Clinics and Research in Hepatology and Gastroenterology (2015) 39, 28—37

Available online at
SciVerse ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

MINI REVIEW

# Epidemiology of HBV subgenotypes D

**Resat Ozaras*, Ilker Inanc Balkan, Mucahit Yemisen, Fehmi Tabak**

*Infectious Diseases Department, Cerrahpasa Medical School, Istanbul University, 34098 Cerrahpasa, Istanbul, Turkey*

Available online 16 July 2014

**Summary** The natural history of hepatitis B virus infection is not uniform and affected from several factors including, HBV genotype. Genotype D is a widely distributed genotype. Among genotype D, several subgenotypes differentiate epidemiologically and probably clinically. D1 is predominant in Middle East and North Africa, and characterized by early HBeAg seroconversion and low viral load. D2 is seen in Albania, Turkey, Brazil, western India, Lebanon, and Serbia. D3 was reported from Serbia, western India, and Indonesia. It is a predominant subgenotype in injection drug use-related acute HBV infections in Europe and Canada. D4 is relatively rare and reported from Haiti, Russia and Baltic region, Brazil, Kenya, Morocco and Rwanda. Subgenotype D5 seems to be common in Eastern India. D6 has been reported as a rare subgenotype from Indonesia, Kenya, Russia and Baltic region. D7 is the main genotype in Morocco and Tunisia. D8 and D9 are recently described subgenotypes and reported from Niger and India, respectively. Subgenotypes of genotype D may have clinical and/or viral differences. More subgenotype studies are required to conclude on subgenotype and its clinical/viral characteristics.


## Introduction

Chronic hepatitis B (CHB) is a main cause of chronic liver disease worldwide. More than 240 million people are chronically infected worldwide and more than 600,000 people die of the complications of CHB, such as liver failure and hepatocellular carcinoma (HCC) [1,2]. The natural history of hepatitis B virus infection is not uniform and several factors including viral and host characteristics affect this highly variable process. Host factors include gender, age, age at transmission of the infection, race, presence of comorbidities, use of immunosuppressive drugs, and socioeconomical status [3]. Among viral factors are HBV genotype [3], mutations of resistance, and most likely, the subgenotypes [4].

The HBV genome is a partially double-stranded circular DNA consisting of 3200 nucleotides. It exhibits high genetic variability due to the lack of proofreading function of polymerase. HBV is classified into genotypes according to a divergence in the entire nucleotide sequence greater than

* Corresponding author. Tel./fax: +90 212 4143095.
*E-mail address:* rozaras@yahoo.com (R. Ozaras).

http://dx.doi.org/10.1016/j.clinre.2014.06.005

7.5% [5]. HBV has been classified in to 10 genotypes (A—J) [6,7]. Epidemiological studies show that distinctive geographic distribution and ethnic association: genotypes B and C are frequent in Asia, while genotypes A and D are prevalent in Europe, the Mediterranean region and the Middle East [8,9].

## An overview of HBV genotypes

Genotype A is seen in Sub-Saharan Africa, India, and South America (A1), Europe, United States, Australia (A2), and West Africa (A3). A1 is suggested to associate with HCC development in young adults without cirrhosis whereas A2 is predicted to cause HCC and cirrhosis in older people [4].

Genotype B is seen in Japan (B1), East Asia (B2—5) and Alaska, Northern Canada, Greenland (B6). While B1 is characterized by an association of HCC and development of cirrhosis in older persons, B2 may cause HCC and cirrhosis in younger persons with an HBeAg seroconversion occurring at relatively older age [4].

Genotype C is seen more frequently in China, Korea, Southeast Asia, Japan, South Pacific Islands, and Australia. Risks for HCC and cirrhosis in this genotype are higher than genotype B. HBeAg seroconversion occurs 1—3 decades later than other genotypes [4].

