Coll. Antropol. **36** (2012) 4: 1379–1384
Original scientific paper

HLA Class I and Class II Polymorphism in the Population of Vojvodina, Serbia

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A B S T R A C T

The HLA (Human Leucocyte Antigens) class I and class II polymorphism in a sample population of 250 Vojvodinians using standard microlymphocytotoxicity test was investigated. The antigens with the highest frequencies were: HLA-A2 (50.4%), A1 (24.1%) and A3 (22.7%); B35 (22.7%), B51(5) (16.9%) and B18 (15.6%); DR11(5) (34.5%), DR7 (20.0%) and DR3 (19.3%); DQ1 (44.8%), DQ7(3) (30.9%) and DQ2 (13.3). The HLA two-locus haplotypes with high frequency (>0.02) in Vojvodinians included DR11(5)DQ7(3) (7.27%), A2DR11(5) (4.85%), DR3DQ2 (4.84%), DR7DQ2 (3.78%), B8DR3 (3.05%), A1B8 (2.79%) and A2B44(12) (2.45%). The antigen DR3 showed the strongest association with DQ2 (Δ=0.0416, χ^2=60.016) as well as antigen DR11(5) with DQ7(3) (Δ=0.0408, χ^2=19.023). Analysis of the population distance dendrogram revealed the closest relationship of Vojvodina population with Romanians, Hungarians, Albanians, Italians and Croats, which is consistent with the historical data about the turbulent migrations in the microregion of Vojvodina in the times past.

***Key words**: HLA polymorphism, gene frequency, linkage disequilibrium, Hardy-Weinberg equilibrium*

Introduction

The major histocompatibility complex is a system of genes encoding proteins, which plays a crucial role in different immunological functions in humans. In anthropological studies, allelic and haplotype frequencies of HLA represent useful parameters for the investigations of relations among populations and for the explanation of their migrations. The highly polymorphic HLA system is a powerful genetic tool for studies of inheritance, ancestry and genetic history of populations[1,2]. Because of its high polymorphism, tight linkage among the loci and non-random association of alleles, HLA system became interesting from the perspective of population genetics. The distribution of different HLA genes and their haplotypes in different ethnic and geographical populations, is of high importance to HLA matching for allogeneic solid organ and hematopoietic stem cell transplantations, as well as in disease association studies, paternity testing and forensic investigations[3–6]. The region of Vojvodina is located in the southern part of Panonic plain and in the northern part of Serbia. According to the census in 2002., at the teritory of Vojvodina, which comprises 21.506 km^2, there are 2.031.992 inhabitants[7,8]. Population of Vojvodina is very different in ethnic structure, which is the result of geographical, historical, political, demographical and other factors. Vojvodina represents an ethnic mosaic of many nationalities with differencies in socio-economical, historical, religious, demographic and other characteristics. It is also a result of various types of migrations, its geographical position and historical events starting from the prehistoric times to the present day[9–12]. The purpose of the present study was to obtain information concerning the distribution of HLA class I and class II antigens in the population of Vojvodina, Serbia, and to compare the results obtained with other neighbouring populations.

Material and Methods

The study included 250 unrelated, randomly chosen individuals, originating from different parts of Vojvodina. Their age ranged between 2 and 64 years. The population consisted of 109 males and 141 females. The allele frequencies data of all other populations used for comparisons were taken from previous studies[13–21]. HLA class I (A,B) and HLA class II (DR,DQ) typing for the

Received for publication May 19, 2010

sample of Vojvodina population, was performed using the complement-mediated lymphocytotoxicity test on T and B lymphocytes, respectively[22,23]. The panel of histotyping anti-leukocyte sera were obtained from commercial sources.

Statistics

Antigen frequencies (A) were calculated according to equation:

$$A = n / N,$$

where n is a number of persons with given antigen and N is a total nuber of persons studied.

Gene frequencies (p) were determined by the following equation:

$$p = 1 - \sqrt{1 - A}$$

where A is an antigen frequency or prevalence of appropriate antigen[24].

Two-locus haplotype frequencies were calculated by direct counting method. Two-locus gametic disequilibrium were calculated by following equation:

$$D_{ij} = x_{ij} - p_i q_j$$

where x_{ij} is an observed frequency of gamete A_iB_j, p_i and q_j are the frequencies of alleles A_i and B_j at loci A and B, respectively[25–27].

