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Polymorphism of 2'-5'-Oligoadenylate Synthetase (*OAS*) Genes, Associated with Predisposition to Severe Forms of Tick-Borne Encephalitis, in Human Populations of North Eurasia

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Abstract—2'-5'-oligoadenylate synthetases are a family of interferon-induced enzymes playing an important role in antiviral defense in mammals. In the human genome, three genes encoding functional synthetases (*OAS1*, *OAS2* and *OAS3*) form a cluster. Previously, we found that particular genotypes and/or alleles of five single nucleotide polymorphisms (SNPs) of *OAS2* and *OAS3* are associated with predisposition to severe forms of tick-borne encephalitis (TBE) in Russians. In the current study, we investigated the distribution of three of the above SNPs, *OAS3* rs2285932 (C/T, Ile438Ile), *OAS3* rs2072136 (G/A, Ser567Ser), and *OAS2* rs15895 (G/A, Trp720Ter relative to p71 isoform), in seven populations of North Eurasia: Caucasians (Russians, Germans from Altai region), Central Asian Mongoloids (Altaians, Khakass, Tuvinians, and Shorians), and Arctic Mongoloids (Chukchi). Interpopulational differences in genotype, allele and haplotype frequencies and in linkage disequilibrium structure for these SNPs were detected. These frequencies correlated with the ethnicity of the populations and with their supposed differential exposure to the TBE virus. In particular, the lowest frequencies of G/G genotype for *OAS3* SNP rs2072136 (which, according to our earlier results, is associated with predisposition to severe forms of TBE) were found in Altaians, Khakass, Tuvinians, and Shorians, who commonly contact with the TBE virus in their habitation regions. Thus, the data obtained suggest that the TBE virus might act as a selection factor for particular *OAS* variants in Central Asian Mongoloids.

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INTRODUCTION

2'-5'-oligoadenylate synthetases (2-5OAS) are an enzyme family constituting a major component of interferon-induced early intracellular antiviral in mammals [1]. Interferon binding to target cell receptors induces a cascade of intracellular reactions (Jak/STAT pathway), activating transcription of certain genes, including *OAS*. 2-5OASs are activated by double-stranded RNA (dsRNA) and use ATP substrate to catalyze AMP polymerization and produce 2'-5'-oligoadenylates (2-5A), which, in turn, bind to latent endoribonuclease, RNAse L, which causes its dimerization and activation. Activated RNAse L hydrolyzes UpXp dinucleotides of single-stranded RNA from the 3' end, thus leading to degradation of both cellular and viral RNA and suppressing virus replication [2, 3].

In human, the *OAS* family comprises three genes encoding active enzymes: *OAS1*, *OAS2*, and *OAS3*, which form an approximately 130 kbp long cluster in 12q24.1. The gene order is as follows: centromere–5'-*OAS1*–*OAS3*–*OAS2*-3'–telomere. The genes are transcribed in the centromere to telomere direction. *OAS1* spans approximately 12 kbp, and each of *OAS2* and *OAS3* is approximately 35 kbp long. *OAS1, OAS2*, and *OAS3* encode the small (p42/44 and other isoforms), medium (p69/71), and large (p100) 2-5OAS proteins, respectively. Numerous *OAS1* and *OAS2* mRNA isoforms are produced by alternative splicing. The OAS1 domain comprising the first 346 amino acid residues and encoded by five exons is repeated with a high degree of homology twice in OAS2 and thrice in OAS3. In addition, *OASL* (12q24.2) is a gene highly homologous to other members of the *OAS* family; however, its product is inactive [2, 4–7].

In spite of the structural similarity of the *OAS*-encoded enzymes, they differ in cellular compartmentalization, oligomerization degree, activation pattern, and the structure of their 2-5A products. For instance,

activated OAS1, OAS2, and OAS3 are tetrameric, dimeric and monomeric, respectively. It is known that OAS1 and OAS2 catalyze the synthesis of oligomeric, and OAS3 catalyze that mainly of dimeric 2−5A products, which bind and activate RNAse L less efficiently than 2-5A oligomers [2, 4, 5]. However, it was recently shown that OAS3 has antiviral activity against the Chikungunya virus (an alphavirus) [8]. In addition, expression of *OAS3* (p100) and *OAS1* (p42 and p46), but not of *OAS2* and other *OAS1* variants, in cell culture blocks the dengue virus replication by the RNAse L-mediated pathway [9]. Therefore, all of the genes *OAS1, OAS2,* and *OAS3* are involved in antiviral defense.

