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TOPIC HIGHLIGHT

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Human genes involved in hepatitis B virus infection

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Abstract

Persistent hepatitis B virus (HBV) infection is a significant public health problem because it is a major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). Roughly one-third of the world population has been infected with HBV and there are about 350 million (5%-6%) persistent carriers. HBV causes 80% of all liver cancer cases and is the second most important carcinogen, after smoking tobacco. There is an approximate 90% risk of becoming a persistent carrier following perinatal infection in infants born to *e* antigen positive carrier mothers and a 30% risk in pre-school children. Only 5%-10% of adults become persistent carriers following infection. Of individuals persistently infected with HBV, 10%-30% will develop liver cirrhosis and HCC. These highly variable outcomes in both clearance rates and disease outcomes in persistently infected individuals cannot be fully explained by differences in immunological, viral or environmental factors. Thus, differences in host genetic factors may affect the natural history of hepatitis B.

Key words: Hepatitis B virus; Hepatocellular carcinoma; Epidemiology; Clearance; Persistance; Genetic; Polymorphism; Outcome; Natural history

Core tip: This manuscript is a review and summary of the advances about human genetic polymorphisms that are associated with hepatitis B virus (HBV) clearance and persistent infection. Especially, large sample size candidate gene association studies and genome-wide association studies, which discovered several gene polymorphisms that are associated with HBV clearance, such as HLA-DPA1 and HLA-DPB1 polymorphisms, are focused.

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INTRODUCTION

The consequences of acute and chronic hepatitis B virus (HBV) infections are a major public health problem worldwide. Approximately 5% of the world population (350 million persons) has chronic HBV infection, which is the leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC)[1]. It is estimated that one to two million people die annually of HBV-related liver disease.

HBV is transmitted by percutaneous or permucosal exposure to infectious body fluids, by sexual contact with an infected person, and perinatally from an infected mother to her infant. Approximately 45% of the world population live in areas where the prevalence of chronic HBV infection is high [8% of the population are positive for HBV surface antigen (HBsAg)], 43% in areas where the prevalence is moderate (2% to 7% of the population are HBsAg positive), and 12% in areas of low endemic-

ity (< 2% of the population are HBsAg positive). Of individuals persistently infected with HBV, 10%-30% will develop liver cirrhosis (LC) and HCC. The mechanisms underlying different outcomes are not yet well understood, but are generally attributed to: (1) immunological factors: HBV clearance relies on an effective host immune response. The cellular and humoral immune responses to HBV infection are complex. Most studies suggest that HBV is not directly cytopathic to infected hepatocytes and that the cellular response to several viral proteins correlates with the severity of clinical disease and viral clearance[2]. It is believed that the antibody response to viral envelope antigens contributes to clearance of the virus and that cytotoxic T cells mediate viral clearance by killing infected cells. In addition, it has been shown that cytotoxic T lymphocytes inhibit HBV gene expression through the secretion of antiviral cytokines and that the expression of these cytokines may be the principal mechanism of viral clearance during HBV infection[3]. It is hypothesized that chronic infection is related to a weak T-cell response to viral antigens; (2) viral factors: many papers have reported that HBV viral loads[4], genotypes[5] and variants[6,7] are associated with HBV infection outcomes; (3) environmental factors: alcohol and aflatoxin are two important environmental exposures that affect the progression of chronic hepatitis B. Alcohol consumption may act by increasing the severity of liver disease[8,9] and increase risk of liver decompensation[10]. Patients with chronic hepatitis B and exposure to aflatoxins are at an increased risk of HCC[11]; and (4) Host genetic factors: a number of polymorphisms in candidate genes have been tested for associations with HBV persistence and disease outcomes. These include MHC class I loci and class II loci, cytokine, chemokine and vitamin D receptor genes. Gneome wide association studies (GWAS) using very large sample sizes have identified genetic loci that are associated with clearance and clinical outcomes in chronic infection. Therefore, this review focuses on recent genetic advances in both candidate gene and whole genome association studies that have identified promising genetic loci associated with outcome of HBV infection and discuss the implications and translation of these findings to clinical care.

