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Baishideng Publishing Group Inc
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Host genetic factors affecting hepatitis B infection outcomes: Insights from genome-wide association studies

Izzet Mehmet Akcay, Seyma Katrinli, Kamil Ozdil, Gizem Dinler Doganay, Levent Doganay

Izzet Mehmet Akcay, Seyma Katrinli, Gizem Dinler Doganay, Department of Molecular Biology and Genetics, Istanbul Technical University, Istanbul 34469, Turkey

Kamil Ozdil, Levent Doganay, Department of Gastroenterology and Hepatology, Umraniye Teaching and Research Hospital, Istanbul 34764, Turkey

ORCID number: Izzet Mehmet Akcay (0000-0001-6364-0062); Seyma Katrinli (0000-0003-1575-8642); Kamil Ozdil (0000-0003-2556-3064); Gizem Dinler Doganay (0000-0002-3586-1287); Levent Doganay (0000-0002-2263-6689).

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Correspondence to: Levent Doganay, MD, Associate Professor, Doctor, Department of Gastroenterology and Hepatology, Umraniye Teaching and Research Hospital, Umraniye, Istanbul 34764, Turkey. levent.doganay@saglik.gov.tr
Telephone: +90-216-6321818/1846
Fax: +90-216-6327124

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Abstract

The clinical outcome of Hepatitis B Virus (HBV) infection depends on the success or failure of the immune responses to HBV, and varies widely among individuals, ranging from asymptomatic self-limited infection, inactive carrier state, chronic hepatitis, cirrhosis, hepatocellular carcinoma, to liver failure. Genome-wide association studies (GWAS) identified key genetic factors influencing the pathogenesis of HBV-related traits. In this review, we discuss GWAS for persistence of HBV infection, antibody response to hepatitis B vaccine, and HBV-related advanced liver diseases. HBV persistence is associated with multiple genes with diverse roles in immune mechanisms. The strongest associations are found within the classical human leukocyte antigen (HLA) genes, highlighting the central role of antigen presentation in the immune response to HBV. Associated variants affect both epitope binding specificities and expression levels of HLA molecules. Several other susceptibility genes regulate the magnitude of adaptive immune responses, determining immunity *vs* tolerance. HBV persistence and nonresponse to vaccine share the same risk variants, implying overlapping genetic bases. On the other hand, the risk variants for HBV-related advanced liver diseases are largely different, suggesting different host-virus dynamics in acute *vs* chronic HBV infections. The findings of these GWAS are likely to pave the way for developing more effective preventive and therapeutic interventions by personalizing the management of HBV infection.

Key words: Genome-wide association studies; Hepatitis B infection; Hepatocellular carcinoma; Cirrhosis; Antigen

presentation; Immune response to hepatitis B virus

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Core tip: Genome-wide association studies (GWAS) have proven to be very useful in uncovering the host genetic factors that influence the clinical outcomes of hepatitis B virus (HBV) infection. Both class I and class II human leukocyte antigen (HLA) genes were implicated in persistence of HBV infection; associated variants affected antigen-binding specificities and expression levels of HLA molecules. HBV persistence and vaccine nonresponse were associated with the same HLA-DP alleles, suggesting a critical role for the surface antigen in HBV pathogenesis. These findings might be exploited for development of potent vaccines based on alternative epitopes. GWAS for HBV-related pathologies identified many other immune-related genes, and provided genetic markers to detect the individuals at high risk for HBV-related diseases.

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INTRODUCTION

Hepatitis B virus (HBV) is the most common viral pathogen of the human liver, and is a prominent cause of acute and chronic hepatitis, liver failure, cirrhosis and hepatocellular carcinoma (HCC). Around 257 million people, or 3.5% of the global population, are estimated to have chronic HBV infection^[1], and more than 800 thousands people lose their life annually due to HBV-related complications^[2]. Perinatal and childhood infections are very common in regions with high endemicity, and mostly result in life-long persistence, whereas infections at adulthood are mostly self-limited^[3]. Chronic HBV carriers are at a high risk of developing end-stage liver diseases, such as cirrhosis and HCC^[4]. Indeed, HBV infection is responsible for 27% of cirrhosis and 53% of HCC cases worldwide^[5]. Hepatitis B vaccine effectively prevents new infections, while antiviral medicines suppress progression of HBV-related liver damage. However, vaccination, safe healthcare practices, and access to treatment do not have full population coverage, and HBV infection still remains a major public health problem^[6].

HBV is generally considered to be non-cytopathic *per se*; the liver injury associated with HBV infection is immune-driven. The clinical outcome of HBV infection varies greatly among individuals, ranging from asymptomatic self-limited infection, inactive carrier state, chronic hepatitis to end-stage liver diseases with life-threatening complications^[3,7-9]. Viral, host and environmental factors affect these outcomes. Viral core/pre-core mutations,

certain viral genotypes (e.g., genotype C in comparison to genotype B), high viral load, early-life (perinatal and childhood) infections, male sex, host genetic factors (e.g., HLA class II homozygosity), suppressed immune status, co-existing metabolic diseases, and exposure to hepatotoxic substances (e.g., aflatoxin, alcohol) are associated with worse prognosis^[7,10]. A complete understanding of these factors is crucial for developing more tailored and effective preventive and therapeutic interventions to reduce the burden of HBV-related complications.

The contribution of host genetic factors to the variation in HBV infection outcomes was most notably evidenced by twin studies^[11], which reported higher concordance rates in monozygotic twins than in same-sex dizygotic twins for HBV carrier status^[12] and for antibody titers in response to hepatitis B vaccine^[13,14]. The host genetic factors were investigated in association studies whereby the frequencies of genetic variants were compared between case and control groups, using candidate gene and whole genome approaches^[15-18]. Candidate gene studies focused on polymorphisms in immunologically relevant genes, especially the classical human leukocyte antigen (HLA) genes^[19-21]. HLA genes encode the molecules that present antigens to T lymphocytes, and polymorphisms in these genes may alter the specificity and strength of antigen binding, affecting the T cell-mediated immune responses. In accordance with this paradigm, HLA typing studies found an ample amount of HLA allelic variations associated with the clinical outcomes of HBV infection^[15]. However, the associations reported in these studies were largely inconsistent, even within the same ethnicity, with few exceptions. The validity of these studies were undermined by inappropriately small sample sizes, lack of replication in an independent cohort, ambiguous allele assignments, genotyping confined to only one or two exons that show the highest genetic variability, low population coverage, and weak statistical evidences^[11,15].

