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## Hepatitis B virus genotypes: Global distribution and clinical importance

Mustafa Sunbul

Mustafa Sunbul, Department of Infectious Diseases, School of Medicine, Ondokuz Mayıs University, 55139 Samsun, Turkey  
Author contributions: Sunbul M contributed to the manuscript.  
Correspondence to: Mustafa Sunbul, MD, Professor, Department of Infectious Diseases, School of Medicine, Ondokuz Mayıs University, Atakum, 55139 Samsun, Turkey. [msunbul@omu.edu.tr](mailto:msunbul@omu.edu.tr)  
Telephone: +90-362-3121919 Fax: +90-362-4576029  
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### Abstract

At least 600000 individuals worldwide annually die of hepatitis B virus (HBV)-related diseases, such as chronic hepatitis B (CHB), liver cirrhosis (LC), and hepatocellular carcinoma (HCC). Many viral factors, such as viral load, genotype, and specific viral mutations, are known to affect disease progression. HBV reverse transcriptase does not have a proofreading function, therefore, many HBV genotypes, sub-genotypes, mutants, and recombinants emerge. Differences between genotypes in response to antiviral treatment have been determined. To date, 10 HBV genotypes, scattered across different geographical regions, have been identified. For example, genotype A has a tendency for chronicity, whereas viral mutations are frequently encountered in genotype C. Both chronicity and mutation frequency are common in genotype D. LC and progression to HCC are more commonly encountered with genotypes C and D than the other genotypes. Pathogenic differences between HBV genotypes explain disease intensity, progression to LC, and HCC. In conclusion, genotype determination in CHB infection is important in estimating disease progression and planning optimal antiviral treatment.

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**Key words:** Hepatitis B virus; Genotypes; Chronic hepatitis B; Anti-viral therapy; Viral mutation

**Core tip:** Hepatitis B virus (HBV) infection is the leading cause of chronic liver disease and death worldwide. The clinical course and consequences of HBV infection are affected by several factors such as viral load, mutation, host, environment, and viral genotypes. Different HBV genotypes are associated with different mutations in the HBV precore and core promoter gene regions. HBV genotypes are closely related with optimal treatment strategy for chronic hepatitis B patients and clinical outcomes.

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### INTRODUCTION

HBV is an enveloped, hepatotropic, non-cytopathic virus that can cause acute and chronic hepatitis<sup>[1]</sup>. Although there is currently a safe vaccine against hepatitis B virus (HBV), it remains a severe public health issue, especially in Asia, Africa and South America, and may result in death. HBV infection may lead to a variety of clinical pictures, ranging from asymptomatic carrier state to acute hepatitis, fulminant hepatitis, chronic hepatitis, liver cirrhosis (LC) and hepatocellular carcinoma (HCC). Progression of chronic hepatitis B (CHB) disease to severe liver diseases, such as LC and HCC, is determined by the genetic characteristics of the host, as well as by viral and environmental factors<sup>[2,3]</sup>.

