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REVIEW ARTICLE

Hepatitis B virus genotypes: epidemiological and clinical relevance in Asia

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Abstract Hepatitis B virus (HBV) is characterized by a high genetic heterogeneity since it replicates via a reverse transcriptase that lacks proofreading ability. Up to now, ten genotypes (A–J) have been described, with genotype A and D being ubiquitous but most prevalent in Europe and Africa, genotype B and C being confined to Asia and Oceania. Infections with other genotypes such as E, F, G and H are also occasionally observed in Asia. Genotype I is rare and can be found in Laos, Vietnam, India and China, whereas genotype J has been described in Japan and Ryukyu. Novel variants generated by recombination and co-infection with other genotypes have gradually gotten worldwide attention and may be correlated with certain clinical features. There are substantial differences in HBV infection regarding prevalence, clinical manifestation, disease progression and response to antiviral therapy. Due to the complex interplay among viral, host and environmental factors, the relationship between HBV genotypes and clinical profiles remains incompletely revealed. In general, genotype A is associated with better response to interferon therapy; genotype C, and to lesser extent B, usually represent a risk factor for perinatal infection and are associated with advanced liver diseases such as cirrhosis and hepatocellular carcinoma; genotype D may be linked with poor response to interferon therapy. Future studies with better design and larger sample size are warranted to further clarify the controversial issues and guide the day-to-day clinical practice.

Keywords Hepatitis B virus · Genotype · Hepatocellualr carcinoma · Antiviral therapy · Asia · Review

Introduction

Thanks to increasing coverage of universal vaccination program against hepatitis B virus (HBV) in infants, the global prevalence of hepatitis B surface antigen (HBsAg) has dramatically declined. However, Western Pacific and African regions were still defined as intermediate to high HBV endemic areas in 2010, with HBsAg prevalence being 5.26 and 8.83 %, respectively [1]. Persistence and progression of HBV infection are determined by a complex interplay among viral, host and environment factors. As a result of evolution, HBV genotypes represent major phylogenetic variants and play certain roles in epidemiology and clinical outcomes. In this review we will summarize the epidemiological and clinical relevance of HBV genotypes in Asia.

Epidemiological relevance of HBV genotypes in Asia

HBV replicates via a reverse transcriptase that lacks proofreading ability and thus confers a high genetic heterogeneity. Based on the sequence divergence in the entire genome, HBV has been classified into ten genotypes (A–J) (the difference is greater than 8 %) and various subgenotypes (the difference is between 4 and 8 %). These

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viral genotypes are partially correlated with serotypes (i.e., ayw1–ayw4, ayr, adw2, adw4, adrq$^-$ and adrq$^+$) classified according to their surface antigen determinants, although some serotypes are encoded by more than one genotype [2].

HBV genotypes are distributed in a characteristic ethnogeographic manner. Genotypes A and D are ubiquitous but most prevalent in Europe and Africa; genotypes B and C are confined to Asia and Oceania [3, 4]. Infections with other genotypes such as E, F, G and H are also occasionally observed in Asia. Though rare, genotype I can be found in Laos, Vietnam, India and China [3, 5–7]. Genotype J has been described in Japan and Ryukyu [3]. Numerous sub-genotypes have been described in Asia, including A1, B1–B5 and B7–B9, C1–C2 and C5–C16, D1–D6 and D9, and I1–I2 [4]. These sub-genotypes appear to be geographically constrained and evolve independently of each other. It has been hypothesized that evolutionary rates are time dependent, and the changes depend on the dynamics of the infected populations and the main transmission routes of the genotypes. The phylogeographic framework would shed light on the geographic origin and global spread of HBV genotypes and sub-genotypes throughout different populations [4].

Novel variants generated by recombination of different genotypes have gradually gotten worldwide attention. More than half of the recombinants are B/C and C/D hybrids [8]. Some recombinant strains have even become dominant in certain populations or regions, such as inter-genotype C/D in Tibetans [9]. The probability of recombination depends on several factors, including circulation of different strains in the same geographical area, viral load, coinfection rate and genetic homology [10].

