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HLA profile of three ethnic groups living in the North-Western region of Russia

Key words:

DNA typing; ethnic groups; HLA DR-DQ alleles, haplotypes; Russia

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Abstract: HLA class II alleles were determined by PCR-SSO and PCR-SSP typing of DNA samples from 55 Nentsy, 81 Saami and 73 Pomor individuals from the North-European part of Russia. The results were compared with similar data from Russians. A high frequency of the DRB1*04-DQA1*0301-DQB1*0302 haplotype and a low frequency of the DRB1*11-DQA1*0501-DQB1*0301 haplotype, observed in all three ethnic groups, may indicate a common aboriginal component in their ancestry. Saami and Pomors displayed a similar pattern of allele and haplotype distribution, with the exception of the DRB1*04-DQA1*0304-DQB1*0301 haplotype, which was significantly higher among Saami compared Nentsy, Pomors and Russians. Nentsy individuals had a particularly high frequency of the DRB1*09-DQA1*0301-DQB1*0303 and the DRB1*12-DQA1*0501-DQB1*0301 haplotypes. Genetic distances and correspondence analysis show that Pomors have a close relationship with Norwegians and Finns, whereas Nentsy and Saami are more closely related to Oriental populations.

Vast territories and exceptional national variety in the Russian Federation makes it an interesting area for anthropological investigations. For HLA studies, the new methods of genotyping offer new ways of studying other populations, as well as contributing to previously reported anthropological data (1). However, HLA allelic frequencies are reported for a limited number of ethnic groups inhabiting the territory of the Russian Federation only (2). No previous studies have been performed on populations of the European North of Russia, although this region is of considerable interest as the area has been inhabited for a long period by the aboriginal populations of the North (Nentsy, Saami and Pomors), closely neighboring the Russian population.

The Nentsy are the aboriginal residents of North-Eastern Russia (total number near 35,000) and are representatives of an Ural transitional ethnic group, with contributions from an Eastern aboriginal group from the Arctic Ocean coast, Samodian tribes from Northern slopes of Sayan plateau and Enets and Ugor groups that joined the Nentsy at a later period. They speak Nenets language, which belongs

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to the Samodiysky group of the Ural family of languages (3, 4). The Saami are an ethnic group of aboriginal people from the North-West of Europe, mostly inhabiting Scandinavia. In Russia they are mostly concentrated on the Kola Peninsula, with a total number of about 2000. They belong to the Lapanoid (Subarctic) anthropological group, which is believed to consist of an ancient blending of European race and Ural tribes, with a Russian population from the Novgorod region contributing later. Saami language belongs to the Ugro-finish group of Ural family of languages (5, 6). Pomors, who have been residing at the White Sea coast since the 4th-5th century AD, belong to the Russian Caucasoid population group and speak Russian, which is from the Slavonic group of the Indo-European family of languages. They number approximately 500 000. It is proposed that both aboriginals from the North and Russians from the Novgorod region contributed to their make up originally (7, 8).

The aim of this study was to determine the genetic diversity of HLA class II alleles among various ethnic groups of European Northern Russia to establish a database for further investigations on ancestry and the genetic factors contributing to complex diseases in this region.

Materials and methods

Population samples

We studied a randomly selected cohort of healthy adults representing the following three ethnic groups from the far North of Russia (Fig. 1): Nentsy from the Nenets Autonomous Area ($N=55$), Saami from the Lovosero village in the Murmansk region of the Kola Peninsula ($N=81$) and Pomors from the Arkhangelsk region on the White Sea coast ($N=73$). The ethnic origin of each volunteer was determined by official documents and family history of three generations (nationality, place of birth and home-speaking language of parents and grandparents). The following populations were used for comparison: Russian, Hungarian, Croatian, German, French, Finn (9), Polish (10), Norwegian (11), Buryat (12), Japanese (13) and Korean (14).

HLA typing

DNA was isolated using a standard salting-out method (15) from peripheral blood samples taken into EDTA. Medium resolution HLA-DRB1 typing was carried out using sequence specific oligonucleotide probes technique (SSOP) on amplified DNA with primers and probes similar to those recommended by the 11th International Histocompatibility Workshop (11th IHWS) (16). Low resolution

HLA-DQB1 and DQA1 typing was achieved using two-round allele specific amplification with a mixture of custom made sequence specific primers (MSSP), designed in the Moscow Institute of Immunology and tested in the 12th International Histocompatibility Workshop (IHWS) quality control (17, 18).

