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HLA CLASS II ANTIGENS AND HAPLOTYPES ASSOCIATED WITH SUSCEPTIBILITY OF LEUKEMIAS AND MYELODYSPLASTIC SYNDROME

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Genetical and environmental factors play an interactive role in the development of acute and chronic leukemias.HLA antigens have been considered as possible genetic risk factors.The aim of this work was to investigate a possible association between HLA class II polymorphisms and leukemias and myelodysplastic syndrome.In the present study we investigated HLA class II antigens,DR/DQ and DR51/DR52/DR53 haplotypes in 100 patients:7 suffering from myelodysplastic syndrome (MDS),37 from acute lymphoblastic leukemia(ALL),32 from acute myeloid leukemia (AML) and 24 from chronic myeloid leukemia(CML).A panel of 210 healthy unrelated individuals of the same origin, from Vojvodina,

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served as controls.HLA phenotyping was performed by two color fluorescence method. In patients suffering from MDS was found a positive association with DR7(RR=2.598,EF=0.175) and DQ7(3)(RR=4.419, EF=0.632), while negative association was found for DR15(2)(RR=0.405, PF=0.172) and DQ6(1) (RR=0.889, PF=0,936).Positive association was found in the group of patients with ALL for DR7(RR=2.391,EF=0.688) and DQ2(RR=1.62, EF=0.15),while negative association was found with DQ5(1)(RR=0.075, PF=0.324).In the group of patients with AML,there were positive associations with DR11(5)(RR=1.732,EF=0.211),DQ2(RR= 1.594, EF=0.151) and DQ7(3) (RR=2.547,EF=0.266),while possible protective antigen was DQ5(1) (RR=0.107,RF=0.701).Higher RR than 1 and EF>0.15, in patients suffering from CML was found for DQ6(1)(RR=1.661,EF=0.232), while negative association was found for DR4 (RR=0.182,PF=0.155).Possible protective haplotype in this study was DR3DQ8(3) for patients suffering from AML(RR=0.007, PF=0.501).The distribution of DR53-DR53 haplotypes showed significant difference in male patients with ALL(6% vs 0.09%), while DR52-DR52 haplotype was significantly less frequent in male patients with CML (4% vs 20.47%) and female patients with MDS (1% vs 18.57%), respectively, in comparison to controls. We deduced that DR7 antigen in male patients with ALL has the greatest impact to the higher frequency of DR53-DR53 haplotype in this type of leukemia.The role of HLA antigens as risk factors for development of leukemias in our population was shown and furthermore it could be useful in clinical practice.

Key words: association, Human Leukocyte Antigens; leukemia

INTRODUCTION

The association between human leukocyte antigens (HLA) and various hematological malignancies has been studied extensivly. The involvement of the HLA system has also been examined in leukemias following the demonstration of a major histocompatibility complex (MHC) influence on the development of mause leukemia (VOJVODIĆ, 2008).In 1964, Lilly and coworkers, reported an increased risk of spontaneous and virus-induced leukemia in congenic mice homozygous for the H-2^k haplotype. Human studies in leukemias point to an association with HLA-A2, HLA-B12 in all types of leukemias as well as with HLA-A9, -A11, -A25, -A32, -B7, -B21, -Cw3 and -Cw4 in acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) (VOJVODIĆ *et al*.,2001, BARION, *et al*.,2007). Despite the excessive number of serological studies on the HLA-DR locus, it was not shown the consistent association with leukemias. The only observed HLA-DR/DQ association was regarded to male-specific homozygosity for the HLA class II supertype DR53 (DORAK *et al*.,2002a, DORAK *et al*.,2002b). There are three HLA class II supertypes: HLA-DR51,-DR52 and -DR53 encoded by *DRB3, DRB4* and *DRB5* genes. HLA-DR53 is an HLA class II supertypic antigen expressed at somewhat lower level than the private HLA-DR antigens (MOHANAPRIYA *et al*.,2010). The supertypic specificity

HLA-DR53 is encoded by HLA-*DRB4* locus in the HLA class II region. HLA-*DRB4* is one of the expressed HLA loci, which exists only on haplotypes possessing HLA-DRB1*04, DRB1*07 and DRB1*09. *DRB3* gene is present on HLA-DRB1*03, DRB1*11, DRB1*12, DRB1*13 and DRB1*14 haplotypes, while *DRB5* gene is present on HLA-DRB1*15 and DRB1*16 haplotypes. The remaining haplotypes DRB1*01, DRB1*08 and DRB1*10, constitute a small fraction that do not belong to any of supertypic groups (DORAK *et al.*,2002a). The HLA-*DRB4* gene or its protein product HLA-DR53 have been associated with increased risk for all major types of leukemias (MACHULA *et al.,*2001). The aim of the present study was to investigate the possible association of HLA class II antigens and haplotypes with leukemias and myelodysplastic sindrome (MDS) in the population of Vojvodina.

