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Association of human leukocyte antigen haplotypes with clearance and persistence of hepatitis B virus infection in northeastern China

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SUMMARY

This study investigated clinical implications of human leukocyte antigen (HLA) I and II haplotypes, in combination with HBV sub-genotype C2, in hepatitis B virus (HBV) infections in northeastern China. Here, HLA haplotypes of 230 HBV-infected patients were compared to 210 healthy, unrelated Han individuals. Of the 230 HBV-infected patients, 54 had acute self-limited hepatitis (ASH) with sub-genotype C2 (ASH-C2), 144 had chronic hepatitis (CH) with sub-genotypes C2 and B2 (CH-C2 and CH-B2), and 32 spontaneously recovered without sub-genotype results. All groups underwent HLA typing and haplotype analysis. The results revealed that A*02-DRB1*12 and A*02-B*15-DRB1*09 carriers were susceptible to HBV infection. A*02-B*15-DRB1*09 is probably associated with acute onset and viral clearance and A*02-DRB1*12, with viral persistence. In HBV infections, B*40-DRB1*12 was associated with HBV persistence, whereas B*46-DRB1*09, A*24-DRB1*14, and B*15-DRB1*04 carriers easily recovered from the disease. By contrast, when infected with the HBV-C2 sub-genotype, A*24-DRB1*14, B*15-DRB1*04, A*02-B*15, A*02-DRB1*15, and A*02-B*15-DRB1*09 carriers displayed an acute clinical course before recovery. This study reveals a relationship between HLA haplotypes and HBV pathogenesis, thereby providing potential therapeutic targets to treat HBV infection.

Key words: Haplotype, hepatitis B virus infection, human leukocyte antigen, sub-genotype.

INTRODUCTION

The human leukocyte antigen (HLA) complex on the short arm of chromosome 6 comprises HLAs A, B, C, and D. HLAs A, B, and C encode class I molecules. The HLA-D region consists of three primary sub-regions designated as DP (DPA1 and DPB1), DQ (DQA1 and DQB1), and DR (DRB1) loci, which encode class II molecules. HLA class I molecules, expressed in many somatic nucleated cells, are largely responsible for presenting pathogen-derived peptides from the cytosol to $CD8^+$ cytotoxic T lymphocytes. HLA class II molecules are expressed on the surface of antigen-presenting cells and target cells. They bind to antigen peptides, which can be recognized by $CD4^+$ T cells, produce an immune reaction, stimulate cytokine production to modulate $CD8^+$ cytotoxic T cells, and promote antibody production [1].

Hepatitis B virus (HBV) infections have various clinical outcomes, such as spontaneous recovery (SR), acute self-limited hepatitis (ASH), and chronic hepatitis

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(CH). CH is associated with a high lifetime risk of developing cirrhosis and hepatocellular cell carcinoma (HCC) [2, 3]. Vigorous $CD4^+$ and $CD8^+$ T lymphocyte responses to various HBV antigens are associated with HBV self-elimination, whereas insufficient $CD4^+$ T-cell activity and defective $CD8^+$ T cells in early stages of infection are associated with viral persistence [4, 5]. However, factors that determine HBV clearance and disease persistence and progress remain unclear. Potential mechanisms may involve interaction between viruses and host immune systems [6, 7].

Studies have analysed the association between clinical outcomes of HBV infection and HLA polymorphism and haplotypes [8, 9]. Currently, HBV is classified into at least eight genotypes (A–H), based on a nucleotide sequence divergence in strains >8% [10, 11]; HBV genotypes are further divided into 34 sub-genotypes. We have previously described the association between sub-genotype distribution and clinical outcomes of HBV infection [12]. We have also previously analysed the association between clinical outcomes of HBV infection and HLA polymorphism combined with HBV sub-genotypes [13, 14]. The present study demonstrates the association of HLA haplotypes, combined with HBV sub-genotypes, with HBV infection outcomes in a northeastern Chinese population.