Three-locus haplotype interactions were performed according to equation:

$$p(A_1B_1C_1) = p(A_1B_1)\, p(B_1C_1) / p(B_1)$$

where $p(A_1B_1C_1)$ is expected three-locus haplotype frequency, $p(A_1B_1)$ is two-locus haplotype frequency of A and B loci, $p(B_1C_1)$ is two-locus haplotype frequency of B and C loci and p(B) is a frequency of appropriate antigen in B locus[28,29].

Three-locus linkage disequilibrium coefficient (D_{kri} or Δ) was calculated by using following formula:

$$D_{kri} = P_{kri} - q_i D_{kr} - \pi_r D_{ki} - p_k D_{ri} - p_k \pi_{rqi}$$

where P_{kri}, p_k, π_r and q_i are haplotype and allele frequencies, D_{kr}, D_{ki} and D_{ri} are the set of two-locus linkage disequilibria[29].

Chi-square test was applied for assesing significance of two- and three-locus linkage disequilibrium coefficient (Δ). χ^2-values exceeding 3.841 (corresponding to $p<0.05$) were regarded as a stable borderline index for significant

TABLE 1
DISTRIBUTION OF HLA CLASS I ANTIGENS IN VOJVODINA

Antigen n=224	AF	GF	Antigen N=224	AF	GF
A1	0.241	0.128	B5	0.071	0.036
A2	0.504	0.295	B51(5)	0.169	0.088
A3	0.227	0.120	B52(5)	0.013	0.006
A9	0.040	0.020	B7	0.116	0.059
A(23)9	0.053	0.026	B8	0.133	0.068
A(24)9	0.218	0.115	B13	0.084	0.042
A10	0.075	0.038	B14	0.044	0.022
A(25)10	0.071	0.036	B15	0.049	0.024
A(26)10	0.035	0.017	B18	0.156	0.081
A11	0.098	0.050	B22	0.026	0.013
A28	0.040	0.020	B27	0.062	0.031
A30	0.026	0.013	B35	0.227	0.120
A31	0.026	0.013	B37	0.013	0.006
A32	0.022	0.011	B16	0.053	0.026
A33	0.031	0.015	B38(16)	0.084	0.042
Blank	0.272	0.146	B39(16)	0.022	0.011
			B40	0.022	0.011
			B60(40)	0.004	0.002
			B41	0.008	0.004
			B12	0.026	0.013
			B44(12)	0.120	0.061
			B21	0.035	0.017
			B49(21)	0.013	0.006
			B50(21)	0.008	0.004
			B57(17)	0.026	0.013
			blank	0.325	0.178

AF – phenotype frequency; GF – gene(allele) frequency

differences between the observed and expected two- and three-locus haplotype frequencies[27]. The population of Vojvodina was tested to fit to Hardy-Weinberg equilibrium (HWE) for each locus, using classical chi-squared goodness-of-fit test. Phylogenetic trees (dendrograms) were constructed from HLA-A allele frequencies by using the Neighbour-Joining (NJ) method[30–33], with the angular distances[34] and MEGA4.0 software[35,36].