MATERIALS AND METHODS

One hundred patients from Vojvodina (51 females, 49 males) were included in study. They were divided into four subgroups according to the type of leukemia/disease: 24 suffering from chronic myeloid leukemia (CML) (8 males, 16 females),7 suffering from MDS (4 males, 3 females), 32 suffering from AML (16 males, 16 females) and 37 suffering from ALL (21 males, 16 females).Control group consisted of 210 healthy individuals who resided in the same geographic area. The HLA-DR and -DQ loci antigens were identified by the two color fluorescence method (VARTDAL *et al.,*1986). Since some haplotypes lack supertypical locus, the presence of supertypic haplotypes partly relies on the results of HLA DR typing. DR52 antigen is present on HLA-DR3, -DR11(5), -DR12(5), -DR13(6) and -DR14(6) haplotypes; DR-53 on HLA-DR4, -DR7 and -DR9 haplotypes; DR51 on HLA-DR15(2) and -DR16(2) haplotypes. HLA-DR1, -DR8 and -DR10 haplotypes do not belong to any of these lineages. A sample was assigned as homozygous for HLA-DR53 lineage when no other supertype was detected or having a double dose of DR53 family (HLA-DR4,-DR7 and -DR9). A sample was assigned as HLA-DR52 homozygote (having double dose of DR52 family (HLA-DR3, -DR11(5), -DR12(5), -DR13(6) and -DR14(6)). Those typed as having only HLA-DR15(2) or -DR16 (2), were assigned as DR51 homozygote.Phenotype and haplotype frequencies were calculated by direct counting method, using following formula: $A = n/N$, where n is number of persons with given antigen and N is total number of persons studied (SHEN *et al.,*2008). Student′s **t** test was used for comparisons of HLA-DR51/52/53 haplotype frequencies between subgroups of patients and controls. Relative risk (RR) for measuring strenght of association with each antigen and haplotype 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 antigen;C^- = is the number of healthy persons who do not have a given antigen;P^- = is the number of patients who do not have a given antigen;C^+ = is the number of healthy persons who have a given antigen.

When RR was higher than 1, we calculated the etiologic fraction, while for RR values less than 1, we calculated the preventive fraction. The etiologic 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 antigen in the subgroup of patients and FAP is the frequency of HLA antigen 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 antigen in the subgroup of patients (GREEN *et al*.,1982). The association was considered positive if the calculated EFs were higher than 0.15 and negative if calculated PFs were more than 0.15. The Pearson χ^2 goodness-of-fit test was used to valuate Hardy-Weinberg genetic equilibrium for phenotypic data (ARMITAGE *et al*., 2002).

RESULTS

The distribution of HLA-DR and -DQ loci specificities in patients with leukemias and MDS and in controls, is shown in Table 1. All of the HLA loci in patients and controls were consistent with Hardy-Weinberg equilibrium. The results showing positive or negative associations are ilustrated in Table 2. Our results demonstrated that there were several HLA class II antigens associated with an increased risk of developing leukemias and MDS, such as: DR6(1) in CML (RR=1.661, EF=0.232), DR11(5) and DQ7(3) in AML (RR=1.732, EF=0.211; RR=2.547, EF= 0.266), respectively, DR7 and DQ2 in ALL (RR=2.391,EF=0.688; RR=1.62,EF=0.15), respectively, and DR7 and DQ7(3) in MDS (RR=2.598,EF=0.175; RR=4.419,EF=0.632), respectively. On the other hand, five antigens were associated with reduced risk of developing leukemias and MDS. The frequency of DR4 in CML (RR=0.182,PF=0.155), DQ5(1) in AML (RR=0.107, PF=0.701), DQ5(1) in ALL (RR=0.075, PF=0.324) and DR15(2) and DQ6(1) in MDS (RR=0.405, PF= 0,172; RR=0.889, PF=0.936), respectively, antigens were decreased in investigated subgroups of patients.

