Amino Acids (2014) 46:1819–1826
DOI 10.1007/s00726-014-1767-2

INVITED REVIEW

Association of variants in *HLA-DP* on chromosome 6 with chronic hepatitis B virus infection and related phenotypes

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Received: 19 April 2014 / Accepted: 21 April 2014 / Published online: 21 May 2014

Abstract Hepatitis B virus (HBV) infection affects more than 2 billion people throughout the world. Among them, more than 240 million have chronic infection. Every year, 0.5–1.2 million people die of chronic hepatitis B virus infection (CHBVI), and approximately 60 % of liver cancers are related to CHBI and subsequent liver cirrhosis (LC). These HBVI-related diseases impose a considerable economic burden as well as morbidity on patients, families, and society. Family and twin studies have indicated that the host genetic constitution greatly influences the clinical outcomes of HBV infection. During the past several years, genome-wide association studies (GWAS) have identified susceptibility variants for various HBVI-related diseases. Of these variants, SNPs rs3077 and rs9277535 in *HLA-DP* on chromosome 6 show the strongest evidence for association with CHBVI and with viral clearance. However, whether there exists an association between *HLA-DP* variants and the progression of CHBVI remains to be determined. Thus, further study should focus not only on identifying more variants in *HLA-DP* that are associated with various HBVI-related diseases but also on characterizing any newly discovered functional variants at the molecular level. Further, given the complexity of CHBV infection and its progression, gene–gene and gene–environment interactions should also be taken into consideration. Moreover, because both smoking and alcohol affect HBV infection and progression, it is important to understand how these factors interact with genetics to influence HBV-related diseases.

Keywords Hepatitis B virus · Infections · *HLA-DP* · Association · SNPs · Functional variants

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Introduction

Hepatitis B virus (HBV) is one of the world's most serious health problems, especially in Asian counties. Although a highly effective hepatitis B vaccine was introduced in 1982, chronic hepatitis B infection (CHBI) remains common, with more than 240 million people now affected (World Health Organization, 2013; http://www.who.int/mediacentre/factsheets/fs204/en/index.html).

The prevalence CHBI is about 5 % worldwide (Lai et al. 2003), but it shows large regional divergences, as well as population differences. Thus, such infection is endemic in sub-Saharan Africa and East Asia, with most people becoming infected during childhood and 5–10 % of the adult population being chronically infected. High CHBI rates also are found in the Amazon Basin and the southern parts of eastern and central Europe. About 2–5 % of the general population is chronically infected in the Middle East and the Indian subcontinent. In contrast, less than 1 % of the population of Western Europe and North America is affected (World Health Organization, 2013; http://www.who.int/mediacentre/factsheets/fs204/en/index.html). In the high-endemic regions, most affected people become infected in the perinatal or preschool period (Lok 2002; Gust 1996), which is associated with a very high

probability of chronic infection (Chen et al. 2000). Most infections are acquired by horizontal transmission in early adult life in low-endemic areas (Gust 1996).

It is estimated that the worldwide mortality of CHBI is 0.5–1.2 million per year (Liaw and Chu 2009). Approximately 60 % of liver cancers are considered to be related to CHBI and subsequent liver cirrhosis (LC) (Lai et al. 2003). About 25 % of persons who acquire HBV as children develop cirrhosis or primary liver cancer as adults (Hsieh et al. 1992; Mahoney 1999). The typical progression of cirrhosis is from compensated to decompensated if treatment is not provided. Patients with decompensated cirrhosis would die without liver transplantation. Because of the high HBV-related morbidity and mortality rates, the economic burden of HBVI is severe. A survey conducted on patients with HBVI-related diseases who were hospitalized for 7 or more days in 13 representative hospitals in Shandong Province of China from April 2010 to November 2010 (Lu et al. 2013) showed, as expected, that the cost escalated with increasing severity of liver disease. It has been estimated that the direct cost in 2010 for CHBI, compensated cirrhosis, decompensated cirrhosis, and primary liver cancer was US$4,552, $7,400, $6,936, and $10,635, respectively. These costs ranged from 78.79 % (for CHBI) to 297.85 % (for primary liver cancer) of the average annual household income of the population, a huge economic burden for the family.