## GLOBAL DISTRIBUTION OF HBV GENOTYPES AND SUBGENOTYPES

HBV is differentiated into many genotypes, according to genome sequence. To date, eight well-known genotypes (A-H) of the HBV genome have been defined. Moreover, two new genotypes, I and J, have also been identified. Some HBV genotypes are further classified as sub-genotypes. HBV sequence is characterized by > 8% nucleotide differences for genotype, and 4%-8% nucleotide differences for sub-genotype. Over 30 related sub-genotypes belonging to HBV genotypes have been determined to date, but the mechanisms of different pathogenic characteristics of HBV genotypes are not known for certain. Many studies have reported that different genotypes and sub-genotypes show different geographical distribution, and are related to disease progression, clinical progression, response to antiviral treatment, and prognosis. A-D and F genotypes are divided into various sub-genotypes; no sub-genotypes have been defined for E, G and H genotypes<sup>[1,3-5]</sup>. Genotype A is widespread in sub-Saharan Africa, Northern Europe, and Western Africa; genotypes B and C are common in Asia; genotype C is primarily observed in Southeast Asia; genotype D is dominant in Africa, Europe, Mediterranean countries, and India; genotype G is reported in France, Germany, and the United States; and genotype H is commonly encountered in Central and South America. Genotype I has recently been reported in Vietnam and Laos. The newest HBV genotype, genotype J, has been identified in the Ryukyu Islands in Japan. Geographic distribution of HBV genotypes may be related to route of exposure. For example, genotypes B and C are more common in high-endemic regions of perinatal or vertical exposure, which plays an important role in viral transmission. Other genotypes are primarily observed in regions of horizontal exposure<sup>[6-9]</sup>. Therefore, genotyping provides an epidemiological clue in the investigation of acquisition, because this lies in the geographical distribution of HBV. Figure 1 shows genotype distribution across the world.

Identification of HBV genotype is important for many reasons. An epidemiological study conducted in China showed that genotype B was primarily distributed in the south and genotype C in the north of the country. Clear HBV genotype-related associations exist between clinical outcomes and treatment efficacy in patients with CHB<sup>[10]</sup>. Genotype G was initially identified in studies conducted in France in 2000. It was found during co-infection with other genotypes, especially HBV/A2. HBV/C and H genotypes have also been reported with co-infection<sup>[11]</sup>. The most important characteristics of HBV epidemiology in India are the dominance of genotype D and the increased frequency of hepatitis B e antigen (HBeAg)-negative chronic infection. To date, nine (D1-D9) sub-genotypes of genotype D have been identified. However, A/D recombinant species of HBV have been identified in chronic HBV patients in Northern India<sup>[12]</sup>.

Genotype distribution shows variations between countries, and even between geographical regions within countries. The HBV genotype and sub-genotype distributions between countries are shown in Table 1.

Pathogenic differences between various HBV genotypes are now partially understood. Intracellular levels of HBV DNA and extracellular levels of HBV DNA and HBeAg have been revealed as higher in genotypes B and C than in genotypes A and D. HBV DNA and intracellular accumulation of viral antigens may play a role in the development of cellular damage in hepatocytes. In addition, the high replication capacity of genotype C may be the reason for increased genotype-related severe hepatic damage<sup>[19]</sup>. The following findings were reported from an *in vitro* study: (1) when a pre-core (PC) or basal core promoter (BCP) region mutation affected HBeAg expression in genotype C, intracellular HBV core protein expression was increased; (2) In PC wild-type HBV genotype C patients, intracellular HBV surface protein expression was lower than in HBV genotype B patients; (3) Extracellular HBV DNA was lower in PC-mutant patients; (4) there was less hepatitis B surface antigen (HBsAg) formation in HBV genotype C than in genotype B; and (5) there was less secretion of HBeAg in HBV genotype B than in genotype C<sup>[38]</sup>.

## CLINICAL IMPORTANCE OF HBV GENOTYPES

A greater understanding of the relationship between HBV genotypes, progression of hepatitis B disease, and clinical outcomes has developed over time. Clinical outcomes of chronic HBV infections are variable, and many viral factors, such as host factors, HBV genotype, specific viral mutations, viral load, and quantitative HBsAg levels are important in their prediction. HBV genotypes in viral factors are not only predictive of clinical progression, but are also related to interferon (IFN)- $\alpha$  treatment response<sup>[6]</sup>. In a study comparing genotypes B and C, alanine aminotransferase (ALT) levels were higher in patients with genotype C. However, the reason for this is not yet known<sup>[39]</sup>. The primary clinical and virological features among HBV genotypes are shown in Table 2<sup>[9]</sup>.

