genet.* **1**, e82.

75. Hancock A.M., Witonsky D.B., Alkorta-Aranburu G., et al. 2011. Adaptations to climate-mediated selective pressures in humans. *PLoS Genet.* **7**, e1001375.

76. Borinskaya S.A., Gureev A.S., Orlova A.A., Sanina E.D., Kim A.A., Gasemian Rodsari 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**, 98–109.

77. Borinskaya S.A., Yankovsky N.K. 2013. Human genetics and genomics. Populations and ethnoses in space and time: Evolutionary and medical aspects. *Vavilov. J. Genet. Selekts.* **17**, 930–942.

Translated by D. Timchenko