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REVIEW

A comparative review of HLA associations with hepatitis B and C viral infections across global populations

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Abstract

Hepatitis B (HBV) and hepatitis C (HCV) viral infection or co-infection leads to risk of development of chronic infection, cirrhosis and hepatocellular carcinoma (HCC). Immigration and globalization have added to the challenges of public health concerns regarding chronic HBV and HCV infections worldwide. The aim of this study is to review existing global literature across ethnic populations on HBV and HCV related human leukocyte antigen (HLA) associations in relation to susceptibility, viral persistence and treatment. Extensive literature search was conducted to explore the HLA associations in HBV and HCV infections reported across global populations over the past decade to understand the knowledge status, weaknesses and strengths of this information in different ethnic populations. HLA DR13 is consistently associated with HBV clearance globally. HLADRB1*11/*12 alleles and DQB1*0301 are associated with HBV persistence but with HCV clearance worldwide. Consistent association of DRB1*03 and *07 is observed with HCV susceptibility and non-responsiveness to HBV vaccination across the population. HLA DR13 is protective for vertical HBV and HCV transmission in Chinese and Italian neonates, but different alleles are associated with their susceptibility in these populations. HLA class I molecule interactions with Killer cell immunoglobulin like receptors (KIR) of natural killer (NK) cells modulate HCV infection outcome *via* regulating immune regulatory cells and molecules. HLA associations with HBV vaccination, interferon therapy in HBV and HCV, and with extra hepatic manifestations of viral hepatitis are also discussed. Systematic studies in compliance with global regulatory standards are required to identify the HLA specific viral epitope, stage specific T cell populations interacting with different HLA alleles during disease progression and viral clearance of chronic HBV or HCV infections among different ethnic populations. These studies would facilitate stage specific therapeutic strategies for clearance of HBV and HCV infections or co-infections across global populations and aid in identification of HBV-HCV combined vaccine. HLA associations of chronic HBV or HCV development with confounding host factors including alcohol, drug abuse, insulin resistance, age and gender are lacking and warrant detailed investigation across global populations.

Key words: Human leukocyte antigen; HBV persistence; HCV persistence; Interferon response to HBV and HCV; HBV vaccination response

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INTRODUCTION

Hepatitis B (HBV) together with hepatitis C (HCV) accounts for 75% of liver diseases and are regarded a major threat to public health worldwide. Hepatitis B and C co-infections have raised major concern in HIV, transplant and other immunosuppressed patients. Intravenous drug abuse is currently the main risk but nosocomial infection is also of concern for HBV and HCV infection. Three independent factors seem to be associated with fibrosis: age, daily alcohol consumption and male gender. Over two billion people are expected to be infected with HBV during their lifetime and about 350 million are estimated to be chronic carriers[1]. Chronic carriers develop life-threatening liver cirrhosis or HCC. Hepatitis C infected patients have greater chances to develop chronic hepatitis and liver cancer. About 54% to 86% of infected individuals develop chronic manifestation, and females and children tend to have lower rate of chronicity. It is estimated that about 200 million people around the world are HCV infected. 4.1 million (1.6%) Americans have been infected with HCV, of whom 80% are chronically infected[2].

The mechanism of HBV and HCV pathogenesis remains elusive. Host genetic factors are proposed to be governing the pathology of disease progression or

regression along with the viral and environmental factors. Interplay of HLA restricted T lymphocytes, antibody-secreting B-lymphocytes, NK cells and cytokines, conditions the immune response to viral infections. Effective presentation of viral antigens to CD4+ T cells and CD8+ T cells by HLA class Ⅱ and class Ⅰ molecules respectively, is the key regulation of optimum immune response against viral infection, and further dictates viral clearance or persistence. Inconsistency is observed in response to HBV vaccination and interferon treatment following HBV and HCV infection. Varied response to vaccination is implicated to specific combinations of polymorphic HLA class Ⅱ alleles that influence the capacity of HLA class Ⅱ molecules to bind and present antigen to CD4+ cells that augment antibody production and cytotoxic T lymphocytes activation. Numerous clinical and laboratory investigations have identified several immunogenetic factors involved in conditioning viral hepatitis. Gene polymorphisms and heterozygosity at HLA loci enable HLA molecules to present a wide array of antigens and diversify the properties of HLA molecules with respect to antigen binding and presentation[3].

HLA associations with respect to HBV and HCV infection susceptibility, protection, disease severity, interferon treatment response and response to vaccination have been intensively investigated across the global populations. We have attempted to review the published literature on HLA associations with HBV and HCV infections with the purpose of identifying common HLA allele association with hepatitis B and C. Convergence of this information would provide but not be limited to (a) insight into the immunopathogenesis of HBV-HCV co-infections and superinfections, (b) identification of genetic markers to predict the course of infection/treatment response and (c) enable designing of combined vaccine strategies for viral hepatitis B and C.

HLA ALLELE ASSOCIATIONS WITH HEPATITIS B INFECTION IN GLOBAL POPULATIONS

Viral persistence and viral clearance

Viral clearance (acute infection) or persistence (chronic infection) is conditioned by immune response mechanisms regulated by HLA molecules. HLA associations with susceptibility and protection from persistent HBV infection, though robust, are inconsistent even within the same population. HLA allele associations with HBV clearance and persistence in global population are outlined in Tables 1 and 2.

HLA Class Ⅰ allele associations: susceptibility to HBV infection and chronicity is attributed to HLA A*0206 allele in Taiwanese, B35 in Chinese[4], B18, B35, B40, Cw3 allele in Russian, A3 and B18 in Kazakhs[5] B8-Cw-7 haplotype in Senegalese[6], and HLA A*01-B*08-DRB1*03, B-44-Cw1601 and B*44-Cw*0501 haplotype in American Caucasians[7] (Table 1). Also, HLAB8 in European Caucasians is associated with non-response to HBV vaccination (Table 3) indicating inefficient immune response against HBV antigen in HLA B8 carriers[7].

HLA B61 in Taiwanese[4], A*26 in Japanese[8] and A*0301 in American Caucasians[7] are protective (Table 2). HLA A2 and A11 are protective alleles for HBV chronicity in Russians and Kazakhs respectively[5]. HLA A-24 and Cw1 are related to lower risk for chronic manifestations of HBV infection in Turkey[9].

HLA Class Ⅱ allele associations: HLA class Ⅱ alleles HLA DRB1*13 and HLA DRB1*11/*12 are consistently associated with viral clearance and viral persistence of HBV infection respectively in major populations (Table 2). In contrast HLA DRB1*11/*12 alleles are associated with HBV clearance in Chinese[10,11] and HLA DRB1*13 is reported as a susceptibility gene for chronic HBV infection in Turkish populations[9]. HLA DR7 and DRB1*15 are also protective for HBV infection in Chinese but associated with chronic infection in Turkish and Indian populations respectively[9,12-14]. HLA DR15 is also reported to be associated with responsiveness to HBsAg vaccine in European Caucasian populations (Table 4). These variations observed in HLA allele associations are confounding and suggest influence of other genes on the effect of these alleles on disease outcome.

HLA DR13 is associated with protection from vertical transmission of HBV and HCV in Chinese and Italian infants[15-17] and with HBV clearance across the population (Table 2). The protectiveness of HLA DR13 is proposed to be either due to proficient antigen presentation by DR13 molecules or linked polymorphisms in neighboring immune regulatory gene.

Hepatitis B viral persistence and disease chronicity is associated with HLA DQA1*0501 and HLA DQB1*0301 in Chinese and African Americans[10,18] and with HLA DR9 in Chinese and Koreans[11,19]. In Chinese populations HLA DR3 is associated with HCV persistence and vertical transmission[10,15]. Pellegris *et al*[20]studied HBV and HCV related HCC in Italian subjects, 73 with liver cirrhosis and 32 without liver cirrhosis. They have suggested the possibility of HLA DQ1 allele association with susceptibility to liver cell destruction and HLA DR3 with absence of cell destruction in HCC subjects showing liver cirrhosis and no cirrhosis respectively.

HLA Class Ⅲ allele associations: Polymorphisms in cytokine genes influence outcome of HBV infection. In Chinese populations tumor necrosis factor-alpha (TNF)alpha-857GG is associated with self-limiting infection while TNF-alpha-857 CC and -238G/A polymorphism[21,22] with chronic HBV infection. Polymorphism at position -238 G/A in TNF alpha is associated with chronic HBV infection and defective viral clearance[23] in German Caucasians. The carriers of the -592A allele in IL-10 promoter and -308G/-238G haplotype homozygotes in the TNF-alpha promoter region have higher risk of persistent HBV infection in Koreans[24]. In Italian patients the genotype -308G/G and haplotype TCGG (-T1031, -C863, -G308, -G238) are associated with an unfavorable prognosis in those with chronic HBV infection[25]. TNF-alpha promoter polymorphism -308A is common in Iranian population but is not associated with hepatitis B disease chronicity[26]. IL18 polymorphism at position -137G is associated with chronic HBV infection while -137C is protective in Chinese. Polymorphism at

Table 1 Association of HLA alleles with Chronic HBV infection across global population

HLA	Effect	Country and cases	Healthy controls	Recovered	Chronic infection	Reference
HLA Ⅰ						
HLA A*0206	VP	Taiwan (Taiwanese Aborigines)	34	229	138	[4]
HLA B-35	VP	Taiwan (Han Chinese)	98	324	98	[4]
HLA A*2	VP/Disease severity	Japan				[8]
HLA B18, B35, B40, Cw3	Susceptibility to chronic HBV infection	Russia				[5]
HLA A3, B18	Susceptibility to chronic HBV infection	Kazakh				[5]
HLA: B8-Cw7 haplotype	Liver cancer associated with HBV infection	Senegal	96		98	[6]
HLA B*8	VP	USA (Caucasians)		342	194	[7]
HLA A*01-B*08-DRB1*03, B*44-Cw*1601 and B*44-Cw*0501 haplotype	VP	USA (Caucasians)		342	194	[7]
HLA Ⅱ						
HLA DRB1*1202#	VP	Taiwan (Han Chinese)	98	324	98	[4]
HLA DQA1*0302	VP	China		148 (R), 212 (AC)	207	[113]
HLA DRB1*0301, DQA1*0501, DQB1*0301	VP	China	106	30	54	[10]
HLA DR9, DQ9	VP	China		56	30	[11]
HLA-DRB1*06, DRB1*08, and DRB1*16	VP	China	200		72	[14]
HLA DR9	VP	Korea (ESRD patients)	946	243	83	[19]
HLA DRB1*11# and DRB1*15	VP	India	100		26	[12]
HLA DQA1 *0501, DQB1 *0301	VP	USA (African American)		60	31	[18]
HLA DR3	Susceptibility to HBV infection & vertical transmission	China (Pregnant women)	40		78	[15]
HLA-DRB1*1201/1202#	Susceptibility to liver cirrhosis	China (Cirrhosis subjects from Hubei area)	108		116	[13]
HLA B13, B8, DR7, DR13, DQ3	Susceptibility to chronic HBV infection	Turkey	50		50	[9]
HLA DQA1 0501, DQB1 0301, DRB1 1102# haplotype	VP	USA (African American)		60	31	[18]

VP: viral persistence/chronic infection; AC: Asymptomatic carriers; Common VP alleles: DQB1*0301, #: DRB1*11/12; ESRD: End stage renal disease; R: Recovered; HBV Hepatitis B virus.

position -137C may be associated with higher production of IL18 that augments IFN-gamma production and thus better immune response against HBV infection[27]. Genetic ability to produce low levels of IFN-gamma is related to susceptibility for chronic HBV infection[28]. Polymorphism of IL10 promoter at position -819T/C and -592A/C is related to chronic infection[29]. Decreased IL10 production owing to -819T and -592A allele contributes to the asymptomatic carrier state and thus is relevant for disease progression in Japanese[30]. Frodsham *et al*[31]have identified an HLA class Ⅱ cytokine receptor gene cluster as a major susceptibility locus for HBV infection *via* genome analysis in Gambian populations. Polymorphism at the type Ⅰ IFN receptor gene, IFN-AR2, and the IL-10RB gene is associated with viral clearance. TNF-alpha polymorphism at position -244G/A is not present in American Caucasian and Egyptian hepatitis B patients but is present in Egyptian healthy individuals suggesting its protective role[32].

Response to HBV vaccination

Variegated antibody response following standard HBV vaccination in otherwise healthy individuals is observed, with 5%-10% showing no response. It is suggested that non-responsiveness may also be associated with antigen-specific HLA determined deficiency in the T cell repertoire and not only with defective antigen presentation or HLA class Ⅱ affinity for hepatitis surface antigen (HbsAg) derived peptide[33]. Clinical evidence suggests strong association of HLA genes with response to HBV vaccination in the global population, which is outlined in Tables 3,4 and 5. Martinetti *et al*[34] explored HBV vaccination response in neonates to identify the genetic predisposing factors influencing the response.

HLA class Ⅰ allele associations: HLA class Ⅰ and class Ⅱ molecules are synergistically involved in the immune response to recombinant HbsAg, with a stronger association of HLA DRB1 locus[35]. HLA class Ⅰ loci (A, B and C) association with vaccine responsiveness is not clear and is considered mainly due to its strong linkage disequilibrium with HLA DR locus. Non-responsiveness to HbsAg vaccination is reported to be associated with HLA A1, B15, and B40 in Indians of Asian origin, HLA A1, A2, B8, and B7 in Caucasians and HLA B54 in Chinese. Responsiveness is associated with HLA A11 in Indians of Asian origin and A10, A1 and B7 in Caucasians (Tables 3 and 4).

