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REVIEW

Molecular epidemiology of hepatitis B virus in Asia

Takako Utsumi, Yoshihiko Yano, Hak Hotta

Takako Utsumi, Indonesia-Japan Collaborative Research Center for Emerging and Re-emerging Infectious Diseases, Institute of Tropical Disease, Airlangga University, Surabaya 60115, Indonesia
Takako Utsumi, Yoshihiko Yano, Hak Hotta, Center for Infectious Diseases, Kobe University Graduate School of Medicine, Kobe 650-0017, Japan
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Correspondence to: Hak Hotta, MD, PhD, Center for Infectious Diseases, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. hotta@kobe-u.ac.jp
Telephone: +81-78-3825500 Fax: +81-78-3825519
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Abstract

Although safe and effective vaccines against hepatitis B virus (HBV) have been available for three decades, HBV infection remains the leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) worldwide, especially in Asian countries. HBV has been classified into at least 9 genotypes according to the molecular evolutionary analysis of the genomic DNA sequence and shown to have a distinct geographical distribution. Novel HBV genotypes/subgenotypes have been reported, especially from Southeast Asian countries. The clinical characteristics and therapeutic effectiveness of interferon (IFN) and nucleos(t)ide analogues vary among different HBV genotypes. Mutations at T1653C in subgenotype C2 from Japan and South Korea, C/A1753T and C1858T in subgenotype C1 from Vietnam, and C1638T and T1753V in subgenotype B3 from Indonesia were reported to be associated with advanced liver diseases including HCC. Genotype distribution in Japan has been changed by an increasing ratio of subgenotype A2 in chronic hepatitis B. While a large number of epidemiological and clinical studies have been reported from Asian countries, most of the studies were conducted in developed countries such as Taiwan, China, South Korea and Japan. In this review, the most recent publications on the geographical distribution of genetic variants of HBV and related issues such as disease progression and therapy in Asia are updated and summarized.

Key words: Hepatitis B virus; Genotype; Subgenotype; Molecular epidemiology; Asia; Pathogenicity; Drug resistance

Core tip: Chronic hepatitis B virus (HBV) infection usually progresses to liver cirrhosis and hepatocellular carcinoma. The variation of the HBV genotype is related to the geographical distribution. Also, the clinical characteristics and therapeutic effectiveness of interferon and nucleos(t)ide analogue vary among different HBV genotypes. A large number of epidemiological and clinical studies have been reported from Asian countries. However, most of the studies were conducted in developed countries such as Taiwan, China, South Korea and Japan. In this review, epidemiologically and clinically important aspects of HBV genotypes/subgenotypes found in East and Southeast Asian countries are updated and summarized.

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INTRODUCTION

Although safe and effective vaccines against Hepatitis B virus (HBV) have been available for more than three decades, HBV infection remains a burden to global public health, resulting in 600000 to 1 million deaths per year worldwide[1]. Two billion people are estimated to be exposed to HBV infection once in their life and it causes a wide spectrum of liver disease, including acute or fulminant hepatitis, inactive carrier state, reactivation, chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC)[2]. More than 420 million individuals in the world are estimated to have chronic HBV infections; 15%-40% of them are at risk of death due to liver failure or HCC[3]. The prevalence of HBV infection varies markedly in different geographical areas of the world. Overall, approximately 45% of the global population live in areas of high HBV prevalence, such as sub-Saharan Africa, the Pacific and particularly Asia[4].

HBV has been classified into at least 9 genotypes (A through H and J) and shown to have a distinct geographical distribution[5,6]. In Asia, HBV genotypes B and C are prevalent, with genotype C having been shown to cause more serious liver diseases than genotype B. High prevalence of HBV mutants with various forms, such as the pre-S mutants, basal core promoter (BCP) mutants, YMDD motif mutants and vaccine escape mutants[7,8], were seen in Asia and these were found to be related to severe liver diseases and resistance to treatment and prevention. This article provides an overview of the molecular-based epidemiology of HBV in Asian countries.

