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Review

Distribution of HBV genotypes in Latin America

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Approximately 2 billion people worldwide are infected with HBV, and 350 million people are chronic carriers. HBV is classified into nine genotypes (A to I). Genotype F is the most prevalent in the Spanish-speaking countries and in the Amerindian population in South America. HBV genotype F was primarily found in indigenous populations from South America and is divided into four subgenotypes (F1 to F4). Subgenotype F1 is further divided into F1a (found in Costa Rica and El Salvador) and F1b (found in in Alaska, Argentina and Chile). Subgenotypes F2 and F3 cocirculate in the north of South America: F2a is found in Brazil and Venezuela, F2b is described only in Venezuela, F3 is frequent in Colombia, Venezuela and Panama, and F4 is reported from the central and south areas of South America, including Bolivia, Argentina and southern Brazil. HBV genotypes and subgenotypes have distinct geographical distributions. It is currently under discussion whether they are associated with different prognoses, considering the patterns of severity of liver diseases in various populations. Furthermore, global human migrations affect the pattern of genotype distribution, introducing genotypes differing from those found in the original inhabitants.

Introduction

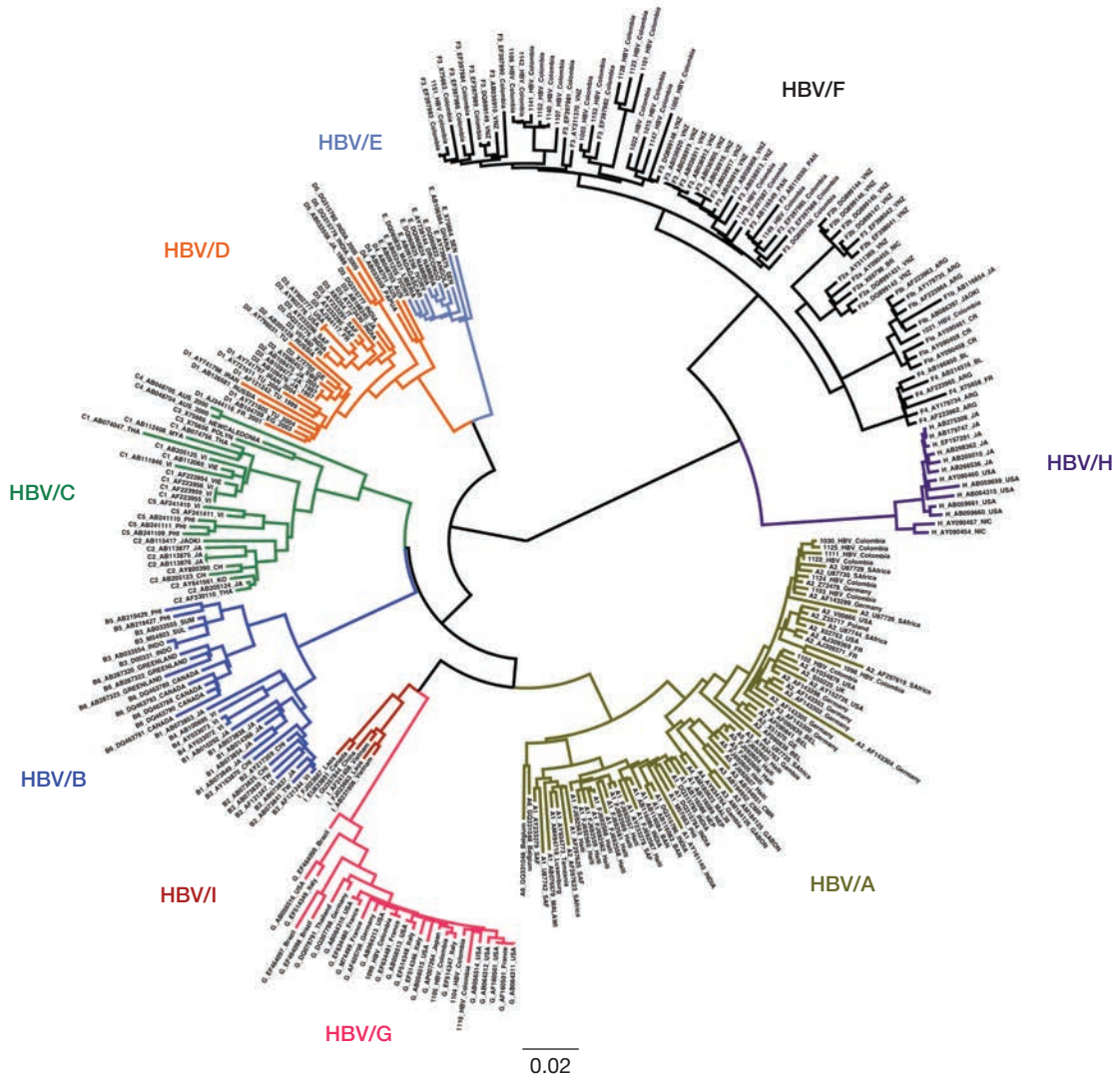
Viral hepatitis is considered one of the major pandemics in the world today and is mainly caused by hepatitis A to E viruses. Chronic hepatitis is caused by HBV, HCV and hepatitis delta virus. HBV infection is a worldwide public health problem affecting approximately 2 billion people, including >350 million chronic carriers worldwide [1]. HBV is classified in the *Orthohepadnavirus* genus of the *Hepadnaviridae* family [2]. HBV has a partial double-stranded DNA genome of approximately 3,200 nucleotides, replicates through a retrotranscription step and contains four partially overlapping open reading frames encoding the polymerase, surface antigens, nucleocapsid (core), hepatitis B e antigen and X protein [3]. Chronic infection may be associated with high or low levels of viral replication, and with severe or absent inflammatory response in the liver [4]. Epidemiological data suggest that 7–12 million Latin Americans are infected with HBV [5]. The routes of transmission in Central and South America are highly variable. An increased prevalence has been reported in individuals ranging from 20–40 years of age, supporting horizontal transmission among adults as the most common route of infection. Moreover, some cultural practices such as tattooing, particularly usual in some Amerindians groups, also contribute to increase the risk of infection [6].

