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EDITORIAL

HLA class Ⅱ associated with outcomes of hepatitis B and C infections

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Abstract

Several factors influence the clinical course of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. The human leukocyte antigen (HLA) system, the major histocompatibility complex (MHC) in humans, has been considered one of the most important host factors with respect to outcomes. To date, conventional genotyping studies have shown that *HLA* class Ⅱ loci are mainly associated with spontaneous clearance of HBV and HCV. However, the specific HLA locus associated with the outcomes of hepatitis virus infection remains unclear. A recent genome-wide association study (GWAS) using a comprehensive approach for human genotyping demonstrated single nucleotide polymorphisms (SNPs) associated with the outcomes of hepatitis virus infection. Examination of large numbers of cohorts revealed that several SNPs in both *HLA-DPA1* and *HLA-DPB1* loci are associated with persistent HBV infection in Asian populations. To date, however, few studies have focused on *HLA-DP* because polymorphisms of *HLA-DP* haplotype do not vary greatly as compared with other loci of *HLA*. There are not enough studies to reveal the function of *HLA-DP*. GWAS additionally detected candidate SNPs within HLA loci associated with chronic HBV or HCV hepatitis, hepatic fibrosis, and the development of hepatocellular carcinoma. The results of one cohort were not always consistent with those of other cohorts. To solve several controversial issues, it is necessary to validate reported SNPs on *HLA* loci in global populations and to elucidate the *HLA*-allele-regulated molecular response to hepatitis virus infection.

Key words: Hepatitis B virus; Hepatitis C virus; Hepatocarcinogenesis; Human leukocyte antigen; Genome-wide association studies; Genotyping; Persistent infection

Core tip: Conventional genotyping studies have shown that human leukocyte antigen (*HLA*) typing was one of the most important host factors with respect to outcomes of hepatitis B and C virus infections. However, the specific HLA locus associated with the outcomes remains unclear. Recently a genome-wide association study for human genotyping demonstrated single nucleotide polymorphisms associated with the outcomes of hepatitis virus infection. Now it has been confirmed that several single nucleotide polymorphisms in both *HLA-DP* loci were associated with persistent hepatitis B virus infection in Asian populations.

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INTRODUCTION

The human leukocyte antigen (HLA) system, the major histocompatibility complex (MHC) in humans, has long been considered the most important region in the human genome with respect to infection, inflammation, autoimmunity, and transplantation medicine[1,2]. In humans, *HLA* complex consists of more than 200 genes located

close together on chromosome 6. Genes in this complex are categorized into three basic groups: class I (*HLA-A, -B*, and *-C*), class Ⅱ (*HLA-DR*, *-DQ*, and *-DP*), and class III (some genes involved in inflammation and other immune-system activities). Interactions among HLA-restricted T lymphocytes, B lymphocytes, natural killer (NK) cells, and cytokines influence immune response to viral infection. *HLA* class I and Ⅱ molecules are expressed as cell surface antigens that bind to peptide epitopes on $CD8^+$ T cells and $CD4^+$ T cells, respectively. Effective presentation of viral antigens by the HLA system induces good immune response.

It is well known that some patients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) spontaneously recover and can escape from persistent infection[3-5]. Progression of liver diseases by chronic viral infection also differs among patients. In addition, the response to HBV vaccination is different in each person. To identify immune systems against invaders in individual patients, *HLA* haplotypes related to persistent viral infection or providing protection against such infection have been examined. Singh *et al*[6] reported a detailed review about associations of *HLA* types with HBV and HCV infections among global populations. They speculated that there was a limited chance of detecting globally common *HLA* types related to outcomes or disease progression associated with hepatitis viral infection because *HLA* loci are diverse owing to racial admixture, environmental and selection pressure, and inherent polymorphic nature, leading to allelic variations among different ethnic groups.

