

# Global Perspective on the Natural History of Chronic Hepatitis B: Role of Hepatitis B Virus Genotypes A to J

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## Abstract

Clinical outcomes of chronic hepatitis B virus (HBV) infection vary widely. In addition to host factors, several viral factors including HBV genotype, viral load, specific viral mutations and quantitative HBsAg levels, have been associated with disease outcomes. Among viral factors, HBV genotype correlates with not only the clinical outcomes, but also with the response to interferon treatment. Currently, 10 HBV genotypes have been identified. Compared with genotype A and B cases, patients with genotypes C and D have lower rates and usually delayed onset of spontaneous HBeAg seroconversion. HBV-genotype C has a higher frequency of basal core promoter (BCP) A1762T/G1764A mutation and preS deletion, and a higher viral load than genotype B. Similarly, genotype D has a higher prevalence of BCP A1762T/G1764A mutation than genotype A. These observations suggest pathogenic differences between HBV genotypes. Genotyping of HBV can help practicing physicians identify chronic hepatitis B patients at risk of disease progression.

## Keywords

- ▶ hepatitis B virus
- ▶ genotype
- ▶ viral load
- ▶ HBsAg level
- ▶ hepatocellular carcinoma
- ▶ cirrhosis

Hepatitis B virus (HBV) infection is endemic in Asia, the Pacific islands, Africa, Southern Europe, and Latin America. In Asian countries, the majority of chronic hepatitis B (CHB) patients acquire the virus in the perinatal period or early childhood through vertical (mother to child) transmission; by contrast, horizontal transmission is the main route in African and Western countries.<sup>1</sup> Long-term outcomes of CHB vary widely. Several viral factors, including HBV genotype, viral load, specific viral mutations, and quantitative hepatitis B surface antigen (qHBsAg) levels, have been shown to predict clinical outcomes in both community- and hospital-based cohort studies.<sup>2,3</sup> However, the precise role of HBV genotype in liver disease progression and response to antiviral therapy remains

to be validated. Accordingly, HBV genotyping is still not recommended as a part of CHB management in the international guidelines.<sup>4,5</sup> In this article, recent advances regarding the impact of HBV genotype on the clinical outcomes in patients with chronic HBV infection are reviewed. In addition, the interactions between HBV genotype and other viral factors, such as viral load and qHBsAg levels, are also discussed.

## Definition and Epidemiology of HBV Genotypes

Based on the extent of divergence in the entire HBV genomic sequence, at least 10 HBV genotypes (A to J) and several

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subtypes have been identified: > 8% for genotypes and 4 to 8% for subtypes.<sup>6–8</sup> Except for the newly identified genotypes I and J, the geographic and ethnic distributions of HBV genotypes and subtypes are well characterized. Genotype A is highly prevalent in sub-Saharan Africa, Northern Europe, and Western Africa. Genotypes B and C are common in Asia. Genotype C mainly exists in East and Southeast Asia. Genotype D is prevalent in Africa, Europe, the Mediterranean region and India. Genotype E is restricted to West Africa. Genotype F is found in Central and South America. Genotype G has been reported in France, Germany, and the United States. Genotype H is found in Central America.<sup>6–10</sup> Recently, genotype I, a novel intergenotypic recombination among genotypes A, C, and G, was isolated in Vietnam and Laos.<sup>11,12</sup> The newest HBV genotype, J, was identified in the Ryukyu Islands in Japan. This genotype has a close relationship with gibbon/orangutan genotypes and human genotype C.<sup>13</sup>

Geographic distribution of HBV genotype may correlate with the modes of transmission. For example, genotypes B and C are prevalent in highly endemic areas where perinatal or vertical transmission plays an important role in the viral spreading, whereas the remaining genotypes are frequently found in areas where horizontal transmission is the main mode of transmission. Therefore, HBV genotyping can serve as an epidemiologic tool for the investigation of transmission, as well as geographic evolution of HBV.<sup>14</sup>

## Clinical Significance of HBV Genotype in the Natural History of HBV Infection

### Toward Chronicity after Acute HBV Infection

Recent studies suggested that acute infection with HBV genotype A was associated with a higher risk of developing chronic infection.<sup>15,16</sup> In Japan, the persistence of HBV infection after acute hepatitis B was higher in patients with genotype A (23%) than those with genotype B (11%) or C (7%) infection.<sup>16</sup> The rate of chronicity after acute genotype D infection has also been reported to be relatively high.<sup>17</sup> Notably, an increase of certain HBV genotype after acute infection would result in redistribution of HBV genotypes among patients with chronic HBV infection in countries where universal hepatitis B vaccination has not yet been launched (► **Table 1**). For example, in a nationwide survey, Matsuura et al found that the prevalence of HBV genotype A in chronic hepatitis B patients in Japan increased from 1.7% in 2000 to 3.5% in 2006.<sup>18</sup>