A study conducted in China investigated the reasons for the longer immune clearance period in HBV patients infected with genotype C compared with genotype B; higher level of viral replication; high hepatic histological activity, recurrent or persistently high ALT levels and IFN, nucleos(t)ide analogs; and low response to treatment. The possible relationship among genotypes B and C and peripheral blood follicular helper T (Tfh) cells in CHB patients under treatment was investigated. Tfh cells play a major role in spreading signals that affect cellular division; help with activation of B cells; and regulate the humoral response. In addition, Tfh cells secrete specific cytotoxic T lymphocyte (CTL) interleukin (IL)-21 in order to sustain long-acting, effective, antiviral immunity in chronic infection. High serum HBV DNA and ALT ra-

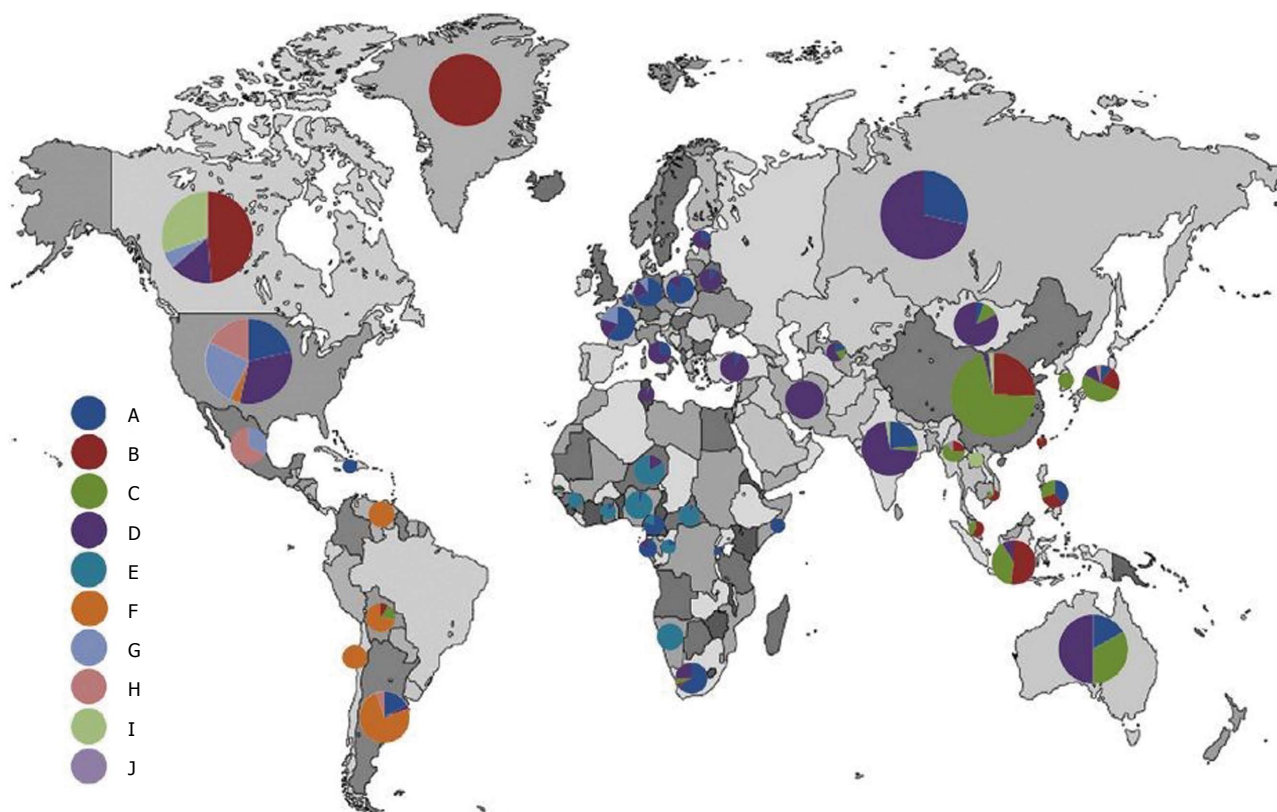


Figure 1 Geographic distribution of hepatitis B virus genotypes worldwide. Permission for Figure 1 has been granted by the Publisher, from Shi *et al*<sup>[4]</sup>.

tios in patients with genotype C might be related to lower peripheral blood Tfh cell levels, which would cause low IL-21 levels, when compared to genotype B. It has been reported that HBV-specific CTL levels are lower<sup>[40]</sup>.