HBV GENOME

HBV contains a partially double-stranded DNA genome of approximately 3200 base pairs. HBV replicates *via* a RNA intermediate anti-genome sequence, which encodes a potentially error-prone polymerase without proof-reading activity. The error frequencies are similar to those of retroviruses and other RNA viruses. The HBV genome encodes viral proteins through four open and partially overlapping reading frames: surface (*S*), core (*C*), polymerase (*P*) and *X* genes. This unusual genomic structure can compress a large amount of information into short sequences but implies a constrained evolution for the virus. This constraint can be reflected on the calculated rate of substitution, 10^{-5} per site per year, slower than the rate displayed by the retroviruses of around 10^{-3} per site per year[9].

EPIDEMIOLOGY OF HBV INFECTION

The prevalence of chronic HBV infection varies greatly in different parts of the world and can be categorized as high (≥ 8%), intermediate (2%-7%) and low (< 2%) endemicity. Table 1 shows the prevalence of hepatitis B surface antigen (HBsAg)-positive individuals in the general population of Southeast Asia and East Asia. HBV infection is highly endemic in Myanmar[10]; has intermediate to high endemicity in Indonesia[11-13], Cambodia[10,14], Thailand[15,16], the Philippines[17-19], Vietnam[20,21] and Laos[10,24]; low to high endemicity in Malaysia[22,23] and China[25-27]; and intermediate endemicity in Singapore[28,29], Brunei[30,31] and South Korea[32,33]. Japan is the only country with low endemicity of HBV infection in Asia[22].

Table 1 Prevalence of hepatitis B surface antigen in the general Asian population

Country	HBsAg positivity (%)	Ref.
Southeast Asia		
Brunei	4.7	Sebastian *et al*[30]
	6.0	Alexander *et al*[31]
Cambodia	7.7	OI *et al*[14]
	10.8	Sa-Nguanmoo *et al*[10]
Indonesia	3.5-9.1	Hasan[11]
	4.9	Achwan *et al*[12]
	2.1-10.5	Lusida *et al*[13]
Laos	6.9	Jutavijittum *et al*[24]
	8.7	Sa-Nguanmoo *et al*[10]
Malaysia	3.0-5.0	Merican *et al*[22]
	0.5-1.8	Yousuf *et al*[23]
Myanmar	9.7	Sa-Nguanmoo *et al*[10]
Philippines	10.0	Lingao *et al*[17]
	2.0-16.0	Lansang *et al*[18]
	16.7	Wong *et al*[19]
Singapore	3.6-4.0	James *et al*[28]
	2.7-4.0	Ang *et al*[29]
Thailand	4.0	Suwannakarn *et al*[15]
	13.8	Louisirirotchanakul *et al*[16]
Vietnam	11.4	Viet *et al*[20]
	7.5	Reekie *et al*[21]
East Asia		
China	2.4	Ting-Lu *et al*[25]
	1.0	Liu *et al*[26]
	10.6	Chen *et al*[27]
Japan	0.8	Merican *et al*[22]
South Korea	3.0-4.0, 6.0	Kim *et al*[32]
	6.0	Hyun *et al*[33]

HBsAg: Hepatitis B surface antigen.

HBV infection is highly endemic in developing regions with a large population such as Southeast Asia and China, where at least 8% of the population are HBV chronic carriers. For example, in Indonesia, which consists of thousands of islands with many ethnicities, the endemicity of HBV infection greatly varies even within the country. The wide range of the HBV prevalence is largely related to differences in age at the time of infection[3].

HBV GENOTYPES/SUBGENOTYPES AND THEIR GEOGRAPHICAL DISTRIBUTIONS

HBV is currently grouped into at least 9 genotypes (A through H and J, with I still being controversial)[6,34,35], based on a full genome diversity of more than 8% at the nucleotide (nt) level, and phylogenetic analyses have shown that most of the genotypes can be further divided into subgenotypes differing by at least 4% of their full genome sequences. The prevalence of each HBV genotype and subgenotype varies in different geographical regions and is strongly associated with ethnicity[36].

