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HLA Class II Polymorphism in Autochthonous Population of Gorski Kotar, Croatia

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A B S T R A C T

*The aim of this study was to examine frequencies and haplotypic associations of HLA class II alleles in autochthonous population of Gorski kotar (Croatia). HLA -DRB1, -DQA1 and -DQB1 alleles were determined by DNA based PCR typing in 63 unrelated inhabitants from Gorski kotar whose parents and ancestors were born and lived in tested area for at least over four generations.. A total of 13 HLA-DRB1, 12 DQA1 and 14 DQB1 alleles were identified. The most frequent HLA class II genes in Gorski kotar population are: HLA-DRB1*13 (af=0.150), -DRB1*03 (af=0.142), -DRB1*07 (af=0.119), and -DRB1*11 (af=0.119), HLA-DQA1*0501 (af=0.278), -DQA1*0102 (af=0.183), -DQA1*0201 (af=0.127) and HLA-DQB1*0301 (af=0.157), -DQB1*0201 (af=0.139), -DQB1*0501 (af=0.111). We have identified 24 HLA class II three-locus haplotypes. The most common haplotypes in Gorski kotar population are DRB1*03-DQA1* 0501-DQB1*0201 (0.120), DRB1*11-DQA1*0501-DQB1*0301 (0.111) and DRB1*07-DQA1*0201-DQB1*0202 (0.094). The allelic frequencies and populations distance dendrogram revealed the closest relationships of Gorski kotar population with Slovenians, Germans, Hungarians and general Croatian population, which is the result of turbulent migrations within this microregion during history.*

Key words: *Croatians, HLA class II alleles and haplotypes, DNA typing, Gorski kotar population*

Introduction

The highly polymorphic HLA system is a power genetic tool for studies of inheritance, ancestry and genetic history of populations[1]. Croats are of Slavic origin coming from Eastern Europe to the Balkan Peninsula by two great migrations of Slavs between the 6th and 7th century[2]. During their history Croats were admixtured by other populations: by other Slavic and Baltic populations, by autochthonous Balkan populations such are Illyrians and Thracians, and recently by immigrated populations of Germans, Austrians, Hungarians, Italians, Turks and other neighbor populations[3].

HLA polymorphism in different regions of Croatia was previously described[4–7]. Gorski kotar is very appropriate for such study because this area was isolated during centuries and geographic features favor settlement of population but nevertheless, this area has experienced several immigration waves from neighbor and even distant, North-European populations, preserving their genes in Gorski kotar population. The history, demography, anthropology, anthroponomy and linguistic of this region are well known[8–10].

The region of the western Croatia, Gorski kotar is a high-risk zone for multiple sclerosis (MS) with the prevalence of 124.3/100,000[11]. Corresponding frequency of MS in Croatia are much lower (24.5/100,000)[11]. The familial occurrence of MS disease related to 36%[12]. The high incidence of familial MS suggests that the disease in Gorski kotar is to a large extent genetically conditioned. There

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is no data concerning immunogenetic structure of the inhabitants of Gorski kotar which can help in the future studies of susceptibility to MS and association with HLA.

With the aim to contribute to the existing knowledge about HLA polymorphism in Croatian population, we determined the frequencies of HLA class II genes and haplotypes in autochthonous population of Gorski kotar to establish a database for further investigations on ancestry and genetic factors contributing to complex, polygenic diseases in this region.

Materials and Methods

Population samples

We studied 63 autochthonous, randomly selected, unrelated inhabitants (9/54 female/male, mean age: 39.8) from Gorski kotar whose parents and ancestors were born and lived in tested area for at least over four generations. The study was approved by the institutional ethics committee and informed consent was obtained from all volunteers.

HLA class II typing and statistical analysis

Genomic DNA was extracted from whole venous blood using the standard proteinase K digestion method followed by salting-out extraction and ethanol precipitation[13]. HLA-DRB1 low resolution, and HLA-DQA1 and DQB1 high resolution genotyping was performed by PCR-SSP method (Olerup SSP™ Products) according to Olerup et al[14]. The DRB1, DQA1 and DQB1 allelic and haplotypic frequencies were calculated using Arlequin software, v.2.000 (http://anthro.unige.ch/arlequin). The significance of differences in allele frequencies among population of Gorski kotar and general Croatian and selected European populations was evaluated using the chi-square analysis by 2x2 contingency tables with Yates's correction factor, while Fisher's exact test was used if any value was less than 5. In order to compare allelic frequencies with other populations, the reference tables used were those published by Terasaki and Gjertson[15–20] and several other authors[21–23]. Dendrogram was constructed with the allelic frequencies by applying the neighbor-joining (NJ) method[24] to obtain the genetic distances between populations (GD)[25], by using DISPAN software designed by T. Ota (Pennsylvania State University, Philadelphia, PA, USA), which contains the GNKDST and TREEVIEW programs[26–27]. The haplotype frequencies were estimated by the maximum likelihood method applying Arlequin software, v.2.000.