Infection with more than one genotype is also possible. Super-infection manifested by acute exacerbation of the chronic disease has been described [11], indicating that an adaptive immune response is not always protective across genotypes. To further investigate the impact of co-infection and explore the genotype-genotype interplay, Datta et al. [12] detected the distribution of HBV genotypes in the serum as well as in the intrahepatic tissues of chronic hepatitis B (CHB) patients with liver cirrhosis (LC) and hepatocellular carcinoma (HCC) in India. They demonstrated that co-infection with different HBV genotypes (i.e., C and D) was a frequent event in LC and HCC in areas with multiple genotypes. The synergistic effect of the co-infected HBV genotypes may promote the development of LC and HCC.

Interestingly, genotype shift and genotype switching have been reported during antiviral therapy. The underlying molecular mechanism of genotype shift is elusive but might be explained by superinfection of another genotype during the treatment. Or, as more widely proposed, individuals are infected with mixed genotypes (dominant genotype detectable but minor genotype undetectable by current methods) before treatment. Different sensitivities of these genotypes to drug selection pressure finally lead to genotype shifts. It has been found that genotype C is more sensitive to adefovir dipivoxil (ADV) and thus is more prone to be associated with genotype shift during ADV therapy [13]. In a study including 67 Indian patients treated with tenofovir disoproxil fumarate (TDF), genotype switching including inter-genotype switching (e.g., A1–D1) and intra-genotype switching (e.g., D1–D3) was detected in 76.1 % patients [14]. The phenomena may possibly be due to the constant antiviral drug pressure.

The geographic distribution of HBV genotypes and HBsAg prevalence in Asia is shown in Fig. 1. Even within one country the distribution of HBV genotypes may also have considerable spatial and temporal variations. For example, in China, HBV genotype B is predominant in the central southern areas, genotype C is predominant in the northeastern area, both genotypes B and C are dominant in the southwestern areas, and the recombinant genotype C/D is predominant in the northwestern areas [15]. A recent report from Fujian Province shows a higher rate of genotype C infection in older patients; genotype B is no longer dominant, as previously reported [16].

HBV genotypes and clinical manifestation in Asia

Numerous studies have revealed the association between clinical manifestations and HBV genotypes. Specific HBV genotypes have been associated with chronicity in patients with acute hepatitis B (AHB) but the association is not consistent. In Shanghai, China, where genotypes B and C prevail, a population-based surveillance showed 8.50 % of the adult patients with AHB became chronic; in the 68 AHB patients with genotype data available, the only identified risk factor for chronicity was sub-genotype C2 [31]. In Japan, a large prospective cohort study showed that the proportion of AHB patients with genotype A (particularly sub-genotype A2, mainly through sexual contact) is increasing year by year, with a chronicity rate of 4 % [32]. A nationwide multicenter cohort study in Japan on 212 AHB patients revealed that genotype A was independently associated with viral persistence following AHB [33]. However, this phenomenon was not confirmed by a hospital-based single-center retrospective study [34] in Okayama including 128 AHB patients, which might be due to the small number of patients and the insufficient follow-up time.

Genotype C or B may be a risk factor for perinatal HBV infection. Despite passive-active immunoprophylaxis with hepatitis B immunoglobulin and HBV vaccine,

