

## HBV endemicity in Mexico is associated with HBV genotypes H and G

Sonia Roman, Arturo Panduro

Sonia Roman, Arturo Panduro, Department of Molecular Biology in Medicine, Civil Hospital of Guadalajara, "Fray Antonio Alcalde", and Health Sciences Center, University of Guadalajara, Guadalajara 44280, Jalisco, Mexico

Author contributions: Roman S and Panduro A contributed equally to this paper.

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Correspondence to: Arturo Panduro, MD, PhD, Department of Molecular Biology in Medicine, Civil Hospital of Guadalajara, "Fray Antonio Alcalde", and Health Sciences Center, University of Guadalajara, Guadalajara 44280, Jalisco, Mexico. [apanduro@prodigy.net.mx](mailto:apanduro@prodigy.net.mx)

Telephone: +52-33-36147743 Fax: +52-33-36147743

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### Abstract

Hepatitis B virus (HBV) genotypes have distinct genetic and geographic diversity and may be associated with specific clinical characteristics, progression, severity of disease and antiviral response. Herein, we provide an updated overview of the endemicity of HBV genotypes H and G in Mexico. HBV genotype H is predominant among the Mexican population, but not in Central America. Its geographic distribution is related to a typical endemicity among the Mexicans which is characterized by a low hepatitis B surface antigen seroprevalence, apparently due to a rapid resolution of the infection, low viral loads and a high prevalence of occult B infection. During chronic infections, genotype H is detected in mixtures with other HBV genotypes and associated with other co-morbidities, such as obesity, alcoholism and co-infection with hepatitis C virus or human immunodeficiency virus. Hepatocellular carcinoma prevalence is low. Thus, antiviral therapy

may differ significantly from the standard guidelines established worldwide. The high prevalence of HBV genotype G in the Americas, especially among the Mexican population, raises new questions regarding its geographic origin that will require further investigation.

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**Key words:** Hepatitis B virus genotypes; Hepatitis B virus genotype H; Hepatitis B virus genotype G; Molecular epidemiology; Mexico; Antiviral therapy; Severity of liver disease; Clinical outcome

**Core tip:** Molecular, clinical, geographical and ethnicity evidence are characteristics that define any hepatitis B virus (HBV) genotype. All of these features are there for HBV genotype H, which is most predominant in Mexico, but not in Central America. Likewise, HBV genotype G has unique molecular characteristics and a similar route of transmission among those infected with this viral genotype, but it lacks a geographic origin. To date, despite the high prevalence of HBV genotype G cases from the Americas, especially among Mexicans, the limited number of complete sequences hinders further investigation to establish a hypothesis of an Amerindian origin.

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### INTRODUCTION

#### **Definition of hepatitis B virus genotypes and their association with human liver disease**

Hepatitis B virus (HBV) and humans share a close re-

relationship through the process of evolution and migration<sup>[1,2]</sup>. Numerous studies have demonstrated that most HBV genotypes are associated with a host population and geographical area of the world, while others tend to have a worldwide distribution, or still remain unknown<sup>[3,4]</sup>.

In 1988, Okamoto *et al.*<sup>[3]</sup> proposed the first genetic classification for HBV strains, defining a genotype as a viral sequence with an intertypic nucleotide divergence of more than 8% based on the entire genome. Later, a 4.2% nucleotide divergence using the S gene sequence was proposed by Norder *et al.*<sup>[5]</sup>. Throughout their discovery, each new genotype was defined by the same criterion and designated with letters in an alphabetical order, from A to J. However, given the wide diversity of HBV genomes worldwide, several authors have proposed over the years that precise criteria be fulfilled in order to identify and describe a specific genotype/subgenotype<sup>[6-9]</sup>. Recently, Kurbanov *et al.*<sup>[10]</sup> have endorsed and updated these recommendations which, in summary, are the following: use of whole genome sequences, divergence of  $\geq 7.5\%$  ( $> 4\%$  to  $< 7.5\%$  in the case of a subgenotype), strong independent clustering on molecular evolutionary analysis, avoidance of recombinants, as well as substantial epidemiological, virological and clinical evidence.

