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ASSOCIATION OF HLA -A, -B AND -DRB1 ALLELES WITH HEMATOLOGICAL DISEASES IN VOJVODINA

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Major histocompatibility complex (MHC) genes are involved in various mechanisms of pathogenesis and immunoediting of hematological diseases. This study aimed to investigate the association between HLA -A, -B and -DRB1 alleles with hematological diseases. In this study, we performed DNA-based HLA typing by polymerase chain reaction analysis with sequence-specific primers (PCR-SSP) to distinguish HLA-A, -B, and -DRB1 alleles. Eighty-two patients with hematological diseases (29 with acute lymphoblastic leukemia (ALL), 19 with acute nonlymphoblastic leukemia (ANLL), 5 with chronic myelogenous leukemia (CML), 2 with chronic lymphocytic leukemia (CLL), 9 with myelodysplastic syndrome (MDS), 9 with lymphomas (M.Hodgkin (HL) and non-Hodgkin (NHL)), 7 with aplastic anemia (AA) and 2 with multiple myeloma (MM)), were included in the study and compared with 111 healthy blood donors, residents from Vojvodina, evaluating the strength of the observed associations by measuring the aetiologic and preventive fractions. Among the alleles significantly associated with hematological diseases, HLA-A*24 showed an aetiologic fraction higher than those of HLA-A*26 and A*25 (RR=1.027,

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EF=1.233, RR=1.047, EF=1.141 and RR=1.213, EF=0.910). Negative association with significant preventive fraction was observed with HLA-B*18 and HLA-DRB1*11 alleles, with RR=0.400, PF=0.179 and RR=0.587, PF=0.176. Our results suggest that HLA-A*24, A*26 and A*25 as associated more frequently than other specificities with a hypothetical disease predisposing genes, may play a role in the pathogenesis of hematological diseases.

Key words: Human Leukocyte Antigens; hematological diseases; association.

INTRODUCTION

The major histocompatibility complex (MHC) encodes the synthesis of human leukocyte antigens (HLA) which represents the polymorphic membrane glycoproteins found on the surface of almost all nucleated cells (HLA class I molecules) and cells mainly involved in the immune response (HLA class II molecules). The HLA molecules serve as markers for self during the thymic maturation of T-cells and these cells always recognize foreign antigenic peptides in the context of self HLA molecules. The loss of HLA antigens by neoplastic cells is considered important for tumor growth and metastasis (NOWAK *et al*., 2009, LIPINS *et al.*, 2001). Since tumor neoantigens on the surface of aberrant cells are recognized by T-cells only in the context of the HLA "self" antigens, loss of the HLA antigens may allow the tumors to escape immunosurveillance. HLA system is a kind of genetic marker of human being, and the most complicated human genetic polymorphic system with hereditary features of haplotype inheritance and allele polymorphism and linkage disequilibrium. It playes an important role in the event of antigen recognition and presentation, immune response and modulation, destroying foreign antigen targeted cells. The alleles of the HLA system control a variety of immune functions and influence the susceptibility to more than 40 diseases, many of which have an autoimmune component (LIN *et al*., 2003, MACHULLA *et al.,* 2001, SAUNTHARARAJAH *et al.,* 2002). More diseases have been shown to be associated with alleles of the HLA region than with any other genetic region (MUNDHADA *et al*., 2004, SAVRAN OGUZ *et al.,* 2003, ZHANG *et al*., 2006, HARTY *et al*., 2002). Conventional serological and cellular typing methods permit identification of the HLA class I and II specificities. However, in many cases reliable assignment of class I and II alleles is impossible due to the small number or poor quality of T- or B-cells or reduced expression of HLA molecules on the cell surface. Genomic HLA typing, using various polymerase chain reaction (PCR)-based typing methods, is accurate for HLA association studies and more importantly, more biologically relevant polymorphism can be detected with DNA-based tissue typing than with serology. The aim of this study was for the first time in the Vojvodina region to determine the frequencies of HLA-A, -B and -DRB1 alleles using genomic tissue-typing methods in order to assess HLA association in hematological diseases.