Recent genome-wide association studies (GWAS) have demonstrated single nucleotide polymorphisms (SNPs) associated with the outcomes of hepatitis virus infection[7-14]. Imputation-based association analysis showed that some of the SNPs are located near *HLA* loci in chromosome 6p21[7,8,15]. Conventional genotyping and GWAS are different approaches for analysis. Conventional genotyping examines selected targeted genes, while GWAS can comprehensively examine hundreds of thousands of SNPs[16]. Although both approaches have suggested that *HLA* loci play important roles in the outcomes of viral hepatitis, the precise regions of *HLA* loci detected by each approach differed. In the present review, we summarize and compare the latest data obtained by GWAS with previous data obtained by conventional *HLA* typing.

ASSOCIATION BETWEEN HEPATITIS VIRAL INFECTION AND *HLA* ALLELES IDENTIFIED BY GENOTYPING

Singh *et al*[6] suggested that an association of *HLA DR*13* alleles in *HLA* Class Ⅱ was protective in both HBV and HCV infections in several populations. *HLA DRB1*11* and *HLA DQB1*0301* were protective in HCV infection, but were associated with persistent HBV infection.

A recent meta-analysis showed that *HLA-DR*03* and *HLA-DR*07* were associated with an increased risk of persistent HBV infection in 19 individual case-control studies including 9 Han Chinese cohorts, 3 Korean cohorts, 2 Iranian cohorts, and 1 cohort each of Caucasian, Gambian, Taiwanese, Thai, and Turkish subjects[17]. In contrast, *HLA-DR*04* and *HLA-DR*13* were associated with clearance of HBV infection. In Chinese Han populations, *HLA-DR*01* was associated with clearance of HBV infection, while in other ethnic groups there was no association between *HLA-DR*01* and HBV infection.

As for HCV infection, a study performed in patients from the United Kingdom and the United States reported that the inhibitory NK cell receptor KIR2DL3 and *HLA-C1* ligand, *HLA* class I interact directly to promote spontaneous viral clearance[18]. In global populations, *HLA* class Ⅱ, especially several alleles in *HLA-DRB1*, has been linked to persistent HCV infection[19,20]. Interestingly, Spanish and American groups reported an association between *MICA* genotypes in *HLA* class Ⅲ and clearance of HCV[21,22].

ASSOCIATION BETWEEN HEPATITIS VIRAL INFECTION AND SNPS IN *HLA* LOCUS IDENTIFIED BY GWAS

A recent GWAS discovered many SNP candidates associated with common diseases[16]. In research on viral hepatitis, several SNPs associated with outcomes, including the *HLA* coding region of chromosome 6p21.3, were detected by GWAS.

HBV infection

Kamatani *et al*[7] reported the results of a case-control association study of HBV infection in 2009. They showed that rs3077 SNP near *HLA-DPA1* gene and rs9277535 SNP near *HLA-DPB1* were associated with persistent HBV infection in Japanese cohorts. In addition, *HLA* haplotype analysis showed that *HLA-DPA1*0202-DPB1*0501* and *HLA-DPA1*0202-DPB1*0301* were risk types for persistent HBV infection, and *HLA-DPA1*0103-DPB1*0402* and *HLA-DPA1*0103-DPB1*0401* were protective types for HBV infection. The same group performed a second GWAS analysis involving a larger number of cohorts[8]. The study validated that rs3077 SNP near *HLA-DPA1* gene and rs9277535 SNP near *HLA-DPB1* were strongly associated with persistent HBV infection. Other SNPs, rs2856718 and rs7453920 within the *HLA-DQ* locus, were also associated with persistent HBV infection. Moreover, HLA haplotype analysis indicated that *HLA-DQA1*0102-DQB1*0303* and *HLA-DQA1*0301-DQB1*0601* were risk types for persistent HBV infection, while *HLA-DQA1*0102-DQB1*0604* and *HLA-DQA1*0101-DQB1*0501* were protective types for HBV infection. GWAS of Han Chinese populations also showed that the *HLA-DPA1* and *HLA-DPB1* genes were related to persistent HBV infection. The first study from China indicated that 4 SNPs related to *HLA-*

Table 1 Single nucleotide polymorphisms within human leukocyte antigen loci associated with outcomes of hepatitis B virus infection

