

HLA Class I Genetic Diversity in the Population of Vojvodina

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ABSTRACT Investigation of HLA antigen's polymorphism has a great advantage in antropological studies and has been extremely useful in population genetics. The purpose of present study is to determine the HLA-A and -B antigens in unrelated subjects of Vojvodina population and analyze the genetical distances among geographically distant and narrow populations. Results of investigation showed that the most common antigens in population of Vojvodina are: A2 (gene frequency=0,293); A9 (gene frequency=0,143); B12 (gene frequency=0,125); B18 (gene frequency=0,162) and B35 (gene frequency=0,107), and that the genetical distances among investigated populations are the highest for the geographically distant or isolated populations (Tuvinians=0,956, Orientals=0,6405, Blacks=0,6315, Chinese=0,561, South Koreans=0,546). Results of this study confirm the assertion, that genetical distances among populations are in accordance with geographical distances.

INTRODUCTION

Vojvodina is north province of Serbia that includes Banat, Backa, and east Srem, and extends on area of 21,506 km². Through the older history and prehistory period, various nations and nationalities have been replaced on territory of Vojvodina.: Agartises, Geths, Kelths, Romans, Goths, Huns, Gepids, Avarians, Slovans, Francks, Hungarians. Among all of them, mostly Slovans and Hungarians have been preserved (Bihalji-Merin 1968; Salinovic 1998).

Nowadays on territory of Vojvodina exist ethnic diversity with various nations: Serbs, Croatians, Montenegrins, Macedonians, Slovenians, Hungarians, Slovacs, Romanians, Germans, Ukrainians, Bulgarians, Czecks, Gipsies, Albanians, Ruthenians and the other.

On the end of XIV century and in beginning of XV century, Serbs started their large migration from Kosovo province and from area around Morava river, provoked by Turkish invasion to the Balcanic peninsula. Serbs passed river Danube and Sava and settled on the south parts of Panonic depression, where they have been ordered to be in border gard of Austro-Hungarian Monarchy.

In XVIII century, after partial emigration of Serbs to the Russia, caused by tendention of

Catholic Church to force the Serbs to the Catholic or Uniatic religion or payment of tribute and serfdom relations, in Vojvodina various nations have been settled on this territory, like: Germans, Hungarians, Slovaks, Ruthenians, Romanians and the other (Bihalji-Merin 1968; Salinovic 1998). With help of that Vojvodina gradually obtained it's ethnic diversity, which is preserved to the nowadays (Grubac 1961; Markovic 1984). Our study includes investigation of HLA-A and -B frequencies in members of all nations presented in population of Vojvodina, with no consideration of ethnic origin of these subjects.

MATERIAL AND METHODS

HLA-A and -B alleles in 350 healthy unrelated persons living in Vojvodina have been typed. HLA-A and -B alleles were determined using standard microlymphocytotoxicity method by Paul Terasaki (Walker 1993; Stites et al. 1989; Labar and Bogdanic 1985).

Phenotype frequencies of Vojvodina population and other compared populations were used for calculating gene (allelic) frequencies using Bernstein's formula: $P_A = 1 - \sqrt{1 - a}$; where: P_A = gene frequency and a = phenotype frequency (Vogel and Motulsky 1986; Zergollern 1991).

Genetical distances (GD) are defined as: $D = 1/2 \sum |X_i - Y_i|$; where X_i and Y_i are the frequencies of allele in population X and Y , and k is size of the frequency vector (Jungerman et al. 1997). A set of sixteen populations from all parts of the world was considered (Tanaka et al. 1997; Alexeev et

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al.1997; Orgad et al. 1997; Jaksic et al. 1989; Siren et al.1996; Mayr 1977; Lazovic et al.1996; Brown et al. 2000).

RESULTS

Table 1 presents the HLA-A and -B phenotype and gene frequencies estimated for population of Vojvodina.

Table 2 presents the HLA-A and -B gene frequencies estimated for sixteen different populations or members of various races.

