PRINT: ISSN 0972-3757 ONLINE: 2456-6360
Int J Hum Genet, 8(4): 331-334 (2008)
DOI: 10.31901/24566330.2008/08.04.03

HLA DRB Alleles in Chronic Hepatitis B Infected Patients

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KEYWORDS Chronic hepatitis B infection; HLA associations; Western India

ABSTRACT Chronic hepatitis B virus (HBV) infection is one of the most common infectious diseases and leads to high morbidity and mortality due to the development of liver cirrhosis and hepatocellular carcinomas. We have analyzed the HLA DRB1 allele associations among 26 clinically definite western Indian chronic hepatitis B infected patients and compared them with 31 ethnically matched clinically normal individuals. HLA DRB1 alleles were defined molecularly using commercial low-resolution DRB1polymerase chain reaction sequence specific priming kit. The study revealed a significant increase of DRB1*15 (57.69% vs 24.19%; OR= 4.27; EF= 0.44; P value 0.0002) allele as well as a significant decrease of DRB1*13 (0% vs 11.29%; P value 0.012), DRB1*04 (0% vs 6.45%; P value 0.062) and DRB1*14 (5.76% vs 16.12%; OR= 0.318; PF= 0.10; P value 0.08) alleles when compared to the controls. This is the first report on HLA DRB1 allele associations from Western Indian HBV infected patients. Further our study indicates that there is a complexity of genetic susceptibility to HBV infection in different populations studied and reported.

INTRODUCTION

HBV infection is a major health challenge worldwide. Over 350 billion people in the world are carrier of HBV, of whom more than 250,000 die annually of HBV related liver disease- chronic hepatitis, cirrhosis and hepatocellular carcinoma (Lee 1997). Prevalence of HBV worldwide has reduced due to availability of effective vaccination, safe blood practice and AIDS campaign against sexual promiscuity and needle sharing (Grob 1995). In Southeast Asian countries HBV carriage rates are 10-20% with major route of transmission being vertical/percutaneous whereas age of infection being perinatal/early childhood (Lok and Conjeevaram 2003). In India HBV prevalence ranges in general population from 1.1 – 12.2% with estimated 40 million people infected (Thyagarajan et al. 2002). Infection with the same HBV virus has been found to cause various clinical outcomes in patients. In adults suffering from primary HBV infection, 90 - 95% of the individuals can successfully clarify the virus through self-limiting hepatitis and only 5 - 10% of adults become chronic HBV carriers (Hohler et al. 1997). There is a different incidence and infection rate among different global ethnic groups. HBV infection is significantly endemic in Asia and Africa, and there is a significantly higher incidence of chronic HBV infection in Chinese compared to Caucasians Hoffmann et al. 2002). HBV infected subjects generally fall into one of the following clinical types: asymptomatic HBV carriers; acute hepatitis; chronic hepatitis; liver cirrhosis with or without liver failure; and primary hepatocellular carcinoma associated with HBV infection (Iino 2002; Thio et al. 2000). Majority of host genetic studies in HBV infection worldwide have concentrated on HLA associations. Different HLA Class II alleles are reported to be important in persistence or clearance of HBV in various studies throughout the world and yet class I associations are to be ascertained (Abel and Dessein 1998). In the present study 26 chronic hepatitis B infected patients were studied for their HLA DRB1 allele associations.

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MATERIALS AND METHODS

Clinically definite 26 chronic HBV infected patients defined according to persistent HbsAg for more than 6 months, attending the gastroenterology department, Bombay hospital Institute of Medical sciences were studied from Jan 2002-Jul 2002. A detailed evaluation of patient history, identified clinical variables, disease severity, age at onset, initial clinical manifestations and

informed consent were recorded for every patient. Thirty-one ethnically age and sex matched normal individuals studied for their HLA in the tissue typing during the same period without the clinical disease symptoms, as well as negative for HbsAg, anti HBc, and anti HBs were compared as controls. The genomic DNA was extracted using commercially procured DNA extraction kit (Qiagen kit), HLA DRB1* low resolution typing was followed using the commercial DRB1 PCR kit protocol (Dynal Oslo). The allele frequencies, odds ratio, probability value, chi-square with Yates correction, etiological and preventive fraction were estimated using our database and computer programs as described earlier (Shankarkumar et al. 2002). Since each individual is tested for several HLA alleles and the same data used for comparing the frequency; it is possible that one of the alleles will by chance deviate significantly. To overcome this error, the P value is corrected by use of Bonferoni inequality method i.e. by multiplying it with the number of alleles compared.