GENETIC FACTORS INFLUENCING OUTCOMES OF HBV INFECTION

HLA

MHC class I genes encode glycoproteins which bind viral peptides for presentation to CD8+ cytotoxic T lymphocytes (CTLs). Upon recognition of antigenic peptides, CTLs induce lysis or apoptosis of the infected hepatocytes. CTLs are readily detectable in the peripheral blood of patients with acute HBV infection and anti-HBs seroconversion and are found to be polyclonal and multispecific. Thio *et al*[12] showed that HLA-A*0301 was associated with HBV clearance and B*08, A*01-B*08-DRB1*03, B*44-Cw*1601 and B*44-Cw*0501 were associated with HBV persistent infection in an European population. Wu *et al*[13] showed that HLA-B*4001 was associated with HBV clearance in Taiwan Aborigines, but not in the Chinese Han population. Albayrak *et al*[14] reported that HLA-B35 and HLA-CW4 were risk factors for persistent HBV infection in an eastern Turkey population. Hu *et al*[15] showed that HLA-C (rs3130542A) was associated with HBV persistent infection in a Chinese Han population.

CD4+ T cell proliferative responses in acute HBV infection are significantly more vigorous than those seen in persistent HBV infection, suggesting that MHC class II polymorphisms influence susceptibility to persistent infection. Several MHC class II alleles have been identified in association with clearance or persistence of HBV infection.

Ramezani *et al*[16] and Kummee *et al*[17] showed that DRB*13 was associated with viral clearance in Iran and Thailand populations. Thio *et al*[12], Thursz *et al*[18], Höhler *et al*[19] and Cho *et al*[20] found that DRB1*1302 was associated with viral clearance in Europeans, Gambia children, German and South Korea adults. Recently, Kamatani *et al*[21] performed a GWAS and identified that HLA-DPA1 and DPB1 were associated with HBV clearance in the Japanese population. An *et al*[22], Guo *et al*[23], Cheng *et al*[24], Yan *et al*[25], Wong *et al*[26], Li *et al*[27], Hu *et al*[28] and Hu *et al*[15] further confirmed that HLA-DPA1 rs3077 T and HLA-DPB1 alleles/haplotypes (rs9277535 non-G, rs9277378 A, rs3128917 T) were strongly associated with viral clearance in a Chinese population. Another GWAS also confirmed that HLA-DPA1 (rs3077) and HLA-DPB1 (rs9277542) were associated with viral clearance in Japan and Korea populations[29]. However, there were two studies, which indicated different mRNA expression levels for HLA-DPA1 and HLA-DPB1. O'Brien *et al*[30] showed the mRNAs of both of HLA-DPA1 (rs3077 GG) and HLA-DPB1 (rs9277535 GG) were lowly expressed in liver cells and monocytes in non-Hispanic Europeans, while Thomas *et al*[31] showed the mRNA level of HLA-DPB1 in subjects with rs9277534 (not rs9277535) GG genotype was significantly higher than that in subjects with AA and AG gentotypes in B cells, in which it was associated with HBV clearance in European-Americans and African-Americans.

Thio *et al*[32] showed that DQA1*0501, DQB1*0301 and DQA1*0501-DQB1*0301-DRB1*1102 were associated with persistent infection in adult African-American injection-drug users. Almarri *et al*[33] found DR7 to be a risk factor and DR2 to be protective in Qatarian adults. Albayrak *et al*[14] showed that HLA-DQ2 and DQ8 were associated with persistent HBV infection in an eastern Turkey population. In the Japanese population, a GWAS showed that HLA-DQ rs2856718 and rs7453920 SNPs, and DQA1*0102-DQB1*0604 and DQA1*0101-DQB1*0501 haplotypes were protective, and DQA1*0102-DQB1*0303 and DQA1*0301-DQB1*0601 were risk factors[34]. Hu *et al*[28] also reported that HLA-DQ rs2856718 and rs7453920 were associated

with HBV clearance and decreased HCC development in the Chinese population. Fletcher *et al*[35] showed that HLA-DRB1*0701 was associated with persistent HBV infection in the South Indian population. Corrêa Bde *et al*[36] showed that HLA-DRB1*08 and DRB1*09 were associated with peraiatent HBV infection in the Brazilian population.

