Evaluation of MHC Class 2 Alleles in Chronic Hepatitis B Patients and Inactive Hepatitis B Carriers

Kronik Hepatit B Hastalari ve İnaktif Hepatit B Taşıyıcılarında MHC Klass II Allellerinin Değerlendirilmesi

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ABSTRACT Objective: We aimed to determine MHC Class 2 allele frequencies of chronic hepatitis B cases (CHB) and inactive hepatitis B (IHB) carriers in our population, and to asses the prognosis of disease according to MHC Class 2 type in early stage. **Material and Methods:** Forty-eight CHB patients, 46 IHB carriers and 100 normal control subjects participiated in this study. DNAs were amplified by PCR using appropriate oligonucleotides. Then, these PCR products were displayed by agarose gel electrophoresis technique by using UV transulliminator. The polymorphism of the alleles HLA-DRB1 and HLA-DQB1 were analyzed based on genotyping including the lengths of the bands displayed on the gel. **Results:** The IHB carriers had significantly higher frequencies of DQB1*01, DRB1*14 and DQB1*05 alleles than the control subjects. When two groups of patients were compared, the frequencies of HLA-DQB1*01 alleles were significantly higher in the CHB patients than in the IHB carriers. The frequencies of HLA-DRB1*14-*15 and HLA-DQB1*01-*01 genotypes were significantly higher in the CHB patients than in the IHB carriers. **Conclusion:** It might be advised to determine HLA-DRB1*14 ve HLA-DQB1* 01 allells and HLA-DRB1*14-*15, HLA-DQB1*01-*01 genotypes in the individuals facing with hepatitis B virus, and if the results are positive, these patients should be followed up for chronicity.

Key Words: Hepatitis B, chronic; genes, MHC class II

ÖZET Amaç: Kronik hepatiti B hastaları (KHB) ve inaktif hepatit B (İHB) taşıyıcılarının MHC klass II allel sıklığını saptamayı ve erken dönemde MHC klass II tipine göre hastalığın prognozunu değerlendirmesi. **Gereç ve Yöntemler:** Kırksekiz KHB hastası, 46 İHB taşıyıcısı ve 100 normal konrol kişi çalışmaya alındı. DNA uygun oligonükleotidler kullanılarak PCR ile amplifiye edildi. Sonra bu PCR ürünleri UV transuliminatör kullanılarak agaroz jel elekroforez tekniği ile gösterildi. HLA-DRB1ve HLA-DQB1allellerinin polimorfizmi jel üzerinde gösterilen bantların uzunluklarını kapsayacak şekilde genotipleme temelinde analiz edildi. **Bulgular:** İHB taşıyıcılarında DQB1*01, DRB1*14 ve DQB1*05 allelleri sağlıklı bireylerden önemli oranda daha yüksekti. Hastaların iki grubu karşılaştırıldığında HLA-DQB1*01 alllelleri KHB hastalarında İHB taşıyıcılarından önemli oranda yüksekti. HLA-DRB1*14-*15 ve HLA-DQB1*01-*01genotiplerinin sıklığı KHB hastalarında İHB taşıyıcılarından daha yüksekti. **Sonuç:** HLA-DRB1*14 ve HLA-DQB1* 01 allellerine ve HLA-DRB1*14-*15, HLA-DQB1*01-*01genotiplerine hepatit B virusu ile karşılaşan bireylerde bakılması ve saptaması durumunda bunların kronikleşme yönünden yakın takip edilmesi önerilebilir

Anahtar Kelimeler: Kronik hepatit B; MHC klas II genleri

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Hepatitis B infection is one of the most important diseases which engender public health both in Turkey and in the world. Although there has been a vaccine available against the disease since 1982, two billion people are infected with hepatitis B virus (HBV) in the world now; the disease may cause a wide variety of clinical pictures such as inac-

tive hepatitis, acute hepatitis, chronic hepatitis, cirrhosis and hepatocellular cancer. These variations in the clinical picture of the disease depend on viral factors and immunological and genetic factors of the host.[1,2]

It is believed that the host immune response rather than viral factors play a role in the development of liver damage. Inactive carriers with high rates of viral replication but with normal liver enzyme levels and normal liver histopathology indicate that the virus does not have a considerable direct cytopathic effect.[3,4]

Complete eradication of the virus from the liver depends on the specific immune response. HLA class I (HLA-A, B and C) and HLA class II (DRB1, DQA1, DQB1, DPA1 and DPB1) genes, primary modulators of the host immune response, are located on the short arm of the sixth chromosome. HLA molecules present the foreign antigen to CD4+T lymphocytes and CD8 cytotoxic T cells, which induces humoral and cellular immune responses.[5]

Most of the studies on HBV infection and the host genetics have focused on HLA molecules. Although HLA class I alleles mediate cytotoxic T lymphocyte responses via HLA class I molecules, no relations between viral persistence and the progression of HBV infection have been detected.[6]

In this study, we performed MHC class II typing in the chronic HBV patients, the inactive HBV carriers and the normal population and attempted to determine which allele frequencies differed between HBV patients and the normal population and to reveal which alleles caused the disease to become chronic.