HBV genotypes and subgenotypes

A genetic classification of HBV genotypes based on the comparison of complete HBV genomes identified nine genotypes [3,7] (Figure 1), which are further subdivided in subgenotypes. More than 8% inter-nucleotide divergence in the whole HBV genome is required to define a 'genotype'. A 'subgenotype' is characterized by inter-genotypic divergence between 4% and 8% and is based on the full-length genome. 'Clades' are intra-subgenotype groups with <4% nucleotide divergence. Recently, the definitions for HBV genotype and subgenotype were updated: the inter-divergence between strains to define a genotype decreased from 8% to 7.5% and, together with the percentage of inter-divergence, a 'high bootstrap value' is required as complimentary support to define a separate cluster as a novel subgenotype [8,9].

HBV genotypes and subgenotypes have distinct geographical distribution. There is current discussion regarding whether they are associated with different prognoses, considering the patterns of severity of liver diseases in different populations. Furthermore, global human migrations affect the pattern of genotype distribution, introducing genotypes differing from those found in the original inhabitants.

Figure 1. Maximum clade credibility tree of the nine hepatitis B genotypes



Genotypes A, B, C, D, E, F, G, H and I are show in the tree.

Genotype A

HBV genotype A (HBV/A) is found mainly in Northern and Western Europe, North America and Africa [10,11]. This genotype is subdivided into seven subgenotypes (A1 to A7) [12,13]. Isolates belonging to subgroup A1 have been mostly identified in African populations and their descendants [11,14]. Subgenotype A2 is primarily found among Europeans, whereas subgenotype A3 has been identified in Central and West Africa [15]. Subgenotype A4 was reported in Gambia [14] and subgenotype A5 was reported in Nigeria and among African descendants in Haiti [16]. Subgenotype A6 includes strains from African-Belgian patients from Congo and Rwanda [17] and A7 was found in Rwanda and Cameroon [13]. When a high bootstrap value is required as complimentary support to separate a cluster of novel subgenotypes, there is some criticism of the current classification: subgenotypes A3 to A5 should be classified as 'quasi-subgenotype' A3 while subgenotype A6 should merge to subgenotype A4 [8]. This might also be true for other new subgenotypes described for genotypes B [18] and C [19], which should be carefully analysed before a final definition of their status.

Genotypes B and C

HBV genotypes B (HBV/B) and C (HBV/C) are prevalent in Southeast Asia and the Far East [20,21].

HBV/B may be classified into non-recombinant (Bj/B1 and B6) and recombinant (Ba/B2–B5) types. Non-recombinant genotypes B1 and B6 are mostly found in Japan and Greenland, respectively. Subgenotypes with evidence of recombination with genotype C include B2–B5; B2 is endemic in China and Taiwan, B3 in Indonesia, B4 in Vietnam and B5 in the Philippines [22]. Genotype C is the most prevalent in Asia. Five subgenotypes have been described; subgenotype C1 was found in Southeast Asia, C2 in East Asia, C3 in Polynesia, C4 in Aboriginal people from Australia, and C5 in the Philippines and Vietnam [23]. In Brazil, specifically in the states of São Paulo and Paraná, there was a great migration of descendants of East Asia, therefore, genotypes C (subgenotype C2) and B [24,25] are found in these regions.

Genotype D

HBV genotype D (HBV/D) is predominant in the Mediterranean basin, Middle East and Central Asia [23]. Genotype D was divided in four subgenotypes (D1–D4) [23] found in different continents, spreading particularly around the Mediterranean basin to the Asian continent. New subgenotypes, D5 to D7, were later described in India [26], Indonesia [27] and in the Mediterranean basin [28], respectively.