HLA class Ⅱ allele associations: HLA DR alleles in several populations are major determinants of response to HBV vaccination. Clinical studies have supported HLA DR3 and DR7 association with non-responsiveness to HBsAg vaccination (Table 3). HLA haplotype

Table 2 Association of HLA allele with protection from chronic HBV infection across global population

HLA	Effect	Country and cases	NC	R	CI	Reference
HLA I HLA B61	Early HBeAg seroconversion	Taiwan (chronically infected children)			81	[114]
HLA A*26	No disease progression in HBV carriers	Japan				[8]
HLA A-24 and Cw1	Low risk for HBV related chronic disease	Turkey	50		50	[9]
HLA A2	VC	Russia				[5]
HLA A11	VC	Kazakh				[5]
HLA A*0301	VC	USA (Caucasians)		342	194	[7]
HLA II						
HLA DRB1*4001	VC	Taiwan (Taiwanese Aborigines)	98	324	98	[4]
HLA DRB1*0406, DRB1*0701	VC	Taiwan (Han Chinese)	98	324	98	[4]
HLA DQA1*0301, DQA1*0102	VC/AC	China		148 (R) & 212 (AC)	207	[113]
HLA DRB1*1101/ *1104, DQA1*0301	VC	China	106	30	54	[10]
HLA DR12 (DRB1*1201)	VC	China		56	30	[11]
HLA-DRB1*07	VC/Protection from HBV infection.	China	200		72	[14]
HLA DR6 (DRB1*13)	VC	Korea (ESRD patients)	946	243	83	[19]
HLA DRB1*13	VC	India	100		26	[12]
HLA DRB1*1301 and DRB1*1302	VC	Gambia (children & Adult men)	891 & 25	218 & 195	185 & 40	[110]
HLA DRB1*1301/1302	VC	Spain	24	11	38	[115]
HLA DRB1*1301/1302	VC	Germany	101		117	[116]
HLA DR13 (DRB1*13)	VC	Germany	208	33	32	[117]
HLA DQB1*0503	Early HBeAg seroconversion	Taiwan (Chronically infected children)			81	[114]
HLA DR13	Resistance to HBV infection & vertical transmission	China (Pregnant women)	40		78	[15]
HLA-DRB1*1501/1502	Protection from liver cirrhosis	China (Cirrhosis subjects from Hubei area)	108		116	[13]
HLA DR5	No disease progression in HBV carriers	Japan				[8]

VC: Viral clearance/self limiting infection, AC: Asymptomatic carriers; Common VC alleles: DRB1*13; ESRD: End Stage Renal Disease; R: Recovered; HBV: Hepatitis B virus.

Bw54CREG, C4RFLP (6.5 kb + 12.0 kb)-DR4-DRw53-DQw4, (DQA1*0301-DQB1*0401) is in increased frequency in Japanese non-responders (NR) while HLA group DR1, DRw6, DQw1 are in low frequency in the non-responders[36] to HbsAg vaccine. HLA DR3, DR4, DR7, DR13 (DRB1*1302), DR14, DR16 is associated with non-responsiveness and HLA DR1, DR5, DR11, DR13 (DRB1*1301) and DR15 with responsiveness (Tables 3 and 4) to HBV vaccination across the population. HLA DR alleles associations were not reported in Indian (Asian) populations. Higher frequency of HLA DR4, DR7 and DR14 is associated with non-responsiveness and HLA DR1 with responsiveness in Japanese, Chinese and Caucasian populations (Tables 3 and 4). HLA DR10 and DR51 association with HBV vaccine responsiveness is reported only in Indian (Asian) population[37]. HLA DRB1*13 alleles carriers are hyper responsive to anti measles vaccine and HLA DR7 with non-responsiveness, resembling the pattern of response for recombinant HbsAg vaccine[38].

HLA DP alleles -DPB1*1101 with non-responsiveness, DPB1*0401 with responsiveness- are significant in determining the HBV vaccination response[39] in Belgian populations. HLA DQ2 (DQB1*02) is predominantly associated with non-responsiveness to HBV vaccine in Indian (Asian) and Caucasian populations (Table 3). HLA DQB1*0202, DQB1*0502, DQB1*0604 and DQA1*0102 alleles are associated with non-responsiveness and DQB1*0301, DQB1*0501, DQB1*0603, DQA1*0101 and 0103 with responsiveness in different European populations to this vaccine. Despite robust association in wide population HLA DQ2 did not qualify to be a non-responder marker[40] for HBV vaccine in European populations. However it was suggested to be an indicator for sub-optimal response to HBV vaccination in homozygous subjects.

HLA class Ⅲ allele associations: HLA class Ⅲ complement allele C4AQ0 is strongly associated with non-responsiveness to anti HBV vaccination[41]. It may contribute to inefficient complement activation and thus failure of B cells to secrete anti-HB immunoglobulin[34,42]. Complement protein production is linked to HLA haplotype[43]. Other HLA class Ⅲ genes including BfF, Cw4, Cw2, and C4A6 are associated with responsiveness to HBV vaccination in the Caucasian population (Table 4). Kramer *et al*[44] studied the TCR/CD3 density in non-responders and responders following vaccination in end stage renal disease (ESRD) patients. In these patients lower density of TCR/CD3 was reported in responders carrying C4A*6 and BfF alleles in comparison to non-carriers. Low TCR/CD3 density is related with non-responsiveness and is found associated with HLA A1-B8-DR3 haplotype. The HLA DR3 (associated with HBV vaccine non responsiveness) positive responders lacked C4A*6 and BfF alleles. HLA A1, C4A*6 and Bf*F alleles

Table 3 HLA allele association with Non-responsiveness to HBsAg vaccine across global population

HLA	Effect	Country	Vaccinees	Rs	NRs	Reference
HLA I HLA B54	Non- responsiveness	China	Healthy vaccinees	30	29	[118]
HLA A*0602, A*1101 and B*35	Non-responsiveness/ antibody production	Japan	Healthy medical students			[35]
HLA A1, A10, B15, B40.	Non responsiveness	India	Healthy volunteers	15 of 87 Rs	15	[37]
HLA A10, CW4	Non-responsiveness	Turkey	Health care workers		12	[119]
HLA A1, B8	Non-responsiveness	Germany, Poland	ESRD Patients on hemodialysis	119	34	[44,46]
HLA B8	Non-responsiveness	Belgium	Homosexual vaccinees	39	9	[120]
HLA A2	Non-responsiveness	Spain	Hemodialysis patients			[121]
HLA II HLA DR7##	Non- responsiveness	China	Healthy vaccinees	30	29	[118]
HLA DRB1*07##	Non-responsiveness	China (Han)	Healthy vaccinees	145	118	[122]
HLA DR14, DR52	Non- responsiveness	Chinese (Taiwan)	Non responder vaccinees		26	[123]
HLA DRB1*0405, DRB1*1101, DR4	Non-responsiveness/ antibody production	Japan	Healthy medical students			[35]
HLA DQ2$	Non responsiveness	India	Healthy volunteers	15 of 87	15	[37]
HLA DR7#	Non-responsiveness	Turkey	Health care workers		12	[119]
HLA DR3, DQ2$	Non-responsiveness	Germany, Poland	ESRD Patients on hemodialysis	119	34	[44,46]
HLA DR3	Non-responsiveness	Belgium	Homosexual vaccinees	39	9	[120]
HLA DRB1*07#, *DQB1*02$, and DPB1*1101	Non-responsiveness	Belgium	Vaccinees	134	117	[39]
HLA DRB1*03, DRB1*14	Non-responsiveness	France	Hemodialysis patients	301	114	[124]
HLA DRB1*1302, DQB1*0604, DQA1*0102	Non-responsiveness	Sweden	Healthy vaccinees	69	53	[48]
HLA DRB1*0701#, DQB1*0202$	Non-responsiveness	UK	Vaccinees	117	86	[125]
HLA DRB1*0701#, DQB1*0202$	Non-responsiveness	UK	HBsAg Non responders			[45]
HLA DQB1*02$	Non-responsiveness	Italy	Neonates	76	49LR, 43SR 19TNR	[34]
HLA DRB1*1601, DQB1*0502, DQA1*0102 Haplotype	Non-responsiveness	Slovenia	Health care workers	60	36	[126]
HLA DR3, DR7#, DQ2$	Non-responsiveness	Spain	Hemodialysis patients			[121]
HLA DRB1*3, DRB1*7, DRB1*14x	Non-responsiveness	Germany	Healthy adults & Infant vaccinees	53 & 56	73 & 62	[127]
HLA-B8, SC01, DR3 and HLA B44-FC31, DR7#	Non-responsiveness	USA	Healthcare worker		20	[33,49]
HLA DRB1*07#	Non-responsiveness	USA	Healthy vaccinees	85	79	[128]
HLA III HLA C4A*6, C4A*Q0##, Bf*F, Bf*S07	Non-responsiveness	Germany, Poland	ESRD Patients on hemodialysis	119	34	[46]
HLA C4AQ0##	Non-responsiveness	Italy	Neonates	40	26LR, 21SR, 10TNR	[41]
HLA C4AQ0##	Non-responsiveness	Italy	Neonates	76	49LR, 43SR 19TNR	[34]
HLA C4AQ0##	Non-responsiveness	Germany	Healthy vaccinees	53	73	[42]

Rs: Responders; NRs: Non-responders; ESRD: End stage renal disease; LR: Low responders, SR: Slow responders; TNR: Total non-responders. Common HLA alleles $: DQ2, #: DR7, ##: C4AQ0, DR3.

are associated with non-responders as well as responders but occur within different haplotypes in non-responders and responders for HBV vaccination.

Homozygous individuals for non-responder haplotype are strongly non-responsive to HBV vaccination when compared to the heterozygous state[45]. Homozygotes for HLA A1, B8, DR3, and DQ2 alleles are found exclusively in non-responders while heterozygotes are mostly non-responders[46] for HBV vaccination.

Non-uniformity observed in HLA association may be due to interaction between HLA factors within a haplotype. In Belgian populations HLA DPB1*0201 is associated with non-responsiveness to HBV vaccine when it occurs with haplotype DRB1*0701/DRB4*0101-DQB1*020*[39]. Also interaction with non-HLA genes in addition to HLA genes may influence responsiveness to HBV vaccination[47]. Presence of certain HLA genes in both responder and non-responder subjects suggests a role for other genes (cytokines, T cell receptors etc) in influencing the response to anti Hepatitis B vaccination and HLA alleles may be markers for such association[48]. Several susceptibility genes for immunoglobulin deficiency associated with haplotype HLA-B8, SC01, and DR3 are found in higher frequency in HBV vaccine non-responders[33,49]. Low levels of IL2 cause hypo-response to HBV vaccination[50]. IL10 ACC haplotype is associated with lower production of IL10 and thus favor strong humoral immune response to HbsAg[51].

HLA ALLELE ASSOCIATIONS WITH HEPATITIS C INFECTION IN GLOBAL POPULATIONS

Viral persistence and viral clearance

Activation of T helper (TH) 1 response is associated with self-resolving viral infection and that of TH2 with chronicity. The reactivation mechanism of T cells contributing to activation of particular TH CD4+ cells during HCV infection is not understood. Since negative finding by Vitte *et al*[52] in Caucasians, several HLA alleles and haplotypes have been found associated with susceptibility and resistance to hepatitis C infection, progression to liver damage and cirrhosis, development of hepatocellular carcinoma and response to interferon

Table 4 HLA association with responsiveness to HBsAg vaccine across global population

HLA	Effect	Country	Vaccinees	Rs	NRs	Reference
HLA Ⅰ, HLA A1, B7, B12	Responsiveness (Low)	Germany Poland	ESRD Patients on hemodialysis	119	34	[46]
HLA A1, A19, B5, B27, Cw2, Cw4	Responsiveness (High)	Germany Poland	ESRD Patients on hemodialysis	119	34	[46]
HLA Ⅱ, HLA DRB1*02	Responsive	China (Han)	Healthy vaccinees	145	118	[122]
HLA DRB1*0101, DRB1*08032, DQA1, DQB1, DPA1 and DPB1	Responsiveness	Japan	Healthy medical students			[35]
HLA DR4	Responsiveness (Low)	Germany, Poland	ESRD Patients on hemodialysis	119	34	[46]
HLA DRB1*010, DR5, DPB1*040, DQB1*0301, DQB1*0501.	Responsiveness	Belgium	Vaccinees	134	117	[39]
HLA DRB1*01, *DRB1*15# and DRB1*16	Responsiveness	France	Hemodialysis patients	301	114	[124]
HLA DRB1*1301, *DR15#, DQA1*0103, DQA1*0102, DQB1*0603,	Responsiveness	Sweden	Healthy vaccinees	69	53	[48]
HLA DRB1*11, DQB1*0301	Responsiveness	Italy	Neonates	76	49LR, 43SR 19TNR	[34]
HLA DRB1*1 DRB1*13, *DRB1*15#	Responsiveness	Germany	Healthy adults & infant vaccinees	109	135	[127]
HLA Ⅲ C4A*6, C4B*2, Bf*F	Responsiveness (High)	Germany Poland	ESRD Patients on hemodialysis	119	34	[46]

Rs: Responders; NRs: Non-responders, ESRD: End stage Renal Disease, LR: Low responders, SR: Slow responders, TNR-total non-responders common HLA alleles: DRB1*01, #: DR15.