METHODS

Subjects

Overall, 440 subjects (230 HBV-infected and 210 healthy) were enrolled from February 2006 to October 2010. HBV-infected individuals were divided into three groups (ASH, CH, and SR groups). In total, 54 individuals had ASH with C2 sub-genotype [ASH-C2, hepatitis B surface antigen ($HBsAg^+$) with high-titre IgM of anti-HBc, and HBV DNA $\geqslant 1{\cdot}0 \times 10^3$ copies/ml, and detectable HBV C2 sub-genotype]. The ASH group was characterized by self-recovery from liver disease, negative HBsAg, and positive anti-HB scores for $\leqslant 24$ weeks after treatment following initial symptom presentation. Overall, 144 individuals had CH with C2 and B2 sub-genotypes (117 CH-C2 and 27 CH-B2 infections). Individuals in the CH group who visited the Department of Infectious Diseases in the Second Affiliated Hospital of Harbin Medical University and had received antiviral therapy showed persistent HBsAg for >6 months, HBV DNA $\geqslant 1{\cdot}0 \times 10^3$ copies/ml, and detectable HBV B2 or C2 sub-genotypes; 32 individuals spontaneously recovered (SR, negative for both HBsAg and HBV DNA, but positive for both anti-HBc and anti-HBs, in a routine physical examination without any clinical symptoms) without sub-genotype results. Individuals in the control group were negative for HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc, and HBV DNA; no familial relationship was identified among them. Subjects were diagnosed in accordance with the Virus Hepatitis Diagnosis Standard of China (2000). None of the subjects was positive for hepatitis viruses A, C, and D (HAV, HCV, and HDV) or human immunodeficiency virus (HIV), based on antibody testing. The study protocol conformed to the 1975 Declaration of Helsinki regulations. The procedures were approved by our ethics committee, and informed consent was obtained from all participants.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

METHODS

Laboratory assays, including HBV serology, serum HBV DNA extraction, HBV sub-genotype analysis, and HLA typing (HLA-A, HLA-B, HLA-DRB1), have been described previously [14]; demographics and detailed descriptions of serology tests are listed in Table 1.

Statistical analysis

Arlequin v. 3.5.1.2 (http://cmpg.unibe.ch/software/) [15], including Hardy–Weinberg equilibrium (HWE) tests, multilocus haplotype inferences, and pairwise global linkage disequilibrium (LD), was used to analyse data. Maximum-likelihood haplotype frequencies were estimated using the expectation maximization (EM) algorithm in Arlequin v. 3.5.1.2. Classic coefficients of LD (Δ) and normalized LD (Δrel) were computed for each individual haplotype, as described previously [16, 17].

HLA haplotype frequencies were analysed with a two-tailed Fisher's exact test in SPSS v. 17.0 (SPSS Inc., USA). $P < 0{\cdot}05$ was considered statistically significant. The odds ratio (OR), indicating the likelihood of carrying a specific HLA haplotype, and 95% confidence intervals (95% CI) were also calculated.

RESULTS

HLA haplotype frequency (HF)

Calculated haplotypes with HF >0·05 are listed in Table 2. A*02-B*15, A*02-B*40, A*30-B*13, A*02-DRB1*09,

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Table 1. *Demographic and serological description of 198 HBV infections*

Characteristics	ASH ($n = 54$)	SR ($n = 32$)	CH ($n = 144$)	Normal group ($n = 210$)	P value
Age, years (mean ± S.D.)	40·06 ± 12·08	42·27 ± 16·18	38·26 ± 12·60	41·00 ± 10·75	0·279
Sex (male:female)	39:15	17:15	111:33	112:98	0·000
ALT level, U/l (mean ± S.D.)	1329·39 ± 802·80	19·40 ± 7·793	241·03 ± 473·84	17·95 ± 7·253	0·000
HBV DNA, copies/ml (mean ± S.D.)	$1{\cdot}92 \times 10^6 \pm 7{\cdot}17 \times 10^6$	$\leqslant 5{\cdot}0 \times 10^2$	$6{\cdot}26 \times 10^7 \pm 1{\cdot}44 \times 10^8$	$\leqslant 5{\cdot}0 \times 10^2$	0·006*
Positive for HBsAg	54 (100%)	0 (0%)	117 (100%)	0 (0%)	0·000
Positive for anti-HBs	0 (0%)	27 (84·4%)	0 (0%)	36 (17·1%)	0·000
Positive for anti-HBc	48 (89·8%)	30 (93·8%)	132 (91·5%)	0 (0%)	0·824
Positive for HBeAg	19 (34·7%)	0 (0%)	110 (76·4%)	0 (0%)	0·000
Positive for anti-HBe	19 (34·7%)	5 (15·6%)	16 (11·3%)	0 (0%)	0·002
Positive for anti-HBc IgM	54 (100%)	n.d.	n.d.	n.d.	