MATERIAL AND METHODS

This study included 46 inactive hepatitis B carriers and 48 chronic HBV patients followed in the Department of Clinical Microbiology and Infectious Diseases, Mersin University Hospital, Mersin, Turkey, and 100 healthy individuals.

Patients with HBsAg positivity for more than 6 months, HBV DNA levels were below 10^5 copy/ml and transaminase levels continuously normal were described as inactive HBV carriers. Chronic hepatitis B patients are the ones having HBsAg positivity for more than 6 months, HBV DNA levels above 10^5 copy/ml, high transaminase levels (one and half times as high as normal) and having necroinflammatory scores above 4 on liver biopsy (indicative of chronic hepatitis). Healty control group was consisted of people who were anti- HBc negative and naive for hepatitis B virus.[7]

The two groups were invited to participate in the study and blood specimens were collected for molecular investigations. Informed consent was obtained from all patients and controls. The study protocol was approved by our hospital's Ethics Committee.

Blood specimens drawn into etylendiaminotetraenoic acid (EDTA) containing tubes were kept at 2-8ºC until the day of examinations.

The parameters studied in all three groups were as follows:

- HLA-DRB1 typing
- HLA-DQB1 typing

TYPING OF HLA CLASS II ALLELES:

DNA from venous blood samples was extracted with High Pure PCR Template (Cat. No.1 796 828) kit. Typing of HLA-DRB1 and HLA- DQB1from DNA samples were performed by SSOP (Sequence Specific Oligonucleotide Probes) in all groups. Lifecodes HLA-DRB (Ref: 628710-50) and HLA-DQB (Ref: 628610) typing kits were used for polymerase chain reaction and hybridization procedures.

Statistical Analyses

HLA analysis tolls in Los Alamos National Laboratory (http://www.hiv.lanl.gov/content/immunology/hla/) were used for statistical analyses. Fisher's exact probability test in the minitab 15 program was used to make comparisons between the groups. P less than 0.05 was considered significant.

RESULTS

GENERAL CHARACTERISTICS

Out of 48 chronic HBV patients, 27 were males and 21 were females; out of 46 inactive HBV carriers, 31

were male and 15 were females; and out of 100 healthy control subjects, 53 were males and 47 were females. Using Lifecodes HLA-SSO typing procedure, we performed HLA-DRB1 and HLA-DQB1 typing.

The mean ages of the chronic HBV patients, inactive HBV carriers and healthy control subjects were 37.9 ± 12.2, 43.1 ± 11.2 and 38.4 ± 13.2 years, respectively.

RESULTS OF HLA-DRB1 ALLELE ANALYSES

Based on Lifecodes HLA-SSO typing, there were 13 different alleles in the chronic HBV patients, 12 different alleles in the inactive HBV carriers and 14 different alleles in the healthy control subjects.

Individuals possessing DRB1*14 alleles have been shown to develop chronic hepatitis B and being inactive carriers more frequently than the healty controls (p= 0.0 OR=9, 95% CI= 3.229-25.084 and p= 0.007 OR= 4.756, 95% CI= 1.576-14.346 respectively). However, the frequency of DRB1*07 was significantly higher in the control group (p= 0.006 OR= 0.171, 95%CI=0.039-0.741) (Table 1). There was no significant difference in the frequency of HLA-DRB1 allele between the patient groups (Table 2).