Genotype E

HBV genotype E (HBV/E) is frequent in West Africa and Central Africa [12]. HBV/E was not found outside of Africa until recently, except for some cases of individuals of African origin. Some studies performed in Afro-descendant populations from Venezuela and Brazil did not find HBV/E among these communities [29,30]. Nevertheless, this genotype was also identified in an African descent community living in Colombia that has not had any known recent contact with the African continent [31]. Genotypes A1 and E are the most frequent in this community and were possibly introduced during periods when slavery existed. The long-term existence of these subgenotypes in this community is also supported by the finding of an HBV recombinant strain subgenotype F3/A1 that was found here for the first time [32]. An extensive review identified recombinants between the following genotypes: A/D, A/E, A/G, A/C, B/C, C/D and C/F, and also interspecies recombinants with viruses found in gibbons and chimpanzees. Some of these intergenotypic HBV recombinants were found in Bolivia, including genotypes A/D, C/B, D/C and F/C [33].

Genotype G

HBV genotype G (HBV/G) was found in several European countries [34] and in the Americas [35], often in coinfection with HIV [36].

Genotypes F and H

HBV genotype F (HBV/F) and H (HBV/H) are found in the Americas, with genotype F described from Alaska to Argentina [23], whereas genotype H has been primarily described in Central America and Mexico [37].

Genotypes I and J

Finally, two new genotypes have been recently characterized: genotype I in Vietnam and Laos [7] and genotype J, from a Japanese patient living in Borneo, which was proposed as a recombinant isolate between human and gibbon viruses [38].

HBV genotypes in Latin America

HBV/F and HBV/H are considered indigenous to the American continents. An HBV strain isolated from the woolly monkey (a New World monkey) is closer to genotype F but with a noteworthy phylogenetic distance from other strains of HBV [23]. Several strains of genotype F have been isolated in different countries in America, particularly among Amerindian populations, and four subgenotypes have been described with genetic divergence among 4.3–6.1% [39]. Although there is a high prevalence of genotype H in Mexico, in other Latin American countries, genotype F prevails with the exception of Brazil, where genotype A is the most prevalent. In each country, there are also other genotypes with varying frequencies, as shown in Figure 2.

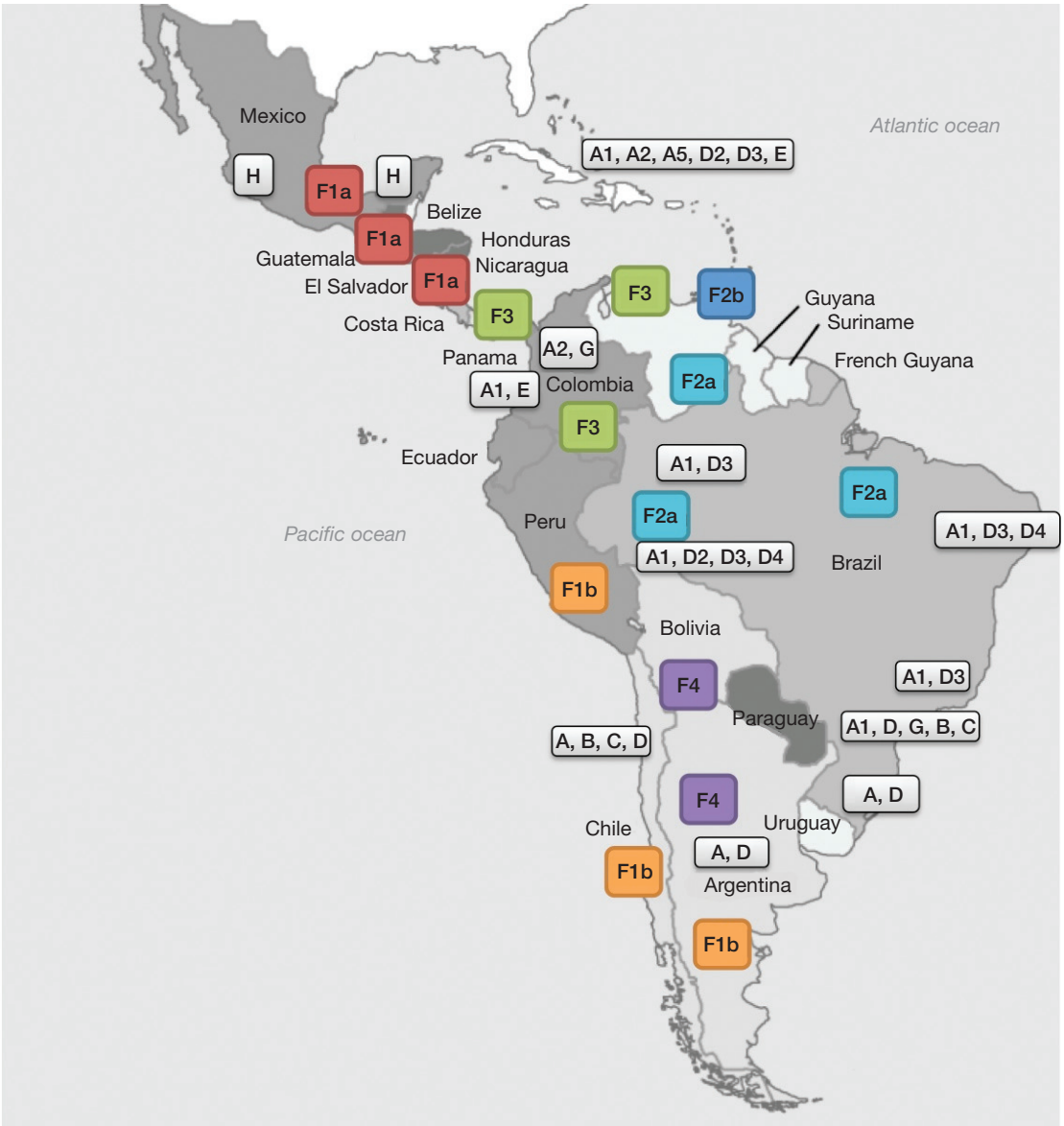
In Mexico, a recent study confirmed a high prevalence of HBV/H and the results also suggest that HBV/G predominates in HBV–HIV-coinfected patients, especially in men who have sex with men, sometimes even in coinfection with HBV/H or HBV/A [40]. HBV/G and HBV/D coinfections were mostly found in patients who were not coinfected with HIV [41].