HBV, Hepatitis B virus; ASH, acute self-limited hepatitis; SR, spontaneous recovery from hepatitis B without clinical syndrome; CH, chronic hepatitis; ALT, alanine aminotransferase; n.d., not detected.
Positive scores for HBsAg, anti-HBs anti-HBc, HBeAg, anti-HBe and anti-HBcIgM are given as number of patients (%).
* ASH *vs.* CH.

and B*13-DRB1*07 (HF = 0·058, 0·071, 0·059, 0·062, and 0·052, respectively) were the most frequent haplotypes. Of these haplotypes, A*02-B*40 had the highest HF (0·071) in this population.

HLA haplotypes associated with HBV infection

As shown in Table 3, the frequencies of A*02-DRB1*08, A*02-DRB1*09, A*02-DRB1*12, A*11-DRB1*15, A*24-DRB1*09, A*33-DRB1*07, B*13-DRB1*12, B*15-DRB1*15, B*40-DRB1*08, B*40-DRB1*09, B*51-DRB1*09, B*51-DRB1*15, and A*02-B*15-DRB1*09 were significantly higher in the infection group (including 32 SR, 54 ASH, and 144 CH) than in the control group. However, frequencies of A*24-B*13, A*02-DRB1*04, A*02-DRB1*07, A*33-DRB1*13, A*33-DRB1*15, B*13-DRB1*09 and A*02-B*40-DRB1*15 were significantly lower in the infection group than in the control group.

HLA haplotypes associated with HBV infection recovery or persistence

In the 230 HBV-infected participants, 86 RH (recovery from hepatitis B) (including ASH and SR) recovered from the disease within 6 months. Frequencies of A*24-DRB1*14, B*15-DRB1*04, B*46-DRB1*09, and A*02-B*15-DRB1*09 were significantly higher than those in the CH group (including CH-C2 and CH-B2, $n = 117$; Table 4). By contrast, frequencies of A*02-DRB1*12 and B*40-DRB1*12 were significantly lower than those in the CH group (including CH-C2 and CH-B2, $n = 117$).

HLA haplotypes associated with acute or occult clinical course of HBV infection recovery

ASH and SR infections were characterized by self-recovery from liver disease. ASH infections had an obvious clinical course, whereas SR infections showed no clinical symptoms. The two groups were compared, and the results showed that the frequency of A*02-B*46 was significantly lower, whereas that of A*02-B*15 was significantly higher in the ASH group than in the SR group (Table 4).

HLA haplotypes associated with outcomes of HBV-C2 sub-genotype infections

Overall, 171 HBV patients were infected with HBV-C2 sub-genotype, including 54 ASH and 117 CH. Frequencies of A*02-B*15, A*02-DRB1*15, A*24-DRB1*14, B*15-DRB1*04, and A*02-B*15-DRB1*09 (Table 4) were significantly higher in the ASH-C2 group than in the CH-C2 group. B2 sub-genotype was also detected in some CH infections; however, low numbers prevented further analysis.

DISCUSSION

The relationship between HLA polymorphisms and HBV infection outcomes has been explored [18–20].

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Table 2. *Frequency of HLA-A, -B, and DRB1 haplotypes in the study group*

HLA haplotype	Total	ASH	SR	RH	CH-B2	CH-C2	CH	Infection group	Control group
A*02-B*15	0·058	0·131		0·087	0·074			0·064	
A*02-B*40	0·071	0·068	0·109	0·091	0·145	0·069	0·084	0·088	0·059
A*02-B*46			0·109	0·052					
A*02-B*51			0·062		0·055	0·057	0·054		
A*11-B*15					0·055				
A*11-B*40			0·062						
A*11-B*54					0·055				
A*24-B*15			0·062						
A*24-B*35					0·055				
A*30-B*13	0·059	0·092		0·069		0·076	0·065	0·066	0·051
A*33-B*58					0·055				
A*02-DRB1*08			0·078	0·051					
A*02-DRB1*09	0·062	0·109	0·141	0·114	0·111	0·081	0·087	0·091	
A*02-DRB1*12						0·087	0·077	0·055	
A*02-DRB1*14				0·055					
A*02-DRB1*15			0·074	0·054	0·074				0·055
A*11-DRB1*08					0·055				
A*11-DRB1*09					0·055				
A*11-DRB1*12					0·074				
A*11-DRB1*15			0·05						
A*24-DRB1*09					0·055				
A*24-DRB1*14			0·062						
A*30-DRB1*07		0·055				0·071	0·062	0·052	
A*33-DRB1*15					0·055				
B*13-DRB1*07	0·052	0·055				0·081	0·069	0·061	
B*13-DRB1*12					0·055	0·062	0·061		
B*15-DRB1*04		0·055							
B*15-DRB1*09		0·055			0·092				
B*15-DRB1*15		0·081		0·053	0·055				
B*40-DRB1*08					0·055				
B*40-DRB1*09			0·062		0·055		0·05		
B*40-DRB1*12						0·051			
B*51-DRB1*09					0·055				
B*52-DRB1*15					0·055				
A*02-B*15-DRB1*09		0·064							
A*02-B*15-DRB1*15					0·074				
A*02-B*40-DRB1*09			0·062						
A*11-B*40-DRB1*04					0·055				
A*30-B*13-DRB1*07		0·055				0·072	0·062	0·054	