### Emergence of HBeAg Seroconversion and HBsAg Seroclearance

Seroconversion of hepatitis B e antigen (HBeAg) and seroclearance of HBsAg have been recognized as important events in the natural history of chronic HBV infection, with an estimated annual incidence rate of 12% and 2%, respectively.<sup>19–21</sup> Earlier HBeAg seroconversion usually confers a favorable clinical outcome, whereas late or absent HBeAg seroconversion after multiple hepatitis flares is likely to be

responsible for the progression from chronic hepatitis to cirrhosis.<sup>22</sup> In our previous observations, CHB patients with HBV genotype C infection were more likely to remain positive for HBeAg despite multiple hepatitis flares,<sup>23</sup> and had a lower likelihood of spontaneous HBeAg seroconversion than those with genotype B infection. Consistent data were found in a cohort of 460 Taiwanese children with chronic HBV infection.<sup>24</sup> Besides, the mean age at HBeAg seroconversion in HBV genotype C patients was generally one decade older than that in genotype B patients.<sup>20,25</sup> Taking these lines of evidence together, HBV genotype C patients may experience delayed HBeAg seroconversion and a lengthier period of active HBV replication than genotype B patients. With these unfavorable features, genotype C patients are prone to develop advanced fibrosis, cirrhosis, and even HCC than genotype B patients. Similar findings on HBV genotype C versus B patients have been reported from China, Hong Kong, and Japan.<sup>26–29</sup>

Regarding genotypes A and D, one prospective study evaluated the clinical outcomes of 258 Spanish patients with chronic HBV infection; mean follow-up was 94 months.<sup>30</sup> Although no difference was observed in the probability of HBeAg seroconversion between HBV genotype A and D patients, the rate of sustained remission after HBeAg seroconversion was higher in genotype A than genotype D patients (55% vs. 32%,  $p < 0.01$ ).

As for spontaneous HBsAg seroclearance, compared with genotypes C and D patients, genotype A and B patients had a higher rate of HBsAg seroclearance.<sup>30,31</sup> Overall, these facts suggest that the clinical phenotypes differ between genotypes B and C, as well as between genotypes A and D during the early phase of chronic HBV infection.

### Disease Progression to Cirrhosis or Hepatocellular Carcinoma

In addition to retrospective or case-control studies, a community-based prospective cohort study on 2,762 Taiwanese HBV carriers demonstrated that HBV genotype C was associated with an increased risk of HCC than was genotype B; the adjusted hazard ratio (HR) was 2.35 (95% confidence interval [CI] 1.68 to 3.30;  $p < 0.001$ ).<sup>32</sup> Of interest, several reports showed HBV genotype B was associated with early-onset HCC, whereas genotype C was associated with the development of HCC at an older age.<sup>24,33</sup> The predominance of HBV genotype B in HCC patients was more prominent in those younger than 35 years, and most were noncirrhotic.

In addition to the differential hepatocarcinogenesis, HBV genotype also influences the clinicopathological features of patients with HCC. In Taiwan, among 193 patients with resectable HBV-related HCC, genotype B patients had a higher rate of solitary tumor (94% vs. 86%,  $p = 0.048$ ), but more satellite nodules (22% vs. 12%,  $p = 0.05$ ) than genotype C patients.<sup>34</sup> These characteristics may contribute to the recurrence patterns and prognosis of HBV-related HCC patients with genotype B or C infection.<sup>34,35</sup> However, a recent case-control study showed that the distribution of HBV genotype was not different between early and nonearly-HCC patients.<sup>36</sup>

**Table 1** Comparison of clinical and virological features among hepatitis B virus genotypes<sup>a</sup>

Genotype	B	C	A	D	E-J
Clinical characteristics					
Modes of transmission	Perinatal /Vertical	Perinatal /Vertical	Horizontal	Horizontal	Horizontal
Tendency of chronicity	Lower	Higher	Higher	Lower	ND
Positivity of HBeAg	Lower	Higher	Higher	Lower	ND
HBeAg Seroconversion	Earlier	Later	Earlier	Later	ND
HBsAg seroclearance	More	Less	More	Less	ND
Histologic activity	Lower	Higher	Lower	Higher	ND
Clinical outcomes (cirrhosis and hepatocellular carcinoma)	Better	Worse	Better	Worse	Worse in genotype F
Response to interferon $\alpha$	Higher	Lower	Higher	Lower	Lower in genotype G
Response to nucleos(t)ide analogues	No significant differences among genotypes A to D				ND
Virologic characteristics					
Serum HBV DNA level	Lower	Higher	ND	ND	ND
Frequency of precore A1896 mutation	Higher	Lower	Lower	Higher	ND
Frequency of basal core promoter T1762/A1764 mutation	Lower	Higher	Higher	Lower	ND
Frequency of preS deletion mutation	Lower	Higher	ND	ND	ND