The development of high-throughput genotyping technologies (e.g., microarrays) and the construction of a detailed map of common genetic polymorphisms in humans enabled genome-wide investigation of genetic variants for association to complex traits and diseases. In contrast to candidate gene-based studies, genome-wide association studies (GWAS) test hundreds of thousands to millions of common SNPs across the genome, providing an unbiased method to investigate genetic risk loci, and allowing the discovery of novel disease-relevant genes. Several GWAS were conducted to identify the risk loci that predisposes to persistence of HBV infection, non-response to hepatitis B vaccine, and progression of liver disease in chronic HBV infections. In this review, we discuss the findings of these GWAS, and we emphasize how GWAS has driven the research on the genetic basis of variability in HBV-related pathologies.

GWAS FOR HBV INFECTION PERSISTENCE

The first GWAS to identify the genetic risk factors for

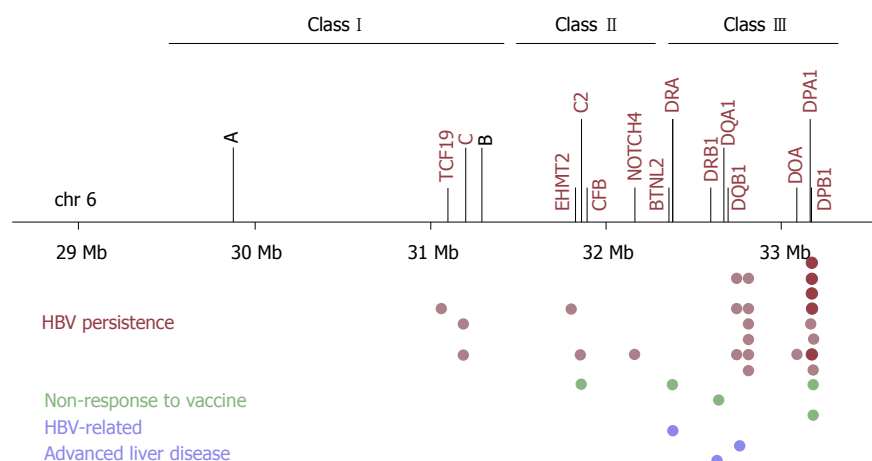


Figure 1 Associations within the human leukocyte antigen locus identified by genome-wide association studies for hepatitis B virus-related traits. GWAS hits for HBV-related pathologies are concentrated on the HLA region. Top SNPs in each GWAS are demonstrated in rows in the chronological order of publication; red for HBV persistence, green for Hepatitis B vaccine non-response, and blue for advanced HBV-related liver diseases. The nearest genes for the identified SNPs are colored in red; *HLA-A* and *HLA-B* are also marked. GWAS: Genome-wide association studies; HLA: Human leukocyte antigen; HBV: Hepatitis B virus; SNPs: Single nucleotide polymorphisms.

susceptibility to HBV infection persistence was performed in a Japanese population, and published in 2009^[22]. Seven hundred and eighty-six chronic hepatitis B (CHB) cases and 2201 HBsAg seronegative controls were used in the discovery phase. This GWAS detected significantly associated SNPs within the *HLA-DP* locus. rs3077 in *HLA-DPA1* 3'UTR and rs9277535 in *HLA-DPB1* 3'UTR were selected, and further replicated in independent Japanese and Thai samples^[22]. The same group employed a second GWAS using additional Japanese case-control samples where they confirmed the associations of *HLA-DP* variants, and, additionally, detected significant associations around the *HLA-DQ* locus^[23]. The *HLA-DQ* SNPs, rs2856718 and rs7453920, were not in LD with the *HLA-DP* SNPs, and their associations remained significant after adjusting for the effect of rs9277535. These findings revealed that *HLA-DP* and *HLA-DQ* variants were independently associated with chronic HBV infection. rs2856718 tagged an LD block comprising *HLA-DQA1* and *HLA-DQB1*, which produce the functional HLA-DQ molecules. rs7453920 was located in *HLA-DQB2*, which, along with *HLA-DQA2*, is thought to be nonfunctional. The association of rs7453920 with functional *HLA-DQ* alleles was shown later^[24].

Additional GWAS for HBV persistence were performed in Japanese^[25], Korean^[26], Han Taiwanese^[27], and Han Chinese populations^[28-30] (Table 1, Figure 1). These GWAS repeatedly mapped the strongest signals within the *HLA-DP* and/or *HLA-DQ* loci, replicating the associations of rs3077, rs9277535, rs7453920 and rs2856718. Furthermore, independent studies genotyping the same SNPs validated these associations with high consistency in diverse Asian populations, including Chinese^[31-39], Japanese^[40], Thai^[41], Indonesians^[42], Tibetans and Uyghurs (Asian-Caucasian mix)^[43]. A meta-analysis of 62050 subjects from 29 case-control studies, mostly from Asian populations, further validated the associations of rs3077 and rs9277535^[44]. Replication studies were also

conducted in non-Asian populations, including Caucasians in Germany^[45], European Americans, African Americans^[46], Saudi Arabians population^[47], and multiethnic Argentine populations (Native American-European Caucasian mix)^[48]. With few exceptions and inconsistencies, probably due to different allele frequencies and LD structures in these populations, the associations of *HLA-DP* (rs3077 and rs9277535) and *HLA-DQ* (rs7453920 and rs2856718) SNPs were validated in these populations, too.

Most of the subsequent GWAS also revealed additional susceptibility loci for HBV persistence. To begin with, a GWAS in Korean chronic HBV carriers and non-infected healthy individuals identified two novel loci within the HLA region^[26]. These two loci, marked by rs652888 in *EHMT2* and rs1419881 in *TCF19*, had independent effects on HBV persistence. *EHMT2* is a histone lysine methyltransferase involved in gene expression regulation, and plays roles in immune cell development and differentiation^[49]. *TCF19* is a transcription factor necessary for cell survival and proliferation^[50]. A previous GWAS associated a non-synonymous SNP in *TCF19* with blood cell counts, including lymphocyte and monocyte (macrophage precursor) cell counts^[51], suggesting a potential mechanism by which *TCF19* variants affected immune mechanisms. However, the associations of rs652888 (*EHMT2*) and rs1419881 (*TCF19*) were not replicated in Chinese and Thai populations, probably due to different genetic structures^[24,30,41]. Additional replication studies are, therefore, necessary for both loci.