Statistical analysis

The allelic and three-locus haplotypic frequency estimation was performed using Arlequin software, v.2000 (<http://anthro.unige.ch/arlequin>). The allele and haplotype frequencies in the four groups were compared using the χ^2 test (2×2 table) or the Fisher's exact test where appropriate. P -values were corrected for the number of comparisons (number of haplotypes with frequency above 5% in any of



Fig. 1. Geographical location of the Nentsy, Saami and Pomors in Northern part of Russia. Places of sampling – Naryan-Mar (latitude 67°N; longitude 52°E), Lovosero (latitude 72°N; longitude 33°E), Arkhangelsk (latitude 64°N; longitude 40°E).

HLA class II allele and DRB1*-DQA1*-DQB1* haplotype frequencies in four populations of North-European Russia

Allel/Haplotype	Pomors n = 73	Saami n = 81	Nentsy n = 55	Russians n = 140 [#]	P corrected (χ^2 test)
DRB1					
*01	0.110	0.136	0.018	0.082	P < 0.05
*04	0.192	0.327	0.209	0.116	P < 0.001
*07	0.123	0.037	0.118	0.127	
*08	0.048	0.074	0.055	0.024	
*09	0.034 ¹	0.043 ²	0.182	0.003 ³	P < 0.05 ^{1,2} ; P < 0.0001 ³
*11	0.055	0.043	0.018	0.147	P < 0.05
*12	0.021 ¹	0.037 ²	0.164	0.027 ³	P < 0.05 ^{1,2} ; P < 0.01 ³
*13	0.103	0.092	0.118	0.079	
*15	0.171	0.117	0.045	0.134	
*17	0.096	0.080	0.055	0.075	
DQB1					
*0201	0.164	0.111	0.127	0.185	
*0301	0.123	0.235	0.227	0.257	
*0302	0.171	0.185	0.209	0.075	P < 0.05
*0303	0.110	0.093	0.218	0.038	P < 0.0001
*0501	0.103	0.148	0.018	0.096	P < 0.05
*0602-8	0.247	0.136	0.136	0.182	
DQA1					
*0101	0.130	0.154	0.027	0.123	P < 0.01
*0102	0.205	0.123	0.055	0.175	
*0103	0.062	0.049	0.091	0.055	
*0201	0.123	0.037	0.109	0.127	P < 0.05
*0301	0.226	0.383 ¹	0.409 ²	0.123	P < 0.001 ^{1,2}
*0401	0.034	0.062	0.045	0.014	P < 0.05
*0501	0.199	0.179	0.255	0.315	
DRB1-DQA1-DQB1					
*01*0101*0501	0.089	0.130	0.018	0.082	
*04*0301*0301	0.014 ¹	0.118	0 ²	0.024 ³	P < 0.05 ^{1,3} ; P < 0.001 ²
*04*0301*0302	0.164	0.172	0.200	0.072	
*07*02*0201	0.068	0.031	0.073	0.096	
*07*02*0303	0.055	0.006	0.018	0.031	
*09*0301*0303	0.034 ¹	0.043 ²	0.181	0.003 ³	P < 0.05 ^{1,2} ; P < 0.001 ³
*12*0501*0301	0.021 ¹	0.025 ²	0.154	0.027 ³	P < 0.05 ^{1,2} ; P < 0.01 ³
*13*0103*0602-8	0.048	0.037	0.054	0.051	
*15*0102*0602-8	0.164	0.068	0.027	0.103	
*17*0501*0201	0.088	0.074	0.045	0.096	

Only alleles and haplotypes with a frequency higher than 0.05 in at least one of the populations are listed. Population data from a mixed Russian group[#], living in Moscow, was published by Alexeev et al (19). The frequency, which deviates the most from the others (or a pair which deviate the most from each other) for certain allele or haplotype, are typed in bold.

Table 1

the three populations, multiplied with the number of populations studied, which was $9 \times 3 = 27$). Correspondence analysis on the basis of the Nei's genetic distances, obtained from HLA-DRB1, DQA1 and DQB1 allele frequencies (19), was carried out using the VISTA v.5.6 software (20).

Results and discussion

Comparative analysis of allelic variation in HLA class II genes (DRB1, DQB1, and DQA1) suggested that Nentsy, Saami and Pomors have common features in their allelic repertoire. Thus, when compared to Russians living in Moscow (21), a high (more than 0.1) frequency of the DRB1*04 allele was characteristic for all the groups studied, although the group of Kola Saami was characterized by an extremely high frequency of this DRB1 allele (0.33) (Table 1). The three northern populations are similar, in that they have relatively high frequencies of the DQB1*0201 and *0302 as well as the DQA1*0301 and *0501 alleles. An analysis of the DRB1-DQA1-DQB1 haplotype frequencies (Table 1) also reveals common peculiar features among the three population groups. A high frequency of the DRB1*04-DQA1*0301-DQB1*0302 haplotype and a low frequency of the DRB1*11-

DQA1*0501-DQB1*0301 haplotype is observed. This common component, which is typical neither for Caucasians nor for Orientals of Asia, distinguishes the three northern ethnic groups from Russians (21) and is characteristic for Amerindians also (22, 24).