The distribution of supertypical haplotypes in patients and controls is presented in Table 3. There was a difference in the distribution of haplotypes between male and female patients. The greatest impact to the difference came from two supertypical haplotypes: increased homozygosity for HLA-DR53 in male ALL patients and decreased homozygosity for HLA-DR52 in male CML patients, in comparison to the control group (t=2.043; t=105.984), respectively.

Table 1. The distribution of HLA class II antigens in patients with leukemias and MDS and in controls

	Patients					Controls
Antigen	**MDS n=7**	**ALL n=37**	**AML n=32**	**CML n=24**	**Total n=100**	**n=210**
DR1	0.285	0.243	0.156	0.208	0.210	0.171
DR3	0.142	0.216	0.312	0.125	0.230	0.195
DR4	0	0.216	0.125	0.041	0.130	0.190
DR11(5)	0.285	0.297	0.500	0.416	0.390	0.366
DR12(5)	0	0.027	0.031	0	0.020	0.004
DR13(6)	0.142	0.189	0.125	0.250	0.190	0.166
DR14(6)	0.142	0.054	0.031	0.041	0.050	0.080
DR7	0.285	0.270	0.093	0.208	0.190	0.133
DR8	0.142	0	0.031	0.041	0.030	0.038
DR9	0	0.027	0	0	0.010	0.009
DR10	0	0	0	0.083	0.020	0.023
DR15(2)	0.142	0.243	0.312	0.291	0.280	0.290
DR16(2)	0.142	0.081	0.156	0.041	0.100	0.066
Blank	0.285	0.135	0.187	0.250	0.190	0.261
DQ5(1)	0.428	0.351	0.281	0.333	0.333	0.785
DQ6(1)	0.428	0.405	0.468	0.583	0.480	0.457
DQ2	0.285	0.405	0.406	0.291	0.370	0.300
DQ7(3)	0.714	0.324	0.531	0.416	0.440	0.361
DQ8(3)	0	0.108	0.093	0.041	0.080	0.152
DQ9(3)	0	0	0	0	0	0.009
DQ4	0	0	0.031	0.041	0.020	0.033
Blank	0.142	0.378	0.250	0.250	0.290	0.376

DISCUSSION

This is the first HLA class II association study in leukemias and MDS in the population of Vojvodina. The distribution of HLA class II antigens in patients suffering from leukemias and MDS in comparison to controls, showed the increase in frequency of DQ6(1)(40.5%), DQ2 (40.5%), DQ7(3) (32.4%) and DR7 (27%) in ALL patients. The most common HLA class II antigens in AML and CML patients were DQ7(3) (53.1%), (41.6%) respectively, DR11(5) (50%), (41.6%) respectively, and DQ6(1) (46.8%), (58.3%) respectively, as well as DQ7(3) (71.4%), DQ6(1) (42.8%) and DQ5(1) (42.8%) in MDS patients (Table 1). The analysis of susceptibility with HLA class II antigens with leukemias and MDS showed that RR to develop ALL is 2.391 in patients having DR7, which is in accordance with study of Von Fliedner and coworkers (DORAK,2008) and that RR to develop AML is 1.732 for patients having DR11(5) (Table 2).

Table 2. Disease susceptibility with HLA class II antigens

Antigen	MDS			ALL			AML			CML		
	RR	**EF**	**PF**	**RR**	**EF**	**PF**	**RR**	**EF**	**PF**	**RR**	**EF**	**PF**
DR1	1.932	0.137	-	1.556	0.086	-	0.900	-	0.017	1.273	0.044	-
DR3	0.683	-	**0.160***	1.137	0.026	-	1.872	0.145	-	0.589	-	0.080
DR4	-	-	-	1.174	0.032	-	0.609	-	0.074	0.182	-	**0.155***
DR11(5)	0.690	-	0.113	0.744	-	0.092	1.732	**0.211***	-	1.233	0.078	-
DR12(5)	-	-	-	5.801	0.022	-	6.688	0.026	-	-	-	-
DR13(6)	0.831	-	0.043	1.170	0.016	-	0.717	-	0.047	1.674	0.100	-
DR14(6)	1.903	0.065	-	0.656	-	0.027	0.367	-	0.050	0.491	-	0.041
DR7	2.598	**0.175***	-	2.391	**0.688***	-	0.668	-	0.044	1.712	0.086	-
DR8	4.190	0.108	-	-	-	-	0.809	-	0.006	1.082	0.003	-
DR9	-	-	-	2.887	0.075	-	-	-	-	-	-	-
DR10	-	-	-	-	-	-	-	-	-	4.053	0.060	-
DR15(2)	0.405	-	**0.172***	0.785	-	0.062	1.110	0.030	-	1.004	0.001	-
DR16(2)	2.342	0.081	-	1.247	0.016	-	2.615	0.096	-	0.605	-	0.026
DQ5(1)	0.748	-	0.143	0.075	-	**0.324***	0.107	-	**0.701***	0.136	-	0.675
DQ6(1)	0.889	-	**0.936***	0.808	-	0.087	0.953	-	0.022	1.661	**0.232***	-
DQ2	0.930	-	0.021	1.620	**0.150***	-	1.594	**0.151***	-	0.957	-	0.012
DQ7(3)	4.419	**0.632***	-	0.848	-	0.049	2.547	**0.266***	-	1.260	0.086	-
DQ8(3)	-	-	-	0.675	-	0.049	0.572	-	0.065	0.240	-	0.129
DQ4	-	-	-	-	-	-	0.937	-	0.002	1.252	0.009	-