ASH, Acute self-limited hepatitis; SR, spontaneous recovery from hepatitis B without clinical syndrome; RH, recovery from hepatitis B; CH-B2, CH-C2, chronic hepatitis with sub-genotypes B2 and C2.
Haplotype frequencies <0·05 are not shown.

However, the relationship between HLA haplotypes and HBV infection outcomes is rarely studied [21, 22]. Furthermore, the influence of HLA-A, HLA-B, DRB1, and HBV sub-genotypes on HBV infection outcomes has not been reported.

Hwang *et al*. [23] reported that the HLA haplotypes A*33-B*44, B*44-DRB1*07, B*46-DRB1*08, A*33-DRB1*07, A*02-DRB1*14, and A*24-DRB1*12 are more frequent in infected than control groups. Moreover, HFs of A*33-B*44-DRB1*07 and A*02-B*46-DRB1*08 are higher in infected than control groups. By contrast, B*44-DRB1*13, B*62-DRB1*04, A*24-DRB1*04, and A*33-B*44-DRB1*14 are more common in control groups. However, the data presented here differ. A*02-DRB1*08, A*02-DRB1*09, A*02-DRB1*12, A*11-DRB1*15, A*24-DRB1*09, A*33-DRB1*07, B*13-DRB1*12, B*15-DRB1*15, B*40-DRB1*08, B*40-DRB1*09, B*51-DRB1*09, B*51-DRB1*15, and A*02-B*15-DRB1*09 haplotypes may pose a higher risk of HBV infection compared

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Table 3. *Comparison of frequency of HLA-A, B, and DRB1 haplotypes between infection and control groups*

	Infection group ($n = 230$)		Control group ($n = 210$)					
HLA haplotype	Freq. (%)	*n*	Freq. (%)	*N*	*P*	*P*(Fisher)	OR	95% CI
A*24-B*13	0·46	2	1·85	8		0·05	0·22	0·05–1·06
B*13-DRB1*09	0·3	1	2·23	9		0·01	0·10	0·01–0·79
B*13-DRB1*12	4·66	21	0·31	1	<0·0001	<0·0001	20·04	2·68–149·68
B*15-DRB1*15	3·89	18	0·77	3	0·00	0·00	5·66	1·66–19·36
B*40-DRB1*08	2·65	12	0·47	2	0·01	0·01	5·60	1·25–25·16
B*40-DRB1*09	4·65	21	1·34	6	0·01	0·01	3·30	1·32–8·26
B*51-DRB1*09	3·02	14	0·24	1	0·00	0·00	13·15	1·72–100·46
B*51-DRB1*15	2·15	10	0·47	2	0·03	0·04	4·60	1·01–21·32
A*02-DRB1*07	1·06	5	3·01	13	0·04	0·05	0·34	0·12–0·97
A*02-DRB1*08	3·61	17	0·92	4	0·01	0·01	3·99	1·33–11·96
A*02-DRB1*09	9·18	42	3·35	14	0·00	0·00	2·91	1·57–5·42
A*02-DRB1*12	5·51	25	2·48	10	0·02	0·02	2·36	1·12–4·97
A*11-DRB1*15	3·55	16	0·72	3	0·01	0·01	5·01	1·45–17·32
A*24-DRB1*09	2·85	13	0·74	3	0·02	0·02	4·04	1·14–14·29
A*33-DRB1*07	1·71	8	0·3	1		0·04	7·42	0·92–59·55
A*33-DRB1*13	0·65	3	2·3	10	0·03	0·05	0·27	0·07–0·98
A*33-DRB1*15	0.000 012	0	1·42	6		0·01	n.a.	n.a.
A*02-B*15-DRB1*09	2·98	14	0·71	3	0·01	0·01	4·36	1·25–15·29
A*02-B*40-DRB1*15	0·23	1	2·84	12	0·00	0·00	0·07	0·01–0·57