Previously, some *OAS1* single nucleotide polymorphisms (SNP) were associated with human susceptibility to certain diseases directly or indirectly caused by viral infections. For instance, the rs2660 SNP of *OAS1* was associated with hepatitis C outcome in Caucasians [10]. The same SNP was associated with susceptibility to severe acute respiratory syndrome (SARS) in Chinese, while rs1131454 (Gly162Ser, earlier designated rs3741981) located in *OAS1* exon 3 was associated with susceptibility to SARS in Vietnamese [11, 12]. The basal *OAS1* activity was correlated to the SNP rs10774671 located in the splice site of this gene [13]. The same SNP is associated with susceptibility to type I diabetes mellitus, whose pathogenesis supposedly involves a viral infection [14]. In addition, rs10774671 apparently is associated with susceptibility to the West Nile virus in the Caucasian population of the United States [15].

Furthermore, susceptibility of certain mouse lines to *Flavivirus* infections depends on particular *Oas1b* variants. In sensitive mice, a nonsense C820T mutation in *Oas1b* exon 4 results in truncation of the protein product by 30% [16−18]. The tick-borne encephalitis (TBE) virus endemic in the forest and forest−steppe zones of North Eurasia (including many Russian regions) also belongs to the *Flavivirus* genus [19]. In our previous study, we investigated the effects of 23 *OAS1, OAS2, OAS3,* and *OASL* SNPs on the clinical course of TBE in Russian residents of Novosibirsk. For five SNPs of *OAS2* and *OAS3*, the genotype, allele, and/or haplotype frequencies differed significantly between the groups of patients with severe (meningoencephalitis et al.) and with milder (fever, meningitis) TBE forms and/or population control. These differences suggest an association of these SNPs with individual TBE susceptibility in Russians [20].

Viral infections can act as natural selection factors and affect allele frequencies of the genes controlling disease susceptibility in populations. For this reason, we thought it interesting to study *OAS* polymorphisms in populations of different ethnicity. This study was concerned with three polymorphisms belonging to the earlier identified group of five SNPs associated with TBE course: rs2285932 (C/T), rs2072136 (G/A) of *OAS3*, and rs15895 (G/A) of *OAS2*. We analyzed their distribution in seven populations of North Eurasia: Russians, Germans, Altaians, Khakass, Shorians, Tuvinians, and Chukchi. The SNPs rs2285932 (Ile438Ile) and rs2072136 (Ser567Ser) resulting in synonymous substitutions are located in *OAS3* exons 6 and 8, respectively. The G $\longrightarrow$ A substitution in *OAS2* (SNP rs15895) generates a stop codon instead of a tryptophan at position 720 truncating the protein by eight amino acid residues (in comparison to the p71 isoform). The selected populations differ in race and ethnicity; moreover, for generations they have been residing in regions associated with different degrees of exposure to the TBE virus.

EXPERIMENTAL

Subjects. The study involved 873 individuals representing seven populations of North Eurasia: Russians (Novosibirsk, $n = 285$), Germans (Nemetskii district, Altaiskii krai, $n = 96$), Altaians (Kosh−Agach district, Altai Republic, $n = 99$), Khakass (Khakass Republic, $n = 85$), Shorians (Orton and Chuvashka settlements, Kemerovo oblast', $n = 86$), Tuvinians (Mongun−Taiga settlement, Tyva Republic, $n = 110$), and tundra Chukchi (Kanchalan settlement, Anadyr district, Chukotskii Autonomous Region $n = 112$). Blood samples were collected during earlier field studies of these populations. Individuals' ethnicity was verified using targeted questionnaires.

DNA was isolated from peripheral blood using the standard phenol−chloroform procedure [21].