Another GWAS in Han Chinese used chronic HBV carriers as cases and individuals who naturally cleared HBV infection as controls, and revealed two additional loci^[28]. The first locus was marked by the lead SNP rs3130542, located near *HLA-C* within the HLA region. Conditional analysis showed that the effect of rs3130542 was independent of *HLA-DP* and *HLA-DQ* variants. Therefore, both class I and class II variants were detected by GWAS for HBV persistence. The second

Table 1 Results of genome-wide association studies for persistence of hepatitis B virus infection

Ref.	Study population	SNP ID	Minor/major alleles	Risk allele	P	OR	Location	Nearest gene	Functional class
Kamatani <i>et al</i> ^[22] Mbarek <i>et al</i> ^[23]	Japanese, Thai (n = 6387) ¹ Japanese (n = 9163) ¹	rs3077	A/G	G	2.31×10^{-38}	0.56	6p21.32	HLA-DPA1	3'UTR
		rs9277535	A/G	G	6.34×10^{-39}	0.57	6p21.32	HLA-DPB1	3'UTR
		rs3077	A/G	G	1.57×10^{-61}	1.87	6p21.32	HLA-DPA1	3'UTR
		rs9277535	A/G	G	2.55×10^{-54}	1.77	6p21.32	HLA-DPB1	3'UTR
		rs2856718	A/G	A	3.99×10^{-37}	1.56	6p21.32	HLA-DQB1, HLA-DQA2	Intergenic
Nishida <i>et al</i> ^[25] Kim <i>et al</i> ^[26]	Japanese (n = 1793) ² Korean (n = 4309) ²	rs7453920	A/G	G	5.98×10^{-28}	1.81	6p21.32	HLA-DQB2	Intron
		rs3077	A/G	G	4.40×10^{-19}	0.46	6p21.32	HLA-DPA1	3'UTR
		rs9277542	A/G	G	1.28×10^{-15}	0.5	6p21.32	HLA-DPB1	Exon
		rs3077	A/G	G	3.74×10^{-40}	0.53	6p21.32	HLA-DPA1	3'UTR
		rs9277535	A/G	G	5.25×10^{-39}	0.53	6p21.32	HLA-DPB1	3'UTR
Hu <i>et al</i> ^[28] Chang <i>et al</i> ^[27] Jiang <i>et al</i> ^[29]	Chinese (n = 11791) ³ Han Taiwanese (n = 2688) ² Chinese (n = 18371) ¹	rs2856718	A/G	A	1.78×10^{-24}	1.6	6p21.32	HLA-DQB1, HLA-DQA2	Intergenic
		rs7453920	A/G	G	6.71×10^{-26}	0.5	6p21.32	HLA-DQB2	Intron
		rs652888	G/A	G	7.07×10^{-13}	1.38	6p21.33	EHMT2	Intron
		rs1419881	G/A	A	1.26×10^{-18}	0.73	6p21.33	TCF19	3'UTR
		rs7453920	A/G	G	4.93×10^{-37}	0.53	6p21.32	HLA-DQB2	Intron
		rs3130542	A/G	A	9.49×10^{-14}	1.33	6p21.33	HLA-C	Intergenic
		rs4821116	A/G	G	1.71×10^{-12}	0.82	22q11.21	UBE2L3	Intron
		rs3077	A/G	G	6.50×10^{-14}	0.75	6p21.32	HLA-DPA1	3'UTR
		rs9277535	A/G	G	4.87×10^{-14}	1.59	6p21.32	HLA-DPB1	3'UTR
		rs7453920	A/G	G	6.66×10^{-15}	2.31	6p21.32	HLA-DQB2	Intron
Li <i>et al</i> ^[30]	Chinese (n = 9569) ³	rs12614	T/C	C	1.28×10^{-34}	1.89	6p21.33	CFB	Exon
		rs422951	G/A	A	5.33×10^{-16}	1.27	6p21.32	NOTCH4	Exon
		rs378352	T/C	T	1.04×10^{-23}	1.26	6p21.32	HLA-DOA	Exon
		rs2853953	A/G	G	5.06×10^{-20}	1.47	6p21.33	HLA-C	Intergenic
		rs1883832	T/C	T	2.95×10^{-15}	1.19	20q13.12	CD40	5'UTR
		rs2856718	G/A	A	7.35×10^{-28}	1.28	6p21.32	HLA-DQB1, HLA-DQA2	Intergenic
		rs7453920	A/G	G	1.28×10^{-60}	2	6p21.32	HLA-DQB2	Intron
		rs9277535	A/G	G	9.84×10^{-71}	1.52	6p21.32	HLA-DPB1	3'UTR
		rs3077	A/G	G	1.15×10^{-53}	1.45	6p21.32	HLA-DPA1	3'UTR
		rs7000921	C/T	T	3.20×10^{-12}	0.78	8p21.3	INTS10	Intergenic
		rs7453920	A/G	G			6p21.32	HLA-DQB2	Intron
		rs9277535	A/G	G			6p21.32	HLA-DPB1	3'UTR

Participant phenotypes: ¹CHB *vs* Non-infected; ²Chronic HBV carriers *vs* Non-infected; ³Chronic HBV carriers *vs* Spontaneously recovered. OR: Odds ratio.

locus was marked by the lead SNP rs4821116, located in *UBE2L3* on chromosome 22. *UBE2L3* encodes an ubiquitin-conjugating enzyme, which enhances NFκB activation upon CD40 stimulation in B cells and TNF stimulation in monocytes^[52]. The protective variant of rs4821116 was associated with higher *UBE2L3* mRNA levels in peripheral blood monocytes^[53]. Moreover, *UBE2L3* was implicated in multiple autoimmune diseases; the risk variants correlated with higher *UBE2L3* expression in B cells and monocytes, enhanced NFκB activation, enhanced B cell proliferation and activation^[52]. Thus, hyperactivity of *UBE2L3*-related immune mechanisms conferred protection from infections on the one hand, but predisposed to autoimmunity on the other hand.