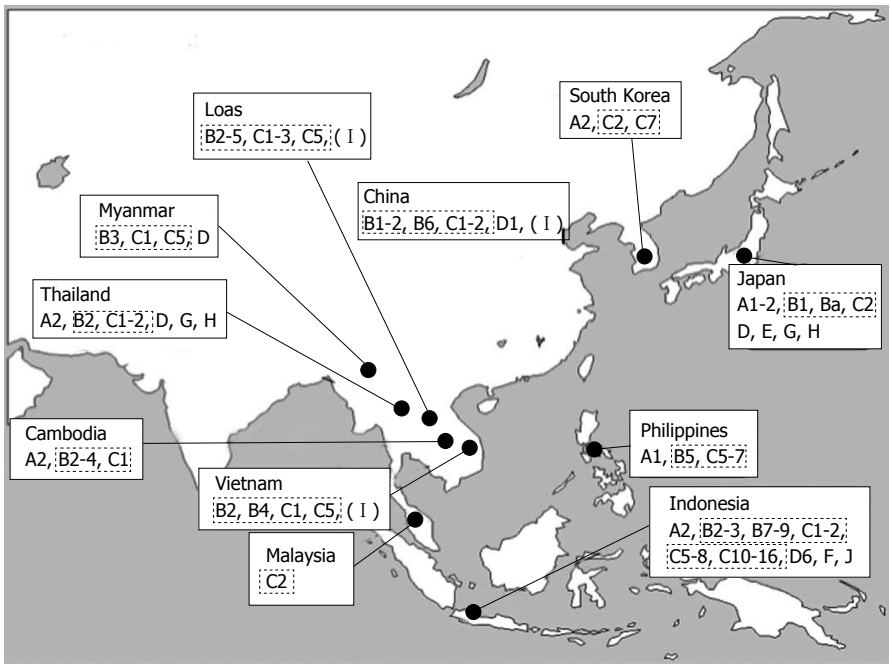

Figure 1 Genotype/subgenotype distribution in East and Southeast Asia. Subgenotypes of genotypes B and C commonly found in Asia are encircled with dotted lines.

Genotype A is highly prevalent in Sub-Saharan Africa (A1 or Aa: a for Africa), Northern Europe (A2 or Ae; e stands for Europe) and Western Africa (A3). Genotypes B and C are the major HBV genotypes circulating in East and Southeast Asia[37] (Figure 1) and co-infection has led to a frequent occurrence of recombination between these two genotypes[38,39]. Subgenotype B1 (or Bj; j for Japan) is found almost exclusively in Japan and B2 (or Ba; a for Asia) is found in the rest of Asia[40,41], but mainly in China and Vietnam. B1 is not a recombinant while B2 is considered to be B/C recombinants with the precore and core genes from genotype C. B3 is mostly found in Indonesia[42] while B4 is in Vietnam[5]. B5 was initially reported in 2006 from the Philippines[43]. B6 was identified in 2007 from the Arctic[39]. B7 to B9 were isolated in eastern Indonesia during the years 2007 to 2011[44-46]. C1 (or Cs: s for Southeast Asia) is the dominant strain in Southeast Asia and southern China, while C2 (or Ce: e for East Asia) is found mainly in East Asia (South Korea and Japan) and the northern part of China, C3 in Oceania[47] and C4 in the Aborigines from Australia[48]. C5 was initially reported in 2006 from the Philippines with B5[44]. C6 was identified from a Papuan population in Indonesia[13,49] and the Philippines[50] in 2008. Surprisingly, ten novel subgenotypes (C7 to C16) were isolated in Indonesia during 2009 to 2012[45,51-54]. Subgenotypes D1 to D4 of genotype D are widely distributed globally[5], D5 in India[55] and D6 in Papua, Indonesia[13]. Genotype E is found mainly in sub-Saharan Africa. Genotypes F and H are found mainly in South and Central America, respectively. Genotype G has been found in Europe, United States and Japan. Genotype I was originally identified in Laos[56], Vietnam and Southern China. However, this classification is still controversial as the sequence divergence hovers at but is slightly less than 8%, with a close relationship to genotype C[35]. Genotype J was found in a Japanese soldier who was thought to have been infected in the forests in Kalimantan, Indonesia, during World War Ⅱ[57]. Thus, novel HBV genotypes and novel subgenotypes have been found in Southeast Asia, especially in Laos, Vietnam, the Philippines and Indonesia, all consisting of many islands and ethnic groups. In addition to genotypes B and C which are common in Asia, an increasing rate of infection with rare HBV genotypes, such as genotypes A, D, E, G and H, has been recognized throughout Asia. Globalization may yield HBV strains of possible novel genotypes containing novel nucleotide sequences in the precore/core region[58]. The distribution of genotypes/subgenotypes varies even in different regions of a country, as observed in Indonesia, which may partly be related to the ethnic origin of the infected patients.