Cytokines

Tumor necrosis factor (TNF)-α is a pro-inflammatory, anti-viral cytokine, and is located within the class III region of the MHC complex, which has been shown in transgenic mice to inhibit the replication of HBV[37]. Patients persistently infected with HBV have increased levels of TNF-α and upregulated TNF-α receptors. There are two polymorphisms in the TNF-α promotor region at positions -308 and -238 that alter TNF-α expression[38,39]. However, a study showed that the -308 polymorphisms did not influence TNF-α expression in healthy people[40]. The -238 promotor variant was significantly associated with HBV persistence in German patients[41]. -308G/-238G haplotype[42] and -1031C/-863A/-857C/-308G/-238G haplotype[35] were found to be associated with persistent HBV infection in Korean and South Indian populations. However, -1031C or T/-863A or C/-857C/-308G/-238G/-163G haplotypes in Koreans[43], -863C/-308G/-238G in Thais[17] and -1031T/-863C/-857C/-308G/-238G[44] in the Chinese population were associated with HBV clearance. There were also several meta-analysis studies that showed that -238A[45] and -308G[46] were associated with HBV persistent infection in European and Chinese populations, respectively; -857T[47] in Asians and -863C[17] in Thais were associated with HBV clearance.

Interleukin-28B (IL-28B) plays an important role in clearance of hepatitis C virus. However, there were many reports that indicated IL-28B polymorphism(s) did not influence the outcome of HBV infection[48-53]. However, Al-Qahtani *et al*[54] showed that IL-28B polymorphisms were associated with HBV clearance. And also, Seto *et al*[51] showed that IL-28B polymorphisms were associated with HBsAg seroconversion. In addition, L-28B polymorphisms were also associated with HBeAg and HBsAg seroconversion in response to interferon treatment[55,56]; however, Holmes *et al*[57] showed that this might not apply in the Asian population.

Interleukin 10 (IL-10) is another important cytokine that influence CD4+ cell proliferation. IL-10 promotor polymorphisms -1082, -819 and -592 haplotype ATA was associated with persistent HBV infection in Japanese and Chinese populations[58,59]. A meta-analysis showed that IL-10 -1082A and -592A were associated with HBV clearance in the Chinese population[60]. Li *et al*[61] showed that interleukin 18 rs1946518A (-838A) was associated with persistent HBV infection in a Chinese population.

Secreted phosphoprotein 1 (SPP1) is also a cytokine that upgulates expression of interferon-gamma and interleukin-12, and therefore, it may influence the outcome of HBV infection. Shin *et al*[62] reported that SPP1 -1800T/-1627T/4645C/5806T/6139A haplotype was associated with HBV clearance and HCC development.

Granulysin (GNLY) is a substance produced by CD8+ cytotoxic T cells. It is expressed in cytolytic granules with perforin and granzymes and functions to create holes in target cell membrance and destroy it. It is able to induce apoptosis and antimicrobial action. Park *et al*[63] reported that GNLY polymorphisms were associated with persistent HBV infection in a South Korean population.

Chemokines

Chemokines are 8-10 kDa proinflammatory proteins involved in the regulation of leukocyte trafficking. Although chemokines are produced by many cell types, CD8+ T cells are a major source[64]. CXC (a) chemokines, such as IL-8 and IP-10, and CC (b) chemokines, such as RANTES, MIP-1a and MIP-1b, have been shown to be dependent on TCR triggering by MHC class I /peptide complex engagement[65-68]. IP-10 and monokine induced by IFN-γ (MIG), which selectively attract activated lymphocytes, are IFN-γ inducible[69,70]. Chemokines and their receptors can regulate T lymphocyte activation or differentiation[71]; TNF-α can also upregulate chemokine expression. Antigen recognition by CTLs leads to both direct release and secondary induction of chemokines at sites of infection. Thus, CTLs can rapidly establish chemotactic gradients when they encounter their target antigens. Ahn *et al*[72] showed that it was CC chemokine receptor 5 (CCR5) promoter 59029G and 59353T, not CCR5 Δ32 or RANTES, that were associated with HBV clearance in a Korean population. However, heterozygosity of CCR5 Δ32 was associated with persistent HBV infection in an Indian population[73].