RESULTS

Among the chronic HBV infected patients group, the mean age of 45 years (range of 21 - 55 years) and male: female ratio of 2.7:1. In the control group mean age was 41 years (range 18 - 62 years) and male: female sex ratio of 2:1. The HLA DRB1 typing revealed that DRB1*15 (57.69% vs 24.19%; OR= 4.27; P=0.0002) was increased among the HBV patients while DRB1*13 (0% vs 11.29%; P = 0.012), DRB1*14 (5.76% vs 16.12%; OR=0.32; P=0.08), and DRB1*04 (0% vs 6.4%; P=0.06) when compared to the controls (Table 1).

DISCUSSION

Most of the reports of human genes associated with HBV infection have currently focused on HLA associations. In world literature different HLA alleles are described for persistence as well as clearance of HBV (Almarri and Batchelor 1994). In our study HLA DRB1*15 was positively associated while DRB1*13, DRB1*14 and DRB1*04 were negatively associated with HBV persistence. In a large cohort of pediatric patients from Gambia HLA DRB1*1302 was associated with self-limiting course of acute hepatitis B (Thurz et al. 1995; Thruz 1997). The haplotype cluster DAQ1*0501-DQB1*0301-DQB1*1102 had a significant association with viral persistence (Thio et al. 1999). However no correlation could be observed between the clearance of HBV or HCV virus and HLA phenotypes in chronic type B, D and C hepatitis (Zavaglia et al. 1996). Further it has been reported that DR13 allele is less frequent in patients with chronic hepatitis B than in healthy controls or subjects with a self-limiting hepatitis B (Diepolder et al. 1998). Negative associations of DRB1*13 have been demonstrated in the past. Among the Gambian children and adults DRB1*1302-DRB3*0301-DQA1*0102-DQB1*0501 appeared to be protective (Thruz et al. 1995). In another study from Germany DRB1*1301-2 was associated with HBV clearance (Hohler et al. 1997), DRB1*13 has a

Table: 1 HLA DRB1 allele distribution in chronic Hepatitis B infected patients, Maharashtra, India

HLA	*Patients N =26*		*Controls N=31*						
	N+	*AF(%)*	*N+*	*AF(%)*	*OR*	*EF*	*PF*	*Ki2*	*P value*
DRB1*01	2	3.84	0	0.00		0.02		2.43	
DRB1*03	5	9.61	10	16.12	0.55		0.07	1.05	
DRB1*04	0	0.00	4	6.45					0.062
DRB1*07	5	9.61	4	6.45	1.54	0.03		0.39	
DRB1*08	0	0.00	2	3.22					
DRB1*09	0	0.00	1	1.61					
DRB1*10	0	0.00	2	3.22					
DRB1*11	6	11.53	5	8.06	1.49	0.04		0.39	
DRB1*12	1	1.92	2	3.22	0.59		0.01	0.19	
DRB1*13	0	0.00	7	11.29					0.012**
DRB1*14	3	5.76	10	16.12	0.32		0.10	2.73	0.083
DRB1*15	30	57.69	15	24.19	4.27	0.44		13.28	0.0002**

N+ = Number positive Ki2 = Chi-square with Yates correction
AF(%)= Allele Frequency percentage OR = Odds ratio
EF= etiological fraction or attributable risk** Significant P value
PF= Preventive fraction

protective role in preventing vertical transmission of HIV, in preventing cervical cancer in HPV infection and also in resistance to severe complicated falciparum malaria (Hohler et al. 1997). This protective effect of DRB1*13 appears to be sustained in all ethnic groups including our study. Further DRB1*13 may be more efficient in presenting immunodominant eptiopes from HBs antigen to CD4+ T cells. HLA DR1 and DR13 were associated with virus elimination among Japanese (Shimbo et al. 1990). Consistent HLA DR2 and its subtype DRB1*1501 associations in infectious diseases like leprosy and tuberculosis have been reported earlier in Indian populations (Hill 1998). Novel alleles DRB1*1506 and DRB1*1508 along with DRB1*1501 has been reported to be associated in multiple sclerosis patients from Western India (Kankonkar et al. 2003). This is the first report on the DRB1*15 allele associations in chronic HBV infected patients from western India. The beneficial effect of HLA DR13 allele on the outcome of HBV infection may either be the result of more proficient antigen presentation by the DR13 molecules themselves or of a linked polymorphism in a neighboring immunoregulatory gene. Further, studies on vitamin D receptor gene polymorphism in Gambian HBV infected patients revealed that **tt** genotype was associated with viral clearance (Bellamy and Hill 1998). Associations between HLA Class I allele and viral persistence or disease progression in HBV infected patients is yet to be identified though class I molecule mediates the cytotoxic T lymphocyte (CTL) response through the cytolytic and noncytolytic mechanisms (Thio et al. 2000).