<sup>a</sup>Due to peculiar distribution of HBV genotype in Asian and Western countries, available data demonstrates only comparisons between genotype B and C or genotype A and D.

Abbreviations: HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ND, no data available.

### Interactions between HBV Genotypes, Viral Load, and Viral Mutants

Accumulating data reveal that HBV viral load and viral mutations are closely associated with long-term outcomes of HBV-related chronic liver diseases.<sup>37,38</sup> In an earlier study, we found that genotype C infections conferred a higher frequency of basal core promoter (BCP) A1762T/G1764A mutation than genotype B. In another prospective study with 4,841 Taiwanese male HBsAg carriers without HCC at enrollment, Yu et al found that HBV viral load was higher in genotype C than genotype B patients. Genotype C-infected patients with high viral loads had a 26-fold higher risk of HCC than those with other genotypes and low or undetectable viral loads.<sup>39</sup> Furthermore, Yang et al reported that among those infected with HBV genotype C, wild-type precore 1896 sequence and BCP A1762T/G1764A mutation were associated with a highest risk of HCC during 13-year follow-up. The adjusted HR was 2.99 (95% CI 1.57–5.70,  $p < 0.001$ ) relative to those with genotype B infection, wild-type precore 1896 and BCP sequences.<sup>32</sup> Similarly, genotype D infected patients who had more progressive liver disease had a higher prevalence of BCP A1762T/G1764A mutation than those with genotype A infection.<sup>40</sup>

Previous reports also showed that deletions within the preS gene may contribute to progressive liver cell damage and hepatocarcinogenesis.<sup>41</sup> In our recent case-control study, the frequency of preS deletion was significantly higher

in genotype C patients than genotype B patients. In addition, the presence of preS deletion was an independent risk factor associated with disease progression (odds ratio [OR], 3.91; 95% CI 1.57–9.76,  $p = 0.003$ ) as well as HCC development (OR, 3.72; 95% CI 1.44–9.65;  $p = 0.007$ ).<sup>42</sup> A meta-analysis further confirmed that the OR of HCC for preS deletion was 3.77 (95% CI 2.57–5.52). Of particular note, the summary OR for preS deletion was higher in genotype C patients than genotype B patients.<sup>43</sup> Additional investigations demonstrated that the combination of viral load, HBV genotype, BCP A1762T/G1764A mutation, and preS deletion is strongly associated with disease progression and development of HCC.<sup>32,44,45</sup>

Recently, several clinical scoring systems or nomograms incorporating independent risk predictors such as sex, age, family history of HCC, alcohol consumption, serum alanine aminotransferase (ALT) level, HBeAg status, serum HBV DNA level, and/or HBV genotype have been developed.<sup>46–48</sup> These easy-to-use nomograms are based on noninvasive clinical parameters and have been found to accurately predict HCC risk in either community- or hospital-based HBV-infected patients. These risk calculators would facilitate communication between practicing physicians and patients in the daily practice. However, the predictive value of these scoring systems in populations with different ethnicities or genotype infections needs to be validated.

## Clinical Significance of Quantitative HBsAg and Its Correlation with HBV Genotypes

### qHBsAg Level Predicts Loss of HBsAg and Development of HCC

In recent years, qHBsAg level has been documented to influence the clinical outcomes of chronic HBV infection.<sup>49–51</sup> For example, the association of HBsAg and HBV DNA levels with subsequent HBsAg loss were investigated in a cohort of 688 HBeAg-negative Taiwanese patients with baseline serum HBV DNA levels < 2000 IU/mL.<sup>50</sup> We found that baseline HBsAg level, but not HBV DNA, was an independent factor for the loss of HBsAg in multivariate analysis. The adjusted HR of HBsAg loss was 13.2 (95% CI 7.8–22.1) for HBsAg level < 10 versus  $\geq 1,000$  IU/mL. Besides, we followed 390 Taiwanese HBeAg-positive patients with chronic hepatitis who had spontaneous HBeAg seroconversion (Study of E Antigen seRoClearance of Hepatitis B [SERACH-B] cohort). We found that serum levels of HBsAg and HBV DNA at 1 year after HBeAg seroconversion were inversely associated with HBsAg loss in a dose–response manner. Compared with patients with HBsAg levels  $\geq 1,000$  IU/mL, the HBsAg loss rate was higher for those with HBsAg levels of 100 to 999 and < 100 IU/mL, with HRs of 4.4 (95% CI 1.1–17.0) and 24.3 (95% CI 8.7–67.5), respectively.<sup>49</sup> An HBsAg level < 100 IU/mL predicted HBsAg loss within 6 years with a diagnostic accuracy of 91.5%, sensitivity of 83.3%, specificity of 92.1%, positive predictive value of 45.5%, and negative predictive value of 98.6% in patients with an HBV DNA level < 200 IU/mL.