The GWAS with the largest sample size (2514 chronic HBV carriers and 1130 healthy controls of Chinese ethnicity in the discovery phase) was published in 2015, revealing five new SNPs independently associated with HBV persistence^[29]. Four of these SNPs, rs12614 in *CFB*, rs422951 in *NOTCH4*, rs2853953 near *HLA-C*, and rs378352 in *HLA-DO* were located within the HLA region, whereas the other SNP, rs1883832, was located in *CD40*

on chromosome 20. rs12614_T/C in *CFB* represents a non-synonymous amino acid polymorphism (R32W) in complement factor B. The complement system is part of the innate immune response against viral infections, and is also involved in enhancing adaptive immune responses^[54]. Chronic HBV carriers and individuals with the risk genotype CC for rs12614 had significantly lower plasma CFB protein levels^[29]. rs422951 in *NOTCH4* also causes a non-synonymous amino acid change (T320A). Notch signaling regulates immune cell development and T-cell mediated immune responses^[55]. rs2853953 tagged *HLA-C* gene; however it was not in LD with the previously reported *HLA-C* tagging SNP rs3130542. Indeed, these two SNPs marked different *HLA-C* alleles; rs2853953 marked *HLA-C*06:02*, whereas rs3130542 marked *HLA-C*07:02*. rs378352 is located in exon 4 of *HLA-DOA*, causing a synonymous codon change. *HLA-DOA* encodes the α chain of the HLA-DO molecule, which, along with HLA-DM, regulates peptide loading to class II molecules. Whether or how this polymorphism affects HLA-DO function is currently unknown. Lastly, rs1883832_T/C is located in the Kozak sequence of

Table 2 Human leukocyte antigen classical alleles associated with hepatitis B virus persistence in more than one study

HLA gene	Associated alleles	Effect on HBV persistence	Study population	Ref.
<i>HLA-C</i>	*07:02	Protective	Chinese	[24,28,29]
<i>HLA-DPA1</i>	*01:03	Protective	Japanese, Korean, Chinese, Thai	[22,24,58]
	*02:02	Susceptible	Japanese, Korean, Chinese	[22,24,58]
<i>HLA-DPB1</i>	*04:01	Protective	Japanese, Chinese	[22,28,58]
	*04:02	Protective	Japanese, Korean	[22,58]
	*02:01	Protective	Chinese, Japanese	[28,58]
	*05:01	Susceptible	Japanese, Korean, Chinese	[22,24,58,59]
	*09:01	Susceptible	Japanese, Chinese	[22,24,58,59]
<i>HLA-DQA1</i>	*06:01	Susceptible	Chinese	[24,28,30]
<i>HLA-DQB1</i>	*03:02	Protective	Japanese, Chinese	[24,28,30,59]
	*03:01	Susceptible	African American, Chinese	[18,28,30]
	*06:01	Susceptible	Japanese	[23,59]
<i>HLA-DRB1</i>	*13:02	Protective	Japanese, Chinese, Gambian, Korean, Germany, European Americans	[24,59,68]

CD40, and was previously shown to affect its translational efficiency^[56]. The risk genotype TT for rs1883832 correlated with lower CD40 levels in the serum in both cases and controls^[29]. CD40 is a co-stimulatory receptor protein found on antigen-presenting cells. Its engagement with CD40 ligand (CD40L) on T cells initiates and promotes humoral and cellular adaptive immune responses^[57]. Intriguingly, rs1883832_T was previously associated with protection against multiple autoimmune diseases^[56]. Thus, CD40 plays an important role in regulating the magnitude of immune responses, and determining immunity vs tolerance. So far, the associations of rs12614 (*CFB*) and rs1883832 (*CD40*) were validated by independent studies in Han Chinese^[24,30]. Additional validation and functional studies are required to establish the roles of other genes and genetic variants in HBV persistence.

The most recent GWAS identified another novel locus (tagged by rs7000921) on chromosome 8 using persistently infected cases and spontaneously recovered controls in a Chinese population^[30]. rs7000921 was an eQTL for the nearby *INTS10* gene; the protective allele was associated with elevated *INTS10* expression in liver. *INTS10* encodes a subunit of the Integrator complex, which has multiple roles in transcriptional regulation. Subsequent analysis showed that *INTS10* was involved in suppressing HBV replication in hepatocyte cell lines, likely through an interferon-dependent mechanism^[30].

To sum up, GWAS for HBV infection persistence revealed many candidate genes with diverse functions in immune responses, improving our understanding of the molecular mechanisms leading to the success or failure of HBV clearance.

CLASSICAL HLA GENE VARIANTS AT THE INTERFACE OF HBV CLEARANCE AND PERSISTENCE

GWAS association signals within the *HLA-DP*, *HLA-DQ* and *HLA-C* loci implicated variable efficiencies in

presenting immunodominant HBV epitopes to T cells. Thus, in the next step after GWAS, the respective HLA genes were typed by direct sequencing or imputation (on the basis of typed SNPs from the study populations and haplotypes from the genetic reference populations), and classical HLA alleles with significant effects on HBV persistence were determined (Table 2). *HLA-DP* susceptible alleles (*DPA1**02:02; *DPB1**05:01, *09:01) and protective alleles (*DPA1**01:03; *DPB1**02:01, *04:01, *04:02) were identified with a high degree of consistency in multiple Japanese, Korean and Chinese populations^[22,24,28,30,58,59]. Moreover, *DPB1**01:01 and *DPB1**04:01 were identified as the most susceptible and the most protective *DPB1* allele, respectively, in European Americans and African Americans^[46]. Alleles with consistent effects in more than one population were also found for *HLA-DQ* and *HLA-C* genes; *DQB1**03:02 was revealed as a protective allele^[24,28,30,59], whereas *DQA1**06:01, *DQB1**03:01, *DQB1**06:01, and *HLA-C**07:02 were revealed as susceptible alleles^[23,24,28-30,59]. Systematic epitope discovery studies are warranted to identify the HBV-derived peptides efficiently presented by protective allotypes, but not by susceptible allotypes. The results of such studies might form the basis for epitope-specific therapeutic interventions.