Regarding these latter points, in 2002, Chu *et al.*<sup>[11]</sup> raised key questions about the association of HBV genotypes with clinical practice: (1) “What is the predominant HBV genotype in each country or geographic region?” (2) “Is the geographic distribution of HBV genotypes related to the endemicity of HBV infection?” (3) “Is there a correlation between HBV genotype and HBV replication activity of liver disease, clinical outcome and treatment response?” and (4) “Is there a correlation between HBV genotype and risk of progression to chronic infection?”

Accordingly, the geographic distribution of HBV genotypes in regard to their regional host population and endemicity has been widely considered. In general, HBV genotypes B and C are associated with the populations of the Asian countries<sup>[3]</sup> while genotypes A and D are prevalent among European countries and the United States<sup>[3]</sup>; genotypes E and F are confined to countries of the African continent<sup>[12]</sup> and the Americas<sup>[12]</sup> (Central and South America), respectively. HBV genotype G (HBV/G) was originally reported in France<sup>[13]</sup> but has a global distribution, and HBV genotype H (HBV/H) was first revealed in Central America<sup>[14]</sup>. HBV genotypes I and J have been reported in dispersed regions of Asia and Japan, respectively<sup>[15,16]</sup>. Likewise, the genetic diversity, disease progression and response to antiviral therapy<sup>[17-20]</sup> of the European and Asian genotypes (A-D)<sup>[21-23]</sup> have received greater attention than those that are typically prevalent in the western hemisphere (E-H)<sup>[24-27]</sup>, while evidence about genotypes I and J is insufficient to respond to such arguments<sup>[10,28]</sup>.

### **Milestones in the discovery of HBV genotypes G and H worldwide and in Mexico**

HBV/G and HBV/H were revealed almost at the same time. Both discoveries represent the culminating results

of investigations carried out in the 1990s by many different laboratories worldwide. HBV/G was first described as an HBV variant<sup>[29,30]</sup> and formally reported by Stuyver *et al.*<sup>[13]</sup> in 2000. In our laboratory, HBV/G was detected in 2000, but not reported until 2002 by Sánchez *et al.*<sup>[31]</sup>. Further on, research studies focused on the development of molecular diagnostic methods<sup>[32]</sup> and the relationship between clinical and virological characteristics in comparison with the other known genotypes<sup>[26,33]</sup>. However, unlike the rest of them, the geographic origin of HBV/G is still unknown<sup>[34]</sup>.

As for HBV/H, Dr. Norder from Sweden and two other laboratories, Dr. Misokami from Japan and Dr. Panduro in Mexico, were studying the genetic variability of HBV that resulted in the identification of HBV/H in the last decade of the preceding century. However, the first HBV/H strains from Mexico were classified as HVB genotype F (HBV/F) by Sánchez *et al.*<sup>[31]</sup> since complete sequences of genotype H were not available for comparison. Later, after discussing our findings with Dr. Norder in Mexico, two strains from Nicaragua and one from the United States were made known as the new genotype H<sup>[14]</sup>. Since then, HBV/H has often been referred to as from Central America, because of the two original Nicaraguan strains. Further discussion regarding the validity of genotype H was provided by Kato *et al.*<sup>[35]</sup>, given that seven HBV isolates (doubtfully H) differed from a number of selected HBV/F strains by a genetic divergence of 7.3%-9.5%, thus proposing a new subtype (F2) of HBV/F.

Overall, in the last ten years, the knowledge on HBV/H regarding the relationship between virological-clinical characteristics and its geographical and host population prevalence has increased significantly, allowing us to have a better understanding of HBV-infected patients. Herein, we provide an updated overview of such evidence concerning the endemicity of HBV infection based on genotypes H and G in Mexico.