Finally, the REVEAL-HBV (Risk Evaluation of Viral Load Evaluation and Associated Liver Disease/Cancer-Hepatitis B Virus) cohort demonstrated that adult HBsAg carriers with serum HBV DNA levels > 10,000 copies/mL will have a significantly higher risk of developing HCC than carriers with serum HBV DNA  $\leq 10,000$  copies/mL. To be noted, carriers with serum HBV DNA < 10,000 copies/mL are still at risk of HCC development. To address whether higher levels of HBsAg increase risk for HCC in this subpopulation, we followed 2,688 Taiwanese HBsAg-positive patients without evidence of cirrhosis for a mean period of 14.7 years (Elucidation of Risk Factors for Disease Control or Advancement in Taiwanese Hepatitis B Carriers [ERADICATE-B] cohort). We found that baseline levels of HBsAg and HBV DNA levels were associated with development of HCC. For HBeAg-negative patients with levels of HBV DNA < 2,000 IU/mL, factors that determined HCC risk included sex, age, and levels of ALT and HBsAg ( $\geq 1,000$  IU/mL). Multivariate analysis showed that the adjusted HR for HCC in patients with levels of HBsAg  $\geq 1,000$  IU/mL versus < 1000 IU/mL was 13.7 (95% CI 4.8–39.3).<sup>51</sup> Our data strongly suggested that among HBeAg-negative patients with low viral loads, the HCC risk is the lowest in patients with serum HBsAg levels < 1,000 IU/mL. These patients can thus be designated “minimal risk HBV carriers.”

All these data suggest that low serum levels of HBsAg, alone or in combination with HBV DNA levels reliably predict the long-term clinical outcomes of chronic HBV infection, including the favorable HBsAg seroclearance in both HBeAg-

negative and HBeAg-positive populations, and the unfavorable development of HCC.

### Correlations Among HBV DNA Level, qHBsAg Level, and HBV Genotype

Recent data further revealed the correlations among serum HBV DNA level, serum HBsAg level, and HBV genotype. A small study evaluated the correlation between HBV DNA and HBsAg level according to HBV genotype in 80 patients with chronic hepatitis B. They found that serum HBsAg level tended to correlate with HBV DNA level for genotype A (correlation coefficient = 0.44,  $p = 0.02$ ); however, such correlation was not significant for genotypes D ( $p = 0.29$ ,  $p = 0.15$ ). We recently followed up 187 patients with chronic HBV infection for a median of 8 years. We found that inactive carriers had a significant lower HBsAg at baseline and during follow-up compared with patients with elevated serum HBV DNA levels. In contrast to previous findings, the longitudinal HBsAg change was independent of genotype B or C, the most common genotype in Taiwan. More studies are needed to clarify the relationships among HBV genotype, viral loads, and qHBsAg level in different clinical situations.

In addition to the untreated cohort, we also investigated the correlation between the declines of HBsAg level and HBV genotype in 32 HBeAg-positive patients receiving interferon (IFN) therapy. After IFN treatment, both serum HBV DNA and HBsAg levels decreased significantly in genotype B, but not genotype C patients. The posttreatment intrahepatic HBsAg level also significantly decreased in HBV genotype B patients. These preliminary results demonstrated genotype-dependent declines of both serum and intrahepatic HBsAg levels after IFN treatment.

## Summary and Perspectives

Over the past decade, we have witnessed advances in research on clinical implications of HBV genotype. Based on accumulating lines of evidence, it is recommended that patients with chronic HBV infection should be routinely genotyped to help identify those who are at higher risk of disease progression.<sup>52</sup> In the foreseeable future, prospective studies including genotype-stratified clinical trials will be required to validate the value of HBV genotype, and the complementary value of HBV genotype, viral load, and qHBsAg level in our clinical practice.

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