### TENDENCY TO CHRONICITY DEVELOPMENT AFTER ACUTE HBV INFECTION

There are differences in date obtained from studies that reviewed genotypes and chronicity. Some recent studies showed that progression to chronic infection was increased in individuals with acute infection due to HBV genotype A<sup>[41,42]</sup>. However, a study conducted in China reported that chronic infection developed more frequently in patients with C2 sub-genotype than in those with sub-genotype B2, and genotype C2 was an independent risk factor for chronicity development<sup>[43]</sup>. Studies using a limited number of patients concluded that in those with genotypes A and D, chronicity ratios were higher than in patients with genotypes B and C<sup>[21,44]</sup>. In a Japanese study, the ratio of persistent HBV infection development after acute hepatitis B infection was higher in patients with genotype A than in those with genotypes B and C. It was also reported that chronicity ratio after HBV infection was relatively higher in patients with genotype D<sup>[6]</sup>. In addition, chronicity of HBV infection after acute hepatitis B infection was explained by genotype, as well as multi-factorial reasons, such as the amount of viral inoculum,

route of acquisition, and different interactions between host and virus<sup>[45]</sup>.

### HBeAg SEROCONVERSION AND HBsAg SEROCLEARANCE

HBeAg seroconversion and HBsAg seroclearance are the most important steps in the natural progression of HBV infection, and the annual incidence of these are 12% and 2%, respectively. Earlier HBeAg seroconversion is generally accepted as a positive outcome. Conversely, delayed seroconversion, or its absence, after recurrent hepatitis attacks may indicate progression of chronic hepatitis to LC. Following their study in Taiwanese patients, Lin *et al*<sup>[45]</sup> reported that spontaneous HBeAg seroconversion in patients with genotype C was lower than that in genotype B patients (27% vs 47%,  $P < 0.025$ ). HBeAg seroconversion rate in genotype B patients is lower than genotype C patients, and a more lengthy persistence of HBV replication explains why LC and HCC development was found in patients with this genotype.

### HBV GENOTYPES AND ANTIVIRAL TREATMENT

#### IFN-based therapy

Predictive parameters for response to IFN treatment are age, HBV DNA level, sex, ALT, hepatic inflammatory activity index, HBeAg status, and genotype. Many studies