A major distinction between *DPB1* protective alleles (*02:01, *04:01, *04:02) and *DPB1* susceptible alleles (*01:01, *05:01, *09:01) was in their amino acid residues at positions 84-87. Protective alleles encoded Gly/Gly/Pro/Met (GGPM), while susceptible alleles encoded Asn/Glu/Ala/Val (DEAV) at 84-87. These residues corresponded to the pocket-1 of the antigen-binding groove, an anchor region that determines the binding specificity of DP molecules^[60,61]. Epitope binding studies revealed that DP molecules with 84GGPM87 strongly bound aromatic and hydrophobic residues in their hydrophobic pocket-1, whereas DP molecules with 84DEAV87 also preferred positively charged residues, owing to the acidic residues at 84 and 85^[61,62]. These distinct binding motifs of DP allotypes likely form the basis of HBV chronicity as multiple risk-associated DP allotypes ineffectively present a common epitope motif

and lead to the failure of viral elimination. The identities of HBV peptides with this motif and their immunogenic properties remain to be determined by further functional assays.

It should be noted that the contribution of HLA-DP allotypes to HBV chronicity might also involve previously unprecedented mechanisms. It was recently shown that Gly-84 residue in DP molecules prevents the binding of the invariant chain *via* its CLIP region on the antigen-binding groove^[63]. CLIP binding is necessary to block endogenous peptide binding to class II molecules till they reach the MHC compartment where exogenous peptide loading takes place. Therefore, DP^{84Gly} molecules are able to present both intracellular and extracellular peptides^[63]. Whether or how this contributes to immunity against HBV needs to be examined in functional studies.

The HLA locus is characterized by high gene density, high genetic diversity and extensive LD structure, limiting the ability to pinpoint the causal variants^[64]. Some class II associations might not reflect primary effects given the strong LD between *DQ* and *DR* loci, and the weak LD between *DQ-DR* and *DP* loci. Hence, uncovering the LD patterns between the *DP*, *DQ* and *DR* alleles in the study population, rather than examining the alleles at a single locus, would help detecting the alleles with primary effects^[59]. Fine mapping studies in which associated loci are interrogated with many more variants than in GWAS prove to be useful in pinpointing the causal variants and revealing potential mechanisms. An interrogation of the entire HLA locus with 5375 variants, including 4356 SNPs, 849 amino acid polymorphisms and 170 classical alleles, in 1888 Chinese case-control individuals (from a previous HBV-persistence GWAS^[28]) identified four independently associated loci by stepwise conditional analysis^[24]. HLA-DPB1 amino acid polymorphisms at positions 84-87 were the strongest association, whereas HLA-C Leu-15 was the second strongest association, conferring the effect of *HLA-C*07:02*. The two other associated loci were novel; *HLA-DRB*13* allele and rs400488. *HLA-DRB*13* was associated with protection against HBV chronicity, and was in partial LD with the CFB-tagging SNP rs12614. *HLA-DRB*13* allele is distinct from other *DRB1* alleles by the presence of Glu-71 in pocket-4, an anchor region for epitope binding of DR molecules, implying a specific binding motif. Remarkably, *HLA-DRB*13* was one of the few classical HLA alleles identified in the pre-GWAS era with highly reproducible associations across different ethnicities^[65-68]. On the other hand, the biological relevance of rs400488, an eQTL for the pseudogene *HLA-J*, is currently unknown^[24].

The effects of associated SNPs on HLA gene expression were also investigated. An eQTL analysis showed that the risk alleles of rs3077 and rs9277535 were associated with lower *HLA-DPA1* and *HLA-DPB1* mRNA levels, respectively, in normal liver tissues^[69]. Furthermore, allelic expression imbalance assays for both SNPs confirmed that the risk alleles were expressed less abundantly than the protective alleles in liver and blood monocyte samples from heterozygous individuals^[69].

Two separate genome-wide gene expression association studies previously found similar trends for the *HLA-DQ* SNP rs7453920 and the *HLA-C* SNP rs3130542. The risk variant of rs7453920 was associated with lower *HLA-DQ* mRNA levels in peripheral blood monocytes^[53], while the risk variant of rs3130542 was associated with lower *HLA-C* mRNA in lymphoblastoid cell lines derived from European subjects^[70]. Moreover, the susceptible *HLA-C*07:02* allele, tagged by rs3130542, have an intact mir-148a binding site, and a low expression due to RNA interference^[71]. These results suggested that reduced expression of HLA-DP and HLA-DQ molecules in antigen-presenting cells, and reduced expression of HLA-C molecule in hepatocytes might result in ineffective antigen presentation to T cells, leading to inability to clear HBV infection, and thus, HBV persistence. However, a discrepant result was noted for rs9277534_A/G, the most significant *HLA-DPB1* SNP in European Americans and African Americans^[46]. The risk allele rs9277534_G correlated with higher HLA-DPB1 surface protein levels in lymphoid cell lines and higher *HLA-DPB1* mRNA levels in B lymphocytes isolated from healthy donors. This conflicting result can be reconciled with the previous findings by taking into account that rs9277534_G was also in strong LD with the most susceptible *HLA-DPB1* allele (**01:01*) in these populations. Thus, the risk-conferring effect of *HLA-DPB1*01:01* probably prevailed over the protective effect of its increased expression.

To sum up, polymorphisms marking the classical HLA genes influence immune responses by altering the antigen-binding properties of HLA molecules and the expression levels thereof. The relative contributions of these effects to susceptibility to HBV persistence vary among populations depending on the allele frequencies of variants and LD relationships among them.

GWAS FOR IMMUNE RESPONSE TO HEPATITIS B VACCINE

The standard 3 doses of hepatitis B vaccine (based on recombinant HBs antigen) have been implemented as part of the routine infantile vaccination program in more than 160 countries, as a result of which substantial declines in the prevalence of chronic HBV carriers and in the incidence of childhood HBV-related liver diseases have been observed^[6,72]. However, there is a large natural variation in the antibody response to hepatitis B vaccine. Post-vaccination antibody titers range from undetectable levels to higher than 2000 mIU/mL^[73]. Anti-HBs titers above 100 mIU/mL are referred to as successful vaccination, whereas anti-HBs titers below 10 mIU/mL as non-protective. Individuals that mount an antibody response below this threshold, *i.e.*, non-responders, are at a high risk of HBV infection. Booster vaccination can trigger an antibody response at protective levels in a subset of non-responders^[74].