In Central America, Arauz-Ruiz *et al.* [42] reported HBV genotype distributions from five different countries (Costa Rica, Nicaragua, Honduras, El Salvador and Guatemala). Genotype F was found in 71 (79%), A in 13 (14%), D in 5 (6%) and C in just 1 sample.

Panduro *et al.* [43] provide a more detailed review on genotypes F and H in Mexico and Central America in this issue of *Antiviral Therapy*. Mexico is a low endemic area for HBV, but interestingly, occult hepatitis B infection (OBI) is commonly found in blood donors [44] and in native Amerindians [45].

In a recent study involving Colombian blood donors, the most prevalent subgenotype of HBV was F3 (75%), followed by A2 (15.3%), G (7.7%) and F1b (2%) [46]. Results of phylogenetic analysis carried out in this population suggested that genotype G had several entries in Colombia, because its sequences did not group in the same clade of the phylogenetic tree. Likewise, the presence of only one sequence of subgenotype F1b suggests

Figure 2. Distribution of HBV genotypes in Latin American



The HBV genotype F subgenotype classification is highlighted in the figure. Subgenotype F1a is prevalent in Central America and subgenotype 1b is prevalent in Peru, Chile and Argentina. Subgenotype F2a is prevalent in Brazil and Venezuela and subgenotype F2b was found in Venezuela. Subgenotype F3 is prevalent in Colombia, Panama and Venezuela. Subgenotype F4 was found in Bolivia and Argentina. Distributions of other HBV genotypes are also shown in the map.

that this strain represents virus from regions where this subgenotype is prevalent, such as Chile or Argentina [47].

In Venezuela, the mean morbidity rate of HBV is approximately 3.8 per 100,000 inhabitants. Moreover, Venezuela is classified with an intermediate prevalence of hepatitis B surface antigen (HBsAg) in urban areas, while the Venezuelan Aboriginal population has a high prevalence of HBsAg [48,49]. HBV genotype F has been well-documented as the most prevalent [49,50].

In Venezuela, OBI was found among a Piaroa community, an Amerindian group who exhibit significant evidence of exposure to HBV but a low presence of HBsAg. Of 150 sera, with 17% anti-HBc and 1.3% HBsAg prevalence, 70 were tested for the presence of HBV DNA and 25 (36%) were found positive for HBV DNA by PCR in the core region. Two of these 25 sera were HBsAg-positive, indicating an overt infection. Of the remaining 68 sera tested, 23 exhibited OBI. Sequence analysis in the core region of the amplified DNA products showed that all the strains belonged to HBV genotype F3. The OBI isolates displayed 96–100% nucleotide identity between them [51].

In Brazil, HBV genotype distribution is distinct from its closer Spanish speaking countries as a reflex of the ethnic mixture of the Brazilian population [24,52]. In the urban centres from the Brazilian Amazon, genotype A was the most frequent, followed by genotypes D and F [52,53]. Nevertheless, genotype F is generally the most prevalent genotype in isolated indigenous communities [54]. Furthermore, conversely from the Colombian data cited above, genotype E was only reported in cases of native Africans who came recently to Brazil [55]. Subgenotype A1 has been reported as a genotype prevalent in Quilombo communities in the state of Mato Grosso [56]. Likewise, four cases infected with subgenotype A1 were characterized in a Quilombo community (Frechal) in the state of Maranhão [57]. In the state of Rondônia, this subgenotype was found in 37.1% of cases, while subgenotypes D3 and F2a were found in 22.8% and 20.0%, respectively [58]. Genotypes B and C have also been found in São Paulo and Paraná states, generally in Asian-descent patients [24,59]. A case of genotype C infection was recently identified in a non-Asian-descent Brazilian women who had lived in Japan [25], emphasizing that the presence of rare genotypes in novel regions is frequently increasing due to globalization and the frequent and rapid travels around different world regions. Finally, one case of genotype H in Brazil has also been identified at Paraná, Southern Brazil, but it was not possible to identify the possible routes of transmission [59].

Sequencing of three complete Peruvian genomes showed that HBV subgenotype F1 is found in Peru [60].

Subgenotype F4 was identified in Bolivia in 2006 [61]. More recently, Khan *et al.* [62] determined the HBV distribution in Japanese imimigrants and Bolivians in this country and reported that immigrants might have introduced HBV/B and HBV/C genotypes to natives in Bolivia, who are also exposed to the indigenous HBV/F genotype. This report provides striking evidence for inter-community transmission of HBV revealed by its genotypes.