RESULTS OF HLA-DQB1 ALLELE ANALYSES

There were six different alleles in the chronic HBV patients and the inactive HBV carriers, and five different alleles in the control group. The frequency of developing chronic hepatitis B was more than the healty controls in individuals having DQB1*01 allele (p= 0.000). However, the frequency of DQB1*06 allele was significantly higher in the control group (p= 0.036 OR=0.428, 95% CI=0.190-0.963). The frequency of being inactive carriers was higher than the healty controls in patients who had had DQB1*01 and DQB1*05 alleles (p= 0.002 and p= 0.009 OR=2.042, 95% CI=1.186-3.516 respectively), but the frequency of DQB1*06 allele was significantly higher in the control group (p= 0.005 OR=0.270, 95%CI=0.102-0.716) (Table 1). When the patients with chronic hepatitis and the carriers were compared, 14.58% of the chronic HBV patients (14/96) and 5.55% of the inactive HBV carriers (5/90) had HLA-DQB1*01 allele (Table 2). As a result, there was a significant relation only between HLA-DQB1*01 allele and chronic hepatitis (p= 0.042 OR= 2.9707, 95% CI= 1.024-8.615).

TABLE 1: The comparison of HLA DQB1 and DRB1 allele frequencies between patients (chronic hepatitis and inactive carriers) and healty control groups.

HLA	Control group	Chronic hepatitis	p-value	Inactive carriers	p-value
DQB1*01	0.0000	0.1458	0.0†	0.0556	0.00266†
DQB1*02	0.2000	0.1250	0.142	0.1444	0.325
DQB1*03	0.3700	0.3021	0.297	0.3111	0.355
DQB1*04	0.0400	0.0208	0.508	0.0667	0.377
DQB1*05	0.2150	0.3229	0.0617	0.3667	0.00913†
DQB1*06	0.1750	0.0833	0.0361†	0.0556	0.00552†
DRB1*01	0.0400	0.0729	0.261	0.0978	0.0612
DRB1*03	0.1000	0.0833	0.832	0.1304	0.428
DRB1*04	0.1100	0.0521	0.132	0.1304	0.695
DRB1*07	0.1150	0.0521	0.0929	0.0217	0.00644†
DRB1*08	0.0400	0.0208	0.508	0.0435	1
DRB1*09	0.0050	0.0000	1	0.0109	0.532
DRB1*10	0.0550	0.0833	0.447	0.0543	1
DRB1*11	0.2200	0.2083	0.881	0.2283	0.88
DRB1*12	0.0100	0.0104	1	0.0217	0.593
DRB1*13	0.0650	0.0521	0.798	0.0109	0.072
DRB1*14	0.0250	0.1875	0.0†	0.1087	0.00727
DRB1*15	0.1150	0.1354	0.704	0.0978	0.84
DRB1*16	0.0950	0.0417	0.162	0.0435	0.163

† Statistically significant.

TABLE 2: The analysis results of HLA-DRB1 and HLA-DQB1 in chronic hepatitis B patients and inactive carriers.

	Allele counts of chronic hepatitis B (n= 96)	Allele counts of inactive carriers (n= 92)	p-value
DRB1*01	8 (7.29%)	9 (9.78%)	0.729
DRB1*03	8 (8.33%)	12 (13.04%)	0.295
DRB1*04	5 (5.20%)	12 (13.04%)	0.061
DRB1*07	5 (5.20%)	2 (2.17%)	0.445
DRB1*08	2 (2.08%)	4 (4.35%)	0.437
DRB1*09	0	1 (1.09%)	0.489
DRB1*10	8 (8.33%)	5 (5.43%)	0.568
DRB1*11	20(20.83%)	21 (22.83%)	0.86
DRB1*12	1 (1.04%)	2 (2.17%)	0.615
DRB1*13	5 (5.21%)	1 (1.09%)	0.212
DRB1*14	18 (18.75%)	10 (10.87%)	0.129
DRB1*15	13 (13.54%)	9 (9.78%)	0.449
DRB1*16	4 (4.17%)	4 (4.35%)	1.000
	Chronic hepatitis B (n= 96)	Inactive carriers (n= 90)#	p value
DQB1*01	14 (14.58%)	5 (5.56%)	0.042†
DQB1*02	12 (12.5%)	13 (14.44%)	0.698
DQB1*03	29 (30.21%)	28 (31.11%)	0.894
DQB1*04	2 (2.08%)	6 (6.67%)	0.159
DQB1*05	31 (32.29%)	33 (36.67%)	0.530
DQB1*06	8 (8.33%)	5 (5.56%)	0.570

One person couldn't genotyping for DQB1 allels.

† Statistically significant.

RESULTS OF HLA-DRB1 GENOTYPE ANALYSES IN PATIENT GROUPS

Based on HLA-DRB1 genotyping, there were 13 different alleles in the chronic HBV patients and 12 different alleles in the inactive HBV carriers. All possible combinations were evaluated for the two groups and statistical analyses were made based on the number of individuals in each group.