Genotyping of rs2285932, rs2072136 (*OAS3*), and rs15895 (*OAS2*) SNPs was performed by PCR−RFLP. The resulting fragments were separated by PAGE in a 4% gel and stained with ethidium bromide. The sequence of the *OAS*-containing fragment of the human 12q24.1 was obtained from the GenBank database (PAC clone RPCI1-71H24, Acc. No. AC004551). Primers were designed with the Vector NTI 9.0 software. PCR−RFLP conditions were optimized using DNA samples with known genotypes. Initially, randomly selected DNA samples containing SNPs in question were sequenced on an automated ABI Prism 310 Genetic Analyzer according to the recommendations of Applied Biosystems in the Interinstitutional DNA Sequencing Center of the Russian Academy of Sciences, Siberian Branch.

rs2285932 (C/T) genotyping. A 421 bp SNP-containing fragment of *OAS3* was amplified with the primers 5'-tggatgctcaggtttgggcc-3' and 5'-ccaacctcagctc-cattgctgta-3'. The reaction mixture (10 µl) contained 75 mM Tris-HCl (pH 8.8), 20 mM $(NH_4)_2SO_4$, 0.01% Tween-20, 0.5 µg total DNA, 0.5 µM each primer, 0.2 mM each dNTP, 2.5 mM $MgCl_2$, and 0.6 units *Taq* DNA polymerase (Sibenzyme). The PCR protocol included denaturation at 95°C for 3 min and 32 cycles of 1 min denaturation at 95°C, 1 min annealing at 63°C, and 1 min elongation at 72°C. Next, the PCR product was digested with 5 units of *Taq*I restriction

Table 1. Allele and genotype frequencies of the *OAS3* SNP rs2285932 in seven North Eurasian populations

Population	N	Genotype frequency, %			Allele frequency, %		χ^2 HW
		C/C	C/T	T/T	C	T	
Russians	265	57.0	35.8	7.2	74.9	25.1	0.57
Germans	96	35.4	57.3	7.3	64.1	35.9	5.73*
Altaians	99	72.7	27.3	0.0	86.4	13.6	2.47
Khakass	85	83.5	14.1	2.4	90.6	9.4	2.52
Shorians	86	89.5	10.5	0.0	94.8	5.2	0.26
Tuvinians	110	90.0	10.0	0.0	95.0	5.0	0.30
Chukchi	112	69.6	28.6	1.8	83.9	16.1	0.39

* Deviation from the Hardy−Weinberg equilibrium due to C/T excess (2.64) and T/T deficiency (2.36).

Note: Here and in Tables 2, 3, and 6, *N* is the sample size.

endonuclease (Sibenzyme) for 12 h at 65°C. DNA samples with the C/C genotype produced two bands, 271 and 98 bp long (a fragment of 52 bp universally produced due to the second *Taq*I recognition site was eluted from the gel), T/T homozygotes produced one fragment of 369 bp, and C/T heterozygotes produced three fragments (369, 271 and 98 bp).

rs2072136 (G/A) genotyping. A 465 bp SNP-containing fragment of *OAS3* was amplified with the primers 5'-gattatccactgtgcagttactgg-3' and 5'-gtggttgccat-gacagtggt-3'. The reaction mixture (10 μl) contained 75 mM Tris-HCl (pH 8.8), 20 mM $(NH_4)_2SO_4$, 0.01% Tween-20, 0.5 μg total DNA, 0.4 μM each primer, 0.2 mM each dNTP, 2.5 mM $MgCl_2$, and 0.6 units *Taq* DNA polymerase. The PCR protocol included denaturation at 95°C for 3 min and 36 cycles of 30 s at 95°C, 30 s at 66°C, and 1 min at 72°C. Next, the PCR product was digested with 5 units of *Taq*I restriction endonuclease (Sibenzyme) for 12 h at 65°C. samples with the genotype G/G produced two fragments (281 and 184 bp), those with the genotype A/A produced one fragment 465 bp, and those with the genotype G/A produced three fragments (465, 281 and 184 bp).