**Table 1** Distribution of genotypes and sub-genotypes among countries

Country	Genotypes	Sub-genotypes	Ref.
China	B, C	B2, C1, C2	Lin <i>et al</i> <sup>[10]</sup>
Indonesia	C, B	C1, B3, B7, C10, B9 and C8	Sibirian <i>et al</i> <sup>[13]</sup> Prasetyo <i>et al</i> <sup>[14]</sup>
Tunisia	D, F	-	Ayari <i>et al</i> <sup>[15]</sup>
Turkey	D	D2, D1, D3	Sunbul <i>et al</i> <sup>[16]</sup>
Brazil	A, F	A1, F2a, A2, F4	Moura <i>et al</i> <sup>[5]</sup> Nabuco <i>et al</i> <sup>[17]</sup>
Vietnam	B, C, I	B2-5, C5-16	Shi <sup>[18]</sup>
Taiwan	B	B2, B5	Kao <sup>[19]</sup>
South Korea	C	-	Kao <sup>[19]</sup>
Hong Kong	C, B	-	Kao <sup>[19]</sup>
Gambia, Nigeria, Haiti, Congo, Rwanda, Cameroon	A	A4, A5, A6, A7	Shi <sup>[18]</sup>
Japan	A, C	C1, C2, C3	Sakai <i>et al</i> <sup>[20]</sup> Kobayashi <i>et al</i> <sup>[21]</sup>
Philippines	A, B, C	A1, B5, C5	Sakamoto <i>et al</i> <sup>[7]</sup>
India	A, C, D	-	Biswas <i>et al</i> <sup>[2]</sup>
Canada	C, B, A, D	-	Congly <i>et al</i> <sup>[22]</sup>
Central African Republic	A, D, E	A1, D4	Komas <i>et al</i> <sup>[23]</sup>
Saudi Arabia	D, E	D1	Khan <i>et al</i> <sup>[24]</sup>
Iran	D	D1	Geramizadeh <i>et al</i> <sup>[25]</sup> Norouzi <i>et al</i> <sup>[26]</sup>
Mongolia	D	-	Oyunsuren <i>et al</i> <sup>[27]</sup>
South Africa	D	D3	Yousif <i>et al</i> <sup>[28]</sup>
Thailand	C, B	C1-5	Louisirirothanakul <i>et al</i> <sup>[29]</sup>
Italy	D	-	Lampertico <i>et al</i> <sup>[30]</sup>
Morocco	D, A	D1, D7, A2	Baha <i>et al</i> <sup>[31]</sup>
Argentina	F	F1, F2, F4	Torres <i>et al</i> <sup>[32]</sup>
Egypt	D	D1	Ragheb <i>et al</i> <sup>[33]</sup>
Pakistan	D	-	Ali <i>et al</i> <sup>[34]</sup>
Australia	C, D	C4, D4	Davies <i>et al</i> <sup>[35]</sup> Sugauchi <i>et al</i> <sup>[36]</sup>
Spain	A, D, F	-	Buti <i>et al</i> <sup>[37]</sup>

have indicated the role of HBV genotypes in response to IFN treatment, and response is greater with regard to genotypes A and B than genotypes C and D, with the worst response to IFN being observed with genotype D<sup>[3,18,46]</sup>. An experimental study investigating the effect of IFN showed that IFN/Peg-IFN was more effective in genotypes A or B than in genotypes C, D and I<sup>[47]</sup>. In a separate study, different serological and virological results were obtained for the varying HBV genotypes. In addition, it was determined that HBsAg and HBV DNA kinetics were specific for genotype. During IFN treatment, the most rapid decrease in quantitative HBsAg level was observed in genotypes A and B, and the best serological responses were obtained after treatment discontinuation in these genotypes. It was indicated that genotype C patients receiving IFN treatment reached HBV DNA negativity the earliest. In the same study, it was reported that genotype E was the most difficult genotype to treat, and that a longer period of time was required for treatment<sup>[46]</sup>.

Biochemical and serological response rates in patients with genotypes A and B were significantly higher than in

patients with genotypes C and D at 6-12 mo after IFN treatment was discontinued. Similarly, it was reported that persistent HBeAg clearance frequency was higher in patients with genotypes A and B, compared to patients with genotypes C and D 3 years after treatment was discontinued. During longer follow-up periods, the HBsAg clearance ratio in HBeAg-negative patients with genotype A who were treated with IFN was markedly higher than in the patients with the other genotypes. Moreover, there were differences between HBV genotypes in HBsAg clearance kinetics during IFN treatment. For example, the mean decrease in HBsAg levels at the end of treatment was the highest in patients with genotype A, was moderate in those with genotypes B and D, and was lowest in patients with genotypes C and E. Although decreases in serum HBsAg levels continued in patients with HBV genotypes A and D during the follow-up period, HBsAg rebound was observed in those with genotypes B and E. In two large global studies, ALT levels were higher in IFN-treated, HBeAg-positive patients with high ALT levels, or in genotype A patients with low HBV DNA levels. In addition, there was a possibility of a persistent response with IFN treatment in genotype B and C patients with lower HBV DNA, and it was concluded that IFN should be assessed for its therapeutic use. Conversely, HBV genotype D patients had the lowest persistent response independently of ALT and HBV DNA levels, so IFN treatment should be recommended for these patients<sup>[19,48]</sup>. In conclusion, identification of HBV genotype provides the clinician with very important clues with regard to the treatment response of disease and disease progression.