Results

The expected and observed antigen frequencies for HLA-A,-B,-DR and -DQ loci do not significantly differ and the population sample is in Hardy-Weinberg equilibrium. Table 1 shows the HLA antigen and gene frequencies found in the population of Vojvodina. Sixteen different HLA-A, 26 different HLA-B antigens were observed in the population of Vojvodina. The frequency of the antigens HLA-A2, -A3, -A1, -A24(9), -B51(5), -B35, -B8 and -B18 were found to be highest among all antigens tested in HLA class I antigens. Among HLA-A group, HLA-A2 with frequency of 50.4% is found to be the most frequent antigen followed by A1 (24.1%), A3 (22.7%) and A24(9) (21.8%) and among HLA-B antigens, HLA-B35 (22.7%), -B51(5) (16.9%), -B18 (15.6%) and -B8 (13.3%), were found to have increased frequency. With regard to the HLA class II antigens, 24 different DR and DQ antigens were found and only 4 had frequency higher than 20% (DR11(5), DR7, DQ1 and DQ7(3)), as shown in Table 2. DQ antigen frequencies reflect the DR locus antigen distribution, because of the strong linkage disequilibrium between the two loci. The most common haplotypes with significant positive linkage disequilibrium are shown in Table 3. The two-locus haplotype analysis revealed significant positive disequilibrium for DR3DQ2 (χ^2=60.01), DR7DQ2 (χ^2=31.57), DR11(5)DQ7(3) (χ^2=19.02), B8DR3 (χ^2=16.41), A1B8 (χ^2=14.41), A1DR3 (χ^2=5.19) and DR2DQ1 (χ^2=4.02). In our results (Table 4) the three-locus haplotype analysis revealed significant positive disequilibrium for A1B8DR3 haplotype (χ^2=6.03). Figure 1 depicts an HLA-A Neighbour-Joining (NJ) dendrogram. Two major clades could be found in dendrogram. Populations of Albanians, Romanians, Hungarians and Turks, were clustered in one clade, that is the northern group. Populations of Greeks, Russians and Germans were clustered into another clade, the southern group. The remaining populations of Italians, Croats, Serbians and Vojvodinians, were in the middle of the two groups.The relationship among populations in the dendrogram was basically in accordance with the geographical distances.

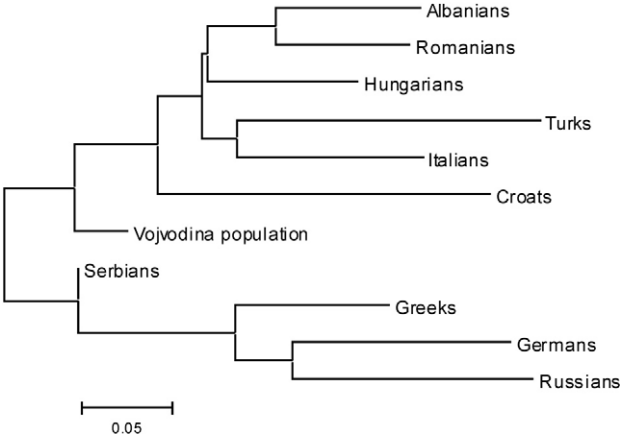

Fig. 1. Neighbour-joining dendrogram based on HLA-A allele frequency data reflecting relationships among population of Vojvodina and other 10 populations.

TABLE 2
DISTRIBUTION OF HLA CLASS II ANTIGENS IN VOJVODINA

Antigen n=165	AF	GF	Antigen N=165	AF	GF
DR 1	0.109	0.056	DQ1	0.448	0.257
DR 2	0.139	0.072	DQ5(1)	0.103	0.052
DR15(2)	0.145	0.075	DQ6(1)	0.121	0.062
DR16(2)	0.072	0.036	DQ2	0.133	0.068
DR 3	0.193	0.101	DQ3	0.193	0.101
DR 4	0.120	0.061	DQ7(3)	0.309	0.168
DR 7	0.200	0.105	DQ8(3)	0.018	0.009
DR 8	0.048	0.024	DQ4	0.048	0.024
DR 9	0.006	0.003	blank	0.381	0.213
DR10	0.012	0.006			
DR11(5)	0.345	0.190			
DR 6	0.030	0.015			
DR13(6)	0.127	0.065			
DR14(6)	0.036	0.018			
blank	0.315	0.172			

AF – phenotype frequency; GF – gene frequency

TABLE 3
HLA TWO-LOCUS INTERACTIONS IN THE ANALYSIS OF LINKAGE DISEQUILIBRIUM IN VOJVODINA (FREQUENCY ?0.02)