rs15895 (G/A) genotyping. A 369 bp SNP-containing fragment of *OAS2* was amplified with the primers 5'-tgtctctggcaatagttaccttcc-3' and 5'-aagggtttgcagtct-tgattga-3'. The reaction mixture (10 μl) contained 75 mM Tris-HCl (pH 8.8), 20 mM $(NH_4)_2SO_4$, 0.01% Tween-20, 0.5 μg total DNA, 0.4 μM each primer, 0.2 mM each dNTP, 1.5 mM $MgCl_2$, and 0.6 units *Taq* DNA polymerase. The PCR protocol included denaturation at 95°C for 3 min and 35 cycles of 30 s at 95°C, 30 s at 65°C, and 1 min at 72°C. Next the PCR product was digested with 5 units *Xba*I restriction endonuclease (Sibenzyme) for 12 h at 37°C. samples with the genotype G/G produced one fragment of 369 bp, those with the genotype A/A produced two fragments (229 and 140 bp), and those with the geno-

type G/A produced three fragments (369, 229 and 140 bp).

Statistical analysis. The correspondence of the genotype frequencies to the Hardy−Weinberg equilibrium was assessed using the χ^2 criterion with the CHIHW software [22]. Interpopulational comparison of the SNP allele frequencies was performed using the χ^2 test with the SPSS 11.0 software. Differences were considered significant at $P < 0.05$. Pairwise SNP linkage was analyzed by the permutation test using the EM algorithm [23]. The most likely haplotype structures for two and more heterozygous SNPs were determined by maximum likelihood analysis with the Arlequin 3.0 software [24]. Interpopulational genetic distances were estimated using multidimensional scaling (MDS) with the XLSTAT software.

RESULTS

We determined the allele and genotype frequencies of the rs2285932, rs2072136 (*OAS3*), and rs15895 (*OAS2*) SNPs in seven ethnically different populations of North Eurasia: Russians, Germans, Altaians, Khakass, Shorians, Tuvinians, and Chukchi (Tables 1−3), and the allele frequencies were compared in all population pairs to detect significant differences with the χ^2 test (Table 4).

In Germans, the rs2285932 (*OAS3*) genotype distribution deviated from the Hardy−Weinberg equilibrium due to the C/T heterozygote excess and T/T homozygote deficiency ($\chi^2 = 5.73$, d.f. = 1) (Table 1). In all other population samples, the genotype distribution agreed with the Hardy−Weinberg equilibrium. The frequency of the less common T allele was the highest in Russians and Germans (25.1 and 35.9%, respectively). In all other populations, its frequency was significantly lower. The lowest T allele frequency was observed in Tuvinians (5.0%) and Shorians (5.2%). There was no significant difference in the T

Table 2. Allele and genotype frequencies of the *OAS3* SNP rs2072136 in seven North Eurasian populations

Population	N	Genotype frequency, %			Allele frequency, %		χ^2 HW
		G/G	G/A	A/A	G	A	
Russians	260	50.0	41.2	8.8	70.6	29.4	0.02
Germans	89	61.8	36.0	2.2	79.8	20.2	1.16
Altaians	98	29.6	51.0	19.4	55.1	44.9	0.10
Khakass	77	29.9	53.2	16.9	56.5	43.5	0.53
Shorians	83	26.5	45.8	27.7	49.4	50.6	0.59
Tuvinians	107	36.4	43.0	20.6	57.9	42.1	1.49
Chukchi	107	53.3	41.1	5.6	73.8	26.2	0.44

Table 3. Allele and genotype frequencies of the *OAS2* SNP rs15895 in seven North Eurasian populations

Population	N	Genotype frequency, %			Allele frequency, %		χ^2 HW
		G/G	G/A	A/A	G	A	
Russians	240	54.2	35.4	10.4	71.9	28.1	3.69
Germans	90	42.2	57.8	0.0	71.1	28.9	14.85*
Altaians	97	85.6	14.4	0.0	92.8	7.2	0.59
Khakass	78	74.3	23.1	2.6	85.9	14.1	0.18
Shorians	86	87.2	12.8	0.0	93.6	6.4	0.40
Tuvinians	110	90.0	10.0	0.0	95.0	5.0	0.30
Chukchi	106	82.1	17.0	0.9	90.6	9.4	0.004

* Deviation from the Hardy−Weinberg equilibrium due to G/A excess (6.10) and A/A deficiency (7.51).

allele frequency among Chukchi (16.1%), Altaians (13.6%), and Khakass (9.4%) (Tables 1, 4).