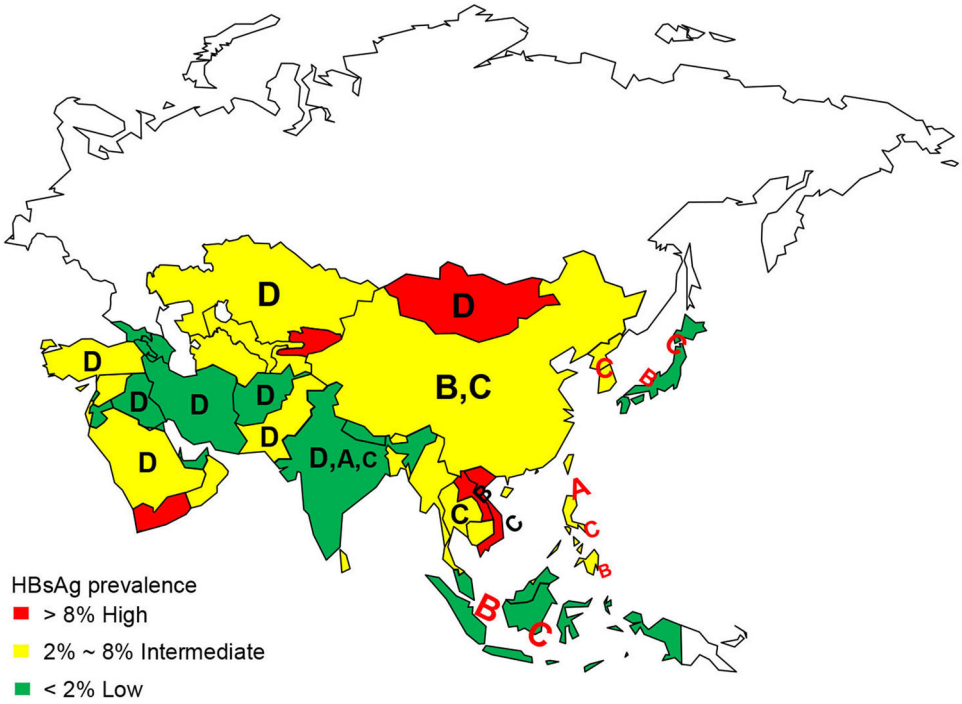

Fig. 1 HBsAg endemicity in 1990–2013 and geographic distribution of HBV genotypes in Asia. The prevalence data are retrieved from a systematic review [1]; this map is prepared according to the literature [1, 6, 15, 17–30]

about 5–10 % of the neonates of mothers with HBsAg positivity still suffer from HBV infection [35]. A report from Shenyang, China, showed that genotype C in pregnant women was a risk factor for mother-to-child transmission of HBV [35]. A report from Taipei also revealed that breakthrough HBV infection occurred more frequently in immunized children born to mothers harboring genotype C when compared with genotype B [36]. However, another study in Shanghai and Ningbo city discovered that in addition to maternal hepatitis B e antigen (HBeAg) positivity, high viral load and male fetus, genotype B2 significantly increased the risk of trans-placental transmission [37].

Genotype C is also implicated in HBsAg-negative HBV infection (HBV occult infection). A study from Zhejiang Province, China, revealed that compared with HBsAg-positive HBV infection, women with occult HBV infection had a higher proportion of genotype C (7/8 versus 8/23, $p = 0.02$) [38]. Moreover, a report from Taipei showed that after a 25-year universal vaccination program, serum HBV-DNA was still detected in 4.2 % of HBsAg-negative and anti-hepatitis B core-positive subjects, all of whom were infected with genotype C [39].

Many studies from Asia have shown that HBV genotype C is independently associated with increased risk of LC and HCC [40–45]. Early-onset HCC accounts for 15–20 % of total HCC cases in Asia. Mechanisms for early-onset (≤30 years) HCC may be different from those for late-onset (≥70 years) HCC, given the low frequency of liver cirrhosis and poor prognosis in the former. In a comparative study of HBV sub-genotypes and HBV-associated HCC from Shanghai, China, Yan et al. found that HBV sub-genotype B2 was predominant in early-onset HCC (mostly without cirrhosis), while C2 was more frequently seen in late-onset HCC [46]. However, in a community-based study from mainland China, HCC-associated mutations were more frequently found in young patients infected with genotype C than in those with genotype B, indicating genotype C might be more apt to cause LC and HCC with increasing age [47].

HBV genotype has also been considered a risk factor for HCC recurrence. In an earlier study in East China, 1-year recurrence of HCC post surgical resection was more frequent in patients with genotype B2 (9/14) than in those with genotype C2 (40/119) [11]. However, another investigation from Kaohsiung including 64 patients who underwent liver resection for HBV-related HCC showed that genotype C was a risk factor for HCC recurrence during a 2-year follow-up and mutation might play a role in carcinogenesis and HCC recurrence in patients infected with genotype C [48].