Table 5 Association of HLA haplotypes with response to HbsAg vaccination across global population

HAPLOTYPE	Effect	Country	Vaccinees	Rs	NRs	References
HLA DR4, 1122 (DRB1*0401-22, 1122)-DR53 (DRB4*0101101, 0102/3)-DQB4 (DQB1*04)	Non-responsiveness	China				[129]
HLA DR14-DR52	Non-responsiveness	Chinese (Taiwan)	Non-responder vaccinees		33	[123]
HLA A1, B8, Bfs, C4AQ0, C4B1, DR3, DQ2 and HLA A1, B8, BfF, C4A6, C4B2, DR3, DQ2	Non-responsiveness	Germany, Poland	ESRD Patients on hemodialysis	34	119	[46]
HLA DRB4*0101-DRB1*0301/DRB3* *0101 DQB1*0202 and DPB1*0201 DRB1*0701/DRB4*0101, DQB1*020*	Non-responsiveness	Belgium	Vaccinees	134	117	[39]
HLA DQB1*0604, DQA1*0102, DRB1*1302 haplotype	Non-responsiveness	Sweden	Healthy vaccinees	69	53	[48]
HLA C4A*Q0, DRB1*0301, DQB1*02	Non-responsiveness	Italy	Neonates	40	26LR, 21SR 10TNR	[41]
HLA C4AQ0, DQB1*02	Non-responsiveness	Italy	Neonates	76	49LR, 43SR 19TNR	[34]
HLA B44-DRB1*0701-DQB1*0202	Non-responsiveness	UK	Vaccinees	117	86	[125]
HLA DRB1*1601, DQB1*0502, DQA1*0102 haplotype	Non-responsiveness	Slovenia	Health care workers	60	36	[126]
HLA B8-DR3	Non-responsiveness	Germany	Healthy adult & infant vaccinees	109	135	[127]
HLA DQB1*0603, DQA1*0102, DR15 and HLA DQB1*0603, DQA1*0103, DRB1*1301 haplotype	Responsiveness	Sweden	Healthy vaccinees	69	53	[48]
HLA DRB1*11, DQB1*0301	Responsiveness	Italy	Neonates	76	49LR, 43SR 19TNR	[34]

ESRD: End stage renal disease. Rs: Responders; NRs: Non responders; LR Low responders; SR: Slow responders, TNR: Total non-responders.

therapy in several populations. These are outlined in Tables 6, 7 and 8. Associations with HLA class Ⅱ genes are reported more often than HLA class Ⅰ. HLA class Ⅰ allelic diversity is suggested to have little influence on fibrosis and disease severity associated with chronic HCV infections[53].

HLA class Ⅰ allele associations: Susceptibility to HCV infections is associated with A*19 in Saudi people[54] and with HLA A*28, A*29, B*14, DR7 in Egyptians[55]. HLA A11-C*04 is associated with HCV persistence in Ireland[56]. HLA B-35 and B8 are strongly associated with chronic HCV infection, with HLA B-35 being positively related to chronic viral infection regardless of viral type[5,57]. In American whites, HCV persistence is associated with HLA Cw*04 and HLA B53, homozygosity of HLA Cw*04 have stronger effect on persistence than single copy of the allele[58].

Protection from HCV infection is associated with HLA-B51, -B52, -B55, -B56, -B61, B70, -Cw1, -Cw3, and -Cw4 in Japanese populations[59]. In Ireland HLA B27 and A*03 have strong association with self-resolving HCV infection[60]. Spontaneous HCV clearance is associated with HLA B-27 in German women cohorts[61] and HLA A*1101, B57 and Cw0102 are reported to be associated with viral clearance in American whites[58]. HLA C allele association with HCV clearance is found in Japanese (Cw1, Cw4)[59], Russian (Cw4)[5] and American populations (Cw0102)[58] (Table 6). HLA Cw*0602 protects from

Table 6 Association of HLA alleles with susceptibility to viral persistence &chronic HCV infection across global population

HLA	Effect	Country	NC	R	Chronicinfection		Reference
					AC	CLD/CHC	
HLA Ⅰ HLA-B61, Cw3,	VP/HCV infection	Japan	293			60	[69]
HLA B54	VP with CLD	Japan	916		33	97	[68]
HLA B55, -B56, B70	VP	Japan	172			113	[59]
HLA A3, B-35, B-46	VP	Korea	206			137	[109]
HLA A28, A29, B14	HCV infection	Egypt					[55]
HLA A-19	HCV infection	Saudi people.	122			146	[54]
HLA-A10, HLA-B35, HLA-B40 and HLA-Cw3	VP-CLD	Russia					[5]
HLA-A30, B35, B41, Cw2, A1-B35, A9-B8	VP-CLD-LC	Russia				107	[57]
HLA B8, B18	VP-CHC	Ireland		86		141	[60]
HLA C*04	VP	Ireland (Whites)		86		139	[56]
HLA B14	VP & active hepatitis C	Italy	489			117	[130]
HLA B18	Susceptibility to CLD	Spain	116		48	93	[131]
HLA-A*2301 and HLA-Cw*04	VP	USA		231		444	[58]
HLA-Cw*07,	Risk factor for vertical infection	Italy (infants born to HCV+ mothers)	44 uninfected infants born to HCV+ mothers			21	[16]
HLA Ⅱ HLA DR4, DQB1*0401 DQB1*0402	VP/ HCV infection	Japan	293			60	[69]
HLA DRB1*0405, DQB1*0401	VP with CLD	Japan	916		33	97	[68]
HLA DRB1*0405, DQB1*0401	VP with LC	Japan	1216		50	67	[70]
HLA DQB1*0503	VP with LC	Japan	201		43	60	[132]
HLA DRB1*0301#, DQB1*0201, DQB1*0502	VP/CHC	Thailand	140	43	21	36	[133]
HLA, DRB1*0803, DQB1*0601 and DQB1*0604	VP	Korea	206			137	[109]
HLA DRB1*0301#	VP	Egypt (Hemophilic and HCV-, HCC+ patients)	15 Healthy & 25 HCV-		10 HCV+	15 (HCV-HCC+)	[134]
HLA DR7	HCV infection	Egypt					[55]
HLA-DRB1*0701, DRB1*15, DRB4*0101	Viral persistence	UK (European)		85		170	[135]
HLA DQB1*0201	VP-CHC	Ireland		86		141	[60]
HLA DRB1*0701 (HCV 1b)	VP	Ireland (females receiving HCV 1b contaminated AntiD immunoglobulin)		84		72	[136]
HLA DRB1*1001, DRB1*1101	VP/CLD	Italy	179		41	99	[137]
HLA DQB1*0502	VP-CLD	Italy	200	35	42	107	[138]
HLA DR14, DR17	VP-CLD	Italy	70		34	39	[139]
HLA DRB1*0301	VP-CHC	Germany	101			105	[140]
HLA DRB1*07	VP-CLD	German & North Europeans	2045			99	[94]
HLA DR B1*13 and DRB1*14	Susceptibility to infection	German & North Europeans	2045			99	[94]
HLA DR3#	Susceptibility to chronic disease	Spain	116		48	93	[131]
HLA DRB1*13 and DRB1*07	Necro inflammatory activity during infection	Poland				134	[95]
HLA DRB1*13 allele	VP	Poland				134	[95]
DRB1*03# and DQB1*0201(male gender)	CLD/LC	France				233	[141]
HLA G*010401, -DRB1*0701, -DRB1*1401 and homozygosity for HLA-G 14bp deletion	Risk factor for vertical infection	Italy(infants born to HCV+ mothers)	44 uninfected infants born to HCV+ mothers			21	[16]
HLA DRB*4001	High viral load	Taiwan					[142]
HLA Ⅲ MICA-A4	Susceptibility to CLD	Spain	116		48	93	[131]

VP: Viral persistence/chronic infection; CHC: Chronic hepatitis C; CLD: Chronic liver disease; NC: Normal control; R: Recovered; AC: Asymptomatic carriers; LC: Liver cirrhosis. Common VP alleles: # DRB1*03, DRB1*0701.

vertical HCV transmission in infants while HLA CW*07 is the susceptibility allele[16] for HCV.

NK cells mediate direct killing of infected and transformed cells contributing to viral clearance and protection from tumor development. This killer activity is under the control of HLA class Ⅰ molecule interaction with inhibitory and activation receptors-killer cell immunoglobulin like receptors (KIR) of NK cells. HLA C molecules interact with KIRs of NK cells and modulate their cell killer activity. Activation receptor KIRDL3 and HLA-C1C1 ligand interact directly to influence viral clearance in HCV infection[62]. KIRDL3 associated protection is not found in individuals lacking HLA-C1C1 allele[62]. HLA C2C2 interaction with NK cell receptor is associated with viral persistence in Spanish populations[63]. KIR3DS1-HLA Bw4180 genotype is associated with protection from development of HCC in HCV carriers[64]. HLA Cw7 inhibitory interaction with NK cells is proposed

Table 7 Association of HLA alleles with Protection from HCV infection and viral clearance

HLA I	Effect	Country	NC	R	Chronic infection		Reference
					AC	CHC/CLD	
HLA I HLA-B51, -B52, B61, -Cw1, Cw3, and Cw4	VC	Japan	172			113	[59]
HLA A2	AC	Japan	172			113	[59]
B50 (21)	VC	Egypt					[55]
HLA-B8,	Protection from infection	Saudi people	122			146	[54]
HLA-Cw4	Protection from chronic infection	Russia					[5]
HLA A*03,B*07,B*27,Cw*01	VC/Protection from chronic infection	Ireland		86		141	[60]
HLA-A*1101,HLA-B*57 and HLA-Cw*0102	Viral clearance	USA		231		444	[58]
HLA-Cw*0602	Protection against vertical infection	Italy (infants born to HCV+ ve mothers)	44 uninfected infants born to HCV+ mothers			21	[16]
HLA Bw4180/KIR3DS1	HCV carriers	Spain	116		51	47 (LC), 54 (HCC)	[64]
HLA-C1/KIR2DL3	VC/protection from infection	UK		352		685	[62]
HLA A*34,B*56	Low viral load	Taiwan					[142]
HLA II HLA-DR9- DQB1*0301 and DQB1*0303	VC/protection from HCV infection	Japan	293			60	[69]
HLA DRB1*1302, DRB1*1101## and DQB1*0604 alleles	AC/no CLD	Japan	916		33	97	[68]
HLA DRB1*12(1201/1202), DQBI*0301, DRB3*03	AC/no CLD	Japan	201		43	60	[132]
HLA DRB1*0901,DQB1*0303	AC-no LC	Japan	1216		50	67	[70]
HLA DRB1*04, DRB1*0701, DQA1*0201,DQB1*0301	VC	Thailand	140	43	21	36	[133]
HLA DRB1*0301, DQA1*0501 and DQB1*0201	VC/protection from HCV infection	Korea	206			137	[109]
HLA DRB1*0101##	VC	Egypt (Hemophilic and HCV- HCC+ ve patients)	15 Healthy & 25 HCV-		10 HCV+	15 HCV-HCC+	[134]
HLA DRI and DR3	VC/Protection from infection	Saudi people	122			146	[54]
HLA DRB1*11#	VC/Protection from infection	Turkey	43			49	[143]
HLA DQA1*03 and DQB1*0302	VC/Protection from chronic infection	N.European whites	177			104	[144]
HLA-DRB1*0301,DRB1*1101#, DRB1*1201# and HLA-DQB1*0301	Viral clearance	UK (European)		85		170	[135]
HLA DRB1*04, DQA1*03 and DQB1*0301	VC/Protection from chronic infection	UK	134	49		55	[145]
HLA DQB1*0302	Protection from infection	UK	134	49		55	[145]
HLA DRB1*01##. (HCV 1b)	VC	Ireland (females who received HCV 1b contaminated AntiD immunoglobulin)		84		72	[136]
HLA DRB1*0101##, DRB1*0401, DRB1*15	VC/Protection from chronic infection	Ireland		86		141	[60]
HLA DRB1*0101##	Viral clearance	Ireland		73		84	[78, 146]
HLA DR5#	Protection from chronic hepatitis C	Italy	489			117	[130]
HLA II HLA DRB1*1601, DQB1*0502	Protection from HCV infection	Sardinia (Thalassemia major for transfusion)	606 healthy & 30 HCV- patients			116	[147]
HLA DRB1*1104, and DRB3*03	Protection from chronic manifestation /carries	Italy	179		41	99	[137]
HLA DRB1*1104,DQB1*0301	VC	Italy	200	35	42	107	[138]
HLA DR 11	VC/Protection from infection	Italy	70		34	29	[139]
HLA DQB1*0301	Protection from HCV related HCC	Italy	144			29	[148]
HLA DRB1*1301 and DQA1*0103	Protection from chronic HCV infection	Germany	101			105	[140]
HLA-DRB1*15011	Viral clearance/ Protection	Germany		21		49	[149]
HLA-DRB1*11(DR5) and HLA-DQB1*03(DQ3)	Protection from CLD	Germany	501			108	[150]

HLA-DR11	AC/Protection from CLD	Spain	116		48	93	[131]
HLA DQB1*0301	Protection from chronic infection	Poland	103			129	[108]
HLA DRB1*11	Mild liver damage	Poland				134	[95]
HLA DQB1*0301 and DRB1*1101	VC	France	800	25		103	[74]
HLA DQB1*0301 and female sex	VC	France	800	63		282	[75]
HLA DRB1*11	Protection from progression of liver disease	France				233	[141]
HLA DRB1*11 (female association)	AC/less severity of chronic hepatitis	France			83	233	[76]
HLA DQB1*0301	VC (strongly in Black subjects)	USA		200		374	[77]
HLA DRB1*0101, DQB1*0501	VC (in white subjects)	USA		200		374	[77]
HLA DR13	Protection against vertical infection	Italy (infants born to HCV+ ve mothers)		17 (serum reverted)		18	[17]
HLA-DQB1*06, -G*0105N, DRB1*1104 and -DRB1*1302 alleles	Protection against vertical infection	Italy (infants born to HCV+ ve mothers)	44 uninfected infants born to HCV+ mothers			21	[16]
HLA DRB1*1502	Low viral load	Taiwan					[142]

VC: Viral clearance; CHC: Chronic hepatitis C; CLD: Chronic liver disease; NC: Normal control; R: Recovered; LC: Liver cirrhosis; AC: Asymptomatic carriers. Common HLA alleles #: DR5 (DRB1*11, DRB1*12 allele), ##: DRB1*0101, DQB1*0301.