## **HBV GENOTYPE H**

### **Molecular characteristics of HBV genotype H**

In the study by Arauz-Ruiz *et al.*<sup>[14]</sup>, the three original samples (1853Nic, 2928Nic, LAS2523) designated as HBV/H diverged from selected genotype F strains by 7.2%-10.2%. In the polymerase region, the three strains had 16 unique conserved amino acid residues not present in genotype F strains. Additionally, HBV/H also differs from them by two distinct substitutions in the surface antigen protein, at Val<sup>44</sup> and Pro<sup>45</sup>, as well as at Ile<sup>57</sup>, Thr<sup>140</sup>, Phe<sup>158</sup> and Ala<sup>224</sup><sup>[4]</sup>. Furthermore, by “TreeOrder Scan” analysis, genotype H strains show evidence of recombination with genotype F within the small S gene (nucleotide 350-500)<sup>[1]</sup>.

As mentioned before, the limited number of sequences available at that time made it difficult to distinguish HBV/H as an independent genotype, due to its close phylogenetic relatedness with HBV/F<sup>[14,35]</sup>. Nevertheless, the amount of HBV/H sequences reported in GenBank

has increased; hence pair-wise analysis of complete sequences of HBV/F compared against the latest Mexican HBV/H strains result in a genetic distance of at least 0.08 (data not shown). Thus, the initial differences reported by the authors could have been related to the fact that the earlier isolates came from subjects with residence outside of Mexico<sup>[14,35]</sup>.

Additionally, the estimated maximum likelihood phylogeny of HBV/H and HBV/F genomes exhibits a distinct genetic divergence from a common ancestor while HBV/H sequences tend to cluster into multiple and nested clades<sup>[36]</sup>. Further phylogeographic studies based on coalescent models are necessary to provide fresh information regarding these evolutionary characteristics, and integrate them to the timeline of migrations of the prehispanic people from ancient Mexico towards South America.

### **Molecular epidemiology of HBV genotype H in Mexico**

During the last 10 years, the geographic origin of HBV/H was referred to as from Central America. Today, it is clearly evident that most HBV/H sequences deposited in GenBank are from Mexico, while those isolated worldwide come from individuals reporting sexual relationships with people from the Americas, and no further H strains have been reported from Central America<sup>[36]</sup>.

Epidemiological studies using only hepatitis B surface antigen (HBsAg) determinations have shown a steady prevalence rate of 0.3% since 1976 to date, ranking Mexico as a region of low endemicity<sup>[37]</sup>. However, by anti-HBc marker and molecular diagnosis of HBV genomes, high endemic areas of HBV infection have been detected in the native population<sup>[37-39]</sup>, similar to the indigenous populations of the Central and South American countries<sup>[40]</sup>.

It has been estimated that nearly 15 million Mexican adults have been infected by HBV during their lifetime, since the anti-HBc prevalence increases with age<sup>[41,42]</sup>. Additionally, estimates suggest that at least another 5 million native people could be at risk of acquiring infection<sup>[41]</sup>. HBV/H infection is acquired primarily during adulthood by horizontal transmission, through sexual relationships and contact with contaminated body fluids, which could explain why the majority of infected patients do not develop chronic liver disease<sup>[41]</sup>.

HBV/H is the predominant genotype in asymptomatic infected patients living in high endemic areas<sup>[36,38]</sup>, as well as in patients with acute and chronic liver disease<sup>[43,44]</sup>. Indeed, HBV/H is prevalent in more than 90% of the cases, followed by HBV/A, HBV/D and HBV/G, whereas other known HBV genotypes are rare<sup>[36]</sup>. Furthermore, the predominance of HBV/H in Mexico is historically related to the migrations of the prehispanic people, the settlement of the Aztecs in Mesoamerica before the Spanish conquest and the successive admixture of the population; hence, it is the predominant genotype detected in both Mexican native (Amerindian) and mestizo populations<sup>[36,38]</sup>.

### **Clinical presentation of HBV/H infected patients**

HBV/H infected patients usually are asymptomatic without clinical or laboratory manifestations of liver disease<sup>[38,43]</sup>; thus, the existence of liver damage is modest or undetectable, whereas occult B infection (OBI) is a common manifestation<sup>[38,45]</sup>. This situation may be attributed to a rapid resolution of the disease, associated with the genetic characteristics of either the virus or the host<sup>[46]</sup>.