Table 3 presents the genetical distances between population of Vojvodina and investigated populations.

Genetical distances will range from 0 to 1.0 with 0 expected within randomly breeding single populatoin and a maximum of 1 between two populations with no shared alleles (Bias 1997).

DISCUSSION

Frequencies of HLA-A and -B loci in Vojvodina population point that most common antigens are A2 with gene frequency of 0.293,

A9: gene frequency=0.143, A10: gene frequency=0.098, B12: gene frequency=0.125, B18: gene frequency 0.085, B35: gene frequency=0.107.

Opposite of that, the lowest frequencies are noticed for following antigens: A33: gene frequency=0.005, B 5(52): gene frequency=0.003, B 12 (45): gene frequency=0.005, B37: gene frequency=0.005 and B47: gene frequency=0.005. Absent antigens in Vojvodina population are A34 and B48.

Table 2 gives gene frequencies of following populations: Japanese, Chinese, Mongolian, South Koreans, Serbs (central area of Serbia, withouth provinces Vojvodina and Kosovo), Austrians (Vienna), English (London), Finlands, Tuvinians, Iraqi Jews, Orientals, European Caucasoids, Africans, Afrocaribians and members of Mongoloids and Negroids groups.

Estimated gene frequencies point to the fact that various populations have own specific genetic structure and exhibit differences in some HLA-A and -B antigens that represent their genetic variability. These differences are higher between populations with uncommon origin,

Table 1: Phenotype and gene frequencies in population of Vojvodina

Antigen	Phenotype and gene frequencies in population of Vojvodina				
	Phenotype fr.	Allelic fr.	Antigen	Phenotype fr.	Allelic fr.
A1	0.277	0.15	B16	0.102	0.053
A2	0.5	0.293	B38	0.034	0.018
A3	0.177	0.093	B39	0.031	0.016
A9	0.134	0.07	B17	0.082	0.042
A23	0.034	0.018	B18	0.162	0.085
A24	0.097	0.05	B21	0.05	0.026
A10	0.031	0.016	B22	0.037	0.019
A25	0.051	0.026	B27	0.12	0.062
A26	0.102	0.053	B35	0.202	0.107
A11	0.094	0.049	B37	0.008	0.005
A28	0.128	0.067	B40	0.071	0.037
A29	0.02	0.011	B41	0.02	0.011
A30	0.04	0.021	B42	0.002	0.001
A31	0.04	0.021	B47	0.008	0.005
A32	0.054	0.028	B48	0	0
A33	0.008	0.005	B67	0.002	0.001
A34	0	0	BX	0.2	0.106
AX	0.262	0.141			
B5	0.214	0.114			
B51	0.014	0.008	0.125		
B52	0.005	0.003			
B7	0.094	0.049			
B8	0.145	0.074			
B12	0.182	0.096			
B44	0.042	0.022			
B45	0.008	0.005	0.125		
B13	0.048	0.025			
B14	0.051	0.026			
B15	0.048	0.025			