Haplotype	Observed HF	Expected HF	Δ	χ^2 values
A1B8	0.0279	0.0087	0.0191	14.410
A2B51(5)	0.0234	0.0259	–0.0025	0.1327
A2B44(12)	0.0245	0.0179	0.00651	1.2089
A2B18	0.0220	0.0238	–0.0018	0.0728
A2B35	0.0212	0.0354	–0.0142	3.0470
B8DR3	0.0305	0.0068	0.0237	16.410
DR2DQ1	0.0330	0.0185	0.0148	4.0280
DR15(2)DQ1	0.0242	0.0192	0.0050	0.4550
DR3DQ2	0.0484	0.0068	0.0416	60.016
DR4DQ3	0.0348	0.0061	0.0287	31.373
DR11(5)DQ1	0.0287	0.0488	–0.0201	2.8068
DR11(5)DQ2	0.0227	0.0129	0.0097	2.1150
DR11(5)DQ7(3)	0.0727	0.0319	0.0408	19.023
DR7DQ2	0.0378	0.0071	0.0307	31.578
A1DR3	0.0323	0.0129	0.0194	5.1910
A2DR11(5)	0.0485	0.0560	0.0075	0.2475
A2DR2	0.2330	0.0212	0.0021	0.0441
A24(9)1DR11(5)	0.0215	0.0218	0.0003	0.0008

TABLE 4
HLA THREE-LOCUS INTERACTIONS IN THE ANALYSIS OF LINKAGE DISEQUILIBRIUM IN VOJVODINA

Haplotype	Observed HF	Expected HF	Δ	χ^2 values
A1B8DR3	0.01251	0.00087	0.00533	6.0330
A2B51(5)DR11(5)	0.00475	0.00493	–0.01418	10.8850
A2B44(12)DR11(5)	0.04333	0.00341	–0.00988	7.4010
A2B18DR11(5)	0.00486	0.00454	–0.01307	9.8260
A2B35DR11(5)	0.00468	0.00672	–0.01717	12.1230
A2B44(12)DR7	0.00361	0.00188	–0.00570	4.0350

Discussion and Conclusion

Analysis of HLA antigens and haplotypes provided invaluable tools for anthropological studies and was reported for many societes. As population of Vojvodina represents a heterogenous mixture of populations, and in view of admixture brought about by the transmigration which province of Vojvodina had witnessed throughout its history, this study was undertaken to analyze HLA class I and HLA class II antigens and haplotypes in population of Vojvodina and to compare them with general Serbian and European populations. The area of Vojvodina had been inhabited since the Paleolithic period. Before the Roman conquest in the 1st century BC, Indo-european peoples of Illyrian, Tracian and Celtic origin inhabited the region[37]. During the early medieval migrations, Slavs (Severans, Abodrites, Braničevci, Timočani and Serbs) settled the present day Vojvodina in the 6th and 7th centuries[38]. Until the Hungarian conquest in the 10th century, the region had dominant Slavic population. In the history of Balcanic peninsula, the most important invasion was by the Turks in 14th century, when some parts of Vojvodina region were added to the Ottoman Empire, which ruled over it until the end of the 17th and the first half of the 18th century. Then, Vojvodina region was incorporated into the Habsburg Monarchy. Many other non-Serbs colonists also settled on the teritory of present day Vojvodina during the 18th and 19th century. They were mainly Germans and Hungarians, but also Ruthenians, Slovaks, Romanians and others. Because of this colonization, the Serbs lost the absolute ethnic majority in the region, and Vojvodina became one of the most ethnically diverse regions in Europe[39,40]. In the present investigation it was observed that HLA-A2, -A1, -A3 and -A24(9), have an increased frequency of 50.4%, 24.1%, 22.7% and 21.8%, respectively, as well as HLA--B35, -B51(5), -B18, -B8, -B12(44) and -B7, with frequency of 22.7%, 16.9%, 15.6%, 13,3%, 12% and 11.6%. Other antigens had frequencies less than 10%, while HLA-A29 and -A34 were not detected in this sample.The

TABLE 5
ANGULAR DISTANCES AMONG POPULATION OF VOJVODINA AND OTHER POPULATIONS

Population	Angular distance
Serbians	0.0010
Romanians	0.1398
Hungarians	0.1814
Albanians	0.1850
Italians	0.3442
Croats	0.3395
Greeks	0.3974
Turks	0.4047
Germans	0.4988
Russians	0.5089