Other candidate genes

Mannose binding protein (MBP), also known as mannose binding lectin (MBL), acts as an opsonin to affect inate immunity[74]. The HBV envelope contain a monnose-rich ologosaccharide to which MBP could potentially bind. There are three mutations in the MBP gene exon 1 (codons 52, 54 and 57). The codon 52 mutation of the MBP gene in British Caucasians, but not in the Asian population, was associated with persistent HBV infection[75]. The codon 54 mutation was associated with symptomatic persistent infection in Chinese patients[76], not in the Korean population[77]. In German Caucasions and in Gambians, these MBP polymorphisms were not associated with chronic infection[78,79]. The mbl2 gene encodes MBL. Thio *et al*[80] showed that mbl2 promoter -221C decreased MBL production and led to HBV persistent infection. A meta-analysis showed that mbl2 exon 1 polymorphisms were not associated with chronicity of HBV infection, but might be associated with disease progression[81].

Vitamin D acting through the vitamin D receptor (VDR) can act as an immunomodulatory hormone that inhibits the Th1 response and activates the Th2 response[82,83]. Bellamy *et al*[84] showed that vitamin D recep-

Table 1 Genes associated with hepatitis B virus clearance and persistence

Associated with clearance or persistence	Ref.	Area/country	Population	Allele or haplotype	Frequency (%)		OR	*P* value	Comments
					Clearance/number	Persistence/number			
Clearance									
HLA	Thio *et al*[12]	United States	Caucasian	A*0301	15.7/342	8.1/194	0.47	0.0005	Several cohorts combined
				DRB1*1302	4.9/342	2.1/194	0.42	0.030	Limited power
	Thursz *et al*[18]	United Kingdom	Gambias	DRB1*1301	7.3/218 (children)	2.7/185 (children)	0.35	0.037	Class I serol typing
				DRB1*1302	26.6/218 (children)	16.2/185 (children)	0.53	0.012	Malaria cases unkown
				DRB1*1302	25.6/195	7.5/40	0.24	0.012	
	Höhler *et al*[19]	Germany	German	DRB1*1301-02	33.3/24	5.7/70	0.12	0.004	Small sample size
				DRB1*1302	12.5/24	0/70		0.018	
	Almarri *et al*[33]	Qatar	Qatarians	D2	26/31	14/21	0.10	0.013	Small numbers and HLA serol typing
	Wu *et al*[13]	Taiwan	Han Chinese	DR*0406	4.0/324	0.0/98	0.057	< 0.001	
				DR*0701	3.1/324	0.5/98	0.18	0.042	
				DR7	3.1/324	0.5/98	0.18	0.042	
			Taiwanese Aborigines	B*4001	32.8/229	26.5/138	0.65	0.045	
	Albayrak *et al*[14]	Turkey	Turks	CW1	26.67/30	5.33/75	6.455	< 0.05	Small sample size
				DR13	36.67/30	8.0/75	6.658	< 0.05	
	Wong *et al*[26]	Hong Kong	Chinese	rs3077 T	27.6/259	20.7/500	1.41	0.0083	
				rs9277378 A	34.0/259	24.2/500	1.61	0.83E-2	
				rs3128917 T	44.6/259	33.5/500	1.54	1.1E-4	
				Haplotype TAT	20.9/259	14.7/500	1.64	0.0013	
	Ramenazi *et al*[16]	Iran	Iranian	DRB1*13	11.67/30	3.13/64	0.22	< 0.03	Small sample size
	Kamatani *et al*[21]	Japan	Japanese	HLA-DPA1*0103-DPB1*0402	9.6/2100	4.2/1300	0.52	6.00E-8	
				HLA-DPA1*0103-DPB1*0401	3.8/2100	1.8/1300	0.57	0.002	
	An *et al*[22]	United States	Chinese	HLA-DPA1 rs3077 (TT/TC/CC)	(14.0/56.0/30.0)/287	(9.0/40.0/51.0)/1218	2.41	3.47E-10	
				HLA-DPB1 rs9277535 (AA/AG/GG)	(61/100/63)/224	(252/546/395)/1193	0.81	0.036	
	Nishida *et al*[29]	Japan	Japanese, Korean,	rs3077 T	18.6/564	8.3/751	0.46	4.40E-19	GWAS-meta-analysis
			Chinese, Thai	rs9277542 T	21.03/561	12.07/646	0.50	1.28E-15	Healthy control
	Cheng *et al*[24]	Taiwan		rs9277535 (GA + AA)	57.0/100	42.0/100	1.83	0.034	
	Hu *et al*[28]	China mainland	Chinese	DP rs9277535 (GG/AG/AA)	(31.5/49.9/18.6)/1344	(43.5/45.4/11.1)/1344	0.60	1.69E-10	
				DQ rs7453920 (GG/AG/AA)	(79.2/19.6/1.2)/1344	(86.5/13.1/0.4)/1344	0.60	7.61E-7	
				DQ rs2856718 (AA/AG/GG)	(25.8/49.4/24.8)/1344	(31.5/50.5/18.0)/1344	0.75	0.001	
				DP rs3077 (GG/AG/AA)	(46.3/42.9/18.6)/1344	(51.5/40.5/8.0)/1344	0.81	0.0083	
	Yan *et al*[25]	China mainland	Chinese	rs3077 AA	21.9/64	8.6/282	0.29	0.0017	Meta-analysis
				rs9277535 AA	25.0/64	9.6/282	0.26	4E-4	
	Cho *et al*[20]	South Korea	Koreans	DRB1*1302	14/80	19/384	4.34	2E-4	Sample bias
				DRB1*1502	12/80	32/384	2.21	0.0376	
				DQB1*0302	20/80	49/384	2.12	0.0172	
				DQB1*0609	8/80	6/384	7.24	0.0006	
	Kummee *et al*[17]	Thailand	Thais	DRB1*13	8.0/100	4.7/150	0.04	0.0008	
	Thomas *et al*[31]	United States	European-American/	DPB1*04:01	59.1/421	48.6/241	0.56	0.003	
			African-American	rs9277534 (AA + AG)	90.15/406	80.17/232	0.37	1E-4	
			European-American	DPB1*04:01	70.3/320	58.4/185	0.55	0.01	
			African-American	DPB1*04:01	22.4/85	8.7/46	0.27	0.05	Small sample size