Three GWAS were implemented to date to identify the genetic factors that underlie the variation in the

Table 3 Results of genome-wide association studies for non-response to hepatitis B vaccine

Ref.	Study population	SNP ID	Minor/major alleles	Risk allele	P	OR	Location	Nearest gene	Functional class
Png <i>et al</i> ^[73]	Indonesian (n = 3614) ¹	rs3135363	C/T	C	6.53×10^{-22}	1.53	6p21.32	<i>BTNL2</i> , <i>HLA-DRA</i>	Intergenic
		rs9277535	A/G	G	2.91×10^{-12}	0.72	6p21.32	<i>HLA-DPB1</i>	3'UTR
		rs9267665	T/C	T	1.24×10^{-17}	2.05	6p21.33	<i>STK19</i>	Intron
Pan <i>et al</i> ^[76]	Chinese (n = 1944) ²	rs477515	T/C	T	2.63×10^{-19}	2.05	6p21.32	<i>HLA-DRB1</i>	Intergenic
Wu <i>et al</i> ^[81]	Taiwanese (n = 285) ³	rs7770370	A/G	G	1.20×10^{-08}	0.33	6p21.32	<i>HLA-DPB1</i>	Intergenic

Participant phenotypes: ¹Low, intermediate and high responders to primary vaccine (ordinal groups); ²High responders to primary vaccine *vs* non-responders to booster vaccine; ³Non-responders *vs* responders to booster vaccine.

immune response to hepatitis B vaccine (Figure 1, Table 3). The first GWAS was conducted in Indonesians by grouping vaccine recipients into three classes (*i.e.*, low, intermediate and high) on the basis of their post-vaccination antibody titers^[73]. Stepwise conditional analysis revealed three independently associated haplotype blocks within the HLA region. The first haplotype block, tagged by rs3135363, encompassed *HLA-DRA* and *BTNL2*. *HLA-DRA* encodes the sole α chain for HLA-DR molecules, and *BTNL2* encodes a transmembrane protein involved in the negative regulation of T cell activation. *BTNL2* was previously associated with autoimmune diseases^[75]. The second haplotype block, tagged by rs9277535, encompassed *HLA-DPA1* and *HLA-DPB1* genes, suggesting that *HLA-DP* variants contribute to both HBV persistence and non-response to vaccine. A shared genetic basis for these traits is conceivable given that anti-HBs antibody production is a marker for both successful immune response to vaccine and clearance of HBV infection^[3]. Lastly, the third haplotype block, tagged by rs9267665, was located within the class III region, consisting of many genes found in strong LD. Therefore, further research is needed to pinpoint the causal genes^[73].

The second GWAS for vaccine nonresponse used Chinese adults with marginal phenotypes: non-responders (< 10 mIU/mL) after booster vaccination *vs* high-responders (> 1000 mIU/mL) after primary vaccination^[76]. The strongest associations (led by rs477515) were detected within the *HLA-DR* locus, and *HLA-DRB1**07:01 was significantly associated with nonresponse to hepatitis B vaccination^[76]. Numerous studies previously associated *DRB1**07:01 with both vaccine non-response and persistent HBV infection in multiple ethnic populations^[77-79]. Furthermore, *DRB1**07 was also associated with decreased risk of HBV-related cirrhosis in a Turkish population^[80], implicating a *DRB1**07-associated hypo-immune profile against HBV.

The third GWAS used subjects with detectable and undetectable (> or < 1 mIU/mL, respectively) post-booster antibody titers from a cohort of booster vaccine recipient Taiwanese adolescents who had not responded to primary vaccination as infants^[81]. Significant associations were mapped to the *HLA-DP* locus. The lead

SNP rs7770370 was in strong LD with rs9277535. *HLA-DPB1* alleles *02:01, *02:02, *03:01, *04:01 and *14:01 (encoding 84GGPM87) were associated with vaccine response, whereas *05:01 and *09:01 (encoding 84DEAV87) were associated with vaccine nonresponse^[74,81]. These associations were further confirmed in a Japanese population^[82]. Hence, *HLA-DPB1* alleles influenced the outcome of vaccine response in the same manner as of HBV persistence, corroborating further that the ability to present the same HBs epitopes is critical in both traits. In line with this, *HLA-DP* SNPs (*e.g.*, rs7770370, rs9277535 and rs3077) were also associated with vaccine nonresponse in independent replication studies in Korean infants^[83] and Japanese medical students^[84]; and vaccine nonresponse-associated rs477515 (*HLA-DRB1*) also correlated with HBV persistence in a Chinese population^[30]. However, *HLA-DQ* SNPs (rs2856718 and rs7453920) were not associated with vaccine responsiveness^[84]. Therefore, the genetic bases of HBV persistence and nonresponse to hepatitis B vaccine overlap considerably, but not completely.

GWAS FOR HBV-RELATED ADVANCED LIVER DISEASES

Host genetic variation underlying the clinical heterogeneity of chronic HBV infections has been the topic of GWAS, too (Figure 1, Table 4). A GWAS used 648 HBV-infected Saudi Arabian subjects, comprising 343 inactive carriers, 249 patients with CHB, and 76 patients with end-stage liver diseases (*i.e.*, cirrhosis and HCC), to study liver disease progression in chronic HBV infection^[85]. The strongest association, rs2724432, was obtained using cases with end-stage liver diseases and controls with inactive HBV infection. rs2724432 was located upstream of *FDX1*, the product of which is involved in electron transfer from NADH to cytochrome P450. *FDX1* plays a role in steroid and vitamin D synthesis in the adrenals, and bile acid synthesis in the liver^[85]. Further functional assays are necessary to confirm the association of rs2724432 and the underlying molecular mechanisms. Some of the GWAS for HBV persistence contained in their case groups chronic HBV carriers with and without

Table 4 Results of genome-wide association studies for hepatitis B virus-related advanced liver diseases