HLA-B51(5) and -B35 were found with higher frequency, similarly to the other European populations (Greeks, Turks, Romanians)[16,17,21]. One of the characteristics of the population of Vojvodina is a very low frequency of HLA-B60 (40) (0.4%) and -B50(21) (0.8%). Among 24 HLA class II antigens determined in this sample, the most frequent were HLA-DR11(5) (34.5%), DR7 (20%), DR3 (19.3%), DR15(2) (14.5%), DQ1 (44.8%) and DQ7(3) (30.9%). High frequency of HLA DR11(5) is in accordance with other Europeans (Croats, Romanians, Turks)[16,17,41]. The percentage of blank antigens is in average of 30% *per* locus, representing a combination of undetected antigens such as HLA-A29, -A34, -B45, -B58, -B61, -B70, -B71, -B72, -B73 and possible homozygous antigens. Approximately one-third of the total percentage of blank antigens are possible homozygous antigens. Relatively high percentage of undetected antigens is partly the result of the usage of typing trays that were not covered by monospecific antisera. Two-locus haplotype analysis between HLA-A-B, -B-DR, -DR-DQ and -A-DR loci, was also performed (Table 3). The most frequent HLA-A-B haplotype was A1B8 (2.79%), but it is less frequent than in Germans (8.29%), Hungarians (5.48%), Samara region in Russia (4.38%) and than in population of Croats (3.42%)[15,19,41]. Among HLA-DR-DQ two-locus haplotype associations, the most frequent is DR11(5)DQ7(3) (7.27%), which is higher than in Croats (6.41%) but less than in Turks (30%)[41,42]. The antigen DR3 showed the strongest association with DQ2 (4.84%, Δ=60.01), as in some European populations (Turks, Croats, Slovenians)[43–46]. Three--locus haplotype analysis showed that the most frequent haplotype with significant positive linkage disequilibrium coefficient is A1B8DR3 (1.251%, Δ=6.033), also found in other European populations (Hungarians, Scottish, Belgians)[19,46,47]. The phylogenetic trees were constructed as shown in Figure 1, and the corresponding angular distances calculated using HLA-A gene frequencies from Vojvodina and other European populations, as shown in Table 5. The closest relationship was observed with general population of Serbia, Romanians, Hungarians, followed by other European populations in the following decreasing order: Albanians, Italians, Croats, Greeks, Turks, Germans and Russians. Estimated angular distances basically correspond to the geographical distances between compared populations. These observations support the historical data regarding the turbulent migrations within the microregion of Vojvodina throught recent and past history. Nevertheless, no definite conclusion about the ancestry of diverse ethnic groups present in the population of Vojvodina, could not be drawn from such a limited sample and because of requisition for defining the HLA polymorphism by molecular typing.

Acknowledgements

Authors are indebted to the technical staff of Tissue Typing laboratory in the Institute for Blood Transfusion of Vojvodina in Novi Sad, for their selfless efforts and contribution to HLA typing. The authors are grateful to Vuk Vojvodić for constructing phylogenetic trees, design work on the computer and technical support.

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POLIMORFIZAM HUMANIH LEUKOCITNIH ANTIGENA KLASE I I KLASE II U POPULACIJI VOJVODINE, SRBJE

S A Ž E T A K

Polimorfizam HLA (Humani Leukocitni Antigeni) klase I i klase II je ispitivan u uzorku od 250 Vojvođana koristeći standardni mikrolimfocitotoksični test. Antigeni sa najvišim frekvencijama su: HLA-A2 (50.4%), A1 (24.1%) i A3 (22.7%); B35 (22.7%), B51 (5) (16.9%) i B18 (15.6%); DR11 (5) (34.5%), DR7 (20.0%) i DR3 (19.3%); DQ1 (44.8%), DQ7 (3) (30.9%) i DQ2 (13.3%). HLA haplotipovi sa visokom frekvencijom (>0.02) u Vojvođanskoj populaciji uključuju DR11 (5)DQ7 (3) (7.27%), A2DR11 (5) (4.85%), DR3DQ2 (4.84%), DR7DQ2 (3.78%), B8DR3 (3.05%), A1B8 (2.79%) i A2B44 (12) (2.45%). Antigen DR3 je pokazao najjaču povezanost sa DQ2 (Δ=0.0416, χ^2=60.016), kao i DR11 (5) sa DQ7 (3) (Δ=0.0408, χ^2=19.023). Analiza dendrograma o genetskoj udaljenosti populacija pokazala je najveću povezanost populacije Vojvodine sa Rumunjima, Mađarima, Albancima, Talijanima i Hrvatima, što je u skladu s povijesnim podacima o turbulentnim migracijama u mikroregiji Vojvodine u prošlosti.