Table 2: Gene frequencies of examined populations and members of some races

<i>Gene frequencies of examined populations and members of some races</i>																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
A1	0.006	0.012	0.039	0	0.074	0.006	0.042	0.085	0.094	0.123	0.131	0.143	0.185	0.206	0.112	0.036
A2	0.118	0.136	0.151	0.141	0.157	0.153	0.092	0.257	0.232	0.079	0.319	0.261	0.282	0.27	0.21	0.357
A3	0.006	0.008	0.016	0.026	0.069	0.008	0.035	0.207	0.094	0.045	0.109	0.140	0.138	0.134	0.09	0.036
A9	/	/	/	/	0.061	0.173	0.067	0.091	0.213	/	0.136	/	/	/	/	/
A23	0	0	0.003	0	/	/	/	0.004	/	0	0.024	0.048	0.014	0.019	0.097	0
A24	0.21	0.117	0.11	0.064	/	/	/	0.087	0.003	0.006	0.11	0.095	0.077	0.071	0.048	0.191
A10	/	/	/	/	0.021	0.037	0.023	0.03	0.102	/	0.085	/	/	/	/	/
A25	0	0.037	0.003	0.023	/	/	/	0.013	0.026	/	0.025	0.026	0.021	0.016	0.004	0
A26	0.056	0	0.035	0.018	/	/	/	0.017	/	0.021	0.059	0.053	0.012	0.036	0.024	0.018
A11	0.048	0.064	0.055	0.121	0.033	0.061	0.01	0.039	0.073	0.061	0.061	0.048	0.067	0.072	0.03	0.036
A28	0	0	0.008	0	0.024	0.011	0.051	0.059	0.03	/	0.038	0.043	/	/	/	/
A29	0	0.003	0.011	0.046	0.015	0.003	0.025	0.007	0.003	0.031	0.007	0.029	0.046	0.036	0.03	0
A30	0	0.025	0.036	0.014	0.018	0.012	0.057	0.005	0.077	0.046	0.007	0.029	0.016	0.02	0.101	0.036
A31	0.053	0.024	0.006	0	0.015	0.027	0.009	0.041	0.077	0.011	0.01	0.025	0.018	0.021	0.011	0
A32	0	0	0.026	0.056	0.02	0.003	0.012	0.036	/	0.015	0.046	0.042	0.037	0.035	0.027	0.036
A33	0.142	0.008	0.006	0	0.008	0.004	0.002	0.003	/	0.008	0.01	0.017	0.005	0.014	0.041	0.072
B5	/	/	/	/	0.042	0.079	0.013	0.049	0.131	/	0.158	0.083	/	/	/	/
B51	/	/	/	/	/	/	/	0.045	0.034	0.031	/	/	0.058	0.034	0.041	0.072
B52	/	/	/	/	/	/	/	0.002	/	0	/	/	0.002	0.079	0.024	0.018
B7	0.035	0.017	0.013	0.02	0.06	0.024	0.063	0.13	0.089	0.021	0.055	0.121	0.14	0.13	0.116	0.018
B8	0	0.0022	0.027	0.005	0.05	0.002	0.028	0.087	0.065	0.019	0.07	0.086	0.144	0.152	0.034	0.053
B12	/	/	/	/	0.066	0.031	0.052	0.075	0.045	/	0.09	0.138	/	/	/	/
B44	0.142	0.045	0.016	0.018	/	/	/	0.074	/	0.062	/	/	0.154	0.169	0.09	0
B45	0	0	0.003	0	/	/	/	0.002	/	0.008	/	/	0.006	0.008	0.014	0
B13	0.006	0.023	0.022	0.061	0.015	0.02	0.009	0.032	0.057	0.034	0.036	0.039	0.021	0.018	0.007	0.072
B14	0	0.003	0.003	0	0.019	0.002	0.015	0.004	0.007	0.031	0.021	0.026	0.04	0.044	0.02	0
B15	/	/	/	/	0.035	0.05	0.023	0.12	0.089	/	0.018	0.065	0.062	0.061	0.034	0.091
B17	0.005	0.03	0.051	0.033	0.015	0.01	0.015	0.016	0.069	/	0.038	0.038	0.011	0.038	0.044	0
B16	/	/	/	/	0.023	0.006	0.009	0.048	0.015	/	0.071	0.046	/	/	/	/
B18	0	0	0.006	0.01	0.028	0.002	0.022	0.049	0.011	0.031	0.04	0.07	0.048	0.041	0.044	0.036
B21	/	/	/	/	0.01	0.004	0.015	0.003	0.017	/	0.041	/	0.015	0.014	0.027	0
B22	0.002	0	0	0	0.015	0.053	0.02	0.022	0.03	0.005	0.025	0.032	0.023	0.023	0.017	0.053
B27	0.003	0.013	0.006	0.014	0.018	0.009	0.01	0.075	0.045	0.005	0.061	0.033	0.042	0.034	0.011	0.053
B35	0.039	0.031	0.034	0.047	0.054	0.053	0.037	0.131	0.026	0.079	0.129	0.095	0.075	0.085	0.079	0.091
B37	0.005	0.007	0.022	0.01	0.009	0.004	0.007	0.009	/	0	0.008	0.013	0.016	0.023	0.007	0.018
B38	0.002	0.007	0.003	0.01	/	/	/	0.009	/	0.034	0.045	/	0.007	0.02	0.004	0.11
B39	0.015	0.012	0.004	0.014	/	/	/	0.039	/	0	0.026	/	0.004	0.011	0.004	0.018
B40	/	/	/	/	0.047	0.096	0.02	0.085	0.14	0.011	0.045	0.068	0.053	0.038	0.004	0.072
B41	/	/	/	/	0.005	0.001	0.012	0.005	0.018	0.021	0.016	0.01	0.004	0.01	0.007	0
B42	/	/	/	/	/	/	/	0	/	0	/	/	0	0	0.048	0
B47	0	0	0	0.005	0.002	0.003	0	0.008	/	/	0.004	/	0.002	0.002	0.007	0
B48	0.005	0.017	0.029	0.027	/	/	/	0.002	/	/	/	/	/	0	0.001	0.053