Five of 48 (10.41%) of the chronic HBV patients (5/48) had HLA-DRB1*14-*15 genotype, but none of the inactive HBV carriers (0/46) had this genotype (Table 3). There was a significant relation between HLA-DRB1*14-*15 genotype and chronic HBV infection (p= 0.024).

RESULTS OF HLA-DQB1 GENOTYPE ANALYSES IN PATIENT GROUPS

Six different alleles were detected in the chronic HBV patients and the inactive HBV carriers. All possible combinations were evaluated in both groups.

Fourteen point fifty-eight percent of the chronic HBV patients had HLA-DQB1*01-*01 genotype, but none of the inactive HBV carriers had this genotype (Table 4). The relation between HLA-DQB1*01-*01 genotype and chronic hepatitis was significant (p= 0.007).

DISCUSSION

We performed MHC class-2 typing in chronic hepatitis patients, inactive HBV carriers and healthy individuals. The frequency of developing chronic hepatitis B was more than the healty controls in individuals having DQB1*01 and HLA- DRB1*14 alleles. In addition, HLA-DQB1*01 allele was more frequent in the chronic HBV patients than inactive carriers. Genotype analyses revealed that the individuals with HLA-DRB1*14-*15 and HLA-DQB1*01-*01 genotypes were more likely to develop chronic HBV infection.

Hepatitis B virus is a well known agent of acute and chronic hepatitis. The disease has a high mortality and morbidity since it causes liver cirrhosis and hepatocellular cancer. Hepatitis presents with a wide variety of clinical spectrums and the factors frequently implicated in the severity and

TABLE 3: The HLA-DRB1 gynotype analysis results of chronic hepatitis B patients and inactive carriers.

Gynotype	Chronic hepatitis B n: 48	Inactive carriers n: 46	p -value
DRB1*01-*01	1/48 (2.08%)	0/46 (0%)	0.325
DRB1*01-*04	0/48 (0%)	1/46 (2.17%)	0.304
DRB1*01-*08	0/48 (0%)	2/46 (4.34%)	0.144
DRB1*01-*10	1/48 (2.08%)	1/46 (2.17%)	0.976
DRB1*01-*11	1/48 (2.08%)	1/46 (2.17%)	0.976
DRB1*01-*12	0/48 (0%)	1/46 (2.17%)	0.304
DRB1*01-*14	2/48 (4.16%)	3/46 (6.52%)	0.611
DRB1*01-*15	1/48 (2.08%)	1/46 (2.17%)	0.976
DRB1*01-*16	0/48 (0%)	1/46 (2.17%)	0.304
DRB1*03-*03	1/48 (2.08%)	2/46 (4.34%)	0.532
DRB1*03-*04	0/48 (0%)	2/46 (4.34%)	0.144
DRB1*03-*07	1/48 (2.08%)	1/46 (2.17%)	0.976
DRB1*03-*10	1/48 (2.08%)	0/46 (0%)	0.325
DRB1*03-*11	1/48 (2.08%)	2/46 (4.34%)	0.532
DRB1*03-*13	1/48 (2.08%)	0/46 (0%)	0.325
DRB1*03-*14	1/48 (2.08%)	1/46 (2.17%)	0.976
DRB1*03-*15	1/48 (2.08%)	2/46 (4.34%)	0.532
DRB1*03-*16	0/48 (0%)	1/46 (2.17%)	0.304
DRB1*04-*04	0/48 (0%)	1/46 (2.17%)	0.304
DRB1*04-*08	0/48 (0%)	2/46 (4.34%)	0.144
DRB1*04-*10	1/48 (2.08%)	0/46 (0%)	0.325
DRB1*04-*11	2/48 (4.16%)	1/46 (2.17%)	0.583
DRB1*04-*14	1/48 (2.08%)	1/46 (2.17%)	0.976
DRB1*04-*15	1/48 (2.08%)	2/46 (4.34%)	0.532
DRB1*04-*16	0/48 (0%)	1/46 (2.17%)	0.304
DRB1*07-*11	3/48 (6.25%)	0/46 (0%)	0.085
DRB1*07-*14	0/48 (0%)	1/46 (2.17%)	0.304
DRB1*07-*15	1/48 (2.08%)	0/46 (0%)	0.325
DRB1*08-*10	1/48 (2.08%)	0/46 (0%)	0.325
DRB1*08-*11	1/48 (2.08%)	0/46 (0%)	0.325
DRB1*09-*10	0/48 (0%)	1/46 (2.17%)	0.304
DRB1*10-*10	1/48 (2.08%)	0/46 (0%)	0.325
DRB1*10-*11	2/48 (4.16%)	1/46 (2.17%)	0.583
DRB1*10-*14	0/48 (0%)	2/46 (4.34%)	0.144
DRB1*11-*11	3/48 (6.25%)	4/46 (8.69%)	0.652
DRB1*11-*12	0/48 (0%)	1/46 (2.17%)	0.304
DRB1*11-*13	0/48 (0%)	1/46 (2.17%)	0.304
DRB1*11-*14	0/48 (0%)	2/46 (4.34%)	0.144
DRB1*11-*15	1/48 (2.08%)	3/46 (6.52%)	0.287
DRB1*11-*16	3/48 (6.25%)	1/46 (2.17%)	0.328
DRB1*12-*14	1/48 (2.08%)	0/46 (0%)	0.325
DRB1*13-*13	1/48 (2.08%)	0/46 (0%)	0.325
DRB1*13-*14	1/48 (2.08%)	0/46 (0%)	0.325
DRB1*13-*15	1/48 (2.08%)	0/46 (0%)	0.325
DRB1*14-*14	3/48 (6.25%)	0/46 (0%)	0.085
DRB1*14-*15	5/48 (10.41%)	0/46 (0%)	0.024†
DRB1*14-*16	1/48 (2.08%)	0/46 (0%)	0.325
DRB1*15-*15	1/48 (2.08%)	1/46 (2.17%)	0.976
DRB1*15-*16	0/48 (0%)	1/46 (2.17%)	0.304