MATERIALS AND METHODS

Eighty two patients from Vojvodina (40 females, 42 males, with a median age of 38,5 years) were included in study. An informed consent of the individuals participating in the study was obtained and all institutional ethics requirements were met. They were divided into subgroups according to the type of disease: 29 suffering from acute lymphoblastic leukemia (ALL), 19 suffering from acute nonlymphoblastic leukemia (ANLL), 5 suffering from chronic myelogenous leukemia (CML), 2 suffering from chronic lymphocytic leukemia (CLL), 9

suffering from myelodysplastic syndrome (MDS), 9 suffering from lymphomas (M.Hodgkin (HL) and non-Hodgkin (NHL)), 7 suffering from aplastic anemia (AA) and 2 suffering from multiple myeloma (MM). Control group consisted of 111 healthy blood donors who resided in the same geographic area. Genomic DNA were extracted from buffy coat using standard proteinase K digestion method followed by spin-column-based method (QIAamp Blood Mini isolation kit, Qiagen) (GREENSPOON *et al*., 1998). Amplification was performed by Polymerase Chain Reaction-Sequence Specific Primer (PCR-SSP) employing Micro SSP^{TM} DNA (One Lambda, Inc. Canoga Park, CA, USA) as well as INNO-TRAIN DiagnostikGmbH (HLA-REDY GENE, Lot: G954011, Kronberg/Taunus,Germany). Assay was performed for DNA typing of alleles HLA-A, -B and -DRB1/3/4/5 (ADIB *et al*., 2004). Pre-opromized primers for the amplification of HLA-A, -B and -DRB1 genes in reaction were distributed in wells of PCR plate for later addition of DNA samples, Taq polymerase (AXITAQ-DNA Polymerase, INNO-TRAIN, Kronberg/ Taunus, Germany, Lot: GOT 120) and dNTP-buffer mix. After amplification, electrophoresis in agarose gel 2% was undertaken, at 180 volts, for approximately 20 minutes. A pair of specific primers amplifying a conserved region of the Human β-globin gene, which is present in all DNA samples, was used to verify the integrity of the PCR reactions performed by Micro SSP^{TM} DNA,One Lambda kits. On the contrary, gene sequence of the human growth hormone**,** HGH, was used as a positive internal control of HLA-REDY GENE, INNO-TRAIN kits.

All statistical analyses were performed with the software Microsoft Office Excel 2002 for Windows. Relative risk (RR) for measuring strenght of association with each allele was calculated by the method of Woolf (ARMITAGE *et al*.,2002), according to following formula:

$$RR = \frac{P^{+} x C^{-}}{C^{+} x P^{-}},$$ where

P^+ = is the number of patients who have a given allele;
C^- = is the number of healthy persons who do not have a given allele;
P^- = is the number of patients who do not have a given allele;
C^+ = is the number of healthy persons who have a given allele.

When RR was higher than 1, we calculated the aetiologic fraction, while for RR values less than 1, we calculated the preventive fraction. The aetiologic fraction (EF) or population atrributable risk, that gives the proportion of disease, due to the HLA marker associated with disease, was calculated according to method of Green, using following formula:

$$EF = \frac{(FAD - FAP)}{(1 - FAP)},$$

where FAD is the frequency of given HLA allele in the subgroup of patients and FAP is the frequency of HLA allele in controls. The preventive fraction (PF), that gives the percentage of cases that can be prevented if a population is exposed to an intervention, compared to an unexposed population, was calculated according to following formula:

$$FP = \frac{(1 - RR)xf}{RRx(1 - f) + f},$$

where RR is relative risk and f is the frequency of HLA allele in the subgroup of patients. The association was considered positive if the calculated EFs were higher than 0.15 and negative if calculated PFs were more than 0.15 (GREEN *et al*.,1982).