Geography of Gorski Kotar

Gorski kotar is surrounded on the north and northwest borders by the Republic of Slovenia and southwest with the Adriatic coast (Figure 1). Gorski kotar is located in the biggest Jurassic limestone zone of the Dinaric Alps. It is a mountainous karst area mostly covered with woods and pastures[8].

Fig. 1. Geographic location and position of Gorski Kotar region.

Demography of Gorski kotar

Demography of Gorski kotar has been recorded for about 150 years. The censuses of population indicate great oscillations in the number of population, depending on social and economic conditions throughout that period. The greatest number of population was recorded in the middle of the 19th century (41,548 in the year 1857), and after that gradual decrease for almost one quarter followed (30,545 in the year 1991), making Gorski kotar a distinctly emigrant area. In such demographic regression influence of the two World Wars should not be neglected According to the census of the 31st of March, 2001, 26,120 inhabitants, equally distributed by sex, lived in the area of 1,273 km^2 in 257 historical settlements (20 inhabitants per km^2)[27]. Gorski kotar is nowadays threatened by natural depopulation, caused mostly by long lasting emigration of younger population and unfavorable economic situation. The last census registers that 85.6% of inhabitants are Croats, 9.8% Serbs, 0.75% Slovenes and 3,8% others[27]. Population speaks Croatian, in smaller part Serbian, and dialects in regions have many terms of German origin[9].

History of Gorski kotar

Antique history

The earliest findings are from the New Stone Age, (Upper Paleolithic), found in the cave nearby Lokve. Illyrian and Celtic tribes Iapodes were settling in these regions in the period from 1000 B.C. till Roman occupation of the regions in the 1st century A.C. when this area was gradually romanized. At the time of the Roman Empire Gorski kotar was partially in the Province of Dalmatian, and its smaller northeastern part was in the Province of Pannonia. In the 6th century Croats from the Pannonia Plane came through the valley of the river Kupa and settled in the east part of Gorski kotar. The

west area (nowadays municipalities of Čabar and Delnice) was settled later; the first settlement was mentioned as late as early 11th century (Gerovo). In 1096 troops of the First Crusade passed through Gorski kotar[8–9].

From Middle Age to nowadays

In the period from 7th to 12th century Gorski kotar was surrounded by powerful estates of the Croatian dukes Frankopans and from northwest across the river Kupa there was the estate of Slovene landowners. At the middle of the 16th century the entire Gorski kotar came into the hands of the feudal lords of Zrinski, who kept these estates until 1670. At the end of 16th century the Eastern area of Gorski kotar (municipality of Vrbovsko) were settled by Vallachians. In the year 1638 the Zrinskis opened a steel forge, and from 1651 to 1665 this region was settled by miners from Slovenia[8–9].

At the beginning of the 18th century Gorski kotar was settled by 48 families from Slovenia, mostly of German origin. From 1809 to 1815 Gorski kotar was a part of the Napoleon Illyrian provinces. The reorganization of Gorski kotar was influenced by a group of Germans from Franconia and Thuringia, Tyrol and Carinthia, who settled in the area of Kocevje, in the north of Gorski kotar in 1401. In 1726 after construction of the Caroline road (by Charles IV) several Czech families settled in Gorski kotar[8–9].