IFN- $\alpha$  shows antiviral, immunomodulatory, antiproliferative, and gene induction activities through binding to type I IFN receptor (IFNAR). In another study conducted in China, hepatic expression of type I IFN- $\alpha$  receptor  $\beta$  subunit (IFNAR2) in CHB infection in response to IFN treatment and its relationships with HBV genotypes was investigated. It was reported that IFNAR2 was expressed at high rates in liver in genotype B patients, and better response rates were obtained with IFN treatment when compared to patients with other HBV genotypes<sup>[48]</sup>.

In a similar manner to chronic hepatitis C patients, correlation between IFN treatment and IL28B polymorphism has been investigated in CHB patients in recent years. Lampertico *et al*<sup>[49]</sup> studied HBeAg-negative CHB patients, who are known to be difficult to treat, investigating the correlation between IFN and IL28B polymorphisms, and HBsAg clearance was accepted as the response at the end of treatment. It was shown that HBsAg seroclearance and persistent viral responses were increased in patients with the IL28B CC genotype. Therefore, IL28B polymorphism might be an additional predictor in HBeAg-negative genotype D patients with regard to the optimization and discontinuation of the treatment.

**Table 2 Comparison of clinical and virological features among hepatitis B virus genotypes**

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
Histological activity	Lower	Higher	Lower	Higher	ND
Clinical outcomes (LC, HCC)	Better	Worse	Better	Worse	Worse in genotype F
Response to INF- $\alpha$	Higher	Lower	Higher	Lower	Lower in genotype G
Response to nucleos(t)ide analogs	No significant differences among genotypes A to D				ND
Virological characteristics					
Serum HBV DNA level	Lower	Higher	ND	ND	ND
Frequency of PC 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

ND: No data available; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; LC: Liver cirrhosis; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus.

### Nucleos(t)-ide analog therapy

Treatment responses similar to lamivudine, adefovir, entecavir and telbivudine have been shown among different HBV genotypes in many clinical studies<sup>[45,50-52]</sup>. A recent meta-analysis showed that there was no difference in the response between HBV genotypes and nucleos(t)-ide analogs<sup>[53]</sup>.

### PROGRESSION TO LC OR HCC

LC and HCC are the most severe complications of hepatitis B. Therefore, studies conducted in the past decade have focused particularly on the correlation between HCC and HBV variants, and correlations between two important mutations of the HBV virus, PC mutant in nucleotide 1896 and BCP mutants in nucleotides 1762 and 1764, as well as clinical intensity of the disease, were investigated in detail. A study conducted in China, on HBeAg-positive patients infected by the HBV/C1 sub-genotype, reported that, in addition to T1762/A1764 BCP mutations, V1753 or/and A1768 mutations were closely correlated with HCC. It has been shown that increased HCC risk caused by BCP variants was partially based on modifications of biological functions of HBx protein<sup>[54]</sup>. In a study conducted in Turkish patients, a correlation between T1773 and T1764/G1766 mutations and high viral load was observed, but a definite correlation between BCP, PC, and/or core region mutations and disease prognosis could not be determined<sup>[55]</sup>. Many similar studies have indicated that genotype C caused more common severe liver diseases, such as LC and HCC, than the other genotypes caused. Concomitant presence of high serum HBV DNA levels, mutations, such as 1653T, 1753V and A1762T/G1764A, as well as acute hepatic failure, LC and HCC have also been noted. In addition, subsequent studies similarly showed that HBV genotype C infection caused mutations more frequently than did genotype B infection. It is currently accepted that there

is a positive correlation between HBeAg expression and HBV DNA level, which is the HBV replication indicator. Some prospective studies have also indicated that HCC risk is increased as basal serum HBV DNA levels are increased<sup>[18,56,57]</sup>.