RESULTS

The allele frequencies of HLA-A, -B and -DRB1 gene in patients suffering from hematological disorders and healthy controls from population of Vojvodina were summarized in Tables 1a and 1b. In total, 14 different HLA-A*, 23 different HLA-B* and 12 different HLA-DRB1* alleles were found in investigated groups from Vojvodina. In HLA-A locus, A*02 was the most frequent allele in both of groups with frequency of 63% in controls and 57.3% in patients, respectively. In locus B, the most frequent alleles in controls were B*18, B*35 and B*51 with frequency of 29.7%, 28.8% and 27%, while in patients B*35 ranked as the first one with the frequency of 23.1% followed by B*44 (17%), B*51 (15.8%), B*07 and B*18 (14.6%). In locus DRB1, DRB1*11 ranked as the first one with the frequency of 42.3% in controls and 30.4% in patients, followed by DRB1*16 and DRB1*03 in controls (with frequency of 24.3% and 22.5%), and DRB1*13 (25.6%) and DRB1*15 (23.1%) in patients.

Table 1a. Allelic frequencies of HLA-A and -DRB1 genes in patiens suffering from hematological disorders and controls from Vojvodina

Allele	Patients	Controls	Allele	Patients	Controls
A*01	0.219	0.315	DRB1*01	0.219	0.198
A*02	0.573	0.630	DRB1*03	0.195	0.225
A*03	0.134	0.216	DRB1*04	0.121	0.126
A*11	0.197	0.135	DRB1*07	0.207	0.135
A*23	0.048	0.063	DRB1*08	0.048	0.054
A*24	0.195	0.189	DRB1*09	0	0.018
A*25	0.097	0.081	DRB1*10	0.024	0.018
A*26	0.085	0.081	DRB1*11	0.304	0.423
A*29	0	0.036	DRB1*12	0.048	0.045
A*30	0.036	0.027	DRB1*13	0.256	0.171
A*31	0.060	0.027	DRB1*14	0.060	0.063
A*32	0.073	0.054	DRB1*15	0.231	0.189
A*33	0.048	0.054	DRB1*16	0.170	0.243
A*34	0.012	0			
A*68	0.060	0.072			
A*69	0.024	0			

The results showing relative risk, aetiologic and preventive fraction are presented in Tables 2a and 2b. Our results pointed to the several HLA-A* alleles associated with an increased risk of developing hematologic diseases, such as: A*24 (RR=1.027, EF=1.233), A*26 (RR=1.047, EF=1.141), respectively as well as A*25 (RR=1.106, EF=0.910), while A*30, A*31 and A*32

showed RR higher than 1 (RR=1.354, RR=2.316, RR=1.368, respectively), but without significant association (EF=0.009, EF=0.033, EF=0.020). Our results showed significantly decreased frequency of B*18 allele (RR=0.400, PF=0.179) and DRB1*11 allele (RR=0.587, PF=0.176) in the group of patients compared to controls, which indicates to their possible protective role from the risk of investigated hematological disorders. The discrepancy of relative risk higher than 1 and nonsignificant association was especially observed for HLA-B*50 and B*55 alleles where RR=4.139 and 4.263, while EF were 0.027 and 0.056, respectively.

The distribution of HLA-A, -B and -DRB1 alleles in investigated subgroups of patients is presented in Tables 3a and 3b, showing the influence of particular subgroups allele frequencies on total frequencies, relative risk and strength of association.