The rs2072136 (*OAS3*) genotype frequency distribution corresponded to the Hardy−Weinberg equilibrium in all populations studied. In all populations, the polymorphism level was fairly high, with the frequency of the less common A allele exceeding 20%. However, in contrast to rs2285932, these frequencies in Russians and Germans were the lowest, 29.4 and 20.2%, respectively. In Central Asian Mongoloids, the A allele frequencies were significantly higher than in Caucasians, ranging from 42.1% in Tuvinians to 50.6% in Shorians (Table 2). Interestingly, the frequency of the A allele in Chukchi (26.2%) was the same as in Caucasians and significantly lower than in all Central Asian Mongoloids (Table 4).

The rs15895 (*OAS2*) genotype frequency distribution deviated from the Hardy−Weinberg equilibrium only in the population of Germans due to heterozygote excess and A/A homozygote deficiency ($\chi^2 = 14.85$, d.f. = 1) (Table 3). The allele frequency distributions in the seven populations studied were similar to those of rs2285932 (*OAS3*). The highest frequencies of the less common A allele were found in Russians and Germans (28.1 and 28.9%, respectively). Among Central Asian Mongoloids, the A allele frequency varied from 5.0% in Tuvinians to 14.1% in Khakass. Chukchi, an Arctic Mongoloid population, did not differ in this respect from other Mongoloid populations (Tables 3, 4).

Thus, the populations differed in allele frequencies of all three SNPs.

In each of the seven populations, we analyzed possible pairwise linkage of the three SNPs located within a 62 kbp chromosome fragment (Table 5). In Russians, Germans, Khakass, and Tuvinians, all SNPs are in

Table 4. Interpopulational differences in the frequencies of the less common alleles of rs2285932, rs2072136 (*OAS3*), and rs15895 (*OAS2*) SNPs

SNP	Population	P (d.f. = 1)					
		Germans	Altaians	Khakass	Shorians	Tuvinians	Chukchi
OAS3 rs2285932	Russians	**0.004**	**0.001**	**1.4×10^{-5}**	**1.8×10^{-8}**	**2×10^{-10}**	**0.007**
	Germans	–	**3.2×10^{-7}**	**2.8×10^{-9}**	**1×10^{-12}**	**2.4×10^{-15}**	**3.3×10^{-6}**
	Altaians	–	–	0.208	**0.007**	**0.002**	0.483
	Khakass	–	–	–	0.138	0.089	0.053
	Shorians	–	–	–	–	0.916	**0.001**
	Tuvinians	–	–	–	–	–	**1.5×10^{-4}**
	Chukchi	–	–	–	–	–	–
OAS3 rs2072136	Russians	**0.017**	**9.3×10^{-5}**	**0.001**	**5.9×10^{-7}**	**0.001**	0.374
	Germans	–	**4.2×10^{-7}**	**4.8×10^{-6}**	**3.5×10^{-9}**	**4.1×10^{-6}**	0.167
	Altaians	–	–	0.794	0.279	0.562	**7.2×10^{-5}**
	Khakass	–	–	–	0.204	0.781	**5.1×10^{-4}**
	Shorians	–	–	–	–	0.097	**9.7×10^{-7}**
	Tuvinians	–	–	–	–	–	**0.001**
	Chukchi	–	–	–	–	–	–
OAS2 rs15895	Russians	0.845	**3.2×10^{-9}**	**4.2×10^{-4}**	**4.5×10^{-9}**	**2.7×10^{-12}**	**5.4×10^{-8}**
	Germans	–	**4.0×10^{-8}**	**0.001**	**3.7×10^{-8}**	**6.8×10^{-11}**	**7.2×10^{-7}**
	Altaians	–	–	**0.035**	0.755	0.345	0.420
	Khakass	–	–	–	**0.020**	**0.002**	0.164
	Shorians	–	–	–	–	0.551	0.277
	Tuvinians	–	–	–	–	–	0.074
	Chukchi	–	–	–	–	–	–

Note: Significant differences are shown in bold ($P < 0.05$).

linkage disequilibrium with each other. Linkage was disrupted between rs2072136 and rs15895 in Altaians, between rs2285932 and rs15895 in Chukchi, and between rs2072136 and both rs2285932 and rs15895 in Shorians. Thus, linkage disequilibrium patterns of the *OAS* SNPs differ among the populations studied.