	Fletcher *et al*[55]	India	Indian	DRB1*03:01	12.94/85	1.2/83	0.08	0.007	Small sample size
	Mbarek *et al*[54]	Japan	Japanese	rs2856718 (AA/AG/GG)	(23.16/48.3/28.54)/6486	(36.06/45.57/18.37)/2662	1.56	3.99E-37	GWAS-meta-analysis
				rs7453920 (A/G)	(2.91/28.08/69.01)/6496	(1.01/17.71/81.28)/2665	1.81	5.98E-28	HBsAg(-) diseases control
				DQA1*0102-DQB1*0604	6.59	1.22	0.16	3.42E-13	
				DQA1*0101-DQB1*0501	4.77	1.68	0.39	1.06E-5	
	Seto *et al*[51]	Hong Kong	Chinese	DP rs3077	25.4/203	19.2/203	0.699	0.035	
				haplotype block GAT (rs3077/rs9277378/rs3128917)	3.7/203	6.9/203	2.17	0.034	
Cytokines									
TNF	Kim *et al*[43]	South Korea	Koreans	TNF-α-863 (A/C)	23.3/279	30.5/1038	1.52-1.58	0.003-0.004	
				TNF-α-863 (C/C)	74.8/279	65.9/1038			
				TNF-α-863 (A/A)	1.9/279	3.6/1038			
				TNF-α-308 (A/G)	11.3/283	6.5/1040	0.56-0.57	0.01	
				TNF-α-308 (A/A)	0/283	0.1/1040			
				TNF-α-308 (G/G)	88.7/283	93.4/1040			
				TNF-α (-1031T; -863C; -857C; -308G; -238G; -163G)	32.6/276[1] 36.2/276[2]	31.3/1038[1] 29.1/1038[2]	0.67-0.78	0.003-0.006	
	Kummee *et al*[17]	Thailand	Thais	-863 C/C	70.0/100	56.6/150	0.46	0.01	
	Zhang *et al*[46]	China mainland	Chinese	TNF-α-857 TT	83/2012	218/5267	0.701	0.032	Meta-analysis
	Shi *et al*[47]	China mainland	Asian	TNF-α-857 T	/2702	/4929	0.82	0.008	Meta-analysis
	Du *et al*[44]	China mainland	Chinese	857 TT	17.48/143	9.18/196	0.48	0.03	
				Haplotype GGCCT	37.59/143	25.74/196	0.59	0.03	
	Al-Qahtani *et al*[54]	Saudi Arabia	Saudi Arabian	rs12979860T	23.0/304	28.0/824	1.307	0.0183	
				rs12980275 G	27.0/304	19.0/824	0.642	1E-4	
				rs8105790 C	22/304	17/824	0.746	0.0133	
IL-10	Cheong *et al*[42]	South Korea	Koreans	IL-10 -592 (CC)	12.7/204	7.5/412	0.40	0.003	
	Zhang *et al*[46]	China mainland	Chinese	-592A			0.799	0.007	Meta-analysis
IL-28B	Seto *et al*[51]	Hong Kong	Chinese	Haplotype block CG (rs12979860/rs8099917)	0.2/203	2.5/203	10.50	0.026	
Other genes									
SPP1	Shin *et al*[62]	South Korea	Koreans	SPP1-ht2[T-T-C-T-A]	45.11/286	37.44/158	1.44	0.006	
CCR5	Ahn *et al*[72]	South Korea	Koreans	59029G	29.6/243	19.8/349	1.71	0.006	
				59353T	29.6/243	19.8/349	1.71	0.006	
Persistence									
HLA	Thio *et al*[12]	United States	Caucasians	B*08	8.1/342	12.2/194	1.59	0.03	
				B*44	11.9/342	19.4/194	1.82	0.001	
				Cw*0501	6.8/342	12.1/194	1.81	0.009	
				Cw*1601	2.4/342	5.3/194	2.14	0.03	
				DQB1*0201	20.1/342	27.8/194	1.56	0.004	
				DRB1*0301	9.6/342	15.1/194	1.66	0.009	
				A*0101-B*08-DQA1*0501-DQB1*0201-DRB1*0301	5.3/342	8.0/194	1.58	0.09	
				B*44-Cw*1601	2.4/342	5.4/194	2.23	0.02	
				B*44-Cw*0501	5.3/342	10.4/194	1.99	0.006	
				B*44-DRB1*0701	4.6/342	7.8/194	1.83	0.03	
				B*44-Cw*1601-DRB1*0701	2.0/342	4.3/194	2.21	0.04	