In Argentina, the presence of genotypes A, D and F was previously reported. Their frequencies varied according to the geographical origin: in the Northern Region, 44 out of the 48 (91.7%) sequences analysed grouped as genotype F, whereas in the Metropolitan Region, the 40 samples grouped as genotype F (30.0%), genotype D (42.5%) and genotype A (27.5%) [63]. A recent study from Buenos Aires detected a differential distribution of genotypes between acute symptomatic and chronic infections. Among the acute cases, genotype F was predominant (65.2%, 30/46) and genotype D was rare (4.3%, 2/46), whereas among the chronic infections a homogeneous distribution of genotypes A (26.8%, 22/82), D (31.7%, 26/82) and F (36.6%, 30/82), with an unusual presence of genotypes B (1.2%, 1/82) and C (3.7%, 3/82) was found [64].

A recent cross-sectional study was carried out in Argentina, including 561 individuals belonging to distinct Amerindian ethnic groups, the Mbyá-Guaraní, the Kolla, the Sagua-Huarpe and the Wichi. The prevalence of HBsAg was 1.7% and 1.4% for the Mbyá-Guaraní and Sagua-Huarpe, respectively. HBV DNA was amplified in 13 out of in 59 reactive samples for anti-HBc total immunoglobulin and/or HBsAg, including 11 identified as OBI. Genotype F was predominant in the Mbyá-Guaraní community with cocirculation of subgenotypes F4, F1b, A2 and D3; subgenotype C2 was only detected among Sagua-Huarpe individuals from the Central Western Region, which may be partially explained by the historical migrations to and from Chile, migrations during the colonial period, and more recently, from China and Japan [65].

In Chile, HBV/F was found to be the most prevalent (84%), whereas genotypes A, B, C and D were found at the frequencies of 3.8%, 3.8%, 6.1% and 2.3%, respectively [66]. Another study showed similar results: genotype F was the most frequent (67.5%), followed by genotypes A, B, C and D [67]. More recently, our group performed phylogenetic analyses of 21 serum samples from antiviral-drug-naive patients with chronic hepatitis B from Santiago, and the results indicated that all sequences were classified as subgenotype F1b and clustered into four different groups, suggesting that diverse lineages of this subgenotype may be circulating within this population of Chilean patients [47].

Origins of genotype F in the Americas

By using Bayesian analyses, it was possible to make inferences about the time points at which the different HBV/F subgenotypes emerged in Latin America [46,68,69]. Subgenotype F3 was reported in Panamá, Venezuela and Colombia [23,39,46]. Alvarado-Mora *et al.* [46] reported subgenotype F3 as the most frequent in the Colombian population, and also determined the time of the most recent common ancestor (tMRCA) for each subgenotype, F1, F2, F3 and F4, circulating in the Americas. As a result, genotype F3 is probably the oldest genotype, and subgenotype F4 is the newest. Likewise, it was observed that subgenotype F3 apparently circulated first in Venezuela then in Colombia. Performing an analysis of nucleotide substitutions peculiar for each of the four subgenotypes of F, it was found that subgenotype F3 has three non-synonymous substitutions (S gene [Glu^{2}] and *Pol* gene [Glu^{359} and Thr^{607}]) in the genome that are not present in the other subgenotypes but are present in genotype H. Thus, it was suggested that the subgenotype F3 is more related to genotype H than any other subgenotype of genotype F.

The emergence of subgenotypes in the Americas would have required favourable transmission circumstances,

including critical host population size, population increase, migration, behavioural patterns, war or civil conflict, for example [68,69]. More recently, Torres *et al*. [69] described in depth the phylogeographical structure of HBV/F (tMRCA=4,393 years), emphasizing the study of subgenotypes F1b and F4, and speculated that during the first viral diversification events, the virus had been transmitted at a low endemic level until the appearance of conditions for further spread. Finally, to date, it has not been possible to infer with certainty when the first HBV/F diversification events took place, or how subgenotypes arose and spread [69].

The issue on the molecular evolution rates of HBV and further studies on the tMRCA for HBV genotypes in the Americas are still open and are discussed in depth in two other manuscripts published in the current issue of *Antiviral Therapy* [70,71].

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Disclosure statement

The authors declare no competing interests.