Ref.	Study population	Participant phenotypes	SNP ID	Minor/major alleles	Risk allele	P	OR	Location	Nearest gene	Functional class
Al-Qahtani <i>et al</i> ^[85]	Saudi Arabian (n = 693)	LC/HCC vs Inactive ¹	rs2724432	T/C	T	4.29×10^{-08}	3.01	11q22.3	<i>FDX1</i>	Intergenic
Zhang <i>et al</i> ^[88]	Chinese (n = 4107)	HCC vs Non-HCC ²	rs17401966	G/A	A	3.40×10^{-19}	0.62	1p36.22	<i>KIF1B</i>	Intron
Chan <i>et al</i> ^[91]	Chinese (n = 1420)	HCC vs Non-HCC ²	rs12682266	A/G	G	3.76×10^{-05}	1.38	8p12	Expressed sequenced tag	Intergenic
Li <i>et al</i> ^[89]	Chinese (n = 12159)	HCC vs Non-HCC ²	rs9272105	A/G	A	5.24×10^{-22}	1.28	6p21.32	<i>HLA-DQA1</i> , <i>HLA-DRB1</i>	Intergenic
Jiang <i>et al</i> ^[90]	Chinese (n = 11799)	HCC vs Non-HCC ²	rs455804 rs7574865 rs9275319	A/C T/G G/A	C G A	5.24×10^{-10} 2.48×10^{-10} 2.72×10^{-17}	0.84 1.21 1.49	21q21.3 2q32.2-2q32.3 6p21.32	<i>GRIK1</i> <i>STAT4</i> <i>HLA-DQB1</i> , <i>HLA-DQA2</i>	Intron Intron Intergenic
Tan <i>et al</i> ^[86]	Chinese (n = 3387)	ACLF vs Inactive ³	rs3129859	C/G	C	2.64×10^{-20}	1.83	6p21.32	<i>HLA-DQB1</i> , <i>HLA-DRA</i>	Intergenic

¹HBV carriers with LC or HCC vs inactive chronic carriers; ²Chronic HBV carriers with HCC vs chronic HBV carriers without HCC; ³Acute-on-chronic liver failure vs inactive chronic HBV carriers. LC: Liver cirrhosis; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus.

end-stage liver diseases. At least one GWAS employed a secondary genome-wide analysis using these subgroups^[25], however, failed to identify any significant association, possibly due to small sample size.

A GWAS in Han Chinese investigated the risk loci for acute-on-chronic liver failure (ACLF) in chronic HBV carriers, a life-threatening condition that develops as a result of sudden acute exacerbation of chronic infection^[86]. rs3129859 within the *HLA-DR* locus was associated with HBV-related ACLF. Subsequent in silico genotyping of *HLA* alleles and conditional association analysis showed that the effect of rs3129859 was dependent on the *HLA-DRB1**12:02 allele^[86]. Concordant with this finding, *HLA-DRB1**12 was previously associated with the development of HBV-related cirrhosis and HCC in Han Chinese^[87].

To find the genetic risk loci for HBV-related HCC, several GWAS were implemented using HBV carriers with HCC as cases and HCC-free HBV carriers as controls^[88-92] (Table 4). All of these GWAS used Chinese cohorts, exploiting the facts that more than half of HCC cases were found in China, and 80% of HCC incidences were attributable to HBV^[93]. The first GWAS identified rs17401966, located in *KIF1B* on chromosome 1^[88]. *KIF1B* encodes a kinesin protein involved in organelle and vesicle transport, and is a putative tumor suppressor^[94]. The protective variant of rs17401966 significantly correlated with higher KIF1B protein levels in tumor-adjacent tissues, but not in HCC tissues^[88]. The haplotype block tagged by rs17401966 also encompassed the entire *PGD* gene and the 3' end of *UBE4B* gene. The products of these genes are involved in pentose phosphate metabolism and multiubiquitin chain assembly, respectively. Additional studies are necessary to identify the causal gene in this locus. Another GWAS identified rs9272105 within the HLA region and rs455804

on chromosome 21^[89]. rs9272105 was located in the intergenic region between *HLA-DQA1* and *HLA-DRB1*. *HLA-DRB1* alleles *04:05 and *09:01 only partially accounted for the association of rs9272105, implying additional risk variants in LD with this SNP. rs455804 was located in intron 1 of *GRIK1*, which encodes an ionotropic glutamate receptor, suggesting involvement of glutamate signaling in hepatocarcinogenesis. Two additional risk loci were revealed in another GWAS: rs7574865 and rs9275319^[90]. rs7574865 tagged *STAT4* on chromosome 2. *STAT4* is a transcription factor with important roles in the regulation of antiviral immune responses; it induces IFN- γ production in response to stimulation by interleukin-12 and type I interferons (IFN- α and IFN- β)^[95]. HCC risk-associated variant of rs7574865 correlated with lower *STAT4* mRNA expression in both HCC and non-tumor tissues^[90]. rs9275319 tagged *HLA-DQB1* and *HLA-DQA2*, and its effect on HCC risk was only partially accounted for by *DQB1**04:01 and *DQA1**03:03 alleles, indicating other risk variants in the associated locus.

SNPs identified in GWAS for HBV-related HCC were further investigated in replication studies. Intriguingly, no evidence was found for the association of rs17401966 (*KIF1B*) with HCC risk in chronic HBV carriers in subsequent GWAS and other replication studies in Chinese^[36,96], Japanese^[97], Korean^[97], and Thai populations^[98]. Moreover, rs17401966 was also not associated with HBV infection persistence in Chinese^[99], Japanese^[23] and Saudi Arabian populations^[100]. Comparable allele frequencies were detected between different subgroups of chronic carriers (namely, inactive carriers, active carriers, cirrhosis and HCC) in Saudi Arabian and Chinese populations^[100,101]. These results indicated that rs17401966 was a risk factor neither for HBV infection persistence nor for advancement of liver disease.

Replication studies for rs7574865 (*STAT4*) produced inconsistent results. The association of rs7574865 with HBV-related HCC was validated in Vietnamese^[102] and Korean^[103] populations, but not in two separate Chinese populations^[38,96]. The effect of rs7574865_T/G on susceptibility to persistent HBV infection was also examined. HCC risk allele rs7574865_G was significantly associated with chronic HBV infection in Koreans^[103] and Chinese^[104]. However, this association was not reproduced in another Chinese population^[38]. Lastly, rs7574865_G was also significantly associated with the risk of HBV-related cirrhosis in a Chinese population^[101]. Overall, these results supported a role for *STAT4* polymorphisms in HBV infection outcomes in a population specific manner.