Table 8 HLA Haplotype association with HCV viral clearance and persistence across global population

HLA	Effect	Country	NC	R	Chronic infection		Reference
					AC	CLC/CHC	
Viral persistence							
HLA Cw3- DR4-DQB1*0401 or *0402, and HLA-B61-DR4 -DQB1*0401 or 0402	VP/chronic infection	Japan	293			60	[69]
HLA B54-DRB1*0405-DQB1*0401 haplotype	VP-CLD	Japan	916		33	97	[68]
HLA DRB1*0405-DQB1*0401 haplotype	VP with LC	Japan	1216		50	67	[70]
HLA DRB1*0301, DQA1*0501, DQB1*0201	VP	Thailand	140	43	21	36	[133]
A*01-B*08-Cw*07-DRB1*03011-DQB1*0201	VP-CHC	Ireland		86		141	[60]
HLA DRB1*15-DQB1*0602	High viral load/increased risk for disease severity	Ireland (viremic females)				57	[71]
HLA A*11, C*04	VP	Ireland (Whites)		86		139	[56]
HLA DQA1*0201-DQB1*0201	Susceptibility to Chronic hepatitis C	Italy	179		41	99	[151]
HLA DR3/MICA-A4/B18	Susceptibility to chronic disease	Spain	116		48	93	[131]
HLA DRB1*0701-DQA1*0201-DQB1*02 and DRB1*1501-DQA1*01-DQB1*0602	VP-CLD	Poland	103			129	[108]
HLA DRB1*0301 -DQB1*0201	VP	USA					[77]
HLA-Cw*04-B*53	VP	USA		231		444	[58]
Viral clearance							
HLA B44-DRB1*1302-DQB1*0604 and DRB1*1302-DQB1*0604	AC/no progression to CLD	Japan	916		33	97	[68]
HLA DRB1*0901-DQB1*0303	AC-no LC	Japan	1216		50	67	[70]
HLA A*03-B*07-DRB1*15-DQB1*0602 and A*02-B*27-Cw*01-DRB1*0101-DQB1*0501	VC/Protection from chronic infection	Ireland		86		141	[60]
DRB1*0701 and DQB1*02	Stable viral load/slow disease progression	Ireland (viremic females)				57	[71]
HLA DRB1*1104, DQA1*0501, DQB1*0301 haplotype	Protection from Chronic hepatitis	Italy	179		41	99	[151]
HLA DRB1*1104, DQB1*0301	VC	Italy	200	35	42	107	[138]
HLA DRB1*0101 -DQB1*0501 haplotype	Viral clearance (in white subjects)	USA		200		374	[77]

VP: Viral persistence; VC: Viral clearance; CHC: Chronic hepatitis C; CLD: Chronic liver disease; NC: Normal control; R: Recovered; AC: Asymptomatic carriers; LC: Liver cirrhosis.

to be associated with HCC in Italian patients[20]. It is notable that HLA B8-Cw7 haplotype is associated with HBV associated liver cancer[6]. In an in vitro study, HLA E is shown to inhibit NK cell mediated lysis of HCV infected cells via interaction with NK cell receptor NKG2A, contributing to HCV persistence[65]. HLA E expression on hepatocytes is stabilized by recognition of HCV core protein by HLA A2 molecules[65]. Increased expression of inhibitory receptor CD94/NKG2A on NK cells was found in chronic hepatitis C patients and is suggested to contribute to immune resistance towards HCV infection and HCV mediated cellular transformation via modulating dendritic cell function and cytokine secretion[66,67].

HLA class Ⅱ allele associations: HLA DRB1*0405 and DQB1*0401/0402 alleles are associated with viral persistence and chronic HCV infection in Japanese[68-70].

Also, DRB1*0405-DQB1*0401/0402 haplotype[59] and HLA B54-DRB1*0405-DQB1*0401 haplotype are associated with HCV induced liver injury[68]. In Thailand and most European Caucasians HLA DRB1*0301, DQB1*0201 and DQA1*0201 are found associated with chronic HCV infection and HLA DRB1*0701 is associated with disease severity throughout the European populations (Table 6). In Irish viremic females increased risk for HCV infection related disease severity and high viral load was associated with HLA DRB1*15-DQB1*0602[71]. In Italy HLA DQB1*0502 and DR14 and DR 17 are associated with risk to liver cirrhosis and progressive liver damage respectively (Table 6).

HLA DRB1*11 alleles and DQB1*0301 is consistently associated with decreased disease severity of Hepatitis C worldwide (Table 7)[72,73]. In French populations DQB1*0301 is associated with viral clearance in females and DRB1*11 with protection from disease progression in males[74,75] for hepatitis C infection. In contrast Reno *et al*[76] found association of DRB1*11 with HCV clearance in the French female gender. HLA DQB1*0301 is linked to HCV clearance in American populations showing stronger association with African-Americans[77]. Carriers of HLA DR11 and DQB1*0301 alleles may present the HCV epitopes more efficiently to CD4+T cells than others and thus show efficient viral clearance[73]. Viral clearance is associated with DRB1*0101 and DQB10501 in American Caucasians and with DRB1*0101 in Irish, Saudi, and Egyptian populations (Table 7). HLA DRB1*0101 allele appears to have better HCV specific T cell response[78]. DRB1*0701-DQB1*02 haplotype is associated with low HCV viral load in Ireland[71]. HLA DR7 is associated with hepatitis C disease severity in several populations and also with HBV infection, except for in Thailand where it is associated with HCV viral clearance along with HLA DQA*0201. HLA DR13 is protective for vertical transmission in infants born to HCV+ ve Italian mothers[16,17]. In infants born to infected mothers HLA DRB1*1104 is associated with seroreversion and DRB1*1101 with viral persistence[79] for HCV infection. In Japanese and the DRB1*0901-DQB1*0303 haplotype is related to protection from cirrhosis in hepatitis C[70] and HLA B44-DRB1*1302-DQB1*0604 and DRB1*1302-DRB1*0604 with asymptomatic carrier phenotype[68].

HLA class Ⅲ allele associations: HLA class Ⅲ and cytokine genes have been reported in influencing HCV infection outcome. HLA DR3/MICA-A*4, B*18 is increased in patients with HCC but absent in HCV carriers[64]. Single Nucleotide Polymorphism (SNP)-863A in TNF alpha gene is associated with HCV clearance in African American patients, while wild-type haplotype -863C/-308G is associated with viral persistence in the same[80]. TNF alpha-308 G is found associated with HBV persistent infection in Chinese and Koreans but its status with American populations for HBV is not known. IL10 ATA haplotype possibly influences HCV clearance in Italians[81]. Positive association is reported between TNF alpha 238.2 promoter variant and chronic active hepatitis B and C in Germans[23]. In Indian (Asian) populations the TNF-beta (A/A) allele is indicated to be associated with disease progression[82].

HLA ALLELE ASSOCIATIONS WITH RESPONSE TO INTERFERON THERAPY IN HEPATITIS B AND C VIRAL INFECTIONS

Interferon treatment is currently the most adopted therapy for chronic hepatitis patients. It upregulates the expression of HLA DR, CD80 and ICAM- Ⅰ molecules on dendritic cells and thus augmenting the immune response[83]. Interferon treatment for chronic HBV and HCV infection is successful only in one third of patients. HLA DR locus appears to be a prominent immunogenetic factor influencing interferon treatment response. HLA association in independent studies on Chinese populations has reported HLA DRB1*14 and DQA1*0501 and DQB1*0301 to be associated with responsiveness in chronic hepatitis B. DRB1*07 allele carriers are prevalent among chronic hepatitis B patients and associated with non-responsiveness to anti HBV vaccination and IFN-alpha treatment (Tables 1, 3 and 9).

In Chinese populations DRB1*04 is associated with non-responsiveness to interferon therapy in HCV as well as HBV infected subjects (Table 9)[84,85]. HLA DRB1*04 is associated with male non-responders while HLADRB1*07 is reported for female responsiveness in Chinese patients with chronic HCV infection[84]. Japanese HLA allele associations with response to interferon treatment is inconsistent (Table 9) and involve HLA class Ⅰ and class Ⅱ alleles for hepatitis C. HLA A24-B54-DR4 haplotype and HLA B54 allele are predictors of poor response to IFN therapy in Japanese hepatitis C subjects[86]. High serum level of IL10 is also suspected to result in poor response to interferon treatment in chronic HCV cases[47]. Low serum levels of IL10 are associated with responsiveness to HBV vaccination[51].

In Spanish populations HLA B44 is associated with responsiveness to interferon + ribavirin therapy but not when interferon therapy is given alone in hepatitis C cases. Also, HLA class Ⅱ does not influence response to interferon treatment in this population[87]. HLA DRB1*0404 is associated with responsiveness in the HCV infected Caucasian population[88]. Piekarsha *et al*[89] did not find any association of HLA DRB1* alleles with response to Interferon alpha 2b treatment of Polish HCV subjects, but in other populations these alleles are reported to influence the response (Table 9). HLA DRB1*07 is associated with non-responsiveness for HBV and for HCV infected subjects from France, but is associated with responsiveness in HCV cases from Poland and Germany and females subjects from China (Table 9).

HLA allele association with interferon treatment response seems to differ for chronic HBV and HCV infections in global populations. This can be attributed to differences in the antigenic determinants of these two different viruses and consequently differences in the HLA molecules involved. However associations of same HLA allele for hepatitis B as well as C with respect to therapeutic response or non-response, though in different population, warrants explanation. HLA typing for interferon treatment receiving cohorts in different population would give an insight towards the mechanism and immune interactions

Table 9 HLA association with response to interferon therapy in chronic hepatitis (B and C) patients across global population

HLA	Effect	Country	R	NR	References
Hepatitis B					
HLA DQA1*0501 and DQB1*0301	Responsiveness	China	32	28	[85]
HLA-DRB1*14	Responsiveness	China	11	24	[14]
HLA DRB1*04,DQA1*0303	Non-responsiveness	China	32	28	[85]
HLA-DRB1*07 (HBV type c)	Non-responsiveness	China	7		[152]
HLA-DQB1*07	Low response	China	11	24	[14]
Hepatitis C					
Non responsiveness					
HLA Ⅰ HLA B54	Non responsiveness	Japan	20	47	[86]
HLA Ⅱ, HLA DR9	Non responsiveness	Japan			[153]
HLA DR6	Non responsiveness	Japan	21	32	[154]
HLA DRB1*04 (males and HCV1b)	Non responsiveness	China	10	11	[84]
HLA B1*13	Non responsiveness	Turkey			[155]
DRB1*07	Non responsiveness	France	50	120	[75]
Responsiveness					
HLA Ⅰ HLA B55, B62 and Cw3	Responsiveness	Japan	54	118	[156]
HLA B51, CW1	Responsiveness	Japan			[153]
HLA B44	Responsiveness to Interfron + Ribavirin	Spain	53	52	[87]
HLA Ⅱ HLA DRB*10101	Responsiveness	Japan	32	106	[157]
HLA DR6	Responsiveness	Japan	21	32	[154]
HLA DRB1*07 (females and HCV 2b)	Responsiveness	China	10	11	[84]
HLA DR2	Responsiveness	Egypt	25	30	[158]
DQB1*06(HCV genotype 1)	Responsiveness	France	50	120	[75]
HLA DRB1*0404	Responsiveness	Canada	6	64	[88]
Haplotypes					
HLA A-24-B54-DR4	Non responsiveness	Japan	20	47	[86]
HLA B7-DRB10101	Responsiveness	Japan	32	106	[157]
DRB1*0701-DQA1*0201-DQB1*02	Responsiveness	Poland	29	26	[108]

R: Responders to Interferon therapy; NR: Non-responders to interferon therapy.

involved. Interferon therapy involves adverse effects; HLA studies will help identifying responder/no responder markers that would help select patients suitable for interferon therapy.

HLA ASSOCIATIONS WITH VERTICAL TRANSMISSION OF HEPATITIS B AND HEPATITIS C VIRAL INFECTIONS

Vertical transmission from infected mothers is a major contributor to increased HCV and HBV infection[92]. Genetic factors in neonates surely influence the outcome of vertical transmission. Liu *et al*[15] reported HLA DR3 carriers to be at risk of vertical transmission of HBV and DR13 carriers to be resistant in Chinese populations. In Italian subjects, HLA DR13 (DRB1*1302) and DRB1*1104 were reported to be protective in neonates for vertical transmission[16,17,79]. HLA DRB1*1104 is associated with seroreversion in infants born to infected mothers but DRB1*1101 is associated with viral persistence in such infants. The difference in association related to sub allelic differences could to be due to glycine/valine dimorphism at position 86 of the antigen binding sites of the DR B1* molecule. HLA DRB1*86GG was associated with HCV infected children while DRB1*86VV homozygotes were seroconverts[79]. HLA-DQB1*06, -G*0105N, -Cw*0602, DRB1*1104 and -DRB1*1302 alleles are protective while HLA-Cw*07, -G*010401, -DRB1*0701, -DRB1*1401 and homozygosity for HLA-G 14bp deletion are risk factors for HCV vertical transmission in Italian children[16].

HLA ASSOCIATIONS WITH THE EXTRA-HEPATIC MANIFESTATIONS OF HEPATITIS B AND HEPATITIS C VIRAL INFECTIONS

HLA associations have been described for extra-hepatic co-morbidities triggered by HCV and HBV infection. HLA DQB1*0603 is associated with development of HBV associated membranous nephropathy in South African black children[90]. HLA DRB1*11 and HLA DRB1*1302, DQB1*0404, DQB1*0604 are associated with susceptibility and protection respectively to HBV related glomerulonephritis in Korea[91]. Sebastiani *et al*[92] proposed involvement of HLA DR6 in extra hepatic manifestation of HCV related diseases. HCV associated oral lichen planus was reported in HLA DR6 carriers (DRB1*13/*14 alleles)[93]. HLA DRB1*13 alleles are reported to be associated with disease severity in chronic HCV infection in European populations[94,95]. Chronic HCV infection also shows association between DQB1*11 and DR3 with formation of cryoglobulins[72]. HLA studies in this aspect would allow finding of HLA marker for extra hepatic manifestations of hepatic viral infections. Such studies may help prevent post transplantation associated liver damage in recipients. A recent study has suggested donor–recipient mismatch at HLA DRB1 locus and HLA B14 to be responsible for severe fibrosis development in the recipient[96]. The knowledge of HLA gene marker

association with risk for HBV/HCV related disease progression/cirrhosis may be helpful while seeking donor-recipient HLA match before transplantation.