Results

In the present study we have studied the HLA class II alleles in a sample of autochthonous unrelated individuals living in Gorski kotar, a small until recently geographic isolated region of the western Croatia at the junction of Central and Mediterranean Europe. The expected and observed genotype frequency values for HLA--DRB1, -DQA1 and -DQB1 loci did not significantly differ and the population sample was in Hardy-Weinberg equilibrium. Table 1 illustrated the frequencies of the -DRB1, DQA1 and DQB1 alleles in Gorski kotar population. A total of 13 HLA-DRB1, 12 DQA1 and 14 DQB1 alleles were identified in Gorski kotar population. The most frequent DRB1 allele was HLA-DRB1*13 (0.150), followed by -DRB1*03 (0.142), -DRB1*07 (0.119) and -DRB1*11 (0.119). DRB1*13 has been observed in lower frequency in two independent studies of general Croatian populations (Table 4), with 0.113[23] and 0.130[7], respectively, while DRB1*03 is presented with 0.105[23] and 0.066[7]. DRB1*07 was observed with lower frequencies in previous studies, with 0.083[7] and 0.066[23], but the differences were not statistically significant in comparison with Gorski kotar data Table 4. These alleles exist with a similar frequencies in other European populations, except alleles DRB1*11 which was found to be significantly higher in Italians (0.265)[20], Greeks (0.261)[19] and Bulgarians (0.225)[18]. DRB1*11 was higher in general Croatian populations but not significantly; 0.177[23] and 0.155[7], respectively, compared to Gorski kotar population data. Specific feature of Gorski kotar is very low frequency of DRB1*14 allele (<0.01) compared to general Croatian population (0.039)[23], but it is not statistically significant (Table 4). Significantly higher frequency revealed neighbor European populations: Bulgarians 0.071[18], Italians 0.066[20], Hungarians 0.068[17] and French 0.051[21]. DRB1*16 allele, one of the most frequent allele in Croatian population[7,23] is signifi-

TABLE 1
FREQUENCIES OF HLA-DRB1, -DQA1 AND -DQB1 ALLELES IN POPULATION OF GORSKI KOTAR-CROATIA

DRB1	DQA1	DQB1			
Alellic groups♦	Frequencies	Alelle	Frequencies	Alelle	Frequencies
*01	0.087	*0101	0.087	*0201	0.139
*03	0.142	*0102	0.183	*0202	0.095
*04	0.095	*0103	0.079	*0301	0.157
*07	0.119	*0104	0.008	*0302	0.089
*08	0.071	*0105	0.032	*0303	0.035
*09	0.016	*0201	0.127	*0402	0.081
*10	0.032	*0301	0.079	*0501	0.111
*11	0.119	*0302	0.016	*0502	0.048
*12	0.008	*0303	0.016	*0503	0.008
*13	0.150	*0401	0.071	*0601	0.008
*14	0.008	*0501	0.278	*0602	0.084
*15	0.102	*0505	0.024	*0603	0.081
*16	0.039			*0604	0.040
* –	0.012			*0609	0.008
				* –	0.016

♦ HLA-DRB1 genotyping was performed by low resolution DNA typing

– »Blank« alleles

cantly lower in population of Gorski kotar (0.124 and 0.108, compared to 0.039 in Gorski kotar).

The most frequent alleles in Gorski kotar population belong to DQA1 locus, (Table 1) DQA1*0501 (0.278), DQA1*0102 (0.183) and DQA1*201 (0.127). Comparison of these allelic frequencies revealed a close similarity of Gorski kotar population with neighbouring European populations. The frequency of DQA1*0505 allele is significantly lower in Gorski kotar (Table 4) compared to general Croatian population (0.024 *versus* 0.091). The DQA1*104 allele is observed in Gorski kotar population with very low frequency (0.008) compared to frequency in general Croatian population 0.039[23], Slovenians 0.046[15], Hungarians 0.068[17,] Germans 0.040[16], Greeks 0.082[19] and Italians 0.033[20].

The most frequent DQB1 alleles in Gorski kotar population were found to be DQB1*0301 (0.157), DQB1*0201 (0.139) and DQB1*0501 (0.111). DQB1*0301 (Table 1), whose frequency is similar to those observed in other European populations (0.164–0.268) is predominant DQB1 allele among Caucasian population[15–19,21]. Among other DQB1 alleles, DQB1*0503, DQB1*0601 and DQB1*0609 alleles had the lowest frequency in Gorski kotar population (0.008). DQB1*0503 allele is more frequent in general Croatian population, 0.030[23], Slovenians 0.031[15], Bulgarians 0.063[18], Italians 0.057[20] and French 0,047[21].

Analysis of three locus haplotypes between DRB1, DQA1 and DQB1 are shown in Table 2. Among 126 possible haplotypes, 24 combinations were observed, from which 14 were found two or more times whereas 10 haplotypes appeared only once. The most common haplotype in Gorski kotar population was DRB1*03-DQA1*0501-DQB1*0201 with a frequency of 0.120, followed by DRB1*11-DQA1*0501-DQB1*0301 (0.111) and DRB1*07-DQA1*0201-DQB1*0202 (0.094). These haplotype frequencies are in concordance with previously published data for regionally different Croatian study groups done by Grubić et al.1995[28,29], Dražić et al. 2003[23] and Grahovac et al. 2005 (unpublished data).