HBV GENOTYPES AND DISEASE PROGRESSION

Chronic HBV infections usually progress to liver cirrhosis and HCC. Several studies revealed that the presence of hepatitis B e antigen (HBeAg) and high levels of HBV DNA were independent risk factors for the development of liver cirrhosis and HCC[59-62]. HBV genotypes are also related to the clinical characteristics[63]. In northeast Asian countries, where genotypes B and C are prevalent, the dominant mode of transmission is vertical (mother-to-child). A large number of studies have shown that genotype B is associated with HBeAg seroconversion at an earlier age, more sustained remission after HBeAg seroconversion, less active hepatic necroinflammation, a slower rate of progression to cirrhosis, and a lower rate of HCC development compared to genotype C[59,64-67]. On the other hand, genotypes D and A are prevalent in the southwest Asian countries, such as India and Pakistan[68]. The transmission route among Pakistanis, includ-

Table 2 Summary of nucleos(t)ide analogues

	Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir	Ref.
Analogue type	Nucleoside	Nucleotide	Nucleoside	Nucleoside	Nucleotide	
Introduction (yr)	1999	2002	2005	2006	2008	
Product name (company)	Zefix (GSK)	Hepsera (Gilead)	Baraclude (BMS)	Sebivo (Novartis)	Viread (Gilead)	
Dose	100 mg Once daily	10 mg Once daily	0.5 mg Once daily	600 mg Once daily	300 mg Once daily	
Advantage	Low cost	Effective for HIV coinfection		Possible for pregnancy	Effective for HIV coinfection	[89]
Disadvantage	High rate of drug resistance	Renal dysfunction Fanconi anemia	Not recommend for pregnancy	Renal dysfunction	Renal dysfunction Fanconi anemia	
Undetectable HBV-DNA						
HBeAg positive	36%	21%	67%	60%	76%	[90]
HBeAg negative	89%	72%	90%	88%	93%	
HBeAg seroconversion	22%	12%	21%	23%	21%	[91]
Drug-resistance	24%	0%	0.2%	4%	0%	[92]
Drug-resistant mutation	V173l, L180M, A181T, M204V/I	A181V/T, N236T	I169T, L180M, T184A/F/L/S, S202G/I, M204V, M250V	M204V/I	A181V/T, N236T	

GSK: Glaxo Smith Kline; BMS: Bristol-Myers Squibb; HIV: Human immunodeficiency virus; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen.

ing Afghan refugees, is not only vertical transmission but also through unsterilized materials and intravenous drug use[69,70]. Reports concerning the risk factors of advanced liver diseases are still limited in those countries.

Mutations in the viral genome, including the X region, are also important factors in association with disease progression. A study from Taiwan revealed that the precore G1896A wild-type and the BCP A1762T/G1764A mutation were strongly associated with HCC development among genotype C[71]. A study from north India also showed that the BCP A1762T/G1764A mutation was associated with progressive liver diseases among genotype D[72]. In Japan and South Korea, the T1653C mutation was reported as a predictive factor for the development of advanced liver diseases in HBV genotype C2 infection[73,74]. Whereas the C/A1753T and C1858T mutations were associated with advanced liver diseases in genotype C1 infection in Vietnam, C1638T and T1753V were independent risk factors for advanced liver diseases in genotype B3 infection in Indonesia[42,75]. In addition, several studies from Taiwan and Japan showed that the pre-S mutation also contributed to the progressive liver disease and HCC[76,77]. The progression from acute hepatitis to chronic infection occurs more frequently in genotype A (23%) compared with genotypes B (11%) and C (7%)[78]. This might change genotype distribution in the future. In Japan, indeed, the prevalence of genotype A in chronic hepatitis B increased from 1.7% to 3.5% during the period between 2000 and 2006[79].