Table 1b. Allelic frequencies of HLA-B genes in patiens suffering from hematological disorders and controls from Vojvodina

Allele	Patients	Controls
B*07	0.146	0.072
B*08	0.121	0.180
B*13	0.109	0.063
B*14	0.085	0.054
B*15	0.048	0.081
B*18	0.146	0.297
B*27	0.109	0.054
B*35	0.231	0.288
B*37	0.012	0.045
B*38	0.097	0.054
B*39	0.048	0.027
B*40	0.085	0.072
B*41	0.024	0.036
B*44	0.170	0.216
B*45	0	0.009
B*48	0.012	0
B*49	0.024	0.018
B*50	0.036	0.009
B*51	0.158	0.270
B*52	0.048	0.054
B*53	0.012	0
B*55	0.073	0.018
B*56	0.036	0.027
B*57	0.036	0.054
B*58	0	0.009

Table 2a. Relative risk, aetiologic and preventive fractions in investigated groups from Vojvodina for HLA-A and -DRB1 alleles

Allele	RR	EF	PF	Allele	RR	EF	PF
A*01	0.602	-	0.126	DRB1*01	1.125	0.026	-
A*02	0.767	-	0.148	DRB1*03	0.824	-	0.040
A*03	0.563	-	0.094	DRB1*04	0.952	-	0.006
A*11	0.684	-	0.042	DRB1*07	1.656	0.083	-
A*23	0.754	-	0.015	DRB1*08	0.888	-	0.006
A*24	1.027	**1.233***	-	DRB1*09	-	-	-
A*25	1.213	**0.910***	-	DRB1*10	1.350	0.006	-
A*26	1.047	**1.141***	-	DRB1*11	0.587	-	**0.176***
A*29	-	-	-	DRB1*12	1.076	0.003	-
A*30	1.354	0.009	-	DRB1*13	1.622	0.102	-
A*31	2.316	0.033	-	DRB1*14	0.955	-	0.002
A*32	1.368	0.020	-	DRB1*15	1.298	0.051	-
A*33	0.888	-	0.006	DRB1*16	0.632	-	0.089
A*34	-	-	-				
A*68	0.841	-	0.010				
A*69	-	-	-				

DISCUSSION

This is the first PCR-based HLA association study in hematological disorders, which analyzed healthy controls as well as patient from a single center using the same technique. Previously reported associations of HLA class I and class II antigens and leukemias reported for region of Vojvodina, were obtained by serological HLA typing. Our results pointed to the importance of HLA DNA typing for the investigation of HLA disease associations, since in contrast to the results of serologic typing, several differences in HLA frequencies between patients and controls were revealed by PCR-based DNA typing. These differences focused mainly on the MHC class II region (VOJVODIĆ *et al*., 2001, VOJVODIĆ, 2008, VOJVODIĆ and ADEMOVIĆ-SAZDANIĆ, 2011a, VOJVODIĆ and ADEMOVIĆ-SAZDANIĆ, 2011b, VOJVODIĆ and ADEMOVIĆ-SAZDANIĆ, 2012). Our study showed that the relative risk to develop hematological disease was obtained in a patients having several HLA alleles such as HLA-B*55, -B*50, -B*07, -B*27, -DRB1*07, -DRB1*13, -DRB1*15, -B*38, -B*14, -A*31 and other, but significant association with EF > 0.15 was observed only for alleles HLA-A*24, -A*25 and -A*26. Analogically, the decreased frequencies in patients than in controls were obtained for many of HLA alleles but the remarkable results with PF > 0.15 were only observed for HLA-B*18 and -DRB1*11 alleles. Analysis of impact of investigated diseases HLA allele frequencies to increased total frequency for HLA-A*24 allele shows that allele frequencies are highest in patients suffering from chronic leukemias and ANLL (0.285 and 0.210). On a contrary, the greatest impact on increased frequency of HLA-A*25 allele showed a high frequency in AML patients (0.210) and bone marrow failure syndromes such as MDS and AA with frequency of 0.187. The different situation is observed with HLA-A*26 total frequency, where the greatest impact on it is manifested for the frequency in patients suffering from ALL (0.172). This results suggest that the HLA-A*24 allele could be the possible