In order to examine the genetic relations between Gorski kotar, general Croatian and neighbouring European populations, a phylogenetic tree was constructed (Figure 2) and the corresponding genetic distances for each pairwise comparison were calculated with HLA-DRB1, -DQA1 and -DQB1 allelic frequencies (Table 3). The closest relationship was observed with Slovenians, Germans, followed almost equidistant by Croatian general population, Hungarians, Russians and French population (Figure 2).

TABLE 2
HLA-DRB1, -DQA1 AND -DQB1 HAPLOTYPE FREQUENCIES IN GORSKI KOTAR POPULATION

DRB1-DQA1-DQB1	Frequencies
DRB1*03-DQA1*0501-DQB1*0201	0.120
DRB1*11-DQA1*0501-DQB1*0301	0.111
DRB1*07-DQA1*0201-DQB1*0202	0.094
DRB1*01-DQA1*0101-DQB1*0501	0.086
DRB1*04-DQA1*0301-DQB1*0302	0.086
DRB1*15-DQA1*0102-DQB1*0602	0.086
DRB1*08-DQA1*0401-DQB1*0402	0.077
DRB1*13-DQA1*0103-DQB1*0603	0.068
DRB1*16-DQA1*0102-DQB1*0502	0.043
DRB1*13-DQA1*0102-DQB1*0604	0.043
DRB1*10-DQA1*0105-DQB1*0501	0.034
DRB1*13-DQA1*0501-DQB1*0301	0.026
DRB1*07-DQA1*0201-DQB1*0303	0.026
DRB1*09-DQA1*0302-DQB1*0303	0.017
DRB1*15-DQA1*0103-DQB1*0601	0.008
DRB1*01-DQA1*0101-DQB1*0502	0.008
DRB1*03-DQA1*0505-DQB1*0201	0.008
DRB1*04-DQA1*0301-DQB1*0303	0.008
DRB1*11-DQA1*0505-DQB1*0301	0.008
DRB1*12-DQA1*0501-DQB1*0301	0.008
DRB1*13-DQA1*0505-DQB1*0301	0.008
DRB1*13-DQA1*0102-DQB1*0609	0.008
DRB1*14-DQA1*0104-DQB1*0503	0.008
DRB1*07-DQA1*0201-DQB1*0302	0.008

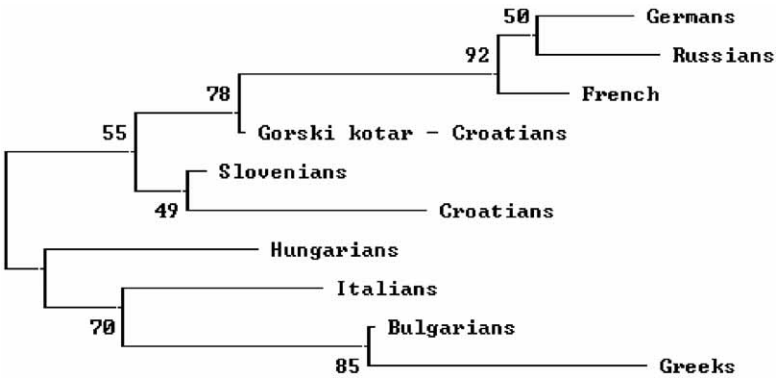

Fig. 2. Neighbor-joining dendrogram based on HLA-DRB1, -DQA1 and -DQB1 allele frequency data showing relatedness between Gorski kotar, general Croatian and selected neighbouring-European populations. Bootstrap values from 1,000 replicates are given.

TABLE 3
GENETIC DISTANCES BETWEEN GORSKI KOTAR POPULATION AND OTHER EUROPEAN POPULATIONS OBTAINED BY USING HLA-DRB1, -DQA1 AND -DQB1 ALLELE FREQUENCIES

Populations	Genetic distances
Slovenians	0.0084
Hungarians	0.0273
Russians	0.0288
French	0.0299
Germans	0.0332
Croatians	0.0388
Italians	0.0441
Bulgarians	0.0713
Greeks	0.1081

Discussion

The results presented here show that Gorski kotar and general Croatian population differ significantly in only two class II genes: -DRB1*16 and DQA1*0505 (Table 4) which are present in Gorski kotar population with low frequencies. The haplotype frequencies in Gorski kotar revealed very similar haplotypes distribution

found in general Croatian population[23,28,29]. Haplotype organisation and distribution in Gorski kotar are similar to neighbouring European populations (Slovenians, Hungarians, Germans, Italians, Russians, Bulgarians, Turks) which reflect influence of population admixture during migration in this region[15–18,20]. The inhabitants of this region are small in number, strictly engaged in wood industry and agriculture, and until construction of communications this area was fully isolated. The mentioned geographic, economic, and cultural obstacles in Gorski kotar conditioned haplotype organization typical for neighbouring and immigrated populations. Particular accumulation of some HLA genes and especially some HLA extended haplotypes, could be useful for further investigations on ancestry and immunogenetic factors contributing to complex, polygenic diseases in this region[11,12].