† Statistically significant.

TABLE 4: The HLA-DQB1 gynotype analysis results of chronic hepatitis B and inactive carriers.

Gynotype	Chronic hepatitis B n= 48	Inactive carriers n=46	p-value
DQB1*01-*01	7/48 (14.58%)	0/46 (0%)	0.007†
DQB1*01-*03	0/48 (0%)	1/46 (2.17%)	0.304
DQB1*01-*04	0/48 (0%)	1/46 (2.17%)	0.304
DQB1*01-*05	0/48 (0%)	3/46 (6.52%)	0.072
DQB1*02-*02	1/48 (2.08%)	2/46 (4.34%)	0.532
DQB1*02-*03	5/48 (10.41%)	5/46 (10.86%)	0.943
DQB1*02-*05	3/48 (6.25%)	3/46 (6.52%)	0.957
DQB1*02-*06	2/48 (4.16%)	1/46 (2.17%)	0.583
DQB1*03-*03	6/48 (12.5%)	5/46 (10.86%)	0.806
DQB1*03-*04	0/48 (0%)	1/46 (2.17%)	0.340
DQB1*03-*05	9/48 (18.75%)	9/46 (19.56%)	0.920
DQB1*03-*06	3/48 (6.25%)	2/46 (4.34%)	0.681
DQB1*04-*04	0/48 (0%)	1/46 (2.17%)	0.304
DQB1*04-*05	2/48 (4.16%)	2/46 (4.34%)	0.965
DQB1*05-*05	7/48 (14.58%)	8/46 (17.39%)	0.710
DQB1*05-*06	3/48 (6.25%)	0/46 (0%)	0.085
DQB1*06-*06	0/48 (0%)	1/46 (2.17%)	0.304

† Statistically significant.

consequences of the disease are viral factors (viral load, genotype and mutations etc.), immunological factors and genetic factors of host. Although there have been extensive research on viral and immunological factors, the relation between persistent infection and host genetics and ethnic factors has not been understood well, and therefore is still the subject of many studies.[8,9]

To date, none of the studies have revealed a single allele associated with HBV persistence and the disease severity, though epidemiological studies on humans suggested the presence of strong genetic components likely to play a role human sensitivity to infectious pathogens. There are about 35 thousand genes in the human genome and most of the alleles have polymorphism. This may explain the wide variety of genetic differences between individuals and ethnic groups.[6] If a specific single nucleotide polymorphism is associated with a good prognosis of HBV infection and low risk of the disease progression, then that allele can be considered resistant to HBV infection. Conversely, if that polymorphism leads the disease to show a quick progression and a high risk of severe disease, that allele can be considered sensitive to HBV.[1] However, since genetic associations are complex, it does not seem to be reasonable to blame a single allele or a single genotype for HBV persistence and sensitivity to HBV.