In a meta-analysis investigating the correlation between HBV genotypes and HCC, HCC detection was 12% for genotype B, and 25% for genotype C (OR = 2.05, 95%CI: 1.52-2.76,  $P < 0.001$ ). Moreover, a correlation between genotype C patients and more severe liver diseases has been reported. Conversely, genotype A (14%) and genotype C (11%) have a similar HCC risk. In accordance with previous studies, another meta-analysis showed that HCC development was associated more with genotype C patients than with patients with the other HBV genotypes<sup>[58]</sup>.

In a study conducted in India, Ghosh *et al*<sup>[59]</sup> showed a correlation between advanced clinical stage and mutation frequency in genotype D patients with HBeAg-negative chronic HBV infection. Many of these mutations were localized in regions that regulated transcription (BCP/EnhII/NRE/SP1). According to the results, deletion at the preS region was the most important predictor of LC. Moreover, the only clinically important mutation was identified as S183P at the HBV core protein C terminus, which was out of the ectopic region, and this caused HBV genotype D to shift from an inactive carrier state to progression to CHB and LC. It was also reported that G1896A and G1899A PC mutants in HBV were correlated with more aggressive liver diseases, as has previously been reported in several studies. Therefore, it was indicated that high-risk patients could be identified before disease progression by the use of viral genomic markers, and thereby incidences of LC and HCC decreased. Conversely, an investigation of correlation between sub-genotypes and severe liver diseases indicated that sub-genotype B1 was related to fulminant hepatitis B infection in Japan, whereas sub-genotype B2 was related to

HCC and HCC recurrence in East Asia. A separate study reported that risk of HCC was high in sub-genotype C2 infections<sup>[18,56,57]</sup>.

A study carried out in South Korea showed that HBV mutations were significantly related to HCC in CHB patients infected by genotype C, especially in major histocompatibility complex class II-restricted regions. In the preC/C region, there are six (preC-W28\*, C-P5H/L/T, C-E83D,C-I97F/L, C-L100I and C-Q182K/\*) and seven (preC-W28\*, preC-G29D, C-D32N/H, CE43K, C-P50A/H/Y, C-A131G/N/P and C-S181H/P) types of mutations that are related to HCC, and these define HBeAg serostatus. The results showed that HBV variants in the C region could lead to HCC progression in chronic patients infected by genotype C by the immune escape pathway against the CD4 T-cell-mediated immune response. Therefore, it was concluded that HCC-related hepatitis B core antigen mutations and HBeAg serostatus could be used as diagnostic markers for early diagnosis of liver disease progression, including HCC<sup>[60]</sup>. Interestingly, many studies reported that HCC development was observed in patients at an advanced age with genotype C, whereas this occurred earlier in genotype B patients<sup>[61-63]</sup>.

Conversely, in the study conducted in India, it was noted that subtypes D1 and D3 were accompanied by chronic and occult infections, respectively<sup>[4,12]</sup>. However, a different study reported that there was a correlation between occult hepatitis and genotype C<sup>[64]</sup>.

## CONCLUSION

Nowadays, There is a large accumulation of knowledge regarding HBV, as well as hepatitis B disease and treatment. HBV genotype varies according to countries and ethnic backgrounds. Chronicity of the disease, response to antiviral treatment, and progression of LC and HCC differ according to genotypes, which also enables the physician to individualize the treatment and to identify disease-related risks. In addition to the existent potent antivirals currently used in treatment, the introduction of new antivirals, such as core inhibitors, which inhibit covalently closed circular DNA activity, may make it possible to achieve more definite treatment outcomes in the near future. The positive outcomes of a routine neonatal vaccination program will be observed more closely in the coming years. However, much remains unknown about HBV disease, so further studies, especially into its complex immunopathogenesis, are required for clarification and understanding.

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