Genotype D is seen in a wide geographic region: Russia, Middle East, Mediterranean, Mongolia, North Africa, Europe, Indian Subcontinent, Arctic, North and South America, Australia. It is associated with precore mutations, HBeAg-negative CHB, HCC and cirrhosis developing in older individuals [4].

Genotype E is seen in West and Central Africa, characterized by both basal core promoter and precore mutations.

Genotype F is seen in Central and South America, and Alaska. Genotype G is seen Europe, United States, and noticed in patients co-infected with HBV genotype A.

Genotype H is seen in Central America and Amazon region. While genotype I is described in Vietnam and Laos, genotype J is defined in Ryukyu Islands of Japan.

The aim of this study is to review the subgenotypes of HBV genotype D and search their correlations with any clinical and/or viral features.

## Materials and methods

Studies that report the subgenotype of genotype D were included. PubMed, MEDLINE was searched for English language articles published from 1964 to November 2013. Search terms included ''subgenotype and hepatitis B''. Articles were included if the reported data included subgenotype of genotype D. Review articles were not used.

## Results

### Genotype D

Genotype D is widely distributed than the other genotypes. Although subgenotypes are different, it is seen in almost every region (Table 1, Fig. 1) [10—75]. It is a common genotype in southern Europe, North Africa, India, China, and West and South Africa [76,77]. Genotype D makes up around 100% of the HBV cases in countries, including Greece [78], Italy [79], Serbia [44,45], Albania [41,80], Turkey [46—51], Lebanon [36] and Iran [27—34].

Genotype D is characterized by some clinical characteristics. Acute hepatitis B patients infected with genotype D were suggested to have a higher chronicity rate than those infected with genotypes B and C [81,82]. Genotype D is characterized by conversion from HBeAg to anti-HBe in adolescence or early adulthood. This seroconversion is generally associated with precore mutations. This period may result in an inactive carrier phase or in HBeAg-negative/anti-HBe-positive chronic hepatitis B. This latter can lead to cirrhosis and HCC [83—85].

Compared to genotype A, genotype D was reported to associate with more severe liver disease and HCC [86]. Another study from Alaska suggested that genotype D was significantly associated with HBV-associated vasculitis (polyarteritis nodosa) when compared to genotypes A2, B6, C2, and F1 [87].

Genotype D associates with lower response rates to interferon treatment. Several studies suggested that IFN/Peg-IFN was more effective in genotypes A or B than the genotypes C and D [88,89].

### Subgenotypes of genotype D

D1: Bulgaria, China (Uyghur region), Egypt, northern India, Turkey, Iran, Lebanon, Morocco, Pakistan, Tunisia, Indonesia and Brazil.

A recent study from Turkey showed that specific mutations of basal core promoter are associated with chronic liver disease in hepatitis B virus subgenotype D1 [49]. They suggested that this subgenotype is characterized by early HBeAg seroconversion and low viral load.

D2: This subgenotype is seen in Albania, Turkey, Brazil, western India, Lebanon, and Serbia.

D3: Subgenotype D3 was reported from Serbia, western India, and Indonesia. In acute HBV outbreaks in Denmark and England, D3 was reported as the predominant subgenotype in injection drug use-related acute HBV infection [90—92]. The D3 subgenotype was responsible from the majority of HBV infection among drug users in Canada [93] and Italy [94]. These reports suggest that transmission of subgenotype D3 may be related with injection drug use [95].

It shows the highest intra-subgenotype divergence [74].

D4: This subgenotype is relatively rare. It has been described from Haiti, Russia and Baltic region, Brazil, Kenya, Morocco and Rwanda. Andernach et al. reported phylogenetic analysis of 179 HBV (+) pregnant women detected during a survey. Genotype was detected in 128 and D in 36. Among them, 29 were of subgenotype D4 [73].

D5: Subgenotype D5 has been reported from India several regions of India. It seems to be relatively common in Eastern India [20].

Ghosh et al. described 13 HBV(+) patients with D5 subgenotype from a primitive tribal community in eastern India (15). It has been also reported from Morocco and Russia and Baltic region [57,58,74].