Ethnic group	Outcome	HLA locus	SNP	Odds	95%CI	HLA haplotype	Odds	Ref.
Japanese	Chronic infection	HLA-DPA1	rs3077	0.56	0.51-0.61			[7]
		HLA-DPB1	rs9277535	0.57	0.52-0.62			
						DPA1*0202-DPB1*0501	1.45	
						DPA1*0202-DPB1*0301	2.31	
						DPA1*0103-DPB1*0402	0.52	
						DPA1*0103-DPB1*0401	0.57	
Japanese	Chronic infection	HLA-DQ	rs2856718	1.43	1.33-1.54			[8]
			rs7453920	1.66	1.49-1.85			
						DQA1*0102-DQB1*0303	19.3	
						DQA1*0301-DQB1*0601	5.02	
						DQA1*0102-DQB1*0604	0.16	
						DQA1*0101-DQB1*0501	0.39	
Chinese	Chronic infection	HLA-DPA1	rs2395309	0.71	0.59-0.86			[9]
		HLA-DPA1	rs3077	0.64	0.53-0.78			
		HLA-DPA1	rs2301220	0.67	0.56-0.81			
		HLA-DPA1	rs9277341	1.77	1.39-2.25			
		HLA-DPB1	rs3135021	0.78	0.64-0.94			
		HLA-DPB1	rs9277535	0.56	0.47-0.68			
		HLA-DPB1	rs10484569	1.60	1.33-1.93			
		HLA-DPB1	rs3128917	1.91	1.59-2.30			
		HLA-DPB1	rs2281388	1.66	1.38-2.01			
		HLA-DPB1	rs3117222	0.51	0.42-0.61			
		HLA-DPB1	rs9380343	0.61	0.50-0.73			
Indonesian	Vaccine response	HLA-DR	rs3135363	1.59	1.45-1.73			[10]
		HLA-DPB1	rs9277535	0.82	0.71-0.96			
		HLA-Ⅲ	rs9267665	2.13	1.82-2.49			
Chinese	HCC	HLA-DQA1/DRB1	rs9272105	1.28	1.22-1.35			[11]
		GRIK1*	rs455804	0.84	0.80-0.89			
Japanese, Korean	Chronic infection	HLA-DPA1	rs3077	0.46	0.39-0.54			[12]
		HLA-DPB1	rs9277542	0.50	0.43-0.60			
Chinese	Chronic infection	HLA-DPB1	rs9277535	0.60	0.51-0.70			[13]
		HLA-DPA1	rs3077	0.81	0.75-0.95			
		HLA-DQ	rs7453920	0.60	0.49-0.73			
		HLA-DQ	rs2856718	0.75	0.64-0.89			
	HCC	HLA-DQ	rs2856718	0.70	0.59-0.83			
		HLA-DPA1	rs3077	0.78	0.67-0.92			
Chinese	HCC	HLA-DQ	rs9275319	1.51	1.38-1.66			[14]
		STAT4*	rs7574865					

HLA: Human leukocyte antigen; SNP: Single nucleotide polymorphism; HCC: Hepatocellular carcinoma.

DPA1 gene, including rs3077, and 7 SNPs related to *HLA-DPB1*, including rs9277535, were associated with chronic HBV infection[9]. Another study showed that rs7453920 and rs2856718 SNPs near *HLA-DQ* were associated with persistent HBV infection in addition to the rs3077 and rs9277535 SNPs[10] (Table 1).

A recent report from another Japanese group showed that rs3077 SNP near *HLA-DPA1* gene and rs9277542 SNP near *HLA-DPB1* gene were associated with persistent HBV infection[12]. Studies using genotyping methods validated that the rs3077 and rs2395309 SNPs near *HLA-DPA1* gene and the rs9277542 SNP near *HLA-DPB1* were associated with HBV infection in Han Chinese populations[23-25].