risk marker for developing chronic leukemias and ANLL, HLA-A*25 could be the possible risk marker for developing AML and MDS/AA while HLA-A*26 allele is susceptibility factor for ALL. The results of this study are in accordance with several reports that suggest that a genetic factors located within or close to the HLA gene loci confers susceptibility to hematological diseases (SHICHISHIMA *et al.,* 2006, STARATSCHEK-JOX *et al.,*2002, DORAK *et al.,* 1999, LECH-MARANDA*, et al.,* 2007, NOWAK *et al*., 2009). The limitation of this study is related to inability for displaying the HLA-A, -B and -DRB1 allele frequencies separately for each subgroup of disease as it would be unrealistic and unsuitable for statistical analysis due to the small number of subjects in individual groups. Despite that, the importance of this study is in the fact that the data processed by using molecular typing method are shown for the first time in a single center and for the studied region.

Table 2b. Relative risk, aetiologic and preventive fractions in investigated groups from Vojvodina for HLA-B alleles

Allele	RR	EF	PF
B*07	2.185	0.079	-
B*08	0.625	-	0.067
B*13	1.269	0.049	-
B*14	1.617	0.032	-
B*15	0.575	-	0.034
B*18	0.400	-	**0.179***
B*27	2.136	0.058	-
B*35	0.735	-	0.076
B*37	0.259	-	0.033
B*38	1.873	0.045	-
B*39	1.829	0.021	-
B*40	1.190	0.014	-
B*41	0.662	-	0.012
B*44	0.737	-	0.057
B*45	-	-	-
B*48	-	-	-
B*49	1.350	0.006	-
B*50	4.139	0.027	-
B*51	0.502	-	0.135
B*52	0.888	-	0.006
B*53	-	-	-
B*55	4.263	0.056	-
B*56	1.354	0.009	-
B*57	0.658	-	0.018
B*58	-	-	-

Table 3a. The distribution of HLA-A and -DRB1 alleles in nvestigated subgroups of patients

Allele	ALL n=29	AML n=19	CLL/CML n=7	HL/NHL/MM n=11	AA/MDS n=16
A*01	0.137	0.210	0	0.454	0.312
A*02	0.551	0.631	0.571	0.545	0.565
A*03	0.172	0.210	0.142	0.090	0.062
A*11	0.068	0.052	0.285	0	0.187
A*23	0.103	0	0	0	0.062
A*24	0.206	0.210	0.285	0.181	0.125
A*25	0.034	0.210	0	0	0.187
A*26	0.172	0.052	0.142	0	0
A*29	0	0	0	0	0
A*30	0	0	0	0.181	0.062
A*31	0.103	0.105	0	0	0
A*32	0.103	0.157	0	0	0
A*33	0.034	0	0	0.181	0.062
A*34	0	0	0	0.090	0
A*68	0.137	0.052	0	0	0
A*69	0	0	0.142	0.090	0
DRB1*01	0.206	0.210	0.428	0.181	0.187
DRB1*03	0.206	0.157	0.142	0.272	0.187
DRB1*04	0.172	0.105	0.142	0.090	0.062
DRB1*07	0.275	0.157	0.428	0.090	0.125
DRB1*08	0.034	0.105	0	0	0.062
DRB1*09	0	0	0	0	0
DRB1*10	0.034	0	0	0.090	0
DRB1*11	0.137	0.315	0.142	0.636	0.437
DRB1*12	0.034	0	0.142	0	0.125
DRB1*13	0.344	0.157	0.142	0.272	0.250
DRB1*14	0.068	0.052	0	0	0.125
DRB1*15	0.275	0.315	0.142	0.090	0.187
DRB1*16	0.137	0.263	0.285	0.090	0.125