Each of the three populations has their own characteristics concerning their HLA class II allele and haplotype distribution. Pomors and Saami have similar frequencies of DRB1*01 (0.11 and 0.14, respectively) which is 5–7 times higher than the Nentsy population (0.02). Conversely DRB1*09 and DRB1*12 are typical of the Nentsy (frequencies of 0.18 and 0.16, respectively) whereas these alleles are less frequent ($p < 0.05$) among Saami (0.04 each) and Pomors (0.03 and 0.02, respectively).

Due to the DR-DQ linkage disequilibrium, the peculiarities of DQA1 and DQB1 allele frequencies in the studied populations correspond in general with the pattern of DRB1 allele distribution. However, there is one important exception: DQB1*0301, which is in strong linkage disequilibrium with DRB1*04, DRB1*11 and DRB1*12, has a relatively high frequency in all four populations, but is mostly characteristic for Saami and Nentsy – in both groups its frequency is 0.23. However the DQB1*0301 allele is found mainly on DRB1*04 haplotypes among Saami, whereas this allele is found mainly on DRB1*12 haplotypes among Nentsy.

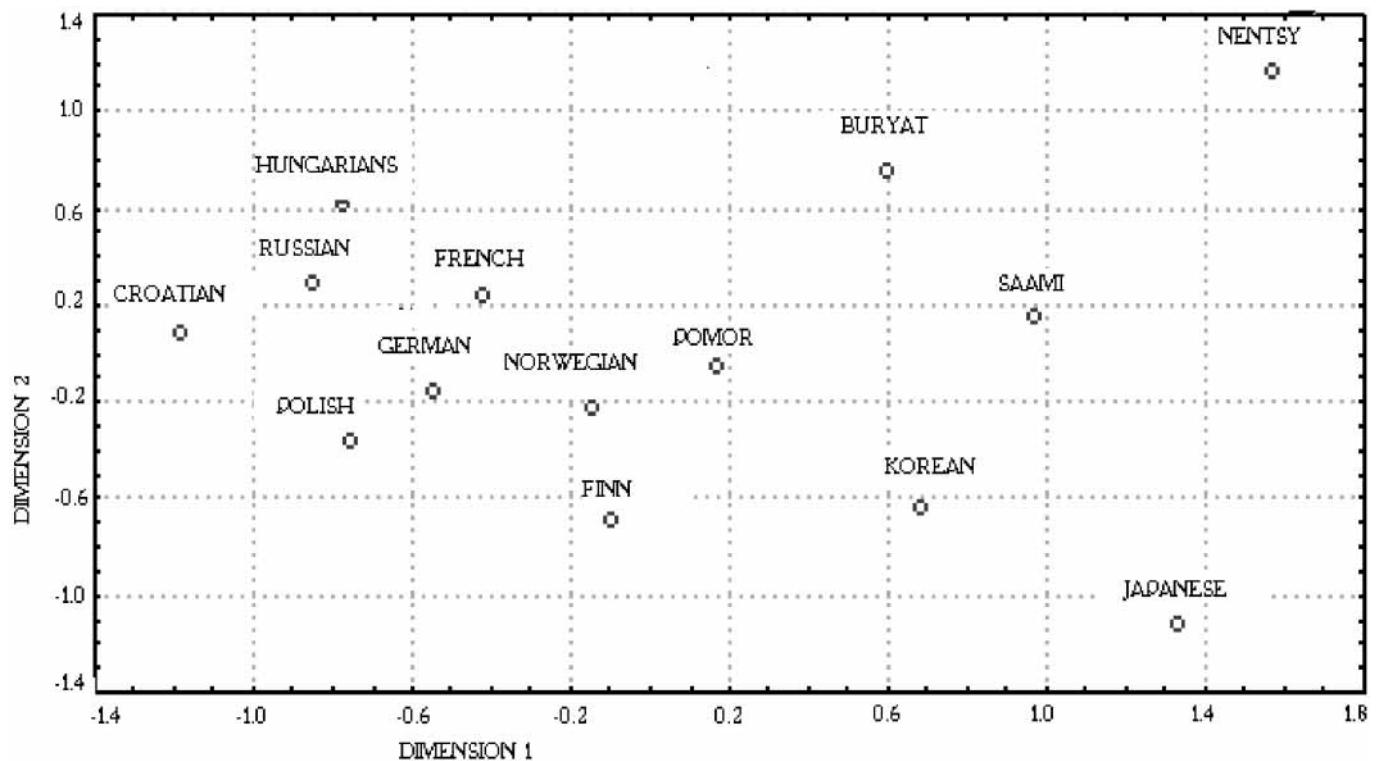


Fig. 2. Diagram of correspondence analysis, based on Nei's genetic distances (calculated from allele frequencies of HLA-DRB1, DQA1, DQB1 genes). Dimension 1 vs dimension 2.