GWAS revealed three independent variants within the *HLA* complex that were related to a poor response to HB vaccine in the Indonesian population. Specifically, rs3135363 SNP near *HLA-DR*, rs9277542 SNP near *HLA-DPB1*, and rs9267665 in *HLA* class Ⅲ were associated with antibody titers after HB vaccination[10].

A comparison between cohorts with and without hepatocellular carcinoma (HCC) showed that rs9272105 SNP near *HLA-DQA1/DRB1* and rs455804 SNP near *GRIK1* were significantly associated with HCC development in Chinese patients with HBV[11]. There was a partial association of the genotype of rs9272105 to *HLA-DRB1*0405* and **0901*. Another study showed that rs2856718 SNP at *HLA-DQ* and rs3077 SNP at *HLA-DPA1* had a protective effect against HCC progression as compared with the dominant SNP of rs2856718 in Han Chinese populations[13]. In 2013, it was reported that rs9275319 at *HLA-DQ* and rs7574865 at *STAT4* were

Table 2 Single nucleotide polymorphisms within human leukocyte antigen loci associated with outcomes of hepatitis C virus infection

Ethnic group	Outcome	No. of cohorts	HLA locus	SNP	Odds	95%CI	Haplotype	Odds	Ref.
Japanese	HCC	721 HCC *vs* 2890 HCV-negative controls	MICA	rs2596542	1.34	1.16-1.53			[30]
Japanese	Cirrhosis	682 cirrhosis *vs* 1045 Chronic hepatitis	C6orf10	rs910049	1.73	1.40-2.15			[31]
			No gene	rs3135363	1.58	1.32-1.90			
							DQA1*0601	2.80	
							DPB1*0405	1.45	

SNP: Single nucleotide polymorphism; HCC: Hepatocellular carcinoma; HLA: Human leukocyte antigen; HCV: Hepatitis C virus.

independently associated with the risk of HCC in Han Chinese populations[14]. There was a moderate association between the genotype of rs9275319 SNPs with *HLA-DQB1*0401* and *HLA-DQA1*0303*. On the other hand, there was no significant association between HCC development by HBV infection and *HLA* alleles in Korean or Japanese populations[26]. It thus remains unclear whether specific HLA loci play important roles in hepatocarcinogenesis in patients with HBV.

HCV infection

It is globally recognized that interleukin-28B (IL-28B) gene polymorphisms originally detected by GWAS are associated with spontaneous clearance of HCV, as well as with the response to combination therapy with pegylated interferon and ribavirin in patients with HCV[27,28]. However, this SNP is not located in HLA loci. A recent study identified rs4273729 SNP near *HLA DQB1*0301* as a candidate allele for spontaneous clearance of HCV in populations with European and African ancestry[29]. *HLA DQB1*0301* and *IL28B* are independently associated with spontaneous resolution of HCV infection.

Comparisons between cohorts with and without HCC showed that rs2596542 SNP at the 5' flanking region of *MICA* in *HLA* class Ⅲ was significantly associated with HCC development in Japanese patients with HCV[30]. Soluble MICA levels in serum were significantly lower in AA genotype of rs2596542 and were associated with a high risk of HCC progression. The same group identified 2 SNPs in the *MHC* region that were associated with progression from chronic hepatitis to cirrhosis. These SNPs were located at rs910049 and rs3135363 on chromosome 6p21.3[31]. Imputation-based association analysis showed that *HLA-DQA1*0601* and *HLA-DPB1*0405* were associated with progression of cirrhosis (Table 2).

FUTURE DIRECTIONS

Ongoing association studies are evaluating the effects of genetic variations on the outcomes of hepatitis virus infection in large groups of patients. However, most SNPs identified by association studies did not link to phenotype, and many other SNPs remained untyped. Imputation-based association analysis exploits information on patterns of multi-marker correlation ("linkage disequilibrium") from publically available databases to estimate ("impute") patient genotypes associated with identified SNPs and thereby assess the relations of such genotypes to phenotypes[32,33]. Owing to this method, the relations between SNPs and *HLA* haplotypes associated with the outcomes of HBV or HCV infection are becoming clearer.