The clinical outcomes of HBVI, from spontaneous clearance to chronic infection that may go on LC and liver cancer, are influenced by viral, environmental, and host factors (Ganem and Prince 2004; Frodsham 2005). Family and twin studies indicate that host genetic constitution is an important factor (Lin et al. 1989). The human leukocyte antigen (HLA) allele *DRB1*1302* was first reported to be associated with a protective effect for CHBI in Gambians (Thursz et al. 1995). Subsequent studies confirmed the involvement of other HLA genes in HBV clearance or persistence (Ahn et al. 2000; Thio et al. 1999, 2000). In addition, non-HLA genes involved in cytokine production, receptor binding, and immune regulation are also significantly associated with HBV infection. These factors include interferon-gamma and tumor necrosis factor (Ben-Ari et al. 2003), estrogen receptor alpha (Deng et al. 2004), vitamin D receptor (Bellamy et al. 1999), mannose-binding protein (Thomas et al. 1996), cytotoxic T-lymphocyte antigen 4 (Thio et al. 2004), and macrophage migration inhibitory factor (Zhang et al. 2013). However, the results of these candidate gene-based association studies are less conclusive in many cases.

In the past several years, genome-wide association study (GWAS) has been used increasingly to identify common genetic variants for complex human disorders such as HBV infection (Wellcome Trust Case Control Consortium 2007). To identify disease-predisposing variants, Kamatani et al. (2009) carried out a two-stage GWAS for CHB, which revealed that several single nucleotide polymorphisms (SNPs) in *HLA-DP* are associated with risk. Since then, many laboratories independently confirmed the association of *HLA-DP* variants with hepatitis B. Together, these studies have led to a new insight and substantial advancement in our understanding of HBV infection in human beings. Thus, the primary objective of this communication is to provide an updated view of recent progress in genetic association studies on the association of variants in *HLA-DP* with various HBV-related diseases.

Association of *HLA-DP* variants with chronic HBV infection and clearance

Using a two-stage GWAS approach, Kamatani et al. (2009) identified an association between CHB and 11 SNPs in *HLA-DP* loci in 786 Japanese CHB cases and 2,201 control individuals in the first discovery stage: rs2395309, rs3077, rs2301220, rs9277535, rs3117222, rs3128917, rs3135021, rs9380343, rs9277341, rs10484569, and rs2281388. Two of these SNPs, namely rs3077 in *HLA-DPA1* and rs9277535 in *HLA-DPB1*, were the most significantly associated SNPs identified from the first discovery stage and were then selected for subsequent validation in three Japanese and Thai samples, which included two independent Japanese case–control samples comprising 274 cases and 274 controls as well as 718 cases and 1,280 controls and one Thai sample comprising 308 cases and 546 controls. A meta-analysis of these samples from both the discovery and replication stages revealed a P value of 2.31×10^{-38} for rs3077 with an odds ratios (OR) of 0.56, 95 % confidence interval (CI) of 0.51, 0.61; and of 6.34×10^{-39} for rs9277535 with OR of 0.57 and 95 % CI of 0.52, 0.62. In addition, after genotyping SNPs in the highly polymorphic exon 2 of *HLA-DP*, it was found that *HLA-DPA1*0103*, *DPA1*0202*, *DPB1*0402*, and *DPB1*0501* were significantly associated with CHBI ($P = 2.93 \times 10^{-11}$, 4.45×10^{-8}, 2.27×10^{-7}, and 6.98×10^{-7}, respectively) (Kamatani et al. 2009). Considering that haplotype and haplotype-based association analysis not only show how these alleles are organized along a chromosomal region but also provide more information than individual SNPs, especially when genotyped SNPs for a region of interest are limited, the authors performed haplotype analysis for 11 SNPs and variants in exon 2. Their analysis revealed a strong linkage disequilibrium (LD) among some of these 11 SNPs, and haplotypes *DPA1*0103-DPB1*0402* and *DPA1*0103-DPB1*0401* showed protective effects for CHBI ($P = 6.00 \times 10^{-8}$; OR = 0.52; 95 % CI 0.35, 0.75; and $P = 0.002$; OR = 0.57; 95 % CI 0.33, 0.96,

respectively). In contrast, they found that haplotypes *DPA1*0202-DPB1*0501* and *DPA1*0202-DPB1*0301* were risk factors for CHBI ($P = 5.79 \times 10^{-6}$; OR = 1.45; 95 % CI 1.16, 1.81 and $P = 0.002$; OR = 2.31; 95 % CI 1.39, 3.84, respectively).