Czaja *et al*[97] have suggested that genetic predisposition, facilitated by viral infection may trigger autoimmune hepatitis (AIH). Similarities in HLA associations in viral hepatitis and AIH are observed. In European and North American Caucasians HLA DRB1*0301 is strongly associated with AIH Ⅰ[97], and in most European population DRB1*0301 is associated with HCV persistence (Table 6). HLA DRB1*0405 is a susceptible allele for AIH Ⅰ as well as HCV viral persistence in Japanese[68,70,97]. In Germans DRB1*07 is a risk factor for AIH Ⅱ, and is also found associated with HCV viral persistence[94,97]. Such associations require an extensive study of HLA association in AIH and viral hepatitis patients.

HLA ALLELE ASSOCIATIONS WITH HEPATITIS A, D AND E VIRAL INFECTIONS

HLA restricted virus specific T cells play an essential role in Hepatitis A related hepatocellular injury, however limited information about the host HLA association in HAV infection is available. HLA-A9 was suggested to be the susceptibility factor in Brazil during an outbreak of hepatitis A infection[98]. HLA-B27[99] and HLA A1, B8, DR3[100] associations with fulminant hepatitis A infection in HCV infected patients is reported. Hepatitis A viral infection (HAV) is suspected to trigger AIH in genetically susceptible patients carrying HLA DRB1*0401[101]. Strong association of DRB1*1301 haplotype with protracted forms of HAV infection that further developed to AIH in pediatric patients is reported[102]. Extensive investigation of HAV infected individuals worldwide will contribute to the limited information regarding its HLA association and its relation to HLA associations of HBV and HCV infections.

HLA association with Hepatitis D and E is not known. Hepatitis E causes acute infections, and Hepatitis D is associated with Hepatitis B infection. A high risk of chronic delta (HDV) infection in Russians is associated with HLA-B8 and HLA-B35, and in Kazakhs with HLA-B35 and HLA-D40[5].

DISCUSSION

Extensive allele diversity is observed in HLA associations with susceptibility and protection regarding HCV and HBV infections and disease progression in different global ethnic populations. HLA loci diversity due to racial admixture, environment and selection pressure and by inherent polymorphic nature results in allelic variation in different ethnic groups, correspondingly we get different HLA associations with disease in different populations. Thus association of disease outcome with HLA alleles appears to depend upon the ethnicity of the infected individual and therefore is inconsistent across the populations despite being robust within an ethnic group.

The specific HLA associations with HBV and HCV infections are different, agreeing to their differences in viral properties and disease pathogenesis, with few exceptions where they share few HLA loci. This could be due to linkage disequilibrium of HLA alleles with disease-associated genes or shared HLA restricted HCV and HBV T cell viral epitopes. It is intriguing that HLA associations are oppositely directed and indicate interactions with other unidentified factors in influencing the HLA mediated immune signaling. It is also observed that HBV and HCV infections tend to suppress each other. HBV and HDV can suppress HCV infection and HCV and HDV can have negative effect on HBV. HCV super infection is seen to reduce HBsAg expression and promote its clearance[103].

HLA DR9 is protective for HCV infection in Japanese[69,70] but is a susceptible factor for chronic HBV in Koreans and Chinese[11,19] (Tables 1 and 6). In a comparative study of HBV and HCV infected subjects, MICA (*) 015 is associated with viral clearance in case of HCV infection but with chronic infection in case of HBV[104]. HLA Class Ⅱ HLA DRB1*11 and DQB1*0301 are protective for HCV infections, but are also associated with chronic HBV infection. Also, HLA DQB1*0301 is associated with responsiveness to interferon therapy in chronic HBV infection[85] and also to anti HBsAg vaccination[39]. Interferon treatment may activate antigen presentation by aiding generation of more DQB1*0301 responding cytototxic T lymphocytes and thus a protective response[85]. Constantini *et al*[105] did not find any association between HCV clearance and alpha interferon therapy with IL1, IL10 and TNF alpha genes. This warrants further investigation with other HLA class Ⅲ genes to know the influence of interferon and a protective association of HLA DQB1*0301 allele in HCV clearance. Cytokine genes should also be investigated for any synergistic association with any of these HLA alleles in HBV infection. Involvement of the same alleles with different outcomes in response to viral infection in different population is intriguing. Collaborative studies involving well-characterized cohorts from different populations are needed.

The difference in influence of HLA DRB1*11 and DQB1*0303 in HCV and HBV infection outcome could be due to variation in viral specific antigen presentation and thus differences in immune responses. Investigating the molecular mechanisms involving HLA DR*11 and DQ*3 associated viral clearance in HCV would provide better understanding of this aspect. Identifying HLA DR*11 and DQ* 3 restricted viral HCV epitopes for CD8+ cells would allow finding or designing similar HBV specific epitopes. This can further be used therapeutically to enhance viral clearance in HLA DR*11 and DQ*3 carrying HBV infected subjects. Investigating involvement of shared epitopes for HBV/HCV may open up opportunities for generating combined HBV-HCV vaccine in the future.

Immunodominant antigenic epitopes have been identified in HCV and they could be investigated for HLA restricted stage specific presentation to develop HLA specific vaccine and peptide-based immunotherapies[106]. HLA B27 restricted HCV specific CD8+ epitope recovered from female subjects has been identified[61]. Such CD8+ specific HLA restricted peptides have been proposed as vaccine and have been shown effective against

human metapneumovirus infection and disease in mice[107].

Since immunization at present is the most effective means of combating HBV infection, non-responders always remain at risk of getting infected. Identifying non-responding immunogenetic marker could help protect non-responders by giving them alternative protective therapy and would also permit avoiding administering vaccine to identified non-responding groups in a given population. Designing HLA restricted epitope based anti-HBV vaccine is an alternative for non-responding groups.

Association of HLA DR13 alleles is protective in both HCV and HBV infections in several populations (Tables 2 and 7) and is proposed to be involved in enhancing immune response to various diseases[17]. In contrast HCV disease susceptibility and severity is linked to DR13 in German and Polish populations[94,95], though other reports from Germany suggest its protective role (Table 7). It is also protective in vertical transmission of HBV and HCV infection (Tables 2 and 7). Recognizing HLA DR13 restricted HBV and HCV T cell epitopes could lead to identification of similar/common antigenic determinants and open possibilities for designing a combined anti HBV-HCV vaccine.

HLA DRB1*07 is positively associated with severe disease outcome in both HBV and HCV infections (Tables 1 and 6). This allele is related to non-responsiveness to anti-HBV vaccination and interferon treatment in subjects with chronic HBV and HCV infections (Table 9), but is reported with responsiveness to interferon treatment in individuals with chronic HCV infection from China and Poland[84,108]. HLA B35 and B40 is associated with chronic HBV and HCV infection in Russian populations[5,57], and the authors suggest chronic hepatitis to be associated with HLA B*35, independent of virus type. HLA B35 involvement is reported with viral persistence of HCV in Koreans[109], and of HBV in Han Chinese[4]. HLA B8 is associated with viral persistence and chronicity for both HBV and HCV infections in Caucasian populations (Tables 1 and 6). HLA Cw*07 is a risk factor for vertical infection in Italians[16] and is associated with HBV related liver cancer in Senegalese[6]. Such associations suggest inability of these alleles to mount efficient immune responses for viral clearance irrespective of the viral type and warrants elaborate studies concentrating these alleles in several populations, to identify predisposing genetic markers for disease severity.

Studies focusing on viral hepatitis in the United States (US) in American populations have suggested differences in HLA allele association for Caucasians and African-Americans. HBV viral persistence is associated with HLA A*01-B*08-DRB1*03, B*44-Cw*1601 and B844-Cw*0501 haplotype in Caucasian Americans while HLA DQA1*0501, DQB1*0301 and DRB1*1102 haplotype in African Americans[7,18]. HLA A*0301 and HLA DRB1*1302 is associated with HBV clearance in Caucasian Americans, the later being associated with HBV viral clearance in Gambian populations[7,110]. HCV persistence is associated with HLA A*2301 in Caucasian Americans and with the HLA-Cw*04 allele in both Caucasian and African American populations. Also, two copies of HLA-Cw*04 showed stronger persistence than one copy of the allele[58]. Viral clearance showed stronger association with HLA A*1101 and B*57 alleles in both Caucasians and African Americans but HLA Cw*0102 showed stronger association with viral clearance only in Caucasians[58]. Another study by Thio *et al*[77] reported HLA DQB1*0301 to be associated with viral clearance showing stronger associations in African Americans than Caucasian Americans. Also HLA DRB1*0101 and DQB1*0501 showed association with HCV viral clearance, but only in Caucasian Americans. No information is available on HLA associations with interferon treatment response and racial differences in US American populations which needs investigation.

Variations in the immune response to viral insult appear to be genetically inherited. Reports on HLA gene associations with viral infections are inconsistent and contradictory. Several factors including (1) alteration in antigen binding affinity, (2) ineffective antigen presentation, (3) ineffective interaction of Ag-MHC and TCRs, (4) absence of specific T cells, (5) cytokine deficiency and (6) inadequate complement activation may contribute to defective/inefficient HLA mediated immune response mechanisms and various disease manifestations. Indirect associations of HLA in disease pathology have also been proposed. Circulating autoantibodies against HLA Class Ⅱ and class Ⅰ molecules have been found, and may represent autoimmune response against HLA molecules that may induce HCV related chronic liver damage[111]. Complement abnormality has been associated with several liver diseases.

Polymorphism of TNF alpha and IL10 promoter has been implicated to influence HBV and HCV infections suggesting a vital role for cytokines in disease outcome. Genes outside the major histocompatibility complex also play a major role in determining the disease/treatment outcome of viral hepatitis. Altered expression of CD45 isoforms influence HCV outcome in humans and transgenic mice studies[112]. NK stimulating and inhibitory signaling receptor and HLA interaction influence viral persistence or clearance. Association of viral persistence and clearance is also reported with chemokine receptors[72].

Due to (1) the highly polymorphic nature of HLA genes, (2) diversity observed in genetic interactions and (3) complexity of immune response, it has not been possible so far to "Tag" any allele or loci as a potential candidate for a particular disease or disease outcome. However clinical evidence vividly indicates such associations. Thus, it is prudent to argue that response to viral hepatitis infection is immunogenetically governed by multiple candidate genes (including HLA and non HLA genes) acting either independently or in association. HLA genes could be directly involved or may be closely linked to genetic markers for true susceptibility, protection and treatment response genes.

CONCLUSION

Racial diversity, variations in the study design, methodology and complex immune-regulatory mechanisms make it difficult to find consistent association of HLA alleles with a given HBV or HCV disease even in the same ethnic group of the global population.

The host-virus interaction resulting in acute or chronic

viral infection depends on cellular immune responses that are regulated by the host's HLA type and HLA restricted viral escape mutants. Much research is required for involving either the CD8 antigenic epitope or NK cell (involving KIR ligands) based HLA associations in individuals undergoing acute *vs* chronic infections in different ethnic populations. Thus, novel strategies are needed to combat the escape mechanisms utilized by viruses in different ethnic populations.

Limited numbers of studies across various ethnic populations have been conducted in relation to HBV vaccination outcome or various therapeutic outcomes against HBV or HCV infections. Thus, global network studies will be useful for HLA disease associations in different ethnic global populations in relation to various therapeutic or HBV vaccination outcome and resulting in viral clearance. Information on HLA association with disease outcome holds immense promise for designing host specific therapeutic strategies. HLA studies involving collaborative analysis of several immune regulatory host genes including T cell repertoire variables in cohorts from around the globe are needed to answer the puzzle regarding various host related immunogenetic factors in conditions resulting in varying outcomes of HBV or HCV hepatitis infection or their co-infections.