In HBV infection, conventional genotyping showed that *HLA* class Ⅱ, DR and DQ haplotypes were the most important regions of host genetic factors for outcomes. However, GWAS showed that rs3077 SNP near *HLA-DPA1* gene and rs9277535 SNP near *HLA-DPB1* gene were associated with persistent HBV infection in Asian populations[7,9,12,13]. *HLA-DPA1* and *DPB1* have also been associated with responsiveness to HB vaccination[10,34,35]. To date, however, few studies have focused on *HLA-DP* because polymorphisms of *HLA-DP* haplotype do not vary greatly as compared with other loci of *HLA*[36]. The structures of *HLA-DP* and *HLA-DP* molecules are similar to those of other *HLA* class Ⅱ molecules. Therefore, similar to the functions of other *HLA* class Ⅱ molecules, *HLA-DP* and *HLA-DP* molecules might affect the ability of *HLA* class Ⅱ molecules to present antigens to CD4-positive helper T cells and result in immune response to HBV. Recently, *HLA-DPA1* and *HLA-DPB1* mRNA expressions in normal liver were respectively associated with SNP types rs3077 and rs9277535 in European populations. The mRNA expressions of *HLA-DPA1* and *HLA-DPB1* were low in genotypes rs3077-G and 9277535-G, which were associated with a high risk of persistent HBV infection[37]. However, another study in European- and African-Americans showed that rs9277534 of the *HLA-DPB1* allele (496-A/G) was a novel variant associated with persistent HBV infection[38]. In contrast to the former study, the 496-GG genotype was associated with both higher mRNA expression of *HLA-DP* and persistent HBV infection.

Inconsistent results have been obtained for the association between *HLA* alleles and HCC in patients with HBV infection. In Han Chinese populations, several SNPs in *HLA* class Ⅱ have been associated with progression of HCC. However, no common SNP was confirmed by independent researchers. In addition, SNPs in chromosomes 1p36.22, 2q32.2, and 21q21.3, were also associated with HBV-related HCC[39]. Further examinations are definitely required to elucidate the role of *HLA* loci on the progression of HCC in patients with HBV.

GWAS indicated that *HLA* loci are related to important host factors involved in several aspects of HCV

infection. First, *HLA DQB1*0301* was reported to be independently associated with spontaneous clearance of HCV infection. Previous HLA haplotype analysis showed that *HLA DQB1*0301* was associated with HCV clearance in French females, African-Americans, and Italian populations[40-42]. Thus, GWAS confirmed the results of previous results. However, the mechanism by which such alleles affect HCV clearance remains undetermined.

In the Japanese population, rs4273729 SNP near *HLA DQB1*0301* and *MICA* SNP in - *HLA* class Ⅲ were respectively associated with progression of hepatitis to cirrhosis[31] and HCC[30] in patients with HCV. This is attractive information for the prediction of clinical course, but several issues remain to be defined. First, HCC most frequently develops in cirrhotic patients infected with HCV. It is not known why different SNPs are identified in continuous pathological conditions such as HCC and hepatic cirrhosis in patients with HCV. Next, an intronic SNP in the *DEPDC-5* gene, without an *HLA* locus, was also associated with HCC development in the Japanese population[43]. In European populations, several SNPs without *HLA* loci were associated with the progression of hepatic fibrosis[44]. The progression of chronic hepatitis C has been confirmed to depend on multiple factors, including age, gender, infection period, obesity, alcohol intake, and treatment[45]. It is suspected that the effects of *HLA* loci on fibrosis progression or the development of HCC (or both) differ in the each population studied.

In conclusion, genome association analysis of large numbers of cohorts indicated that *HLA* loci are one of the most important host determinants of the clinical characteristics of HBV and HCV infections, acting in conjunction with factors such as viral load, viral genotype, age, alcohol intake, and hepatic fibrosis. However, it is necessary to validate reported SNPs on *HLA* loci in global populations and to elucidate *HLA*-allele-regulated molecular responses to hepatitis virus infection.

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