NEA=negative association (PF>0.15) PA=positive association(EF>0.15)

Table 3. Supertypical haplotypes (%) in patients and controls and t test values

Supertypical haplotypes	MDS				ALL				AML				CML				Controls	
	males		females		males		females		males		females		males		females		male	female
	%	t test	%	t test	%	t test	%	t test	%	t test	%	t test	%	t test	%	t test	%	%
DR52-DR52	2	**5.91**	1	**13.41**	6	**3.94**	3	**3.98**	7	**3.55**	8	**3.70**	4	**105.9**	4	**4.37**	20.47	18.57
DR52-DR53	1	**2.67**	0	**4.83**	2	**2.38**	8	0.58	3	1.58	2	**3.20**	2	1.92	2	**3.19**	6.19	10
DR52-DR51	0	**4.68**	0	**4.01**	4	**2.66**	1	**3.00**	3	**2.46**	3	1.78	2	**3.04**	4	1.18	9.52	7.14
DR53-DR53	1	0.03	0	**4.01**	6	**2.04**	2	**2.27**	0	1.41	0	**4.01**	0	1.41	1	**3.00**	0.95	7.14
DR53-DR51	0	**2.68**	0	**2.26**	0	**2.68**	0	**2.26**	1	1.46	0	**2.26**	0	**2.68**	1	0.95	3.33	2.38
DR51-DR51	0	**3.80**	1	**2.11**	3	1.34	2	1.35	2	1.92	3	0.77	0	**3.72**	1	**2.11**	6.19	4.76
Other haplotypes*	0	**2.01**	1	0.32	0	**2.01**	0	1.71	0	**2.01**	0	1.73	0	**2.01**	3	0.83	1.90	1.42

*-haplotypes lacking an HLA class II supertype

V=307, border value=1.97

Our study revealed positive associatin between DQ6(1) antigen and CML which is also reported by MUNDHADA and coworkers (MUNDHADA *et al.*,2004),but was not consistent to the findings of AMIRZARGAR and coworkers (AMIRZARGAR *et al.*,2007), who reported negative association of DQ6(1) in CML patients. In our population, HLA-DR4 (RR=0.182, PF=0.155) antigen was shown to have negative association with CML. The only significant positive association with AML against control group was HLA-DR11(5) (RR=1.732), which is also reported by SARAFNEJAD and coworkers (SARAFNEJAD *et al.*,2006),and DQ7(3) (RR=2.547). HLA-DQ5(1) antigen was found in lower frequency in AML patients in comparison to controls (RR=0.107, PF=0.701), suggesting to be a protective factor against AML. In our study, there were two HLA class II antigens in positive and three in negative association with MDS. Positive association was found with DR7 (RR=2.598, EF=0.175) and DQ7(3) (RR= 4.419, EF=0.632), while negative association was observed with DR3 (RR=0.683, PF=0.16), DR15(2) (RR= 0,405, PF=0.172) and DQ6(1) (RR=0.889, PF=0.936). Our findings regarding positive association with MDS patients do not correspond with an earlier reports, since, as SAUNTHARARAJAH and coworkers (SAUNTHARARAJAH *et al.*,2002), and XIAO and coworkers (XIAO *et al.*,2009) reported, HLA-DR15(2) was shown as genetic susceptibility marker for developing MDS. In our population, any positive association between HLA class II haplotypes and leukemias and MDS, was not found. On the other hand, the only negative association was found between HLA-DR3DQ8(3) haplotype and AML, suggesting to possible protective role of this haplotype against AML. This study provided evidence for HLA class II supertypical haplotypes role in developing leukemias and MDS. The main finding was different gender specific frequency of supertypical HLA-DR53 homozygous haplotype in male ALL patients in comparison to controls (6% vs 0.9%, t=2.043). HLA-DR53 associated susceptibility to ALL in male specific manner was also described in the previous studies (DORAK *et al.*,2002a, DORAK *et al.*,2002b).Significant difference in HLA-DR53 homozygous haplotype was observed for ALL females in comparison to controls (2% vs 7.1%, t=2.274), but with protective role, in contrast to male ALL patients.