HBV/H is often detected in patients with acute liver damage. This clinical symptom is observed in male patients, such as men who have sex with men, mainly during the acute phase, and then with viral clearance or OBI after acute infection and flares during immunosuppressive conditions<sup>[46]</sup>. In chronic patients, HBV/H is predominant also; however, OBI is common so that the association of the HBV/H with the progression and severity of liver disease is masked by the presence of other co-morbidities, such as alcoholism, obesity and co-infection with hepatitis C virus (HCV) or human immunodeficiency virus (HIV)<sup>[36]</sup>. HBV/H-infected patients tend to have low viral loads, usually < 4000 UI/L, that are easily detected as they increase, up to 100000 UI/L or above when patients are infected with mixtures of HBV genotypes<sup>[36]</sup>.

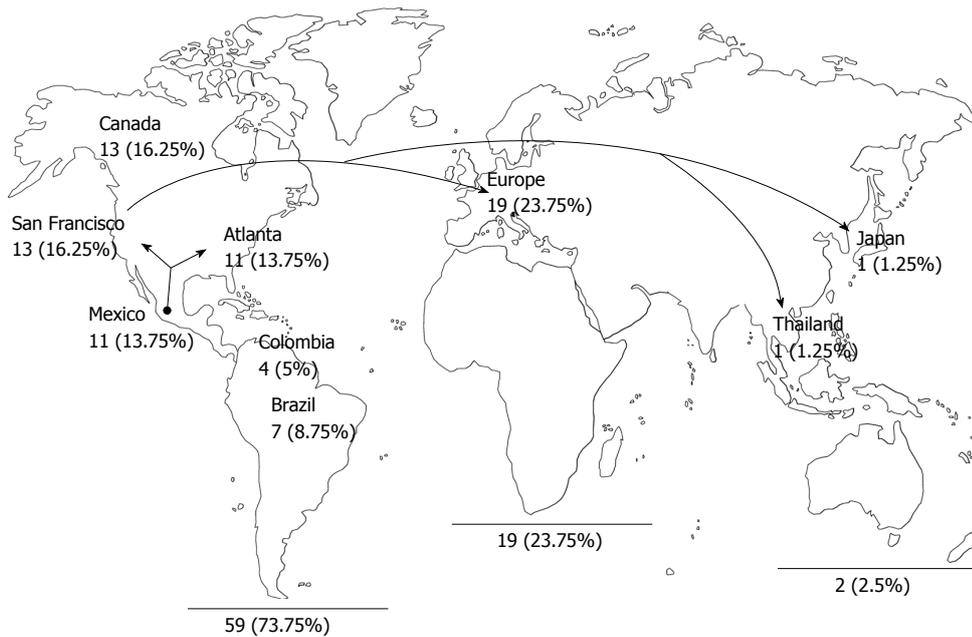
Lastly, the low prevalence of HBV infection among the Mexican population is associated with a low prevalence of hepatocellular carcinoma (HCC) from 1953 to date<sup>[47-49]</sup>. This is contrary to what occurs in the Asian countries, where acute and chronic HBV infection with genotypes B and C and HCC are highly prevalent. Thus, the predominance of HBV/H among the Mexican population is associated with low endemicity, low viral load, minimum cases of acute and chronic liver diseases due to HBV infection and a low prevalence of HCC.

This matter raises a word of caution regarding the strategy for antiviral therapy in Mexico since the main cause of liver disease may be attributed to co-morbidities, such as HCV or HIV infection, alcoholism or obesity, but not to HBV infection exclusively. Therefore, antiviral therapy for HBV/H-infected patients should be given with precaution until the usefulness of the conventional antivirals is fully demonstrated for this genotype, considering that the international guidelines for the treatment of chronic B infection have been designed for populations of other geographic regions that have different HBV genotypes, endemicity and progression of liver disease.