	Thio *et al*[32]	United States	African-Americans	DQA1*0501	20/60	40/31	2.6	0.05	Small sample size
				DRB1*0301	12/60	32/31	3.9	0.01	
				DQA1*0501-DQB1*0301	11/60	27/31	3.0	0.005	
				DQA1*0501-DQB1*0301-DRB1*1102	0.8/60	8.5/31	10.7	0.01	
	Almarri *et al*[33]	Qatar	Qatarians	D7	16/31	57/21	3.73	0.05	Small sample size
	Wu *et al*[13]	Taiwan	Han Chinese	B35	1.9/324	4.6/98	2.63	0.034	
				DR12	13.6/324	23/98	2.1	0.0022	
				DR*1202	9.9/324	16.8/98	1.81	0.024	
			Taiwanese Aborigines	A*0206	3.9/229	8.7/138	2.85	0.0029	
	Albayrak *et al*[14]	Turkey	Turks	B35	0.2/30	46.7/75	0.286	< 0.005	Small sample size
				CW4	13.33/30	44.0/75	0.286	< 0.005	
				DQ2	6.67/30	28.0/75	0.184	< 0.005	
				DQ8	6.67/30	25.33/75	0.211	< 0.005	
	Hu *et al*[15]	China mainland	Chinese	rs3130542			1.33	9.49E-14	GWAS-Meta-analysis
				rs4821116			0.82	1.71E-12	
	Kamatani *et al*[21]	Japan	Japanese	HLA-DPA1*0202-DPB1*0501	34.7/2100	42.8/1300	1.45	5.79E-6	
				HLA-DPA1*0202-DPB1*0301	1.8/2100	3.6/1300	2.31	0.002	
	Mbarek *et al*[34]	Japan	Japanese	DQA1*0102-DQB1*0303	0.25/614	1.91/748	19.03	8.39E-5	
				DQA1*0301-DQB1*0601	0.42/614	2.45/748	5.02	7.34E-5	
	Li *et al*[27]	China mainland	southern Chinese	HLA-DP rs2395309 G	257/524	1367/2107	1.31	9.63E-7	
				rs9277535 G	208/524	1195/2107	1.33	1.67E-7	
			northern Chinese	HLA-DP rs2395309 G	121/304	302/600	1.2	0.021	
				rs9277535 G	75/304	206/600	1.26	8.37E-5	
	Fletcher *et al*[35]	India	Indian	DRB1*07:01	24.71/85	57.83/83	3.76	< 0.005	Small sample size
				HLA-B*44	3.45/85	18.07/83	6.23	0.007	
	Ramezani *et al*[16]	Iran	Iranian	A*33	0/30	10.16/64		< 0.008	Small sample size
	O'Brien *et al*[30]	United States	European	rs3077				3.00E-7	Liver tissues
				rs9277535				0.001	Gene expression study
	Thomas *et al*[31]	United States	European-American/ African-American	DPB1*01:01	14.3/421	21.2/241	1.86	0.01	
			African-American	DPB1*01:01	37.7/85	60.9/46	2.7	0.01	Small sample size
	Cho *et al*[20]	South Korea	Koreans	DRB1*0701	7/80	69/384	0.43	0.0458	Sample bias
				DQB1*0301	17/80	126/384	0.55	0.047	
	Guo *et al*[23]	China mainland	Chinese	rs9277535 G	553/571	498/521	0.56	5.61E-9	
				rs2395309 G	564/571	496/521	0.71	2E-4	
				rs3077 G	562/571	514/521	0.64	6.00E-6	
				rs2301220 T	557/571	509/521	0.67	4.44E-5	
				rs9277341 C	563/571	511/521	1.77	1.28E-5	
				rs3135021 G	566/571	514/521	0.78	3.00E-3	
				rs10484569 A	564/571	514/521	1.6	3.20E-6	
				rs3128917 G	566/571	519/521	1.91	4.62E-11	
				rs2281388 A	556/571	502/521	1.66	4.65E-7	
				rs3117222 T	552/571	511/521	0.51	2.70E-11	
				rs9380343 T	562/571	501/521	0.61	4.95E-7	
	Corrêa Bde *et al*[36]	Brazil	Brazilian	DRB1*09	3.6/256	12.5/64	4.2	0.016	Male gender
				DRB1*08	12.2/256	27.3/64	2.54	0.031	Aged 39 years or younger
Cytokines									