Since the first GWAS, which revealed a significant association of genetic variants in *HLA-DP* with CHBI, association of this genomic region on chromosome 6 with CHBVI has been replicated in a number of studies (Wong et al. 2013; Seto et al. 2013; Kim et al. 2013; Hu et al. 2013; Vermehren et al. 2012; Hu et al. 2012; Nishida et al. 2012; Mbarek et al. 2011; Li et al. 2011; Wang et al. 2011; Guo et al. 2011; An et al. 2011; Al-Qahtani et al. 2014). For example, after genotyping 11 SNPs in 521 chronic HBV carriers and 819 controls (571 individuals with HBV natural clearance and 248 healthy individuals), Guo et al. (2011) reported that this region was significantly associated with chronic HBV infection and clearance in the Han Chinese population from northern China. Moreover, they found that haplotype AACT (defined as block 1 in the original report), formed by the protective alleles of SNPs rs2395309, rs3077, rs2301220, and rs9277341 in *HLA-DPA1*, was significantly associated with a lower risk of chronic HBV infection (OR = 0.54; $P = 8.73 \times 10^{-7}$). In addition, they found that haplotypes GAGATT, all formed by the susceptibility minor alleles of SNPs rs9277535, rs10484569, rs3128917, rs2281388, rs3117222, and rs9380343, and GGGGTC, formed by the same SNPs with the minor alleles for rs9277535, rs3128917 and rs3117222 (defined as block 2), were significantly associated with a higher risk of chronic HBV infection (OR = 1.98, $P = 1.37 \times 10^{-10}$ and OR = 1.7, $P = 0.002$; respectively). Further, these two blocks were tested for their joint effects, which showed that the joint protective haplotypes AACT and AGTGCC from each block exerted a significant protective effect against chronic HBV infection. In addition, the joint haplotypes that included the protective haplotype AGTGCC from block 2 showed significant protective effects. From these results, we can infer that individuals with protective haplotypes should have a lower risk of chronic HBV infection.

In addition, a number of studies have been conducted to investigate the association of rs3077 in *HLA-DPA1* and rs9277535 in *HLA-DPB1* with chronic HBV infection and spontaneous clearance in different populations (Table 1). Generally speaking, the "A" alleles of both rs3077 and rs9277535 have protective effects against CHBI and encourage HBV clearance in the Han Chinese population (Wang et al. 2011; Li et al. 2011), as does the "A" allele of rs2395309 (Li et al. 2011). Moreover, An et al. (2011) reported that the protective effect of the rs3077/A allele was mainly attributable to more efficient viral clearance (OR = 2.41; 95 % CI 1.83, 3.18; $P = 4.65 \times 10^{-10}$) rather than reduction of the possibility of infection (OR = 0.62; 95 % CI 0.47, 0.83; $P = 0.0013$). Additionally, Seto et al. (2013) reported that the probability of viral clearance was further reduced in younger patients; among patients aged ≤50 years, the OR of HBV clearance was 0.56 ($P = 0.027$) (Fig. 1), whereas rs3077 had no association with HBV clearance among patients aged ≥50 years ($P = 0.617$). Also, there was no difference between male and female patients in the association of rs3077 with HBV clearance ($P = 0.091$ and $P = 0.190$, respectively). In Asians, rs3077/A was the minor allele. On the contrary, in one study with 201 chronic HBV carriers and 235 healthy people, it was found that the rs3077/A allele was the major allele in a Caucasian population (Vermehren et al. 2012). In the HapMap project, frequencies of rs3077/A and rs9277535/A were higher in European populations than in the corresponding population from Asia. One possible reason for such a discrepancy is that the higher prevalence of HBV infection in Asia may be secondary to fewer protective alleles in *HLA-DP*. Nevertheless, Wang et al. (2011) reported that rs3077 was not significantly associated with CHBI in the Chinese Zhuang ethnic population (OR = 0.8; $P = 0.206$). A meta-analysis conducted by Yan et al. (2012) showed that rs3077 was significantly associated with CHBI (OR = 0.57; 95 % CI = 0.44, 0.75; $P < 0.001$). However, the sample size in the study of Wang et al. (2011) was small, with only 177 CHBI and 208 spontaneous clearance subjects included, so the study might not have had sufficient power to detect significance.