References

1. Okamoto H, Tsuda F, Sakugawa H, *et al*. Typing hepatitis B virus by homology in nucleotide sequence: comparison of surface antigen subtypes. *J Gen Virol* 1988; **69:**2575–2583.
2. Schaefer S. Hepatitis B virus taxonomy and hepatitis B virus genotypes. *World J Gastroenterol* 2007; **13:**14–21.
3. Magnius LO, Norder H. Subtypes, genotypes and molecular epidemiology of the hepatitis B virus as reflected by sequence variability of the *S*-gene. *Intervirology* 1995; **38:**24–34.
4. Mutimer D. Hepatitis B virus infection: resistance to antiviral agents. *J Clin Virol* 2001; **21:**239–242.
5. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine* 2012; **30:**2212–2219.
6. Te HS, Jensen DM. Epidemiology of hepatitis B and C viruses: a global overview. *Clin Liver Dis* 2010; **14:**1–21.
7. Yu H, Yuan Q, Ge SX, *et al*. Molecular and phylogenetic analyses suggest an additional hepatitis B virus genotype 'I'. *PLoS ONE* 2010; **5:**e9297.
8. Pourkarim MR, Amini-Bavil-Olyaee S, Lemey P, Maes P, Van Ranst M. Are hepatitis B virus 'subgenotypes' defined accurately? *J Clin Virol* 2010; **47:**356–360.
9. Kramvis A, Arakawa K, Yu MC, Nogueira R, Stram DO, Kew MC. Relationship of serological subtype, basic core promoter and precore mutations to genotypes/subgenotypes of hepatitis B virus. *J Med Virol* 2008; **80:**27–46.
10. Bowyer SM, van Staden L, Kew MC, Sim JG. A unique segment of the hepatitis B virus group A genotype identified in isolates from South Africa. *J Gen Virol* 1997; **78:**1719–1729.
11. Kramvis A, Kew MC. Molecular characterization of subgenotype A1 (subgroup Aa) of hepatitis B virus. *Hepatol Res* 2007; **37:**S27–S32.
12. Olinger CM, Venard V, Njayou M, *et al*. Phylogenetic analysis of the precore/core gene of hepatitis B virus genotypes E and A in West Africa: new subtypes, mixed infections and recombinations. *J Gen Virol* 2006; **87:**1163–1173.
13. Hübschen JM, Mbah PO, Forbi JC, *et al*. Detection of a new subgenotype of hepatitis B virus genotype A in Cameroon but not in neighbouring Nigeria. *Clin Microbiol Infect* 2011; **17:**88–94.
14. Hannoun C, Soderstrom A, Norkrans G, Lindh M. Phylogeny of African complete genomes reveals a West African genotype A subtype of hepatitis B virus and relatedness between Somali and Asian A1 sequences. *J Gen Virol* 2005; **86:**2163–2167.
15. Kurbanov F, Tanaka Y, Fujiwara K, *et al*. A new subtype (subgenotype) Ac (A3) of hepatitis B virus and recombination between genotypes A and E in Cameroon. *J Gen Virol* 2005; **86:**2047–2056.
16. Andernach IE, Nolte C, Pape JW, Muller CP. Slave trade and hepatitis B virus genotypes and subgenotypes in Haiti and Africa. *Emerg Infect Dis* 2009; **15:**1222–1228.
17. Pourkarim MR, Lemey P, Amini-Bavil-Olyaee S, Maes P, Van Ranst M. Novel hepatitis B virus subgenotype A6 in African-Belgian patients. *J Clin Virol* 2010; **47:**93–96.
18. Shen T, Gao JM, Zou YL, Dong H, Yan XM. Novel hepatitis B virus subgenotype in the southern Yunnan Province of China. *Intervirology* 2009; **52:**340–346.
19. Mulyanto, Depamede SN, Wahyono A, *et al*. Analysis of the full-length genomes of novel hepatitis B virus subgenotypes C11 and C12 in Papua, Indonesia. *J Med Virol* 2011; **83:**54–64.
20. Sugauchi F, Kumada H, Sakugawa H, *et al*. Two subtypes of genotype B (Ba and Bj) of hepatitis B virus in Japan. *Clin Infect Dis* 2004; **38:**1222–1228.
21. Mahtab MA, Rahman S, Khan M, Karim F. Hepatitis B virus genotypes: an overview. *Hepatobiliary Pancreat Dis Int* 2008; **7:**457–464.
22. Sakamoto T, Tanaka Y, Orito E, *et al*. Novel subtypes (subgenotypes) of hepatitis B virus genotypes B and C among chronic liver disease patients in the Philippines. *J Gen Virol* 2006; **87:**1873–1882.
23. Norder H, Courouce AM, Coursaget P, *et al*. Genetic diversity of hepatitis B virus strains derived worldwide: genotypes, subgenotypes, and HBsAg subtypes. *Intervirology* 2004; **47:**289–309.
24. Sitnik R, Pinho JR, Bertolini DA, Bernardini AP, Da Silva LC, Carrilho FJ. Hepatitis B virus genotypes and precore and core mutants in Brazilian patients. *J Clin Microbiol* 2004; **42:**2455–2460.
25. Alvarado-Mora MV, Santana RA, Sitnik R, *et al*. Full-length genomic sequence of hepatitis B virus genotype C2 isolated from a native Brazilian patient. *Mem Inst Oswaldo Cruz* 2011; **106:**495–498.
26. Chandra PK, Biswas A, Datta S, *et al*. Subgenotypes of hepatitis B virus genotype D (D1, D2, D3 and D5) in India: differential pattern of mutations, liver injury and occult HBV infection. *J Viral Hepat* 2009; **16:**749–756.
27. Utama A, Purwantomo S, Siburian MD, *et al*. Hepatitis B virus subgenotypes and basal core promoter mutations in Indonesia. *World J Gastroenterol* 2009; **15:**4028–4036.
28. Meldal BH, Moula NM, Barnes IH, Boukef K, Allain JP. A novel hepatitis B virus subgenotype, D7, in Tunisian blood donors. *J Gen Virol* 2009; **90:**1622–1628.
29. Quintero A, Martinez D, Alarcon De Noya B, *et al*. Molecular epidemiology of hepatitis B virus in Afro-Venezuelan populations. *Arch Virol* 2002; **147:**1829–1836.
30. Motta-Castro AR, Martins RM, Yoshida CF, *et al*. Hepatitis B virus infection in isolated Afro-Brazilian communities. *J Med Virol* 2005; **77:**188–193.