Furthermore, a retrospective analysis on 829 patients performed in Korea suggested that even after HBsAg seroclearance, HCC surveillance should be considered in cirrhotic patients as well as non-cirrhotic male patients aged ≥50 years, especially in those infected with HBV genotype C [49].

HBV genotypes and response to antiviral therapy in Asia

HBV genotypes and response to interferon (IFN)-based therapies

HBV genotypes are significantly associated with sustained response to IFN-based therapies. In general, for HBeAg-positive patients, the probability of sustained response is in a descending order from genotype A–D [50]. A meta-analysis showed that patients with genotype B might respond better than those with genotype C in HBeAg positive CHB [51], but some later studies failed to find a difference between these two genotypes in response to pegylated interferon (PEG-IFN) therapy [52, 53].

For HBeAg-negative CHB patients, Raimondi et al. reviewed clinical trials carried out up to 2009 and found that among the Chinese population, genotype B appeared to response better than genotype C to IFN-based therapy [54]. Later, a prospective study [55] including 80 treatment-naive HBeAg-negative patients in Guangdong province showed that compared with the standard course (48 weeks), the extended course (72 weeks) improved HBsAg clearance and seroconversion in patients with genotype B and increased the number of patients achieving a viral load below 2000 IU/ml in patients with genotype C.

Additionally, in HBeAg negative CHB patients treated with PEG-IFN-α-2a, HBV genotypes are associated with serum HBsAg kinetics. A multicenter, randomized, phase III trial [56] conducted at 54 sites in 13 countries (Asian 61.3 %, European 37.2 %) found that baseline HBsAg levels were significantly higher for genotype A than genotypes B, C and D; the cutoff value of HBsAg levels for identification of treatment response was lowest for genotype B at 50 IU/ml, followed by 75 IU/ml for genotype C, 400 IU/ml for genotype A and highest for genotype D at 1000 IU/ml. This study provided an HBsAg kinetics of pre-, intra- and post-treatment across genotypes, but may still need to be confirmed by a larger sample size before being routinely used to predict the response to or stopping of IFN treatment in clinical practice. These data are summarized in Table 1.

HBV genotypes and response to nucleos(t)ide analog (NA) therapy

Overall, HBV genotypes do not have a strong and clear impact on the response to NAs therapies [54, 57–59]. However, a certain association seems to exist as indicated by some studies.

Patients infected with genotype B or C had a lower chance to achieve serological response to TDF. In a study [60] including 266 HBeAg-positive CHB patients (51.9 % Caucasian and 36.1 % Asian), after up to 5 years of TDF treatment, HBsAg loss more likely occurred in Caucasians with genotypes A and D, but was not observed in Asian patients with genotype B and C. Similarly, a recent double-blind study [61] including 126 immune-tolerant HBeAg-positive patients (89 % Asian) with predominantly genotypes B or C observed that after 192 weeks' treatment with TDF alone or combined with emtricitabine, no patients achieved HBsAg loss or seroconversion; only 5 and 3 patients experienced HBeAg loss and seroconversion, respectively.

In a 9-year longitudinal study [62] including 791 CHB patients in Tokyo who received lamivudine (LAM) as their first drug and then received NA rescue therapy when drug-resistant mutations emerged, HBV genotype A was independently associated with HBsAg clearance in both HBeAg-positive and -negative cohorts compared with other genotypes. In another Japanese study [63], ADV was added to 28 consecutive LAM-resistant patients, and the virologic response to this add-on therapy was significantly earlier in patients with genotype B than in genotype C.

The BE-LOW study (49 % Asian) [64] investigated the association between changes in HBsAg levels and response to entecavir (ETV) with or without TDF for 100 weeks and found that HBV genotype A was associated with higher baseline HBsAg levels and more pronounced on-treatment HBsAg decline than genotype non-A. These data are summarized in Table 2.