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TABLE 4
FREQUENCIES OF HLA-DRB1, -DQA1 AND -DQB1 ALLELES IN POPULATION OF GORSKI KOTAR AND GENERAL CROATIAN POPULATION

HLA-DRB1 alleles	Gorski kotar – Croatia n=126	Croatian general population n=362
DRB1*01	0.087	0.111
DRB1*03	0.142	0.105
DRB1*04	0.095	0.086
DRB1*07	0.119	0.066
DRB1*08	0.071	0.055
DRB1*09	0.016	0.003
DRB1*10	0.032	0.017
DRB1*11	0.119	0.177
DRB1*12	0.008	0.022
DRB1*13	0.150	0.113
DRB1*14	0.008	0.036
DRB1*15	0.102	0.102
DRB1*16	0.039♦	0.108
DQA1*0101	0.087	0.102
DQA1*0102	0.183	0.249
DQA1*0103	0.079	0.069
DQA1*0104	0.008	0.039
DQA1*0105	0.032	0.017
DQA1*0201	0.127	0.066
DQA1*0301	0.079	0.064
DQA1*0302	0.016	0.003
DQA1*0303	0.016	0.028
DQA1*0401	0.071	0.039
DQA1*0501	0.278	0.224
DQA1*0505	0.024♦	0.091
DQB1*0201	0.139	0.111
DQB1*0202	0.095	0.055
DQB1*0301	0.157	0.238
DQB1*0302	0.089	0.066
DQB1*0303	0.035	0.014
DQB1*0402	0.081	0.033
DQB1*0501	0.111	0.130
DQB1*0502	0.048	0.108
DQB1*0503	0.008	0.030
DQB1*0601	0.008	0.008
DQB1*0602	0.084	0.091
DQB1*0603	0.081	0.066
DQB1*0604	0.040	0.025
DQB1*0609	0.008	0.011

♦ $p<0.05$

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POLIMORFIZAM HLA GENA RAZREDA II U AUTOHTONOJ POPULACIJI GORSKOG KOTARA, HRVATSKA

S A Ž E T A K

Svrha ove studije bila je analizirati frekvencije HLA alela razreda II i njihovu haplotipsku organizaciju u autohtonoj populaciji Gorskog kotara (Hrvatska). Izabrana je skupina od 63 nesrodna stanovnika Gorskog kotara. Roditelji i preci ispitanika rođeni su i živjeli u ispitanom području kroz četiri generacije. HLA-DRB1, -DQA1 and -DQB1 aleli određivani su metodom DNK-tipizacije pomoću lančane reakcije polimerazom. Ukupno je pronađeno 13 HLA-DRB1 alela, 12 DQA1 alela i 14 DQB1 alela. Najučestaliji HLA aleli razreda II u ispitivanoj populaciji su: HLA-DRB1*13 (af=0.150), -DRB1*03 (af=0.142), -DRB1*07 (af=0.119), and -DRB1*11 (af=0.119), HLA-DQA1*0501 (af=0.278), -DQA1*0102 (af=0.183), -DQA1*0201 (af=0.127) and HLA-DQB1*0301 (af=0.157), -DQB1*0201 (af=0.139), -DQB1*0501 (af=0.111). Utvrđena su 24 HLA-DRB1-DQA1-DQB1 haplotipa. Najučestaliji haplotipovi u Gorskom kotaru su: DRB1*03-DQA1*0501-DQB1*0201 (HF=0.120), DRB1*11-DQA1*0501-DQB1*0301

(HF=0.111) i DRB1*07-DQA1*0201-DQB1*0202 (HF=0.094). Usporedbom frekvencija HLA alela i izračunatih genetskih udaljenosti između skupine ispitanika iz Gorskog kotara i susjednih populacija, pokazali smo da je populacija Gorskog kotara imunogenetskom strukturom najbliža općoj populaciji Hrvatske, Slovenije, Njemačke i Mađarske, što je neposredni rezultat migracija u toj mikroregiji tijekom povijesti.