OR, Odds ratio; CI, confidence interval; n.a., not available.
P(Fisher) values <0·05 are shown in the Table; values ⩾0·05 have been omitted.

to that posed by controls. By contrast, A*24-B*13, B*13-DRB1*09, A*02-DRB1*07, A*33-DRB1*13, A*33-DRB1*15, and A*02-B*40-DRB1*15 may protect subjects from HBV infection.

Cho *et al.* [8] reported that HLA haplotypes DRB1*1302-DQB1*0609, DQB1*0609-DPB1*0201, and DRB1*1302-DQB1*0609-DPB1*0201 are strongly associated with viral clearance, which differs from our study. Our previous [14] and current studies have found that DRB1*13 and A*33-DRB1*13 carriers are not susceptible to HBV infection, whereas no association with DRB1*13 and A*33-DRB1*13 infections and clearance and persistence was found. HLA-DQB1 and DPB1 were not investigated in our study, and if LD with HLA-DRB1*13–DQB1*06 and HLA-DRB1*13–DQB1*06-DPB1*02 is associated with HBV clearance, this aspect has not been reported previously and, hence, needs to be investigated. Thio *et al.* [24] reported that A*01-B*08-DRB1*03, B*44-Cw*1601, and B*44-Cw*0501 haplotypes are associated with viral persistence. Zhu *et al.* [1] reported that HLA-A*1101-B*4601-C*0102 and DQA1*0302-DQB1*0303-DRB1*09 haplotypes have lower HFs in patients who may be responsive to interferon-α treatment than those in the group non-responsive to chronic HBV infection. Pan *et al.* [25] have reported that A*110 101G-C*070201G, A*110101G-C*140201G, A*110101G-B*510101G-C*140201G, A*330301G-B*580101G, B*580101G-C*030201G, A*330301G-B*580101G-C*030201G, and B*510101G-C*140201 G haplotypes are positively associated with HCC, whereas A*020701G-B*460101G, B*460101G-C*010201G, and A*020701G-B*460101G-C*010201 G are negatively associated with HCC. However, these results focus on the influence of either HLA class I or HLA class II haplotypes on HBV infection outcomes. No result has been reported from the combined study of HLA class I and class II alleles. In our study, A*02-DRB1*12 and B*40-DRB1*12 haplotypes may be associated with viral persistence. Furthermore, A*24-DRB1*14, B*15-DRB1*04, B*46-DRB1*09, and A*02-B*15-DRB1*09 haplotypes may be associated with viral clearance. However, A*02-B*15 and A*02-DRB1*15 carriers may easily clear the virus with acute clinical onset. B*46-DRB1*09 was no longer associated with viral

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Table 4. *Comparison of frequency of HLA-A, B, and DRB1 haplotypes in infection groups*

HLA haplotype	Freq. (%)	*n*	Freq. (%)	*n*	*P*	*P*(Fisher)	OR	95% CI
RH *vs.* CH		86		144				
B*15-DRB1*04	4·97	9	0·73	2		0·00	7·90	1·69–36·99
B*40-DRB1*12	0·73	1	4·49	13	0·02	0·02	0·12	0·02–0·95
B*46-DRB1*09	3·85	7	1·07	3		0·04	4·03	1·03–15·80
A*02-DRB1*12	2·71	5	7·72	22	0·04	0·04	0·36	0·13–0·97
A*24-DRB1*14	3·80	7	0·37	1		0·01	12·18	1·49–99·83
A*02-B*15-DRB1*09	4·65	8	1·55	4		0·04	3·46	1·03–11·68
ASH-C2 *vs.* CH-C2		54		117				
A*02-B*15	13·11	14	4·70	11	0·01	0·01	3·02	1·32–6·89
B*15-DRB1*04	5·56	6	0·59	1		0·00	13·71	1·63–115·31
A*02-DRB1*15	4·63	5	0·47	1		0·01	11·31	1·31–98·03
A*24-DRB1*14	3·70	4	0·43	1		0·04	8·96	1·00–81·16
A*02-B*15-DRB1*09	6·48	7	0·85	2		0·01	8·04	1·64–39·38
ASH *vs.* SR		54	32					
A*02-B*15	13·11	14	3·13	2	0·03	0·05	4·62	1·01–21·02
A*02-B*46	2·00	2	10·94	7		0·01	0·15	0·03–0·76