Association of *HLA-DP* variants with LC and hepatocellular carcinoma (HCC)

Although chronic HBV infection is an important factor in LC and HCC (Lai et al. 2003) and contributes to 70 % of the HCC in Asian and African populations (Llovet et al. 2003), only 0.06 % of persistent carriers develop HCC per year (Chen et al. 2010). So far, only four studies reported the relation between *HLA-DP* variants (rs3077, rs9277535, and rs2395309) and LC and HCC (An et al. 2011; Hu et al. 2012; Li et al. 2011; Nishida et al. 2012). Most of these studies reported that there is no association of *HLA-DP* variants with LC and HCC (An et al. 2011; Li et al. 2011; Nishida et al. 2012). Even though rs9277535 and rs2395309 were initially reported to be strongly associated with CHBI and HBV clearance in the initial GWAS (Li et al. 2011; Kamatani et al. 2009), when compared with asymptomatic HBV carriers, Li et al. (2011) revealed that these two SNPs were not associated with CHBI, LC, and HCC, indicating there was no association of these two SNPs in *HLA-DP* with progression of chronic HBV infection. In an independent study, Zhang et al. (2010)

Table 1 Reported associations of rs3077 and rs9277535 with CHB and HBV clearance

dbSNP ID	Cases	Controls	Ethnicity	Studies	No. of cases	No. of controls	OR[a]	95 % CI	References
rs3077	CHB	Healthy	Japanese	1	606	1,267	0.57	0.49, 0.66	(Kamatani et al. 2009)
				2	272	274	0.53	0.41, 0.69	
				3	711	1,278	0.55	0.47, 0.63	
				4	300	545	0.61	0.49, 0.75	
		NI	Japanese	1	458	2,056	0.51	0.43, 0.59	(Mbarek et al. 2011)
				2	606	2,022	0.57	0.50, 0.66	
				3	379	1,539	0.54	0.46, 0.65	
				4	1,226	879	0.52	0.46, 0.59	
		NINV	Korean	1	400	1,000	0.55	0.43, 0.71	(Kim et al. 2013)
	IC	NINV	Chinese	1	499	245	0.64	0.50, 0.83	(Wong et al. 2013)
	CHI	NI	Japanese	1	181	183	0.42	0.30, 0.58	(Nishida et al. 2012)
				2	255	236	0.48	0.37, 0.62	
			Korean	1	215	145	0.47	0.35, 0.65	
			Saudi Arabian	1	779	587	0.83	0.70, 0.99	(Al-Qahtani et al. 2014)
		NINV	Caucasian	1	201	222	0.68	0.49, 0.95	(Vermehren et al. 2012)
			Chinese	1	514	808	0.58	0.49, 0.68	(Guo et al. 2011)
				2	1,218	227	0.67	0.54, 0.82	(An et al. 2011)
	SC	CHB	Chinese	1	736	782	0.52	0.45, 0.61	(Wang et al. 2011)
				2	177	208	0.80	0.57, 1.13	
		IC	Chinese	1	259	500	0.68	0.53, 0.87	(Wong et al. 2013)
				2	1,336	1,328	0.83	0.74, 0.94	(Hu et al. 2012)
			Japanese	1	181	183	0.42	0.30, 0.58	(Nishida et al. 2012)
				2	255	236	0.48	0.37, 0.62	
			Korean	1	215	145	0.47	0.35, 0.65	
		CHI	Chinese	1	287	1,218	0.57	0.47, 0.68	(An et al. 2011)
				2	933	947	0.71	0.61, 0.81	(Hu et al. 2013)
				3	1,235	1,245	0.73	0.65, 0.83	
				4	1,803	997	0.80	0.71, 0.90	
rs9277535	CHB	Healthy	Japanese	1	606	1,267	0.59	0.51, 0.69	(Kamatani et al. 2009)
				2	272	272	0.54	0.42, 0.69	
				3	708	1,276	0.56	0.48, 0.64	
			Thai	1	304	535	0.56	0.46, 0.69	
		NINV	Chinese	1	770	573	0.56	0.48, 0.67	(Li et al. 2011)
				2	197	380	0.65	0.51, 0.83	
			Korean	1	400	1,000	0.57	0.44, 0.72	(Kim et al. 2013)
		NI	Japanese	1	458	2,056	0.51	0.44, 0.60	(Mbarek et al. 2011)
				2	606	2,023	0.61	0.53, 0.70	
				3	379	1,539	0.55	0.46, 0.65	
				4	1,225	879	0.57	0.50, 0.65	
	IC	Healthy	Chinese	1	498	794	0.55	0.47, 0.64	(Guo et al. 2011)
	CHI	NINV	Chinese	1	2,202	573	0.52	0.43, 0.64	(Li et al. 2011)
				2	611	380	0.50	0.36, 0.68	
				3	1,193	224	0.80	0.65, 0.98	(An et al. 2011)
			Caucasian	1	201	235	0.92	0.67, 1.25	(Vermehren et al. 2012)
		NI	Saudi Arabian	1	765	571	0.83	0.70, 1.00	(Al-Qahtani et al. 2014)
	SC	CHB	Chinese	1	736	782	0.69	0.60, 0.80	(Wang et al. 2011)
				2	177	208	0.60	0.43, 0.82	
		CHI	Chinese	1	281	1,193	0.74	0.62, 0.89	(An et al. 2011)
				2	937	951	0.78	0.68, 0.88	(Hu et al. 2013)
				3	1,236	1,229	0.59	0.52, 0.66	
				4	1,757	994	0.73	0.65, 0.81	