TNF	Kim *et al*[43]	South Korea	Koreans	TNF-α (-1031C; -863A; -857C; -308G; -238G; -163G)	23.2/276[1] 1.8/276[2]	288.8/1038[1] 3.4/1038[2]	1.42-1.46	0.01-0.02	
	Fletcher *et al*[35]	India	Indian	TNF-rs1800630 AA	4.1/150	11.9/137	2.28	< 0.01	
				TNF-rs1799964 CC	15.0/150	20.8/137	2.21	< 0.01	
	Zheng *et al*[45]	China mainland	European	TNF-α-238 (GA + AA)	/3181	/5245	2.22/4.46	0.032/0.002	Meta-analysis
	Du *et al*[44]	China mainland	Chinese	-238GG	93.01/143	97.96/196	4.08	0.02	
				-863CA	16.08/143	25.51/196	1.79	0.04	
				haplotypes GGCAT	13.72/143	31.40/196	2.85	1E-4	
				haplotypes GGTAT	3.46/143	6.93/196	4.15	4E-4	
	Höhler *et al*[41]	Germany	German	-238 A	6.0/32	25.0/71		< 0.04	
	Cheong *et al*[42]	South Korea	Korean	TNF-α -308 (GG/GA/AA)	(85.8/13.7/0.5)/204	(88.8/10.9/0.2)/412	0.58	0.039	
				TNF-α haplotype (-308/-238)	75.5/204	82.8/412	0.56	0.007	
	Zhang *et al*[46]	China mainland mainland	Chinese	TNF-α-308A	/2012	/5267	0.585	0.002	Meta-analysis
IL28B	Kim *et al*[50]	South Korea	Koreans	rs12979860 CC	85.9/220[2]	93.5/154[2]		0.013	
				rs12980275 AA	85.6/243[2]	91.1/203[2]		0.042	
				rs8099917 TT	89.3/241[2]	94.1/204[2]		0.035	
IL-18	Li *et al*[61]	China mainland	Chinese	rs1946518 AA	60/301	141/501	1.573	0.009	
Other genes									
SPP1	Shin *et al*[62]	South Korea	Koreans	SPP1-ht2-bearing genotype	37.44/428	45.11/331	1.44	0.006	
GNLY	Park *et al*[63]	South Korea	Koreans	rs2886767 TT	2.76/107	10.78/206	2.44	0.015	
				rs1561285 CC	1.25/107	2.77/206	3.78	0.008	
				rs11127 CC	2.01/107	10.28/206	3.26	0.004	
CCR5	Suneetha *et al*[73]	India	Indian	CCR5Delta32	0.73/408	4.2/214		0.005	
MBL	Thomas *et al*[75]	United Kingdom	Caucasian	codon 52	4.0/98	27.0/33		4E-4	
	Thio *et al*[80]	United States	American	-221C	17.7/338	23.4/189	1.38	0.04	