REFERENCES

1 **Rizzetto M**. Hepatitis B vaccination: current status. *Minerva Gastroenterol Dietol* 1999; **45**: 199-205
2 **Armstrong GL**, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006; **144**: 705-714
3 **Martin MP**, Carrington M. Immunogenetics of viral infections. *Curr Opin Immunol* 2005; **17**: 510-516
4 **Wu YF**, Wang LY, Lee TD, Lin HH, Hu CT, Cheng ML, Lo SY. HLA phenotypes and outcomes of hepatitis B virus infection in Taiwan. *J Med Virol* 2004; **72**: 17-25
5 **Popov EA**, Levitan BN, Alekseev LP, Pronina OA, Suchkov SV. Immunogenetic HLA markers of chronic viral hepatitis. *Ter Arkh* 2005; **77**: 54-59
6 **Dieye A**, Obami-Itou V, Barry MF, Raphenon G, Thiam A, Ndiaye R, Ndiaye M, Diaw ML, Diakhate L. Association between Class I HLA alleles and HBs antigen carrier status among blood donors in Senegal. *Dakar Med* 1999; **44**: 166-170
7 **Thio CL**, Thomas DL, Karacki P, Gao X, Marti D, Kaslow RA, Goedert JJ, Hilgartner M, Strathdee SA, Duggal P, O'Brien SJ, Astemborski J, Carrington M. Comprehensive analysis of class I and class II HLA antigens and chronic hepatitis B virus infection. *J Virol* 2003; **77**: 12083-12087
8 **Zeniya M**, Watanabe F, Aizawa Y, Toda G. Immunogenetic background of hepatitis B virus infection and autoimmune hepatitis in Japan. *Gastroenterol Jpn* 1993; **28** Suppl 4: 69-75; discussion 76-80
9 **Karan MA**, Tascioglu NE, Ozturk AO, Palanduz S, Carin M. The role of HLA antigens in chronic hepatitis B virus infection. *J Pak Med Assoc* 2002; **52**: 253-256
10 **Jiang YG**, Wang YM, Liu TH, Liu J. Association between HLA class II gene and susceptibility or resistance to chronic hepatitis B. *World J Gastroenterol* 2003; **9**: 2221-2225
11 **Meng XQ**, Chen HG, Ma YL, Liu KZ. Influence of HLA class II molecules on the outcome of hepatitis B virus infection in population of Zhejiang Province in China. *Hepatobiliary Pancreat Dis Int* 2003; **2**: 230-233
12 **Amarapurpar DN**, Patel ND, Kankonkar SR. HLA class II genotyping in chronic hepatitis B infection. *J Assoc Physicians India* 2003; **51**: 779-781
13 **Cheng YQ**, Lin JS, Huang LH, Tian DY, Xiong P. The association of HLA-DRB1 allele polymorphism with the genetic susceptibility to liver cirrhosis due to hepatitis B virus. *Zhonghua Yixue Yichuanxue Zazhi* 2003; **20**: 247-249
14 **Han YN**, Yang JL, Zheng SG, Tang Q, Zhu W. Relationship of human leukocyte antigen class II genes with the susceptibility to hepatitis B virus infection and the response to interferon in HBV-infected patients. *World J Gastroenterol* 2005; **11**: 5721-5724
15 **Liu HY**, Kong BH, Luo X, Xu YP, Dai MS, Jiang S. Study on the association between maternal-infantile vertical transmission of hepatitis B virus and human leukocyte antigen DR gene domain. *Zhonghua Fuchanke Zazhi* 2003; **38**: 599-603
16 **Martinetti M**, Pacati I, Cuccia M, Badulli C, Pasi A, Salvaneschi L, Minola E, De Silvestri A, Iannone AM, Maccabruni A. Hierarchy of baby-linked immunogenetic risk factors in the vertical transmission of hepatitis C virus. *Int J Immunopathol Pharmacol* 2006; **19**: 369-378
17 **Bosi I**, Ancora G, Mantovani W, Miniero R, Verucchi G, Attard L, Venturi V, Papa I, Sandri F, Dallacasa P, Salvioli GP. HLA DR13 and HCV vertical infection. *Pediatr Res* 2002; **51**: 746-749
18 **Thio CL**, Carrington M, Marti D, O'Brien SJ, Vlahov D, Nelson KE, Astemborski J, Thomas DL. Class II HLA alleles and hepatitis B virus persistence in African Americans. *J Infect Dis* 1999; **179**: 1004-1006
19 **Ahn SH**, Han KH, Park JY, Lee CK, Kang SW, Chon CY, Kim YS, Park K, Kim DK, Moon YM. Association between hepatitis B virus infection and HLA-DR type in Korea. *Hepatology* 2000; **31**: 1371-1373
20 **Pellegris G**, Ravagnani F, Notti P, Fissi S, Lombardo C. B and C hepatitis viruses, HLA-DQ1 and -DR3 alleles and autoimmunity in patients with hepatocellular carcinoma. *J Hepatol* 2002; **36**: 521-526
21 **Li HQ**, Li Z, Liu Y, Li JH, Dong JQ, Gao JR, Gou CY, Li H. Association of-238G/A and -857C/T polymorphisms of tumor necrosis factor-alpha gene promoter region with outcomes of hepatitis B virus infection. *Biomed Environ Sci* 2006; **19**: 133-136
22 **Lu LP**, Li XW, Liu Y, Sun GC, Wang XP, Zhu XL, Hu QY, Li H. Association of -238G/A polymorphism of tumor necrosis factor-alpha gene promoter region with outcomes of hepatitis B virus infection in Chinese Han population. *World J Gastroenterol* 2004; **10**: 1810-1814
23 **Höhler T**, Kruger A, Gerken G, Schneider PM, Meyer zum Büschenefelde KH, Rittner C. A tumor necrosis factor-alpha (TNF-alpha) promoter polymorphism is associated with chronic hepatitis B infection. *Clin Exp Immunol* 1998; **111**: 579-582
24 **Cheong JY**, Cho SW, Hwang IL, Yoon SK, Lee JH, Park CS, Lee JE, Hahm KB, Kim JH. Association between chronic hepatitis B virus infection and interleukin-10, tumor necrosis factor-alpha gene promoter polymorphisms. *J Gastroenterol Hepatol* 2006; **21**: 1163-1169
25 **Niro GA**, Fontana R, Gioffreda D, Valvano MR, Lacobellis A, Facciorusso D, Andriulli A. Tumor necrosis factor gene polymorphisms and clearance or progression of hepatitis B virus infection. *Liver Int* 2005; **25**: 1175-1181
26 **Somi MH**, Najafi L, Noori BN, Alizadeh AH, Aghah MR, Shavakhi A, Ehsani MJ, Aghazadeh R, Masoodi M, Amini S, Baladast M, Zali MR. Tumor necrosis factor-alpha gene promoter polymorphism in Iranian patients with chronic hepatitis B. *Indian J Gastroenterol* 2006; **25**: 14-15
27 **Zhang PA**, Wu JM, Li Y, Yang XS. Association of polymorphisms of interleukin-18 gene promoter region with chronic hepatitis B in Chinese Han population. *World J Gastroenterol* 2005; **11**: 1594-1598
28 **Ben-Ari Z**, Mor E, Papo O, Kfir B, Sulkes J, Tambur AR, Tur-Kaspa R, Klein T. Cytokine gene polymorphisms in patients infected with hepatitis B virus. *Am J Gastroenterol* 2003; **98**: 144-150
29 **Zhang PA**, Li Y, Yang XS. Associated study on interleukin 10 gene promoter polymorphisms related to hepatitis B virus infection in Chinese Han population. *Zhonghua Yixue Yichuanxue Zazhi* 2006; **23**: 410-414

30 **Miyazoe S**, Hamasaki K, Nakata K, Kajiya Y, Kitajima K, Nakao K, Daikoku M, Yatsuhashi H, Koga M, Yano M, Eguchi K. Influence of interleukin-10 gene promoter polymorphisms on disease progression in patients chronically infected with hepatitis B virus. *Am J Gastroenterol* 2002; **97**: 2086-2092

31 **Frodsham AJ**, Zhang L, Dumpis U, Taib NA, Best S, Durham A, Hennig BJ, Hellier S, Knapp S, Wright M, Chiaramonte M, Bell JI, Graves M, Whittle HC, Thomas HC, Thursz MR, Hill AV. Class II cytokine receptor gene cluster is a major locus for hepatitis B persistence. *Proc Natl Acad Sci USA* 2006; 103: 9148-9153

32 **Zein NN**, Germer JJ, El-Zayadi AR, Vidigal PG. Ethnic differences in polymorphisms of tumor necrosis factor-alpha, interleukin-10, and transforming growth factor-beta1 genes in patients with chronic hepatitis C virus infection. *Am J Trop Med Hyg* 2004; **70**: 434-437

33 **Alper CA**. The human immune response to hepatitis B surface antigen. *Exp Clin Immunogenet* 1995; **12**: 171-181

34 **Martinetti M**, De Silvestri A, Belloni C, Pasi A, Tinelli C, Pistorio A, Salvaneschi L, Rondini G, Avanzini MA, Cuccia M. Humoral response to recombinant hepatitis B virus vaccine at birth: role of HLA and beyond. *Clin Immunol* 2000; **97**: 234-240

35 **Mineta M**, Tanimura M, Tana T, Yssel H, Kashiwagi S, Sasazuki T. Contribution of HLAclass I and class II alleles to the regulation of antibody production to hepatitis B surface antigen in humans. *Int Immunol* 1996; **8**: 525-531

36 **Hatae K**, Kimura A, Okubo R, Watanabe H, Erlich HA, Ueda K, Nishimura Y, Sasazuki T. Genetic control of nonresponsiveness to hepatitis B virus vaccine by an extended HLA haplotype. *Eur J Immunol* 1992; **22**: 1899-1905

37 **Das K**, Gupta RK, Kumar V, Singh S, Kar P. Association of HLA phenotype with primary non-response to recombinant hepatitis B vaccine: a study from north India. *Trop Gastroenterol* 2004; **25**: 113-115

38 **Hayney MS**, Poland GA, Jacobson RM, Schaid DJ, Lipsky JJ. The influence of the HLA-DRB1*13 allele on measles vaccine response. *J Investig Med* 1996; **44**: 261-263

39 **Desombere I**, Willems A, Leroux-Roels G. Response to hepatitis B vaccine: multiple HLA genes are involved. *Tissue Antigens* 1998; **51**: 593-604

40 **Desombere I**, Van der Wielen M, Van Damme P, Stoffel M, De Clercq N, Goilav C, Leroux-Roels G. Immune response of HLA DQ2 positive subjects, vaccinated with HBsAg/AS04, a hepatitis B vaccine with a novel adjuvant. *Vaccine* 2002; **20**: 2597-2602

41 **De Silvestri A**, Pasi A, Martinetti M, Belloni C, Tinelli C, Rondini G, Salvaneschi L, Cuccia M. Family study of non-responsiveness to hepatitis B vaccine confirms the importance of HLA class III C4A locus. *Genes Immun* 2001; **2**: 367-372

42 **Höhler T**, Stradmann-Bellinghausen B, Starke R, Sänger R, Victor A, Rittner C, Schneider PM. C4A deficiency and nonresponse to hepatitis B vaccination. *J Hepatol* 2002; **37**: 387-392

43 **Truedsson L**, Awdeh Z, Yunis EJ, Mrose S, Moore B, Alper CA. Quantitative variation of C4 variant proteins associated with many MHC haplotypes. *Immunogenetics* 1989; **30**: 414-421

44 **Kramer J**, Stachowski J, Barth C, Ujhelyi E, Tarján V, Sulowicz W, Füst G, Baldamus CA. Genetic regulation of the impaired immune response to hepatitis-B vaccine associated with low TCR density in end stage renal disease patients: contribution of complement C4 and factor B alleles. *Immunol Lett* 1997; **59**: 13-19

45 **McDermott AB**, Cohen SB, Zuckerman JN, Madrigal JA. Human leukocyte antigens influence the immune response to a pre-S/S hepatitis B vaccine. *Vaccine* 1999; **17**: 330-339

46 **Stachowski J**, Kramer J, Füst G, Maciejewski J, Baldamus CA, Petrányi GG. Relationship between the reactivity to hepatitis B virus vaccination and the frequency of MHC class I, II and III alleles in haemodialysis patients. *Scand J Immunol* 1995; **42**: 60-65

47 **Kuzushita N**, Hayashi N, Katayama K, Kanto T, Oshita M, Hagiwara H, Kasahara A, Fusamoto H, Kamada T. High levels of serum interleukin-10 are associated with a poor response to interferon treatment in patients with chronic hepatitis C. *Scand J Gastroenterol* 1997; **32**: 169-174

48 **Langö-Warensjö A**, Cardell K, Lindblom B. Haplotypes comprising subtypes of the DQB1*06 allele direct the antibody response after immunisation with hepatitis B surface antigen. *Tissue Antigens* 1998; **52**: 374-380

49 **Alper CA**, Kruskall MS, Marcus-Bagley D, Craven DE, Katz AJ, Brink SJ, Dienstag JL, Awdeh Z, Yunis EJ. Genetic prediction of nonresponse to hepatitis B vaccine. *N Engl J Med* 1989; **321**: 708-712

50 **Xie J**, Wang X, Zhuang G, Xu H, Hao B, Tang X, Wu Q. Relationship between interleukin-2, interleukin-2 receptor and the non-and hypo-responsiveness to hepatitis B vaccine. *Zhonghua Ganzangbing Zazhi* 2000; **8**: 332-334

51 **Höhler T**, Reuss E, Freitag CM, Schneider PM. A functional polymorphism in the IL-10 promoter influences the response after vaccination with HBsAg and hepatitis A. *Hepatology* 2005; **42**: 72-76

52 **Vitte RL**, Fortier C, Richardet JP, Grimbert S, Trinchet JC, Beaugrand M, Lepage V, Raffoux C. HLA antigens in patients with chronic hepatitis C. *Tissue Antigens* 1995; **45**: 356-361

53 **Patel K**, Norris S, Lebeck L, Feng A, Clare M, Pianko S, Portmann B, Blatt LM, Koziol J, Conrad A, McHutchison JG. HLA class I allelic diversity and progression of fibrosis in patients with chronic hepatitis C. *Hepatology* 2006; **43**: 241-249

54 **Hadhoud A**, Abdulaziz AM, Menawi LA, Shaheen FA, Abdulghaffar A, Abas FA, Al Mobrak MF. The relationship between HLA typing and HCV infection and outcome of renal transplantation in HCV positive patients. *Exp Clin Transplant* 2003; **1**: 19-25

55 **Zekri AR**, El-Mahallawy HA, Hassan A, El-Din NH, Kamel AM. HLA alleles in Egyptian HCV genotype-4 carriers. *Egypt J Immunol* 2005; **12**: 77-86

56 **Fanning LJ**, Kenny-Walsh E, Shanahan F. Persistence of hepatitis C virus in a white population: associations with human leukocyte antigen class 1. *Hum Immunol* 2004; **65**: 745-751

57 **Bondarenko AL**, Baramzina SV. Role of HLA phenotype in the formation of chronic hepatitis C virus infection. *Zh Mikrobiol Epidemiol Immunobiol* 2002; : 55-57

58 **Thio CL**, Gao X, Goedert JJ, Vlahov D, Nelson KE, Hilgartner MW, O'Brien SJ, Karacki P, Astemborski J, Carrington M, Thomas DL. HLA-Cw*04 and hepatitis C virus persistence. *J Virol* 2002; **76**: 4792-4797

59 **Kondo Y**, Kobayashi K, Kobayashi T, Shiina M, Ueno Y, Satoh T, Shimosegawa T. Distribution of the HLA class I allele in chronic hepatitis C and its association with serum ALT level in chronic hepatitis C. *Tohoku J Exp Med* 2003; **201**: 109-117

60 **McKiernan SM**, Hagan R, Curry M, McDonald GS, Kelly A, Nolan N, Walsh A, Hegarty J, Lawlor E, Kelleher D. Distinct MHC class I and II alleles are associated with hepatitis C viral clearance, originating from a single source. *Hepatology* 2004; **40**: 108-114

61 **Neumann-Haefelin C**, McKiernan S, Ward S, Viazov S, Spangenberg HC, Killinger T, Baumert TF, Nazarova N, Sheridan I, Pybus O, von Weizsäcker F, Roggendorf M, Kelleher D, Klenerman P, Blum HE, Thimme R. Dominant influence of an HLA-B27 restricted CD8+ T cell response in mediating HCV clearance and evolution. *Hepatology* 2006; **43**: 563-572