31. Alvarado Mora MV, Romano CM, Gomes-Gouvea MS, Gutierrez MF, Carrilho FJ, Pinho JR. Molecular epidemiology and genetic diversity of hepatitis B virus genotype E in an isolated Afro-Colombian community. *J Gen Virol* 2010; **91:**501–508.
32. Alvarado Mora MV, Romano CM, Gomes-Gouvea MS, Gutierrez MF, Carrilho FJ, Pinho JR. Phylogenetic analysis of complete genome sequences of hepatitis B virus from Afro-Colombian community: presence of HBV F3/A1 recombinant strain. *Virology Journal* 2011; **54 Suppl 1:**886A.
33. Simmonds P, Midgley S. Recombination in the genesis and evolution of hepatitis B virus genotypes. *J Virol* 2005; **79:**15467–15476.
34. Jardi R, Rodriguez-Frias F, Schaper M, *et al*. Analysis of hepatitis B genotype changes in chronic hepatitis B infection: influence of antiviral therapy. *J Hepatol* 2008; **49:**695–701.
35. Bottecchia M, Souto FJ, Ó KMR, *et al*. Hepatitis B virus genotypes and resistance mutations in patients under long-term lamivudine therapy: characterization of genotype G in Brazil. *BMC Microbiol* 2008; **8:**11.
36. Silva AC, Spina AM, Lemos MF, *et al*. Hepatitis B genotype G and high frequency of lamivudine-resistance mutations among human immunodeficiency virus/hepatitis B virus co-infected patients in Brazil. *Mem Inst Oswaldo Cruz* 2010; **105:**770–778.
37. Arauz-Ruiz P, Norder H, Robertson BH, Magnius LO. Genotype H: a new Amerindian genotype of hepatitis B virus revealed in Central America. *J Gen Virol* 2002; **83:**2059–2073.
38. Tatematsu K, Tanaka Y, Kurbanov F, *et al*. A genetic variant of hepatitis B virus divergent from known human and ape genotypes isolated from a Japanese patient and provisionally assigned to new genotype J. *J Virol* 2009; **83:**10538–10547.
39. Devesa M, Loureiro CL, Rivas Y, *et al*. Subgenotype diversity of hepatitis B virus American genotype F in Amerindians from Venezuela and the general population of Colombia. *J Med Virol* 2008; **80:**20–26.
40. Mata Marín JA, Arroyo Anduiza CI, Calderon GM, *et al*. Prevalence and resistance pattern of genotype G and H in chronic hepatitis B and HIV co-infected patients in Mexico. *Ann Hepatol* 2012; **11:**47–51.
41. Sánchez LV, Tanaka Y, Maldonado M, Mizokami M, Panduro A. Difference of hepatitis B virus genotype distribution in two groups of Mexican patients with different risk factors. High prevalence of genotypes H and G. *Intervirology* 2007; **50:**9–15.
42. Arauz-Ruiz P, Norder H, Visona KA, Magnius LO. Genotype F prevails in HBV infected patients of Hispanic origin in Central America and may carry the precore stop mutant. *J Med Virol* 1997; **51:**305–312.
43. Panduro A, Maldonado-Gonzalez M, Fierro NA, Roman S. Distribution of HBV genotypes F and H in Mexico and Central America. *Antivir Ther* 2013; **18:**475–484.
44. García-Montalvo BM, Ventura-Zapata LP. Molecular and serological characterization of occult hepatitis B infection in blood donors from Mexico. *Ann Hepatol* 2011; **10:**133–141.
45. Roman S, Tanaka Y, Khan A, *et al*. Occult hepatitis B in the genotype H-infected Nahuas and Huichol native Mexican population. *J Med Virol* 2010; **82:**1527–1536.
46. Alvarado-Mora MV, Romano CM, Gomes-Gouvea MS, *et al*. Molecular characterization of the hepatitis B virus genotypes in Colombia: a Bayesian inference on the genotype F. *Infect Genet Evol* 2011; **11:**103–108.
47. Venegas M, Alvarado-Mora MV, Villanueva RA, *et al*. Phylogenetic analysis of hepatitis B virus genotype F complete genome sequences from Chilean patients with chronic infection. *J Med Virol* 2011; **83:**1530–1536.
48. Machado IV, Carvajal J, Mondolfi A, Marcano N, Yarzabal L, Bianco NE. Seroepidemiological differences of HBV infection between urban areas and Amerindian population in Venezuela. In Zuckerman AJ (Editor). *Viral Hepatitis and Liver Disease*. New York: Alan R Liss 1988; pp. 174–176.
49. Devesa M, Pujol FH. Hepatitis B virus genetic diversity in Latin America. *Virus Res* 2007; **127:**177–184.
50. Machado IV, del Pilar Fortes M, Vargas-Lovelle B, *et al*. Genotype F prevails in Venezuelan urban patients with chronic hepatitis B. *Ann Hepatol* 2010; **9:**172–176.