[1]Heterozygosity; [2]Homozygosity. HLA: Human leukocyte antigen; TNF: Tumor necrosis factor; IL: Interleukin; SPP1: Secreted phosphoprotein-1; CCR5: C-C chemokine receptor type 5; GNLY: Granulysin; MBL: Mannose-binding lectin; GWAS: Genome-wide association study.

tor polymorphisms influence susceptability to persistent HBV infection and were associated with HBV clearance in Gambian patients. Suneetha *et al*[73] showed that VDR a/a allele was associated high HBV level.

Toll-like receptors (TLRs) were identified as transmembrane signal transduction proteins in recent years. As a group of pattern recognition receptors (PRRs), TLRs play important roles in the innate immunity by recognizing pathogen associated molecular patterns (PAMPs). PAMPs trigger TLR signaling cascades, leading to the release of proinflammatory cytokines, and play critical roles in infectious diseases. Wu *et al*[85] showed that TLR 4 rs4986790 was associated with HBsAg seroconversion, and TLR 5 rs5744174 and TLR 9 rs5743836 were associated with HBeAg seroconversion. Al-Qahtan *et al*[86] showed that TLR 3 rs1879026 and rs1879026G-rs5743313C-rs5743314G-rs5743315A haplotype were associated with persistent HBV infection in Saudi Arabian patients.

Ubiquitin-conjugating enzyme E2 L3 is a protein encoded by the UBE2L3 gene. It is an important enzyme for degradation of abnormal or shor-lived protein. Hu *et al*[15] showed that the UBE2L3 rs4821116 polymorphism was associated with HBV clearance.

CONCLUSION

Recently, many gene polymorphisms (single neucleotide polymorphisms, SNPs) have been reported to be associated with HBV clearance or persistent infection including some not mentioned above, such as HLA-DPA1 rs3077 and HLA-DPB1 SNPs[15,21-28], TNF-alpha promoter SNPs and/or haplotypes[43] (Table 1). It is clear that polymorphisms in

several genes contribute to the outcomes of HBV infection, such as HLA-DPA1 and HLA-DPB1. However, it is difficult to validate in different populations for other genes. And also, since human traits are inherited polygenically, single gene or SNP cannot fully explain disease susceptibility. The major strength of genetic association analysis is that it uses distortions of compared population genetic frequency distributions to detect disease-associated genes. Yet this advantage is accompanied by potential pitfalls that can lead to false positive associations as well as to missing important loci. False positive associations can arise from sampling errors in sub-structured study populations, from variation associated with multiple statistical tests, and from linkage disequilibrium of marker SNPs with the actual disease-associated SNPs. Thus, optimum studies include: (1) large sample size; (2) replication in different study populations, multicohort and global coopration studies; (3) functional study relating the SNP association with gene function; (4) high relative hazards or relative risks; (5) high attributable risk; and (6) gene-gene interaction study. Gene-gene interactions influence disease susceptibility, but unfortunately, no reliable methods are available to detect these interactions in large datasets now.

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