62 **Khakoo SI**, Thio CL, Martin MP, Brooks CR, Gao X, Astemborski J, Cheng J, Goedert JJ, Vlahov D, Hilgartner M, Cox S, Little AM, Alexander GJ, Cramp ME, O'Brien SJ, Rosenberg WM, Thomas DL, Carrington M. HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. *Science* 2004; **305**: 872-874

63 **Montes-Cano MA**, Caro-Oleas JL, Romero-Gomez M, Diago M, Andrade R, Carmona I, Aguilar Reina J, Nunez-Roldan A, Gonzalez-Escribano MF. HLA-C and KIR genes in hepatitis C virus infection. *Hum Immunol* 2005; **66**: 1106-1109

64 **López-Vázquez A**, Rodrigo L, Martínez-Borra J, Pérez R, Rodríguez M, Fdez-Morera JL, Fuentes D, Rodríguez-Rodero S, Gonzáez S, López-Larrea C. Protective effect of the HLA-

Bw4I80 epitope and the killer cell immunoglobulin-like receptor 3DS1 gene against the development of hepatocellular carcinoma in patients with hepatitis C virus infection. *J Infect Dis* 2005; **192**: 162-165

65 **Nattermann J**, Nischalke HD, Hofmeister V, Ahlenstiel G, Zimmermann H, Leifeld L, Weiss EH, Sauerbruch T, Spengler U. The HLA-A2 restricted T cell epitope HCV core 35-44 stabilizes HLA-E expression and inhibits cytolysis mediated by natural killer cells. *Am J Pathol* 2005; **166**: 443-453

66 **Takehara T**, Hayashi N. Natural killer cells in hepatitis C virus infection: from innate immunity to adaptive immunity. *Clin Gastroenterol Hepatol* 2005; **3**: S78-S81

67 **Jinushi M**, Takehara T, Tatsumi T, Kanto T, Miyagi T, Suzuki T, Kanazawa Y, Hiramatsu N, Hayashi N. Negative regulation of NK cell activities by inhibitory receptor CD94/NKG2A leads to altered NK cell-induced modulation of dendritic cell functions in chronic hepatitis C virus infection. *J Immunol* 2004; **173**: 6072-6081

68 **Kuzushita N**, Hayashi N, Moribe T, Katayama K, Kanto T, Nakatani S, Kaneshige T, Tatsumi T, Ito A, Mochizuki K, Sasaki Y, Kasahara A, Hori M. Influence of HLA haplotypes on the clinical courses of individuals infected with hepatitis C virus. *Hepatology* 1998; **27**: 240-244

69 **Higashi Y**, Kamikawaji N, Suko H, Ando M. Analysis of HLA alleles in Japanese patients with cirrhosis due to chronic hepatitis C. *J Gastroenterol Hepatol* 1996; **11**: 241-246

70 **Aikawa T**, Kojima M, Onishi H, Tamura R, Fukuda S, Suzuki T, Tsuda F, Okamoto H, Miyakawa Y, Mayumi M. HLA DRB1 and DQB1 alleles and haplotypes influencing the progression of hepatitis C. *J Med Virol* 1996; **49**: 274-278

71 **Fanning LJ**, Levis J, Kenny-Walsh E, Whelton M, O'Sullivan K, Shanahan F. HLA class II genes determine the natural variance of hepatitis C viral load. *Hepatology* 2001; **33**: 224-230

72 **Yee LJ**. Host genetic determinants in hepatitis C virus infection. *Genes Immun* 2004; **5**: 237-245

73 **Hong X**, Yu RB, Sun NX, Wang B, Xu YC, Wu GL. Human leukocyte antigen class Ⅱ DQB1*0301, DRB1*1101 alleles and spontaneous clearance of hepatitis C virus infection: a meta-analysis. *World J Gastroenterol* 2005; **11**: 7302-7307

74 **Alric L**, Fort M, Izopet J, Vinel JP, Charlet JP, Selves J, Puel J, Pascal JP, Duffaut M, Abbal M. Genes of the major histocompatibility complex class Ⅱ influence the outcome of hepatitis C virus infection. *Gastroenterology* 1997; **113**: 1675-1681

75 **Alric L**, Fort M, Izopet J, Vinel JP, Bureau C, Sandre K, Charlet JP, Beraud M, Abbal M, Duffaut M. Study of host- and virus-related factors associated with spontaneous hepatitis C virus clearance. *Tissue Antigens* 2000; **56**: 154-158

76 **Renou C**, Halfon P, Pol S, Cacoub P, Jouve E, Bronowicki JP, Arpurt JP, Rifflet H, Picon M, Causse X, Canva V, Denis J, Tran A, Bourliére M, Ouzan D, Pariente A, Dantin S, Alric L, Cartier V, Reville M, Caillat-Zucman S. Histological features and HLA class II alleles in hepatitis C virus chronically infected patients with persistently normal alanine aminotransferase levels. *Gut* 2002; **51**: 585-590

77 **Thio CL**, Thomas DL, Goedert JJ, Vlahov D, Nelson KE, Hilgartner MW, O'Brien SJ, Karacki P, Marti D, Astemborski J, Carrington M. Racial differences in HLA class II associations with hepatitis C virus outcomes. *J Infect Dis* 2001; **184**: 16-21

78 **Barrett S**, Ryan E, Crowe J. Association of the HLA-DRB1*01 allele with spontaneous viral clearance in an Irish cohort infected with hepatitis C virus via contaminated anti-D immunoglobulin. *J Hepatol* 1999; **30**: 979-983

79 **Martinetti M**, Pacati I, Daielli C, Salvaneschi L, Maccabruni A. Critical role of Val/Gly86 HLA-DRB dimorphism in the neonatal resistance or susceptibility to maternal hepatitis C virus infection. *Pediatr Infect Dis J* 1997; **16**: 1001-1002

80 **Thio CL**, Goedert JJ, Mosbruger T, Vlahov D, Strathdee SA, O'Brien SJ, Astemborski J, Thomas DL. An analysis of tumor necrosis factor alpha gene polymorphisms and haplotypes with natural clearance of hepatitis C virus infection. *Genes Immun* 2004; **5**: 294-300

81 **Mangia A**, Santoro R, Piattelli M, Pazienza V, Grifa G, Iacobellis A, Andriulli A. IL-10 haplotypes as possible predictors of spontaneous clearance of HCV infection. *Cytokine* 2004; **25**: 103-109

82 **Goyal A**, Kazim SN, Sakhuja P, Malhotra V, Arora N, Sarin SK. Association of TNF-beta polymorphism with disease severity among patients infected with hepatitis C virus. *J Med Virol* 2004; **72**: 60-65

83 **Yu YS**, Tang ZH, Han JC, Xi M, Feng J, Zang GQ. Expression of ICAM-1, HLA-DR, and CD80 on peripheral circulating CD1 alpha DCs induced in vivo by IFN-alpha in patients with chronic hepatitis B. *World J Gastroenterol* 2006; **12**: 1447-1451

84 **Jiao J**, Wang JB. Hepatitis C virus genotypes, HLA-DRB alleles and their response to interferon-alpha and ribavirin in patients with chronic hepatitis C. *Hepatobiliary Pancreat Dis Int* 2005; **4**: 80-83

85 **Zang GQ**, Xi M, Feng ML, Ji Y, Yu YS, Tang ZH. Curative effects of interferon-alpha and HLA-DRB1 -DQA1 and -DQB1 alleles in chronic viral hepatitis B. *World J Gastroenterol* 2004; **10**: 2116-2118

86 **Kikuchi I**, Ueda A, Mihara K, Miyanaga O, Machidori H, Ishikawa E, Tamura K. The effect of HLA alleles on response to interferon therapy in patients with chronic hepatitis C. *Eur J Gastroenterol Hepatol* 1998; **10**: 859-863

87 **Romero-Gómez M**, González-Escribano MF, Torres B, Barroso N, Montes-Cano MA, Sánchez-Muñoz D, Núñez-Roldan A, Aguilar-Reina J. HLA class I B44 is associated with sustained response to interferon + ribavirin therapy in patients with chronic hepatitis C. *Am J Gastroenterol* 2003; **98**: 1621-1626

88 **Sim H**, Wojcik J, Margulies M, Wade JA, Heathcote J. Response to interferon therapy: influence of human leucocyte antigen alleles in patients with chronic hepatitis C. *J Viral Hepat* 1998; **5**: 249-253

89 **Piekarska A**, Woszczek G, Sidorkiewicz M, Kuydowicz J. HLA class II alleles and response to hepatitis C treatment with interferon alpha2b. *Przegl Epidemiol* 2002; **56**: 123-128

90 **Bhimma R**, Hammond MG, Coovadia HM, Adhikari M, Connolly CA. HLA class I and II in black children with hepatitis B virus-associated membranous nephropathy. *Kidney Int* 2002; **61**: 1510-1515

91 **Park MH**, Song EY, Ahn C, Oh KH, Yang J, Kang SJ, Lee HS. Two subtypes of hepatitis B virus-associated glomerulonephritis are associated with different HLA-DR2 alleles in Koreans. *Tissue Antigens* 2003; **62**: 505-511

92 **Sebastiani GD**, Bellisai F, Caudai C, Rottoli P, Valensin PE, Pippi L, Morozzi G, Porciello G, Donvito A, Bilenchi R, Giannini F, Galeazzi M. Association of extrahepatic manifestations with HLA class II alleles and with virus genotype in HCV infected patients. *J Biol Regul Homeost Agents* 2005; **19**: 17-22

93 **Carrozzo M**, Francia Di Celle P, Gandolfo S, Carbone M, Conrotto D, Fasano ME, Roggero S, Rendine S, Ghisetti V. Increased frequency of HLA-DR6 allele in Italian patients with hepatitis C virus-associated oral lichen planus. *Br J Dermatol* 2001; **144**: 803-808

94 **Kallinowski B**, Scherer S, Mehrabi A, Theilmann L, Stremmel W. Clinical impact of HLA DR B1 genotypes in chronic hepatitis C virus infection. *Transplant Proc* 1999; **31**: 3346-3349

95 **Kryczka W**, Brojer E, Kalińska A, Urbaniak A, Zarebska-Michaluk D. DRB1 alleles in relation to severity of liver disease in patients with chronic hepatitis C. *Med Sci Monit* 2001; **7** Suppl 1: 217-220

96 **Belli LS**, Burra P, Poli F, Battista Alberti A, Silini E, Zavaglia C, Fagiuoli S, Prando D, Espadas de Arias A, Boninsegna S, Tinelli C, Scalamogna M, de Carlis L, Pinzello G. HLA-DRB1 donor-recipient mismatch affects the outcome of hepatitis C disease recurrence after liver transplantation. *Gastroenterology* 2006; **130**: 695-702

97 **Czaja AJ**, Doherty DG, Donaldson PT. Genetic bases of autoimmune hepatitis. *Dig Dis Sci* 2002; **47**: 2139-2150

98 **Arce-Gomez B**, Moliterno RA, Rodrigues AL, Barbosa J, deOliveira MR, Abreu JC, SpeckdoNascimento VA, Sasaki MG. Association of viral hepatitis A with HLA-A9. *Hum Immunol* 1987; **18**: 205-209

99 **Brncić N**, Matić-Glazar D, Visković I, Grzetić M, Racki S. Acute renal failure complicating nonfulminant hepatitis a in HLA-B27 positive patient. *Ren Fail* 2000; **22**: 635-640

100 **Vento S**. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *J Viral Hepat* 2000; **7** Suppl 1: 7-8

101 **Hilzenrat N**, Zilberman D, Klein T, Zur B, Sikuler E. Autoimmune hepatitis in a genetically susceptible patient: is it triggered by acute viral hepatitis A? *Dig Dis Sci* 1999; **44**: 1950-1952

102 **Fainboim L**, Cañero Velasco MC, Marcos CY, Ciocca M, Roy A, Theiler G, Capucchio M, Nuncifora S, Sala L, Zelazko M. Protracted, but not acute, hepatitis A virus infection is strongly associated with HLA-DRB*1301, a marker for pediatric autoimmune hepatitis. *Hepatology* 2001; **33**: 1512-1517

103 **Liaw YF**. Role of hepatitis C virus in dual and triple hepatitis virus infection. *Hepatology* 1995; **22**: 1101-1108

104 **Karacki PS**, Gao X, Thio CL, Thomas DL, Goedert JJ, Vlahov D, Kaslow RA, Strathdee S, Hilgartner MW, O'Brien SJ, Carrington M. MICA and recovery from hepatitis C virus and hepatitis B virus infections. *Genes Immun* 2004; **5**: 261-266

105 **Constantini PK**, Wawrzynowicz-Syczewska M, Clare M, Boron-Kaczmarska A, McFarlane IG, Cramp ME, Donaldson PT. Interleukin-1, interleukin-10 and tumour necrosis factor-alpha gene polymorphisms in hepatitis C virus infection: an investigation of the relationships with spontaneous viral clearance and response to alpha-interferon therapy. *Liver* 2002; **22**: 404-412

106 **Gerlach JT**, Ulsenheimer A, Grüner NH, Jung MC, Schraut W, Schirren CA, Heeg M, Scholz S, Witter K, Zahn R, Vogler A, Zachoval R, Pape GR, Diepolder HM. Minimal T-cell-stimulatory sequences and spectrum of HLA restriction of immunodominant CD4+ T-cell epitopes within hepatitis C virus NS3 and NS4 proteins. *J Virol* 2005; **79**: 12425-12433

107 **Herd KA**, Mahalingam S, Mackay IM, Nissen M, Sloots TP, Tindle RW. Cytotoxic T-lymphocyte epitope vaccination protects against human metapneumovirus infection and disease in mice. *J Virol* 2006; **80**: 2034-2044

108 **Wawrzynowicz-Syczewska M**, Underhill JA, Clare MA, Boron-Kaczmarska A, McFarlane IG, Donaldson PT. HLA class II genotypes associated with chronic hepatitis C virus infection and response to alpha-interferon treatment in Poland. *Liver* 2000; **20**: 234-239