Summary

Among the described ten genotypes, genotypes A–D are frequently seen in Asia. Novel variants generated by recombination and co-infection with other genotypes may be correlated with certain clinical features. Genetic differences in viral genotypes may underlie the differences in clinical behaviors. Generally, genotype A is associated with a better response to interferon therapy; genotype C and, to lesser extent, B usually represent a risk factor for perinatal infection and are associated with advanced liver conditions such as cirrhosis and HCC; genotype D may be linked with poor response to interferon therapy. HBV infections with distinct genotypes in epidemiological and clinical settings might be due to differences in the expression of viral proteins, possibly due to different transcriptional efficiencies between genotypes. Future studies with better designs and larger sample sizes are warranted to further clarify the controversial issues and guide the day-to-day clinical practice.

Table 1 HBV genotype and response to IFN-based therapies

Study	Baseline HBeAg status	Number of (Asian) patients	IFN/control group, duration	Treatment endpoint	Efficacy across genotypes	Significance	References
Buster (2009)	Positive	808 (526)	PEG-IFN-α-2a for 48 weeks/ PEG-IFN-α-2b for 52 weeks	HBeAg loss + HBV-DNA <2000 IU/ml 6 months post-treatment	A (OR, 1; reference); B (ORB vs. ORA, 0.46); C (ORC vs. ORA, 0.30); D (ORD vs. ORA, 0.08)	Yes	[50]
Piratvisuth (2008)	Both	1040 (1040)	PEG-IFN-α-2a/PEG-IFN-α-2a + LAM/ LAM for 48 weeks	HBeAg seroconversion in HBeAg+ patients; HBV-DNA <20,000 cps/ml + ALT normalization in HBeAg- patients	No difference across genotype	No	[52]
Liaw (2011)	Positive	544 (473)	PEG-IFNa-2a for 24 or 48 weeks	HBeAg seroconversion 6 months posttreatment	Similar in B and C in the PEG-IFNa-2a 180 ug/48-week arm	No	[53]
Chen (2014)	Negative	80 (80)	PEG-IFNa-2a for 48 (standard therapy) and 72 weeks (extended therapy)	–	Extended therapy improved HBsAg clearance and seroconversion in genotype B; increased the number of genotype C patients achieving HBV-DNA <2000 IU/ml	Yes	[55]
Brunetto (2013)	Negative	230 (141)	PEG-IFNa-2a ± LAM for 48 weeks	On-treatment HBsAg kinetics vary between HBV genotypes	Difference in on-treatment HBsAg kinetics between responders and non-responders was greatest for genotype A from weeks 12–24; for genotypes B and D from baseline to week 12 and no difference for genotype C	Yes	[56]

Table 2 HBV genotype and response to NAs therapies

Study	Baseline HBeAg status	Number of (Asian) patients	NA/control group, duration	Efficacy across genotypes	Significance	References
Marcellin (2014)	Positive	266 (96)	TDF for 5 years	Patients with genotypes A or D were more likely to lose HBsAg compared with genotype B and C	Yes	[60]
Chan (2014)	Positive	126 (112)	TDF/ TDF + emtricitabine for 192 weeks	Rate of HBeAg seroconversion and HBsAg loss was low in genptype B and C	No	[61]
Wang (2015)	Positive	38 (38)	ADV for a year	Patients with dominant genotype C response better including the reduction of ALT and rate of HBeAg seroconversion than genotype B	Yes	[13]
Hosaka (2013)	Both	791 (791)	LAM/LAM + rescue therapy for 9 years	Genotype A was associated with HBsAg clearance compared with other genotypes	Yes	[62]
Inoue (2011)	Both	28 (28)	LAM + ADF for around 47 months	Cumulative probability of undetectable HBV DNA was higher in genotype B than in genotype C	Yes	[63]
Zoulim (2015)	Both	379 (186)	ETV/ETV + TDF for 100 weeks	Mean HBsAg decline was more pronounced in patients with genotype A than in non-A	Yes	[64]

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Compliance with ethical standards

Ethical requirements This article does not contain any studies with human participants or animals performed by either of the authors.

Conflict of interest Qiuju Tian and Jidong Jia declare that they have no conflict of interest.

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