## **HBV GENOTYPE G**

### **Molecular characteristics of HBV genotype G**

The HBV/G genome has some unique characteristics. It contains a 36-nt/12 amino acid insertion with pleiotropic effects on core protein expression, genome replication and virion secretion, not found in any other HBV genotype<sup>[50]</sup>. It also has two stop codons in the preC region at position 2 and 28, which prohibits the translation of the hepatitis B e antigen (HBeAg)-precursor; thus, patients



**Figure 1** Geographic distribution of the worldwide epidemiology of the hepatitis B virus genotype G isolates. Fifty-nine genome sequences out of a total of 80 have been reported from the Americas (73.75%), whereas 23.75% are from Europe and 2.5% from Asia. The high prevalence of hepatitis B virus genotype G in America may be related to a common source of infection and transmission route.

who are mono-infected with HBV/G are negative for HBeAg<sup>[51]</sup>. Other molecular characteristics include two deletions, one at the carboxyl terminal region of HBcAg and another in the preS1 region<sup>[51]</sup>.

At the nucleotide level, the majority of the complete genome sequences of HBV/G strains share a remarkable sequence conservation of more than 99%<sup>[52]</sup>. Furthermore, there is a high nucleotide similarity within the S gene sequence (94.6%-97.5%), considered as evidence of recombination with genotype A (HBV/A) in the small S fragment (nucleotide 250-350)<sup>[11]</sup> and a 30 base pair fragment in the preS region that is almost identical to genotype E<sup>[34]</sup>.

### Molecular epidemiology of HBV/G in Mexico

Worldwide, a significant number of HBV/G strains have been detected in men who have sex with men<sup>[13,26,29,30,52-54]</sup>, suggesting that sexual genital-anal contact may play a significant role in the transmission of HBV infection<sup>[55]</sup>. However, parenteral transmission has been reported, mainly as mono-infection, such as in blood donors<sup>[56-58]</sup> and hemodialysis patients<sup>[59]</sup>.

In the past years, several publications continue to report that little is known about the geographical origin of HBV/G, and yet it is considered ubiquitous. Such statements have arisen due to earlier HBV/G cases reported from France<sup>[13]</sup>, Germany<sup>[54]</sup> and the cities of San Francisco, CA<sup>[26,29,52]</sup> and Atlanta, Georgia<sup>[13]</sup> in the United States. However, despite the limitations of using RFLPs or strip molecular methods for the detection of HBV/G, instead of complete genome sequences<sup>[10]</sup>, most of the cases of this genotype have been reported from the Americas (73.5%), including Mexico<sup>[31,38,46,55,60,61]</sup> and to a

lesser degree from Europe<sup>[30,50,56,62-65]</sup> (23.75%) and other regions of the world (2.5%)<sup>[66-68]</sup> (Figure 1).

As mentioned before, the geographic origin of HBV/G is still unknown, due to its low global prevalence combined with the lack of epidemiological and clinical data. The genomic characteristics of this genotype are puzzling. On one hand, HBV/G complete sequences share such a close similarity that a specific molecular epidemiological route of transmission among the international cases or a simple evolutionary history cannot be elaborated. On the other hand, the similarity of certain regions of the HBV/G genome with genotypes A<sup>[1]</sup> and E<sup>[34]</sup> suggest co-evolutionary processes among themselves<sup>[10]</sup>. These features have created considerable difficulties to pinpoint a distinct geographic origin for HBV/G.

A hypothesis on a plausible African geographic origin of HBV/G was proposed by Lindh<sup>[34]</sup> in 2005, based on its similarity with HBV/E which is prevalent in Africa and that the worldwide spread of HIV infection from Africa may have been the cause of the dispersion of HBV/G. Unfortunately, HBV/G African sequences have not been deposited in GenBank nor have G/E recombinants been associated with a host population to date. Furthermore, based on the low genetic diversity of HBV/E (1.67%) and its short evolutionary history<sup>[69]</sup>, it has been suggested that it was introduced into the African population after the Atlantic slave trade<sup>[69-71]</sup>. This is consistent with the fact that HBV/E is virtually absent in the Americas, despite the significant number of African slaves introduced into the United States and Latin America (including Mexico), both regions having a high presence of black population, the former of Afro origin and the latter mixed descendents of a large black popula-