51. Cardona NE, Loureiro CL, Garzaro DJ, *et al*. Unusual presentation of hepatitis B serological markers in an Amerindian community of Venezuela with a majority of occult cases. *Virol J* 2011; **8:**527.
52. Mello FC, Souto FJ, Nabuco LC, *et al*. Hepatitis B virus genotypes circulating in Brazil: molecular characterization of genotype F isolates. *BMC Microbiol* 2007; **7:**103.
53. Moraes MT, Niel C, Gomes SA. A polymerase chain reaction-based assay to identify genotype F of hepatitis B virus. *Braz J Med Biol Res* 1999; **32:**45–49.
54. Castilho MC, Costa de Oliveira CM, Gimaque JB, Leao JD, Braga WS. Epidemiology and molecular characterization of hepatitis B virus infection in isolated villages in the western Brazilian Amazon. *Am J Trop Med Hyg* 2012; **87:**768–774.
55. Sitnik R, Sette H, Jr., Santana RA, *et al*. Hepatitis B virus genotype E detected in Brazil in an African patient who is a frequent traveler. *Braz J Med Biol Res* 2007; **40:**1689–1692.
56. Motta-Castro AR, Martins RM, Araujo NM, *et al*. Molecular epidemiology of hepatitis B virus in an isolated Afro-Brazilian community. *Arch Virol* 2008; **153:**2197–2205.
57. Alvarado-Mora MV, Botelho L, Gomes-Gouvea MS, *et al*. Detection of hepatitis B virus subgenotype A1 in a Quilombo community from Maranhao, Brazil. *Virol J* 2011; **8:**415.
58. Santos AO, Alvarado-Mora MV, Botelho L, *et al*. Characterization of hepatitis B virus (HBV) genotypes in patients from Rondonia, Brazil. *Virol J* 2010; **7:**315.
59. Bertolini DA, Gomes-Gouvea MS, Carvalho-Mello IM, *et al*. Hepatitis B virus genotypes from European origin explains the high endemicity found in some areas from southern Brazil. *Infect Genet Evol* 2012; **12:**1295–1304.
60. von Meltzer M, Vasquez S, Sun J, *et al*. A new clade of hepatitis B virus subgenotype F1 from Peru with unusual properties. *Virus Genes* 2008; **37:**225–230.
61. Huy TT, Ushijima H, Sata T, Abe K. Genomic characterization of HBV genotype F in Bolivia: genotype F subgenotypes correlate with geographic distribution and T(1858) variant. *Arch Virol* 2006; **151:**589–597.
62. Khan A, Tanaka Y, Saito H, *et al*. Transmission of hepatitis virus (HBV) genotypes among Japanese immigrants and natives in Bolivia. *Virus Res* 2008; **132:**174–180.
63. Piñeiro y Leone FG, Pezzano SC, Torres C, *et al*. Hepatitis B virus genetic diversity in Argentina: dissimilar genotype distribution in two different geographical regions; description of hepatitis B surface antigen variants. *J Clin Virol* 2008; **42:**381–388.
64. Pezzano SC, Torres C, Fainboim HA, *et al*. Hepatitis B virus in Buenos Aires, Argentina: genotypes, virological characteristics and clinical outcomes. *Clin Microbiol Infect* 2011; **17:**223–231.
65. Delfino CM, Berini C, Eirin ME, *et al*. New natural variants of hepatitis B virus among Amerindians from Argentina with mainly occult infections. *J Clin Virol* 2012; **54:**174–179.
66. Venegas M, Munoz G, Hurtado C, *et al*. Prevalence of hepatitis B virus genotypes in chronic carriers in Santiago, Chile. *Arch Virol* 2008; **153:**2129–2132.
67. Di Lello FA, Pineiro YLFG, Munoz G, Campos RH. Diversity of hepatitis B and C viruses in Chile. *J Med Virol* 2009; **81:**1887–1894.
68. Holmes EC. Evolutionary history and phylogeography of human viruses. *Annu Rev Microbiol* 2008; **62:**307–328.
69. Torres C, Pineiro y Leone FG, Pezzano SC, Mbayed VA, Campos RH. New perspectives on the evolutionary history of hepatitis B virus genotype F. *Mol Phylogenet Evol* 2011; **59:**114–122.
70. Bouckaert R, Alvarado-Mora MV, Rebello Pinho JR. Evolutionary rates and HBV: issues of rate estimation with Bayesian molecular methods. *Antivir Ther* 2013; **18:**497–503.
71. Godoy BA, Alvarado-Mora MV, Gomes-Gouvêa MS, Rebello Pinho JR, Fagundes NJR. Origin of HBV and its arrival in the Americas – the importance of natural selection on time estimates. *Antivir Ther* 2013; **18:**505–512.

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