Since the three SNPs were linked in most populations studied, we also determined the respective haplotype frequencies (Table 6). The nucleotide order in the haplotype structure reflects the physical order of the SNPs on the chromosome (rs2285932, rs2072136, and rs15895). The haplotype frequencies were determined using only the samples genotyped for all three

SNPs. Five of the eight possible combinations (CGG, CAG, TGA, CGA, and TGG) were found in all populations; the TAA haplotype was detected in only one Shorian. The TAG haplotype was not observed in any populations. The haplotype frequencies of CGG (ranging from 36.4% in Russians to 54.3% in Chukchi) and CAG (from 20.2% in Germans and Chukchi to 49.7% in Shorians) were high in all groups. The TGA frequency was the highest in Caucasians, reaching 18.4% in Russians and 23.4% in Germans; in Mongoloid populations it did not exceed 7%. The TGG haplotype was common in Chukchi (15.9%) and Germans (11.5%); in other groups its frequency was less than 10%. The CAA haplotype was present in Chukchi

Table 5. Pairwise linkage disequilibrium between rs2285932 and rs2072136 (*OAS3*) and rs15895 (*OAS2*) SNPs in seven North Eurasian populations assessed by the permutation test using the EM algorithm

SNP pair	P						
	Russians	Germans	Altaians	Khakass	Shorians	Tuvinians	Chukchi
rs2285932/rs2072136	1.9×10^{-11}	1.1×10^{-4}	5.1×10^{-4}	6.4×10^{-3}	0.069*	7.7×10^{-3}	8.3×10^{-4}
rs2285932/rs15895	5.0×10^{-21}	6.5×10^{-8}	8.7×10^{-9}	3.1×10^{-3}	8.8×10^{-4}	7.3×10^{-3}	0.299*
rs2072136/rs15895	1.8×10^{-8}	1.2×10^{-3}	0.055*	0.014	0.121*	8.7×10^{-3}	5.6×10^{-3}

* No significant linkage ($P > 0.05$).

Table 6. Haplotype frequencies of the rs2285932 (C/T), rs2072136 (G/A) (*OAS3*), and rs15895 (G/A) (*OAS2*) SNPs in seven North Eurasian populations

Population	N	Haplotype frequency, %						
		CGG	CAG	TGA	CGA	TGG	CAA	TAA
Russians	211	36.4	29.2	18.4	7.9	6.7	1.4	–
Germans	86	39.2	20.2	23.4	5.0	11.5	0.7	–
Altaians	97	40.7	44.9	6.7	0.5	7.2	–	–
Khakass	77	40.1	42.2	4.4	7.9	4.1	1.3	–
Shorians	83	41.2	49.7	1.9	3.7	2.5	–	1.0
Tuvinians	107	49.8	42.1	1.7	3.4	3.0	–	–
Chukchi	105	54.3	20.2	0.8	2.8	15.9	6.0	–

Note: Nucleotide order in the haplotypes structure corresponds to the SNP order on the chromosome (rs2285932, rs2072136, and rs15895).

(6.0%) and in a small number of Caucasians and Khakass.

To analyze interpopulational differences, the haplotype frequencies of the three SNPs were used to calculate genetic distances (Figure). In the chart, the populations of Shorians, Tuvinians, Altaians, and Khakass are lying close to each other, while the populations of Russians and Germans, on the one hand, and Chukchi, on the other hand, are isolated.