The matrix of Nei's genetic distances ($\times 10^2$) between Nentsy, Saami, Pomors and some other populations, obtained from using HLA-DRB1, DQA1 and DQB1 allele frequencies

Population	Nentsy	Population	Saami	Population	Pomors
Nentsy	0	Saami	0	Pomors	0
Buryat	9.6	Buryat	6.3	Norwegian	1.2
Saami	13.2	Pomors	7.0	German	2.8
Korean	14.7	Norwegian	8.6	French	3.9
Pomors	19.1	Finn	9.4	Polish	4.0
Japanese	21.0	Korean	9.5	Finn	4.4
Norwegian	24.5	Japanese	11.1	Russian	4.9
French	26.0	French	11.4	Saami	7.0
German	26.8	Nentsy	13.2	Buryat	7.3
Russian	28.4	German	14.2	Korean	7.4
Hungarian	28.4	Hungarian	15.5	Hungarian	7.7
Finn	29.1	Russian	17.2	Croatian	7.7
Croatian	37.4	Croatian	19.3	Japanese	14.4
Polish	37.8	Polish	19.3	Nentsy	19.1

Table 2

The three-locus (DRB1-DQB1-DQA1) haplotype repertoire in the Nentsy population is restricted, as compared to the other two aboriginal groups, the most frequent haplotypes being the following: DRB1*04-DQA1*0301-DQB1*0302, DRB1*09-DQA1*0301-DQB1*0303 and DRB1*12-DQA1*0501-DQB1*0301 (Table 1). Saami are characterized by high frequencies of the DRB1*04-DQA1*0301-DQB1*0301, the DRB1*04-DQA1*0301-DQB1*0302, and the DRB1*01-DQA1*0101-DQB1*0501 haplotypes. Moreover, the haplotypic repertoire of Saami is varied. Several rare haplotypes were identified among Saami which was not observed in the other groups, i.e., the DRB1*15-DQA1*0102-DQB1*0501, DRB1*08-DQA1*0301-DQB1*0401, DRB1*08-DQA1*0401-DQB1*0301 and DRB1*04-DQA1*0301-DQB1*0303 haplotypes. In Pomors, the DRB1*15-DQA1*0102-DQB1*0602-8, and DRB1*04-DQA1*0301-DQB1*0302 haplotypes were the most prevalent with frequencies of 0.16 each (Table 1).

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Estimation of the standard genetic distances between populations (Table 2) and correspondence analysis, based on this distance matrix, were performed to present the genetic relationships between studied ethnic groups and other populations. According to the historical data, the Russian expansion from the Novgorod region to the North started in the 11th century AC. It is believed that the assimilation with the aboriginal arctic population was not significant due to differences in religion and culture, so ethnographically, the Pomors have a Russian origin and are considered to be one of the Russian Caucasoid subgroups (7, 8). However, our analysis revealed a closer relationship to Norwegians and Finns rather than the European cluster, including Russian Muscovites (Fig. 2), which could be a trace of a common arctic component in the origin of northern populations.

Nentsy have the most distant position from the European group, being more closely related to Mongoloid populations (Japanese, Koreans, Buryats), which corresponds to the anthropological data indicating their belonging to the transitional Ural race (3, 4).

The origin of Saami people is still debatable. Ethnological findings have suggested that Nentsy and Saami have common Ural ancestors. Their languages belong to the Ugro-Finnish group of the Ural family and they have much in common regarding their culture, way of life and traditional trades (26). In our analysis we can also see some similarity in the HLA Class II allele and haplotype distribution in Nentsy and Saami, which relates them closely to each other and rather far from the European cluster (Fig. 2). The large disparity between the Saami and European group is somewhat unexpected, as previous anthropological data suggest Saami to be a result of ancient admixture of European, Oriental and Ural people, with European genes having the greatest prevalence (5).

In conclusion, based on the comparative analysis of the HLA-class II allele and haplotype frequencies, we suggest that Nentsy, Saami and Pomors have different proportions of Oriental and Caucasoid origins contributing to their ancestry, with relatively large genetic distances between them. However, a common ancestral component, which is characteristic not only for Nentsy and Saami but also for their Slavonic neighbors – Pomors, could reflect the influence of Ural ethnic groups on their origin.

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