109 **Yoon SK**, Han JY, Pyo CW, Yang JM, Jang JW, Kim CW, Chang UI, Bae SH, Choi JY, Chung KW, Sun HS, Choi HB, Kim TG. Association between human leukocytes antigen alleles and chronic hepatitis C virus infection in the Korean population. *Liver Int* 2005; **25**: 1122-1127

110 **Thursz MR**, Kwiatkowski D, Allsopp CE, Greenwood BM, Thomas HC, Hill AV. Association between an MHC class II allele and clearance of hepatitis B virus in the Gambia. *N Engl J Med* 1995; **332**: 1065-1069

111 **El Aggan HA**, Sidkey F, El Gezery DA, Ghoneim E. Circulating anti-HLA antibodies in patients with chronic hepatitis C: relation to disease activity. *Egypt J Immunol* 2004; **11**: 71-79

112 **Dawes R**, Hennig B, Irving W, Petrova S, Boxall S, Ward V, Wallace D, Macallan DC, Thursz M, Hill A, Bodmer W, Beverley PC, Tchilian EZ. Altered CD45 expression in C77G carriers influences immune function and outcome of hepatitis C infection. *J Med Genet* 2006; **43**: 678-684

113 **Lu LP**, Liu Y, Li XW, Sun GC, Zhu XL, Wu YZ, Hu QY, Li H. Association of polymorphisms of human leucocyte antigen -DRB1 and -DQA1 allele with outcomes of hepatitis B virus infection in Han population of north China. *Zhongguo Yixue Kexueyuan Xuebao* 2006; **28**: 134-142

114 **Wu JF**, Chen CH, Hsieh RP, Shih HH, Chen YH, Li CR, Chiang CY, Shau WY, Ni YH, Chen HL, Hsu HY, Chang MH. HLA typing associated with hepatitis B E antigen seroconversion in children with chronic hepatitis B virus infection: a long-term prospective sibling cohort study in Taiwan. *J Pediatr* 2006; **148**: 647-651

115 **Cotrina M**, Buti M, Jardí R, Rodríguez-Frías F, Campins M, Esteban R, Guardia J. Study of HLA-II antigens in chronic hepatitis C and B and in acute hepatitis B. *Gastroenterol Hepatol* 1997; **20**: 115-118

116 **Höhler T**, Gerken G, Notghi A, Lubjuhn R, Taheri H, Protzer U, Löhr HF, Schneider PM, Meyer zum Büschenfelde KH, Rittner C. HLA-DRB1*1301 and *1302 protect against chronic hepatitis B. *J Hepatol* 1997; **26**: 503-507

117 **Diepolder HM**, Jung MC, Keller E, Schraut W, Gerlach JT, Grüner N, Zachoval R, Hoffmann RM, Schirren CA, Scholz S, Pape GR. 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* 1998; **113**: 244-251

118 **Liu P**, Xu H, Wang X, Li H, Zhuang G, Wu Z, Zhang K. Field epidemiological and experimental study on relationship between genetic factor and nonresponse or hyporesponse to hepatitis B vaccine. *Chin Med J (Engl)* 2000; **113**: 547-550

119 **Durupinar B**, Okten G. HLA tissue types in nonresponders to hepatitis B vaccine. *Indian J Pediatr* 1996; **63**: 369-373

120 **Vingerhoets J**, Goilav C, Vanham G, Kestens L, Muylle L, Kegels E, Van Hoof J, Piot P, Gigase P. Non-response to a recombinant pre-S2-containing hepatitis B vaccine: association with the HLA-system. *Ann Soc Belg Med Trop* 1995; **75**: 125-129

121 **Peces R**, de la Torre M, Alcázar R, Urra JM. Prospective analysis of the factors influencing the antibody response to hepatitis B vaccine in hemodialysis patients. *Am J Kidney Dis* 1997; **29**: 239-245

122 **Qian Y**, Zhang L, Liang XM, Hou JL, Luo KX. Association of immune response to hepatitis B vaccine with HLA-DRB1*02, 07, 09 genes in the population of Han nationality in Guangdong Province. *Diyi Junyidaxue Xuebao* 2002; **22**: 67-69

123 **Hsu HY**, Chang MH, Ho HN, Hsieh RP, Lee SD, Chen DS, Lee CY, Hsieh KH. Association of HLA-DR14-DR52 with low responsiveness to hepatitis B vaccine in Chinese residents in Taiwan. *Vaccine* 1993; **11**: 1437-1440

124 **Caillat-Zucman S**, Gimenez JJ, Wambergue F, Albouze G, Lebkiri B, Naret C, Moynot A, Jungers P, Bach JF. Distinct HLA class II alleles determine antibody response to vaccination with hepatitis B surface antigen. *Kidney Int* 1998; **53**: 1626-1630

125 **McDermott AB**, Zuckerman JN, Sabin CA, Marsh SG, Madrigal JA. Contribution of human leukocyte antigens to the antibody response to hepatitis B vaccination. *Tissue Antigens* 1997; **50**: 8-14

126 **Vidan-Jeras B**, Brinovec V, Jurca B, Levicnik Steyinar S, Jeras M, Bohinjec M. The contribution of HLA-Class II antigens in humoral non-response and delayed response to HBsAG vaccination. *Pflugers Arch* 2000; **440**: R188-R189

127 **Höhler T**, Meyer CU, Notghi A, Stradmann-Bellinghausen B, Schneider PM, Starke R, Zepp F, Sänger R, Clemens R, Meyer zum Büschenfelde KH, Rittner C. The influence of major histocompatibility complex class II genes and T-cell Vbeta repertoire on response to immunization with HBsAg. *Hum Immunol* 1998; **59**: 212-218

128 **Wang C**, Tang J, Song W, Lobashevsky E, Wilson CM, Kaslow RA. HLA and cytokine gene polymorphisms are independently associated with responses to hepatitis B vaccination. *Hepatology* 2004; **39**: 978-988

129 **Li M**, Li R, Huang S, Gong J, Zeng X, Li Y, Lu M, Li H. The relationship between nonresponse to hepatitis B vaccine and HLA genotype/haplotype. *Zhonghua Yufangyixue Zazhi* 2002; **36**: 180-183

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

131 **López-Vázquez A**, Rodrigo L, Miña-Blanco A, Martínez-Borra J, Fuentes D, Rodríguez M, Pérez R, González S, López-Larrea C. Extended human leukocyte antigen haplotype EH18.1 influences progression to hepatocellular carcinoma in patients with hepatitis C virus infection. *J Infect Dis* 2004; **189**: 957-963

132 **Yoshizawa K**, Ota M, Saito S, Maruyama A, Yamaura T, Rokuhara A, Orii K, Ichijo T, Matsumoto A, Tanaka E, Kiyosawa K. Long-term follow-up of hepatitis C virus

infection: HLA class II loci influences the natural history of the disease. *Tissue Antigens* 2003; **61**: 159-165
133 **Vejbaesya S**, Songsivilai S, Tanwandee T, Rachaibun S, Chantangpol R, Dharakul T. HLA association with hepatitis C virus infection. *Hum Immunol* 2000; **61**: 348-353
134 **Hamed NA**, Hano AF, Raouf HA, Gamal M, Eissa M. Relationship between HLA-DRB1*0101, DRB1*0301 alleles and interleukin-12 in haemophilic patients and hepatitis C virus positive hepatocellular carcinoma patients. *Egypt J Immunol* 2003; **10**: 17-26
135 **Thursz M**, Yallop R, Goldin R, Trepo C, Thomas HC. Influence of MHC class II genotype on outcome of infection with hepatitis C virus. The HENCORE group. Hepatitis C European Network for Cooperative Research. *Lancet* 1999; **354**: 2119-2124
136 **Fanning LJ**, Levis J, Kenny-Walsh E, Wynne F, Whelton M, Shanahan F. Viral clearance in hepatitis C (1b) infection: relationship with human leukocyte antigen class II in a homogeneous population. *Hepatology* 2000; **31**: 1334-1337
137 **Asti M**, Martinetti M, Zavaglia C, Cuccia MC, Gusberti L, Tinelli C, Cividini A, Bruno S, Salvaneschi L, Ideo G, Mondelli MU, Silini EM. Human leukocyte antigen class II and III alleles and severity of hepatitis C virus-related chronic liver disease. *Hepatology* 1999; **29**: 1272-1279
138 **Mangia A**, Gentile R, Cascavilla I, Margaglione M, Villani MR, Stella F, Modola G, Agostiano V, Gaudiano C, Andriulli A. HLA class II favors clearance of HCV infection and progression of the chronic liver damage. *J Hepatol* 1999; **30**: 984-989
139 **Scotto G**, Fazio V, D'Alessandro G, Monno L, Saracino A, Palumbo E, Angarano G. Association between HLA class II antigens and hepatitis C virus infection. *J Biol Regul Homeost Agents* 2003; **17**: 316-321
140 **Höhler T**, Gerken G, Notghi A, Knolle P, Lubjuhn R, Taheri H, Schneider PM, Meyer zum Büschenfelde KH, Rittner C. MHC class II genes influence the susceptibility to chronic active hepatitis C. *J Hepatol* 1997; **27**: 259-264
141 **Hüe S**, Cacoub P, Renou C, Halfon P, Thibault V, Charlotte F, Picon M, Rifflet H, Piette JC, Pol S, Caillat-Zucman S. Human leukocyte antigen class II alleles may contribute to the severity of hepatitis C virus-related liver disease. *J Infect Dis* 2002; **186**: 106-109
142 **Wang LY**, Lin HH, Lee TD, Wu YF, Hu CT, Cheng ML, Lo SY. Human leukocyte antigen phenotypes and hepatitis C viral load. *J Clin Virol* 2005; **32**: 144-150
143 **Yenigün A**, Durupinar B. Decreased frequency of the HLA-DRB1*11 allele in patients with chronic hepatitis C virus infection. *J Virol* 2002; **76**: 1787-1789
144 **Tibbs C**, Donaldson P, Underhill J, Thomson L, Manabe K, Williams R. Evidence that the HLA DQA1*03 allele confers protection from chronic HCV-infection in Northern European Caucasoids. *Hepatology* 1996; **24**: 1342-1345
145 **Cramp ME**, Carucci P, Underhill J, Naoumov NV, Williams R, Donaldson PT. Association between HLA class II genotype and spontaneous clearance of hepatitis C viraemia. *J Hepatol* 1998; **29**: 207-213
146 **Barrett S**, Sweeney M, Crowe J. Host immune responses in hepatitis C virus clearance. *Eur J Gastroenterol Hepatol* 2005; **17**: 1089-1097
147 **Congia M**, Clemente MG, Dessi C, Cucca F, Mazzoleni AP, Frau F, Lampis R, Cao A, Lai ME, De Virgiliis S. HLA class II genes in chronic hepatitis C virus-infection and associated immunological disorders. *Hepatology* 1996; **24**: 1338-1341
148 **De Re V**, Caggiari L, Talamini R, Crovatto M, De Vita S, Mazzaro C, Cannizzaro R, Dolcetti R, Boiocchi M. Hepatitis C virus-related hepatocellular carcinoma and B-cell lymphoma patients show a different profile of major histocompatibility complex class II alleles. *Hum Immunol* 2004; **65**: 1397-1404
149 **Lechmann M**, Schneider EM, Giers G, Kaiser R, Dumoulin FL, Sauerbruch T, Spengler U. Increased frequency of the HLA-DR15 (B1*15011) allele in German patients with self-limited hepatitis C virus infection. *Eur J Clin Invest* 1999; **29**: 337-343
150 **Tillmann HL**, Chen DF, Trautwein C, Kliem V, Grundey A, Berning-Haag A, Böker K, Kubicka S, Pastucha L, Stangel W, Manns MP. Low frequency of HLA-DRB1*11 in hepatitis C virus induced end stage liver disease. *Gut* 2001; **48**: 714-718
151 **Zavaglia C**, Martinetti M, Silini E, Bottelli R, Daielli C, Asti M, Airoldi A, Salvaneschi L, Mondelli MU, Ideo G. Association between HLA class II alleles and protection from or susceptibility to chronic hepatitis C. *J Hepatol* 1998; **28**: 1-7
152 **Chu RH**, Ma LX, Wang G, Shao LH. Influence of HLA-DRB1 alleles and HBV genotypes on interferon-alpha therapy for chronic hepatitis B. *World J Gastroenterol* 2005; **11**: 4753-4757
153 **Korenaga M**, Hino K, Okita K. A possible role of human leukocyte antigen(HLA) typing for predicting response to interferon therapy in chronic hepatitis C. *Nihon Rinsho* 2001; **59**: 1345-1350
154 **Muto H**, Tanaka E, Matsumoto A, Yoshizawa K, Kiyosawa K. Types of human leukocyte antigen and decrease in HCV core antigen in serum for predicting efficacy of interferon-Alpha in patients with chronic hepatitis C: analysis by a prospective study. *J Gastroenterol* 2004; **39**: 674-680
155 **Dinçer D**, Besisik F, Oğuz F, Sever MS, Kaymakoglu S, Cakaloglu Y, Demir K, Türkoglu S, Carin M, Okten A. Genes of major histocompatibility complex class II influence chronic C hepatitis treatment with interferon in hemodialysis patients. *Int J Artif Organs* 2001; **24**: 212-214
156 **Miyaguchi S**, Saito H, Ebinuma H, Morizane T, Ishii H. Possible association between HLA antigens and the response to interferon in Japanese patients with chronic hepatitis C. *Tissue Antigens* 1997; **49**: 605-611
157 **Nishiguchi S**, Kaneshiro S, Tanaka M, Enomoto M, Akihiro T, Habu D, Takeda T, Fujino K, Tanaka T, Yano Y, Shiomi S. Association of HLA alleles with response (especially biochemical response) to interferon therapy in Japanese patients with chronic hepatitis C. *J Interferon Cytokine Res* 2003; **23**: 135-141
158 **Almarri A**, El Dwick N, Al Kabi S, Sleem K, Rashed A, Ritter MA, Batchelor JR. Interferon-alpha therapy in HCV hepatitis: HLA phenotype and cirrhosis are independent predictors of clinical outcome. *Hum Immunol* 1998; **59**: 239-242

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