A number of studies on HBV infection and the host genetics have focused on HLA molecules. Since HLA Class I and II genes are primary modulators of the host immune response, they present foreign antigens to both $CD4^+$ T and $CD8^+$ T cytolytic cells. Subsequently, humoral and cellular responses appear.[10]

Removal of the virus depends on a specific immune response. While there is a strong CD^+4 and CD^+8 T cellular response in acute infection, there is a considerable decrease in CD^+4 and CD^+8 T cellular responses in chronic infections in which the virus is not easily eliminated.[11,12]

Thio et al. showed a significant relation between DQB1-0301 and DQB1 1102 haplotypes and HBV persistence in African Americans in 1999.[13] They also clearly demonstrated a relation between HLADQB1-0201 and HBV persistence in Asians in 2003.[14] Jiang et al. in their study on Chinese Han population in 2003 found that HLA-DRB1*0301 and HLA-DQB1*0301 alleles were significantly more frequent in chronic hepatitis patients than in the control group.[15] Shen et al. showed that DRB1 *10 allele was more frequent in the chronic hepatitis patients than controls in

North China, and reported that DRB1 *10 allele was associated with susceptibility to chronic HBV infection.[16] Their finding suggested that the abovementioned alleles were closely related to, and probably responsible for, susceptibility to chronic HBV infection. Zhu et al. reported that HLA-DRB1 *0502 allele was an independent factor in susceptibility to chronic HBV infection.[17] As a result, studies on HLA gene polymorphisms in different populations have yielded different results. Based on DQB1 and DRB1 typing in this study, the frequency of developing chronic hepatitis B infection was significantly higher in the patients with DQB1*01 and DRB1*14 alleles than the healty controls, and possessing the genotypes of HLA- DRB1 *14-*15 and HLA- DQB1 *01-*01 were related to developing chronic infection rather than becoming inactive carries.

In some studies on the relation between HLA alleles and the prognosis of HBV infection, some HLA alleles were claimed to be associated with the clearance of the disease. In fact, Thursz et al. showed a relation between HLA-DRB1 *1302 allele and viral clearance, consistent with a similar study from Germany.[18] Jiang et al. revealed that HLA-DRB1 1101/1104 and HLA- DQA1 *0301 alleles were less frequent in the chronic HBV patients than in the acute HBV patients.[15]

Cotrina et al. analyzed HLA-DRB1 *1302 genotype in chronic and acute hepatitis patients and found that HLA- DRB1* 1301 and *1302 alleles were associated with clearance of HBV infection and protective against chronic HBV infections.[19] Likewise, Diepolder et al. reported a strong virus specific $CD4^+$ and $CD8^+$ T lymphocyte response associated with clearance of the virus and showed that acute HBV patients with HLA- DR13 had a stronger $CD4^+$ T cell response against HBV core protein.[20] Their finding could explain how HBV infection was self-limited in the patients with HLA-DR13. Diepolder et al. observed that HLA-DRB1 1101/1104 alleles were significantly less frequent in the chronic HBV patients than the acute HBV patients. This suggested that HLA DRB1 1101/1104 alleles were associated with resistance to chronic HBV infection. Zavaglia et al., however, did not determine any correlations between HBV clearance and HLA phenotypes.[21] Similar to the study of Zavaglia et al., our results did not show any significant relation between HLA-DQB1*01 and HLA-DRB1*14 allele frequencies and resistance to the disease or virus clearance.

Since the study sample included the hepatitis patients presenting to our hospital, the high rates of HLA-DQB1*01 and HLA-DRB1*14 alleles may indicate that the disease was becoming chronic in the region. To our knowledge, this is the first study to show a relation between these alleles and chronic HBV infection. Higher frequencies of DQB1*06 and DRB1*07 alleles in the healthy controls were considered a random distribution of the alleles in the normal population.

In conclusion, host response to HBV has an impact on the prognosis of the disease and in this context, HLA is a genetic factor which determines individual differences in immune response. Since the HLA gene plays a role in the host response to HBV, individuals with different HLA types can be expected to differ in resistance and susceptibility to the disease. The results of this study showed that changes in the genes ruling the immune response to HBV infection might explain the variety of clinical pictures caused by HBV infection.

Further studies with larger sample sizes are required to obtain more significant results. Since the relation between various alleles and the disease varies in different populations (in terms of race, ethnic origin and geographical factors), the results obtained will mainly reflect the populations studied. Further analyses of the association of HBV infection with HLA genetic polymorphism may help to prevent and determine treatment strategies for chronic HBV infection.

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