OR, Odds ratio; CI, confidence interval; RH, recovery from hepatitis B; CH, chronic hepatitis; ASH, acute self-limited hepatitis; C2, sub-genotype B2; SR, spontaneous recovery from hepatitis B without clinical syndrome.
P(Fisher) values <0·05 are shown in the Table; values ⩾0·05 have been omitted.

clearance when HBV-C2 infection was observed. When infected with HBV-C2, A*02-DRB1*12 and B*40-DRB1*12 were no longer associated with HBV persistence. This study is the first to report such findings. In a previous study, class I alleles were most strongly associated with HBV infection, suggesting that $CD8^+$ cytotoxic T lymphocytes are important to viral clearance or persistence [24]. Viral peptides differ in their ability to bind to particular HLA glycoproteins; this suggests an internal mechanism underlying the association of HLA class II allele polymorphisms with HBV infection outcomes and response to vaccination [26]. Therefore, further investigation of the influence of combined HLA class I and class II alleles on HBV infection outcomes is required.

HLA haplotype distribution has been investigated in many Chinese regions [26–28]. For instance, A*02-B*46 (HF = 0·071) and A*11-B*15 (HF = 0·051) are the predominant haplotypes in the Han population. A*02-B*46 and A*30-B*13 have significantly strong LD, whereas A*02-B*15 and A*02-B*40 have low LD [26]. However, A*30-B*13-DRB1*07 is the most frequent haplotype in the northern Chinese Han population. In addition, A*30-B*13, A*33-B*58, A*01-B*37, A*30-DRB1*07, A*33-DRB1*13, A*01-DRB1*10, B*37-DRB1*10, B*08-DRB1*17, B*13-DRB1*07, and B*58-DRB*17 exhibit a significant positive LD [27]. In this study, the A*02-B*15, A*02-B*40, A*30-B*13, A*02-DRB1*09, and B*13-DRB1*07 haplotypes were the most frequent HLA-A, HLA-B, and DRB1 haplotypes. Of these haplotypes, A*02-B*40 exhibited the highest HF in the northeastern Chinese Han population. By contrast to the haplotypes described in other studies, A*30-B*13 and B*13-DRB1*07 (not A*02-B*15 and A*02-B*40) showed a significantly high LD in this study. This discrepancy may be due to regional differences. Various HLA class I and class II alleles are related to HBV infection outcomes in different ethnic populations. However, finding consistent associations in different studies is difficult due to racial diversity, variations in study design, methodology, and complex immune-regulatory mechanisms [25]. Furthermore, the sample size involved in each study may be insufficient and findings may be incidental [1]. Therefore, further validation studies considering other ethnic groups and a larger sample size are required.

In conclusion, our results revealed that B*46-DRB1*09 is probably associated with viral clearance, whereas B*40-DRB1*12 may be related to viral persistence. A*02-DRB1*12 and A*02-B*15-DRB1*09 haplotype carriers were susceptible to HBV infection, whereas the presence of A*02-DRB1*12 may indicate HBV persistence, and the presence of A*02-B*15-DRB1*09 may indicate HBV clearance.

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Additionally, HBV infections, including ASH-C2 and SR without the detected subtypes, were associated with A*02-B*15-DRB1*09. A*24-DRB1*14 and B*15-DRB1*04 carriers may be associated with viral clearance and recovery from the disease with acute clinical onset, when infected with HBV-C2. In patients infected with the HBV-C2 sub-genotype, A*02-B*15 and A*02 -DRB1*15 carriers also showed acute clinical onset before recovery. HLA haplotypes in ASH and SR infections were compared, and the results showed that A*02-B*46 carriers were more likely to recover from a disease with an occult clinical course. The data obtained in these and previous studies suggest a link between HLA haplotypes and HBV pathogenesis, thereby providing potential therapeutic targets to treat HBV infections.

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DECLARATION OF INTEREST

None.

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