tion forced into slavery. Thus, the worldwide spread of HBV/G appears to have not co-dispersed HBV/E, since G/E recombination or G-E co-infection is absent among the admixture populations. Interestingly, the similarity of the 150 base pair fragment between HBV/A and HBV/G could be related to the most common dual HBV G/A infection reported in the United States<sup>[26,52]</sup>, Canadian<sup>[53]</sup> and European cases<sup>[56]</sup>. Given that HBV/A is common in Europe, it may be speculated that genotype G could have reached the Americas by way of the Caucasian people. However, despite the fact that HBV/A is a minor strain in Mexico<sup>[36]</sup>, HBV G/H co-infection is more frequent than G/A<sup>[55]</sup>. Thus, G/H co-infection may be related to the plausibility that genotype G is endemic to Mexico, as well as genotype H. Furthermore, HBV/G has been detected in patients with chronic liver disease; pathogenesis of liver fibrosis has been documented in *in vitro* experiments<sup>[60,72]</sup> and corroborated in patients with co-infection with other HBV genotypes.

The relationship of HBV/G sequences with the Mexican population is based on the following observations: (1) the high prevalence of HBV/G sequences in the American continent (73.75%) (Figure 1); (2) 16 HBV/G cases were detected among 77 HIV/HBV co-infected individuals (21%)<sup>[61]</sup>; (3) 5 HBV/G cases out of 49 high risk individuals (10.2%)<sup>[27]</sup>; and (4) HBV/G sequences have been identified in an ongoing study cohort of young children with HBV infection in our laboratory. These findings lead us to ask ourselves: "Is HBV/G endemic to the Americas, including Mexico, Colombia, and Brazil or was it introduced into the continent?" The evidence that could support an Amerindian hypothesis requires that sequences from native and mestizo populations be analyzed. To date, 11 sequences from Mexico<sup>[31,38,55,60]</sup>, 7 from Brazil<sup>[73-75]</sup> and 4 from Colombia<sup>[58]</sup> have been retrieved from mestizo populations, except for one Mexican case belonging to a native from the Huichol community<sup>[38]</sup>. The presence of HBV/G in this community could be explained by the fact that native individuals engage in multi-partner sexual relationships and male-to-male sexual activity<sup>[38,76,77]</sup>. However, further phylogeographic studies are required in order to determine if these findings may be related to the transmission of HBV/G infection among distinct Amerindian communities before the global dissemination of blood-borne infectious diseases.

Nevertheless, Mexican and United States HBV/G strains share a close genetic homology<sup>[55]</sup>. This is consistent with the fluent migration events that have occurred for centuries across the United States-Mexican border, especially from the western states of Jalisco, Michoacan and Guanajuato, towards the large United States Hispanic communities, such as in Los Angeles, San Francisco and Atlanta, among others<sup>[78]</sup> (Figure 1). However, despite this feasible epidemiological association, further evidence is required to verify if the transmission of HBV/G infection may have occurred among same-sex couples/transgender individuals traveling to and from Mexico and the United States<sup>[79,80]</sup>.

## CONCLUSION

The predominance of HBV genotype H among the Mexican population is associated with a definite geographic region and historical context. The endemicity of HBV infection in Mexico manifests with a low HBsAg seroprevalence, due to a rapid response to the infection, low viral loads and a high prevalence of occult B infection. During chronic infections, HBV infection may be undetectable and associated with co-morbidities, such as obesity, alcoholism and co-infection with HCV or HIV. These manifestations correlate with the low prevalence of hepatocellular carcinoma. Based on these features, antiviral therapy may differ significantly from the international guidelines that have been established for patients within the regions of high endemicity. As for the high prevalence of HBV/G cases reported in Mexico, more detailed phylogenetic analysis of other HBV/G complete sequences will be required in order to elucidate its geographic origin.

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