An association between HLA antigens and diseases may be attributable to either direct effect of the marker antigen or to another antigen in linkage disequilibrium with it. The analysis of HLA-DR antigens belonging to HLA-DR53 supertypic group, showed the strong susceptibility of HLA-DR7 antigen in the group of ALL patients, due to its higher frequency (RR=2.391, EF=0.688) in comparison to controls. Other HLA-DR antigens belonging to DR53 supertypical lineage (HLA-DR4 and -DR9) were present with increased frequency in ALL patients in comparison to controls, but with no positive association, due to lower EFs than 0.15 (EF=0.032, EF=0.075), respectively (Table 2). Therefore, we considered them having no impact on DR53 supertype susceptibility to develop ALL, in contrast to HLA-DR7 antigen.

Our study showed the protective role of homozygous HLA-DR52 haplotype in other investigated diseases: CML (t for male group=105.98, t for female group 4.37), MDS (t for male group=5.91, t for female group 13.41), AML (t for male

group=3.55, t for female group 3.70) and ALL (t for male group=3.94, t for female group 3.98) (Table 3). These results are consistent to the previous studies reporting the protective role of HLA-DR52 supertype family in other leukemias (DORAK *et al*., 2002a, DORAK *et al*., 2002b). The protective role of other combination of supertypical haplotypes was shown in our study for some of investigated diseases but not for all diseases at the same time, in contrast to HLA-DR52 haplotype.

CONCLUSION

The results of present study suggest that homozygosity for HLA-DR53 is a genetic risk factor for development of ALL in males. The positive and negative associations between HLA class II antigens and haplotypes and leukemias and MDS was shown in population of Vojvodina, and furthermore the results of our study could be useful in clinical practice.

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HLA ANTIGENI II KLASE I PREDISPOZICIJA ZA LEUKEMIJE I MIJELODISPLAZNI SINDROM

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Uslovi spoljne sredine i genetski faktori imaju uzajamnu ulogu u razvoju akutnih i hroničnih leukemija. HLA antigeni se smatraju mogućim genetskim faktorom rizika. Clij ovog rada je utvrđivanje moguće udruženosti polimorfizama II HLA klase i leukemija i mijelodisplaznog sindroma. U ovoj studiji ispitivana je distribucija HLA antigena II klase, DR/DQ i DR51/DR52/DR53 haplotipova u 100 bolesnika: 7 koji boluju od mijelodisplaznog sindroma (MDS), 37 od akutne limfoblastne leukemje (ALL), 32 od akutne mijeloblastne leukemije (AML) i 24 od hronične mijeloidne leukemije (CML). Grupa od 210 zdravih nesrodnih osoba sa teritorije Vojvodine, čini kontrolnu grupu. HLA fenotipizacija je vršena dvokolornom fluorescentnom metodom. U svim isptivanim grupama leukemija i MDS uočene su pozitivne i negativne udruženosti sa II klasom HLA antigena u populaciji Vojvodine. Moguć zaštitni haplotip u ovoj studiji je DR3DQ8(3), kod bolesnika koji boluju od AML (RR=0.007, PF=0.501). Distribucija DR53-DR53 supertipskog haplotipa je pokazala značajnu razliku u muških bolesnika sa ALL (6% vs 0.09%), dok je frekvencija DR52-DR52 haplotipa značajno niža u svim grupama obolelih u odnosu na kontrolnu. Prema rezultatima studije izveden je zaključak da DR7 antigen u muških bolesnika sa ALL ima najveći efekat na višu frekvenciju DR53-DR53 haplotipa u ovom tipu leukemije. Uloga HLA antigena kao faktora rizika u nastanku leukemija u našoj populaciji je pokazana a rezultati ove studije mogu biti upotrebljena u kliničkoj praksi.

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