CONCLUSIONS

Thus far, worldover studies have shown inconsistent associations with regard to the effects of host genetic factors on HBV clearance and persistence. This ambiguity could be due to a complex interaction between the virus and host multiple alleles; and/or the ethnic differences in the studied population groups; and/or association with a gene in linkage disequilibrium with an HLA allele. Further, since genetic interactions are complex it is unlikely that a single allelic variant is responsible for HBV resistance or susceptibility. Future studies have to investigate whether one of these HLA allele polymorphisms or a yet unidentified immunoregulatory gene is possibly associated with a more successful immune response against HBV.

REFERENCES

Abel L, Dessein AJ 1998. Genetic epidemiology of infectious diseases in human: design of population-based studies. *Emerg Infect Dis*, **4**: 593-603.

Almarri A, Batchelor JR 1994. HLA and hepatitis B infection *Lancet*, **344**: 1194 -1195.

Bellamy R, Hill AV 1998. Genetic susceptibility to mycobacteria and other infectious pathogens in humans. *Curr Opin Immunol*, **10**: 483-487.

Diepolder HM, Jung MC, Keller E, Schraut W, Gerlach JT, Gruner N, Zachoral R, Hoffmann RM, Schirren CA, Scholz S, Pape GR 1998. A vigorous virus-specific CD4+ T cell response may contribute to the association of HLA DR13 with viral clearance in hepatitis B. *Clin Exp Immunol*, **113**: 244-251.

Grob P 1995. Introduction to epidemiology and risk of hepatitis B. *Vaccine*, **13**: 514.

Hill AVS 1998. The immunogenetics of human infectious diseases. *Ann Rev Immunol*, **16**: 593-617.

Hohler T, Gerken G, Notghi A, Lubjuhn R, Taheri H, Protzer U, Lohr HF, Schneider PM, Meyer Zum, Buschenfelde KH, Rittner C 1997. HLA DRB1*1301 and *1302 protect against chronic hepatitis B. *J Hepatol*, **26**: 503-507.

Hoffmann SC, Stanley EM, Cox ED, DiMercurio BS, Koziol DE, Harlan DM, Kirk AD, Blair PJ 2002. Ethnicity greatly influences cytokine gene polymorphism distribution. *Am J Transplant*, **2**: 560-567.

Iino S 2002. Natural history of Hepatitis B and C virus infections. *Oncology*, **62 (s1)**: 18-23.

Kankonkar S, Jeyanthi G, Singhal BS, Shankarkumar U 2003. Evidence of novel DRB1*15 allele associations among clinically definite multiple sclerosis patients from Mumbai, India. *Hum Immunol*, **64**: 478-482.

Lee WM 1997. Hepatitis B virus infection. *N Engl J Med*, **11**: 1733-1745.

Lok AS, Conjeevaram HS 2003. *Hepatitis B Schiff's diseases of the liver.* Schiff ER, Sorrell MF, Maddrey WC (Eds.); 9th Ed:, Lippincott: Williams & Wilkins Publisher, pp. 763-806.

Shankarkumar U, Devaraj JP, Ghosh K, Mohanty D 2002. Seronegative spondarthropathies and human leukocyte antigen associations. *Br J Biomed Sci*, **59**: 38-41.

Shimbo M, Ohtsuka S, Sakaya S, Sakamoto S, Ikeda H, Sekiguchi S 1990. Immunogenetic factors influencing HBV carrier state, the seroconversion and the development of chronic liver disease. *Hokkaido Igaku Zasshi*, **65**: 67-73.

Thio CL, Carrington M, Marti D, O'Brien SJ, Vlahov D, Nelson KE, Astemborski J, Thomas DL 1999. Class II of HLA alleles and hepatitis B virus persistence in African Americans. *J Infect Dis*, **179**: 1004-1006.

Thio CL, Thomas DL, Carrington M 2000. Chronic viral hepatitis and the human genome. *Hepatology*, **31**: 819-827.

Thurz MR, Kwiatkowski D, Allsopp CE, Greenwood

BM, Thomas HC, Hill AV 1995. Association between an MHC class II allele and clearance of hepatitis B virus in the Gambia. *N Engl J Med,* **332**: 1065-1069.

Thurz MR 1997. Host genetic factors influencing the outcome of hepatitis. *J Viral Hepatol,* **4**: 215-220.

Thyagarajan SP, Jayaram S, Hari R, Mohan KVK, Murugavel KG 2002. Epidemiology of hepatitis B in India- A comprehensive analysis. In: SK Sarin, K Okuda (Eds.): *Hepatitis B and C – carrier to Cancer.* 1st Ed. Harcourt India Pvt. Ltd. Publishers pp. 25-39.

Zavaglia C, Bortolon C, Ferrioli G, Rho A, Mondazzi L, Bottelli R, Ghessi A, Gelosa F, Iamoni G, Ideo G 1996. HLA typing in chronic type B, D and C hepatitis. *J Hepatol,* **24**: 658-665.