The associations of the two HBV-related HCC risk SNPs within the *HLA-DQ/DR* locus (rs9275319 and rs9272105) were validated by an independent replication study in Chinese subjects^[105], whereas two separate studies in Koreans^[103] and in Chinese^[106] failed to replicate the association of rs9275319. rs9275319 was also associated with susceptibility to HBV persistence in the original GWAS^[90], and in other replication studies performed in Korean^[103] and Chinese populations^[30,106]. Moreover, rs9275319 was associated with increased risk of cirrhosis in Chinese HBV carriers^[101]. Therefore, it might be speculated that rs9275319 was associated with an ineffective immune profile against HBV that is too weak to clear HBV infection, yet strong enough to maintain a state of basal liver necroinflammation leading to advanced liver diseases. On the other hand, the effect of rs9272105 on HBV persistence is not yet clear. HCC risk-associated variant of rs9272105 conferred susceptibility to chronic HBV infection in one Chinese population^[30], and protection against chronic HBV infection in another Chinese population^[89]. These conflicting results indicated that rs9272105 did not have a primary effect on HBV persistence.

To fully explore whether the genetic bases of HBV persistence and HBV-related liver diseases overlap, SNPs identified in GWAS for HBV persistence were also examined for possible effects on the development of advanced liver diseases. Most studies showed that *HLA-DP* variants (rs3077 and rs9277535) were associated neither with progression from inactive carrier state to disease-active states^[35,37,39,45], nor with development of end-stage liver diseases^[31,35,38,39,47]. Similar results were found for *HLA-DQ* variants (rs2856718 and rs7453920) regarding the development of end-stage liver diseases^[38,39,47]. Only few studies reported significant associations of these SNPs with HBV-related HCC risk^[36,89,107]. A meta-analysis with 4864 HBV-positive HCC cases and 29790 HBV-infected controls also failed to associate rs3077 and rs9277535 with HCC risk^[44]. Lastly, none of the 13 HBV persistence risk SNPs that were identified hitherto in GWAS were found to be associated with HBV-related HCC in a population of 1161 cases and 1353 controls^[29]. Therefore, SNPs that were associated with HBV persistence/clearance had minimal, if any, ef-

fects on progression of liver disease in chronic carriers. These results implied that distinct immune mechanisms might be critical at different stages of HBV infection, probably reflecting the evolving dynamics between HBV and the host immune system during chronic infections.

CONCLUSION

It is important to have a comprehensive understanding of the mechanisms of failure to clear HBV infection, and translate this knowledge into effective therapies to prevent the development of chronicity and other adverse outcomes. With this motive, many GWAS were performed to dissect the genetic basis of HBV-related traits. These GWAS provided novel insights into the pathogenesis of HBV persistence and non-response to hepatitis B vaccine. For instance, the association of *HLA-DPB1* with HBV persistence was unknown before GWAS. *DPB1* gene was neglected in previous candidate gene-based association studies, mainly because it was less polymorphic than *DQB1* and *DRB* genes^[46]. In addition to the classical HLA genes *HLA-DP*, *HLA-DQ* and *HLA-C*, GWAS for HBV persistence provided candidate genes including non-classical HLA genes (*EHMT2*, *TCF19*, *CFB*, *NOTCH4*) and non-HLA genes (*UBE2L3*, *CD40*, *INTS10*), indicating that genetic susceptibility to HBV persistence is determined by regulation of immune responses at multiple levels. Many of these candidate genes had known roles in immune responses, whereas some were novel. Besides improving our understanding of the molecular mechanisms underlying HBV-related pathologies, GWAS findings are likely to have other immediate and long-running clinical implications. For instance, genetic markers provided by GWAS can be used to predict the individuals that are at a higher risk for worse prognosis, demanding a closer medical surveillance. Furthermore, identification of novel protective HLA allotypes might be exploited for the development of more effective vaccines based on alternative epitopes.

Despite their initial success, some of these GWAS also had certain limitations, including small sample sizes, lack of information on age at first infection, transmission route, maternal status and HBV genotype, unknown infection history of controls, unknown infection status for HCV and HIV, and imperfect match of age, gender and genetic background among some case-control groups. GWAS for HBV-related advanced liver diseases additionally suffered from the stochasticity of disease pathogenesis. For instance, the randomness of HBV DNA integration events in the host genome adds to the heterogeneity of HBV-related HCC^[108]. Cirrhosis and HCC typically occur more than 20 years after the initial infection^[109]. Smoking, alcohol consumption, aflatoxin exposure, obesity, diabetes, and treatment interventions during this period are strong confounders that also lead to clinical heterogeneity^[110]. The lack of consistent associations in GWAS for HBV-related advanced liver diseases might be due to these confounders. Hence, these GWAS must be designed in a better way to ac-

count for each of these factors^[111,112].

Interestingly, the susceptible alleles in the *HLA-DP/DQ* locus are more frequent in Asian populations than in Caucasians, which might be one of the causes for higher prevalence of chronic HBV infections in Asia^[22,113]. However, most of these susceptible alleles are not frequent in Africa, too, even though chronic hepatitis B is as prevalent in Africa as in Asia. Given that the predominant mode of transmission and HBV genotypes are different in Asia and Africa (vertical vs horizontal; B, C vs A, D, E; respectively), the genetic architecture for predisposition to chronic HBV infection also varies among these populations^[7,113]. Hence, allele frequency distributions across human populations might give important insights into human-HBV co-evolution.

GWAS for HBV-related traits have almost exclusively been implemented in Asian populations. So far, there is no GWAS in Africans, and only one GWAS in Saudi Arabians, where the dominant HBV genotype is D^[7]. Populations with different ancestries harbor different haplotype structures and allele frequencies; therefore, implementing GWAS in other populations might also help narrow down the associated loci. This is especially desirable for fine mapping studies. Fine mapping studies on the HLA locus, where extensive LD structure hampers the detection of causal variants, are of utmost importance since immune-related genes are concentrated in this region. The findings of such studies would reveal novel insights into the pathogenesis of HBV-related traits. Therefore, additional GWAS and fine mapping studies, implemented with more refined case-control designs, larger samples, and in other ethnic populations, would further improve our understanding of HBV infection pathophysiology.

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