(Tanaka et al.1997; Alexeev et al.1997; Orgad et al. 1997; Jaksic et al. 1989; Siren et al.1996; Mayr 1977; Lazovic et al.1996; Brown et al. 2000).

Legend: 1=Japanese population, 2=South Korean, 3=Mongolian, 4=Chinese, 5=Whites, 6=Mongoloids, 7=Blacks, 8=Finlands, 9=Tuvinians, 10=Iraqi Jews, 11=Central area of Serbia, 12=Austrians, 13=English, 14=European Caucasoids, 15=Africans-Afrocaribians, 16=Orientals.

different evolution and dinamysm, like geographically distant populations without possible mixing between them in the history. Small differences in HLA-A and -B antigens were found between geographically narrow populations such as: Austrian: genetical (GD)=0.289, English: GD=0.3655, European Caucasoid: GD=0.428, Serbia (central area): GD=0.3525.

It is interesting to stress, that GD is shorter towards population of Austria than GD towards population of Serbia (central area), which is probably caused by the fact that Vojvodina, in the past, was part of Austro-Hungarian Monarchy. Present GD values between

population of Vojvodina and central area of Serbia could be explained by the higher ethnic diversity in population of Vojvodina than in population of Serbia.

Relatively high values of GD are seen in populations of Tuvinia GD=0.956 which is isolated population (probably by geography and/or religion), Yellow race GD=0.653, Blacks GD=0.6315, South Koreans GD=0.5465, Japanese GD=0.484, Iraqi Jews GD=0.485, Finlands GD=0.6405, Chinese GD=0.561, Orientals GD=0.645, Mongolia GD= 0.583, Africans and Afrocaribians GD= 0.527. Because Vojvodina exhibits small amount of shared alleles with those populations, we could give the suppositions that

Table 3: Genetical distances between population of Vojvodina and examined populations

<i>Genetical distances between population of Vojvodina and examined populations</i>	
<i>Population</i>	<i>GD values</i>
Japanese	0.484
South Korean	0.546
Mongolian	0.583
Chinese	0.561
Whites	0.525
Mongoloids	0.653
Blacks	0.631
Finlands	0.640
Tuvinians	0.956
Iraqi Jews	0.488
Serbs (central area of Serbia)	0.352
Austrians	0.289
English	0.365
European Caucasioids	0.428
Africans- Afrocaribians	0.527
Orientalis	0.640

those populations donot have common origin with population of Vojvodina and that there was no mixing in the past between them with inhabitants of Vojvodina.

CONCLUSION

Investigation of HLA polymorphism is very important in view of determining the contribution of certain evolution factors to genetic variability, giving in that way information about origin, evolution and dinamysm of populations.

Results of our investigation clearly suggest that there are genetical connections between geographically narrow populations probably caused by the historical influence of neighboring populations. Genetical distances are in accordance to the geographical distances.

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