Table 3b. The distribution of HLA-B alleles in nvestigated subgroups of patients

Allele	ALL n=29	AML n=19	CLL/CML n=7	HL/NHL/MM n=11	AA/MDS n=16
B*07	0.206	0.210	0.142	0	0.062
B*08	0.068	0.210	0	0.090	0.187
B*13	0.103	0.105	0.142	0.181	0.062
B*14	0.068	0	0.142	0.181	0.125
B*15	0.103	0	0	0	0.062
B*18	0.137	0.105	0.285	0.090	0.187
B*27	0.103	0.157	0.285	0	0.062
B*35	0.172	0.315	0.142	0.454	0.125
B*37	0	0	0	0.090	0
B*38	0.137	0.052	0.142	0	0.125
B*39	0.034	0.105	0.142	0	0
B*40	0.034	0.210	0	0.181	0
B*41	0.034	0	0	0.090	0
B*44	0.206	0.105	0.142	0.090	0.250
B*45	0	0	0	0	0
B*48	0	0	0	0	0.062
B*49	0	0	0	0.090	0.062
B*50	0.103	0	0	0	0
B*51	0.137	0.157	0.142	0.272	0.125
B*52	0.068	0.052	0	0	0.062
B*53	0.034	0	0	0	0
B*55	0.034	0.105	0	0.090	0.125
B*56	0.034	0	0.142	0	0.062
B*57	0.034	0.052	0	0.090	0
B*58	0	0	0	0	0

CONCLUSION

The results of the present study suggest that HLA-A*24, -A*25 and -A*26 are a genetic risk factors for hematological diseases. HLA-B*18 and -DRB1*11 alleles may be the possible protective factor for developing investigated diseases. We hope that these results will be used as a guide for further functional studies and that they would have diagnostic and prognostic implications.

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ISPITIVANJE UDRUŽENOSTI GENA HLA-A, -B I -DRB1 LOKUSA SA HEMATOLOŠKIM BOLESTIMA U VOJVODINI

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Izvod

Geni glavnog kompleksa histokompatibilnosti (MHC) su uključeni u različite mehanizme etiopatogeneze i imunološkog nadzora hematoloških bolesti. Cilj ove studije je da se istraži udruženost HLA-A,-B i -DRB1 alela sa hematološkim bolestima. U ovoj studiji primenjena je molekulska metoda HLA tipizacije putem lančane reakcije polimeraze sa prajmerima specifičnim za sekvencu (PCR-SSP) za determinisanje HLA-A,-B i -DRB1 alela. Osamdeset-dva bolesnika sa hematološkim oboljenjima (29 sa akutnom limfoblastnom leukemijom (ALL), 19 sa akutnom nelimfoblastnom leukemijom (ANLL), 5 sa hroničnom mijelogenom leukemijom (CML), 2 sa hroničnom limfocitnom leukemijom (CLL), 9 sa mijelodisplastičnim sindromom (MDS), 9 sa limfomima (M.Hodgkin (HL) i Non-Hodgkin (NHL)), 7 sa aplastičnom anemijom (AA) i 2 sa multiplim mijelomom (MM)), su uključeni u studiju. Kontrolna grupa od 111 zdravih dobrovoljnih davaoca krvi sa teritorije Vojvodine poslužila je za procenu stepena udruženosti merenjem etiološke i preventivne frakcije. Među alelima koji su značajno udruženi sa hematološkim bolestima, kod HLA-A*24 alele uočena je viša vrednost etiološke frakcije u odnosu na one kod HLA-A*26 i A*25 alele (RR = 1.027, EF = 1.233, RR = 1.047, EF = 1.141 i RR = 1.213, EF = 0.910). Negativna asocijacija sa značajnom preventivnom frakcijom je uočena za HLA-B*18 i HLA-DRB1*11 alele, sa RR = 0.400, PF = 0.179 i RR = 0.587, PF= 0.176. Naši rezultati sugerišu da su HLA-A*24, -A*26 i -A*25 alele hipotetički predisponirajući geni koji mogu imati ulogu u patogenezi hematoloških bolesti.

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