CHB = chronic hepatitis B, *CHI* = chronic HBV infection, *CI* = confidence interval, *IC* = including CHB and carrier, *NI* = no evidence of HBV infection, *NINV* = no evidence of either HBV infection or HBV vaccination, *OR* = odds ratio, *SC* = serum clearance

[a] OR of A allele from two-by-two allele frequency table

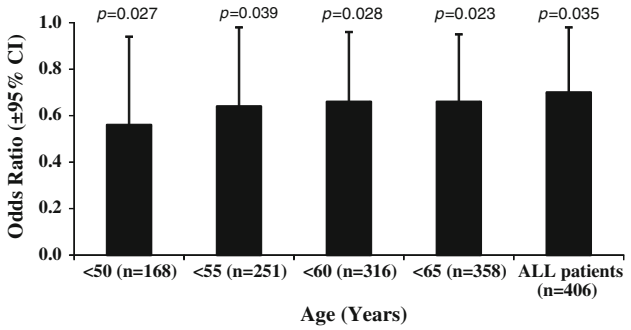

Fig. 1 Odds ratios (OR) of *HLA-DP* rs3077/A in association with hepatitis B virus (HBV) clearance at different ages [Adopted from Seto et al. (2013)]

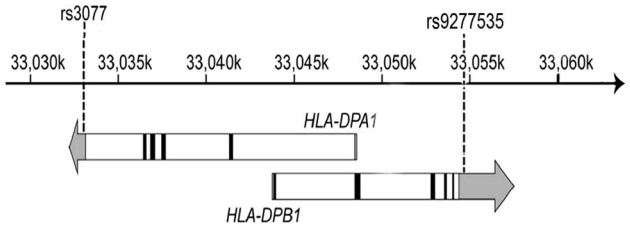

Fig. 2 Relative locations of SNPs rs3077 and rs9277535 in *HLA-DPA1* and *HLA-DPB1* loci on chromosome 6. The names of two SNPs are shown on the *top*, and their chromosomal positions are marked on the ruler in the *middle*. The *HLA-DPA1* and *HLA-DPB1* genes are shown as *arrows* at the *bottom*, with the exons shown as *black boxes*, introns as *open boxes*, and untranslated regions as *gray boxes/arrows*

conducted GWAS for HCC in a Chinese population and identified a new susceptibility locus in the *UBE4B-KIF1B-PGD* region on 1p36.22. This region involves in numerous cellular functions such as proliferation, apoptosis, DNA repair, and other intracellular actions (Hoeller et al. 2006). Based on this work, it is likely that different genes play distinct roles in chronic HBV infection and progression in different populations. *HLA-DP* or other genes might be the primary cause of chronic HBV infection, but an intracellular pathway, such as ubiquitin or others, is mainly involved in the progression of chronic infection (Li et al. 2011). Unfortunately, such association of the genomic region on chromosome 1 has not been replicated in other studies (Li et al. 2012; Hu et al. 2012), and the exact reason for this discrepancy remains to be examined.