HBV GENOTYPE AND ANTIVIRAL THERAPY

The purpose of antiviral therapy for chronic hepatitis B is the sustained suppression of HBV replication, biochemical remission, HBeAg seroconversion and ultimately HBsAg seroconversion. The annual rate of spontaneous HBsAg seroclearance is approximately 0.4%-2.3%, and the HBsAg seroclearance rates of genotypes A and B are higher than that of genotypes C and D[80,81].

Interferon (IFN) and nucleos(t)ide analogues (NA) are commonly used for the treatment of chronic hepatitis B. Antiviral regimens for chronic hepatitis B are decided based on the age, HBV-DNA viral load, alanine aminotransferase (ALT) levels and the degree of fibrosis. In general, younger patients with high ALT levels are recommended to be treated with IFN therapy and older and/or clinically advanced patients with NA. Due to the economic growth, the treatment of chronic hepatitis B has become universal in most developed and developing Asian countries. However, most of the clinical studies about antiviral therapy were reported from developed countries, with few studies being reported from developing countries. IFN has antiviral, antiproliferative and immunomodulatory effects. The response to IFN treatment is poorer in Asian patients compared with Caucasian patients, which may be due partly to the difference in the genotype distribution[82]. It was shown that patients infected with HBV genotypes A and B showed better response than those with genotypes C and D[83-87]. A meta-analysis also revealed that IFN therapy was more effective in patients infected with genotype A than in those with genotype D, and also more effective in genotype B than in genotype C infection[88].

Currently, lamivudine, adefovir, entecavir, telbivudine and tenofovir have been approved for the treatment of chronic hepatitis B (Table 2). Lamivudine (Zeffix®) was first introduced in 1999 and the clinical efficacy was shown by a long-term follow-up study[93,94]. However, drug-resistant mutations, especially multidrug-resistant mutations, are the major concern with patients receiving long-term NA treatment. It was reported that the drug resistance against lamivudine monotherapy reached 70% after 4 years of treatment[95,96]. Entecavir (Baraclude®) is widely used and a first-line drug in many Asian countries, including China, South Korea, Thailand, Hong Kong and Japan. Entecavir is still expensive but the occurrence of drug resistance is very low for naïve patients.

However, the chemical structure of entecavir is similar to lamivudine, which resulted in the cross-resistance between lamivudine and entecavir. Recent long-term follow up studies conducted in South Korea and Hong Kong revealed that entecavir reduced liver-related death and HCC[97,98]. Adefovir (Hepsera®) is effective against lamivudine-resistant mutants and add-on therapy of adefovir and lamivudine is common for suppression of lamivudine-resistant mutants. Tenofovir (Viread®) and telbivudine (Sebivo®) are also safe and effective drugs but their introduction to clinical use is still limited. Telbivudine has recently been approved and is being used as a first-line drug in Indonesia. Unlike IFN therapy, meta-analysis revealed no significant difference between genotypes and response to NA[88]. However, as entecavir and telbivudine were introduced recently in developing countries, further studies will be needed to assess their efficacy against the different HBV genotypes/subgenotypes prevailing in those countries.

CONCLUSION

HBV is widespread in Asian countries and contributes to the mortality from HCC. To reduce HBV infection and HCC mortality, appropriate national immunization programs are required in HBV-endemic countries, including Japan. Although HBV infection is predominant and a number of novel genotypes/subgenotypes have been discovered in Asian countries, studies have not been sufficient regarding disease prognosis and antiviral treatment. It is possible that certain genotypes or variants of HBV prevailing in these regions possess stronger pathogenicity and are associated with more severe outcomes of liver diseases. The studies on HBV genotypes related to their pathogenicity in chronic liver diseases, including liver cirrhosis and HCC, and their effects on treatment outcome are awaited with great interest, especially in Southeast Asia, which is the most endemic region of HBV in Asia with unique HBV genotypes/subgenotypes.

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