DISCUSSION

Central Asian Mongoloid populations of Shorians, Tuvinians, Khakass, and Altaians have been residing in South Siberia for generations and must have regularly been exposed to endemic TBE virus-transmitting ixodic ticks. Caucasian populations of Russian and Germans arrived in Siberia in relatively recent times and have probably had less contact with the TBE virus. The Chukchi, an Arctic Mongoloid population, live in the area not endemic for ticks and have not been exposed to the TBE virus at least for a very long time [25]. In the previous study, we found that the frequencies of the *OAS3* genotypes T/T (SNP rs2285932) and G/G (SNP rs2072136) and of the *OAS2* allele A (SNP rs15895) were significantly higher in patients with severe TBE forms in comparison to patients with milder TBE and/or population controls [20]. This study showed the frequency of the T allele of rs2285932, whose homozygous form is associated with severe forms of TBE, was the lowest in Shorians, Tuvinians, and Khakass, and the highest was in Russians and Germans. A similar pattern was observed for the A allele of rs15895. The frequency of the G/G genotype (rs2072136) in all Central Asian Mongoloid populations was significantly lower than in Germans, Russians, or Chukchi (Table 1−4). This fact suggests that the above alleles and genotypes could have been eliminated from the populations due to selection pressure, with the TBE virus probably acting as a selection factor. In other words, seeing that, until recently, there were no efficient means of TBE prevention and treatment, carriers of these alleles and genotypes were probably less fit to survive in the TBE virus exposure area. Moreover, Chukchi who have not been exposed to the TBE virus do not differ from Caucasian populations in rs2072136 allele frequencies (*OAS3*).
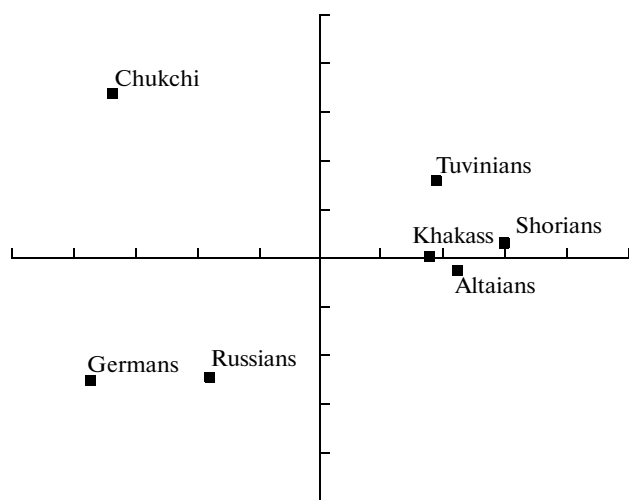
Genetic distances among seven populations of North Eurasia based on the haplotype frequency matrix for rs2285932, rs2072136 (*OAS3*), and rs15895 (*OAS2*) SNPs. The chart was obtained by multidimensional scaling (MDS) using the XLSTAT software package.

In addition, the intensity of the populations' contact with the TBE virus is apparently reflected in the haplotype distribution of the three SNPs (Table 6, figure). For instance, the TGA haplotype includes the unfavorable alleles of rs2285932, rs2072136, and rs15895, associated (individually or in the homozygous form) with severe TBE forms [20]. It is significantly less frequent in Central Asian Mongoloid populations (1.7 to 6.7%) than in Russians or Germans (18.4 and 23.4%, respectively). In Chukchi, the TGA frequency is even lower (0.8%); however, the frequency of the TGG haplotype was the highest (15.9%). The CAG haplotype comprising the alleles alternative to those predisposing to severe forms of TBE was most frequent in Altaians, Khakass, Shorians, and Tuvinians (over 40%).

Different prevalence of certain genome loci variants among human populations can be a result of selection. It is known that infectious diseases act sometimes as selection factors. For instance, it has been proved that, in regions endemic for malaria, selection acts in favor of resistant heterozygotes carrying a hemoglobin S-producing mutation [26]. The frequency of the 32 bp deletion in the chemokine receptor gene *CCR5*, which has been associated with human susceptibility to certain viral infections, also varies among different ethnic groups, presumably, due to selection [27−29]. The above examples back up the hypothesis suggesting that interpopulational differences in the allele and haplotype frequency distributions of the three *OAS2* and *OAS3* SNPs can reflect the differential fitness to living in contact with the TBE virus.

Thus, we have determined the genotype, allele, and haplotype frequencies of three *OAS* SNPs in seven eth-

nically different populations of Russia and detected highly significant interpopulational differences. Considering that these populations have had different TBE virus contact intensity, we suppose that the interpopulational divergence results from the virus acting as a selection factor. These data indirectly support our previous results implicating the above SNPs in human susceptibility to severe TBE forms.

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