Regarding the variants on chromosome 6 reported by Kamatani et al. (2009), Hu et al. (2012) found that SNP rs3077 AG and AA genotypes significantly decreased host HCC risk (OR = 0.78; 95 % CI 0.67, 0.92; $P = 3.63 \times 10^{-3}$) when compared with persistent HBV carriers with GG genotype in dominant genetic models. But after meta-analysis by combining the results from An et al. (2011), this association becomes non-significant (Hu et al. 2012). Thus, further research, with a larger sample and in the same or different populations, needs to be conducted in order to demonstrate whether there exists any association of *HLA-DP* variants with the susceptibility and progression of chronic HBV infection.

Association of *HLA-DP* variants with the immune system

The outcomes of HBV infection depend mainly on the immune response. *HLA* class II molecules (*HLA-DR*, *-DQ* and *-DP*) encode proteins expressed on the surface of antigen-presenting cells and are crucial in that they present peptides to $CD4^+$ helper T-cells (Pieters 2000). Although *HLA-DP* has a structure similar to that of other classical *HLA* class II molecules, the roles of *HLA-DP* molecules in the immune response have not been well characterized. Using single amino acid substitutions in *HLA-DPB1*02012* to analyze the role of polymorphic residues of the *HLA-DPB1* domain on peptide binding and T-cell allorecognition, Diaz et al. (2003) demonstrated that HLA-DPβ peptide residues 9, 11, 35, 55, 56, 69, and 84–87 play crucial roles in peptide binding and T-cell allorecognition, probably by influencing the binding of peptide in the groove of HLA-DPB and altering the conformation of the MHC–peptide complex which is recognized by T-cell receptor. However, there is still very limited information about peptide interactions and the roles of variants in *HLA-DP* both in peptide binding and in T-cell recognition. Because none of the identified 11 SNPs in *HLA-DP* on chromosome 6 leads to a change of amino acids in the encoded protein, it is likely that these 11 SNPs influence binding or presentation of viral peptides, resulting in either chronic HBV infection or viral clearance.

Up to now, the most convincing and well-investigated SNPs regarding chronic HBV infection and clearance are rs3077 and rs9277535, which are about 22 kb away from each other and located in the 3′-untranslated regions (UTRs) of *HLA-DPA1* and *HLA-DPB1* (Fig. 2), respectively. Because they are not located in the *HLA-DP* coding region, their biological effects could be realized through influencing the antigen-binding site indirectly, changing the expression of *HLA-DP* genes through altering some microRNA-binding sites, which leads to changes in the stability and translation of mRNA, and/or through altering transcription factor binding (An et al. 2011; O'Brien et al. 2011). These SNPs upregulate *HLA-DPA1* and *HLA-DPB1* expression in normal liver tissues (Figs. 3, 4) (O'Brien et al. 2011). High *HLA-DPA1* and *HLA-DPB1* expression might be more effective in presenting viral antigens to $CD4^+$ helper T-cells, increasing the immune response to encourage HBV clearance and aiding in the clearance of

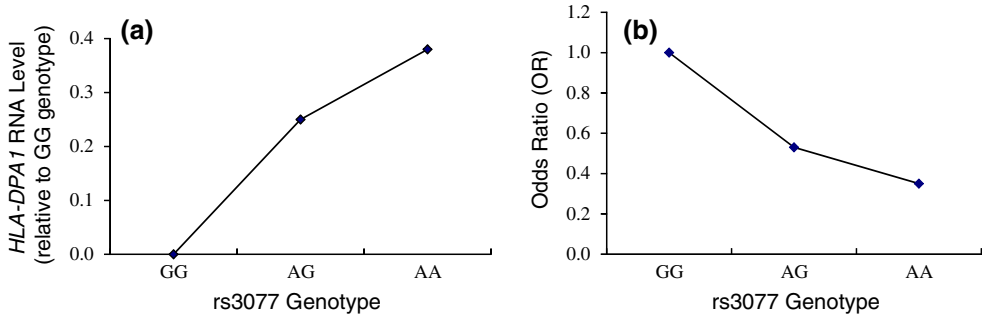

Fig. 3 Relationship of SNP rs3077 genotypes in HLA-DPA1 with HLA-DPA1 RNA expression level (**a**) and odds ratios (OR) for its association with chronic hepatitis B virus infection (**b**). Gene expression values represent the arithmetic increase in mean-log gene expression compared with the risk GG genotype, which has been set to zero as a reference [Adopted from O'Brien et al. (2011)]

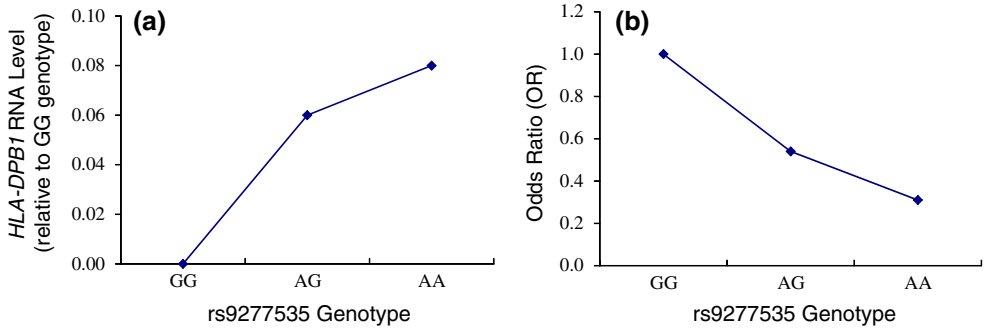

Fig. 4 Relationship of SNP rs9277535 in *HLA-DPB1* with HLA-DPB1 RNA expression level (**a**) and odds ratios (OR) for its association with chronic hepatitis B virus infection (**b**). Gene expression values represent the arithmetic increase in mean-log gene expression compared with the risk GG genotype, which has been set to zero as a reference [adopted from O'Brien et al. (2011)]

chronic HBV infection. The reason these SNPs had no obvious impact on disease progression to cirrhosis or HCC remains to be explored.

Conclusion and future research directions

Both GWAS and candidate gene-based association studies have revealed significant association of variants in *HLA-DP* with viral clearance and chronic HBV infection. In addition, GWAS demonstrated that rs9277535 has a great impact in the response to booster hepatitis B vaccination in adolescents who received postnatal hepatitis B vaccination. The concordance of alleles associated with protective effects for both chronic infection and vaccine response indicates that these two HBV-related phenotypes share some major aspects of genetic etiologies, and the lesser effectiveness of the vaccine in those individuals carrying those risk alleles may attributable to their high likelihood of being infected with HBV (Wu et al. 2013). But whether there exists any association of *HLA-DP* variants with the progression of chronic HBV infection remains to be confirmed with larger samples and different origins of samples.

As reviewed here, most current researches focus mainly on SNPs rs3077 and rs9277535 in *HLA-DP* on chromosome 6. Because none of them can lead to an amino acid change, future study should focus on identifying more variants in this genomic region on chromosome 6 and illustrate how these variants affect gene expression and biological function of the product. A detailed elucidation of the molecular mechanism of *HLA-DP* variants and HBV infection will shed light on its pathogenesis and promote development of new therapies for HBV infection and prevention of disease progression.

Moreover, smoking and alcohol drinking are risk factors for HBV infection and progression (Ohnishi et al. 1987). How they contribute to such processes is rarely addressed in the reported studies; thus, if possible, these factors should be considered when one designs a new genetic study on HBV infection and analyzes this type of data, given the information available for the dataset of interest. Besides, gene–gene and gene–environment interactions should be taken into account. It is our hope that such comprehensive studies will lead to a better understanding of the involvement of variants within this genomic region on chromosome 6 in chronic HBV infection and

progression and eventually lead to targeted and effective epidemic control strategies.

Acknowledgments The preparation of this review was supported in part by the Ministry of Science and Technology of China (2012AA020405) and the National Natural Science Foundation of China grant 81273223.

Conflict of interest The authors declare that they have no conflict of interest on this report.

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