

Evolution of Hepatitis B Genotype D in the Middle East and South Asia

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Hepatitis B virus (HBV) has been classified into 8 genotypes, from A to H and there are some hints that the outcome of the disease and the response to therapy might be correlated to these genomic groups (although not as serious as hepatitis C virus [HCV]).

Hepatitis B virus genotypes show a characteristic geographic distribution with a proposed association with human migration. Several scientific fields are employed for the study of human population history, including archaeology, linguistics, anthropology and, recently, genetics. Thanks to the introduction of modern technology into genetics in the past two decades, humans have been facing some very interesting findings about their history. Besides mitochondrial DNA sequence analysis, persistent viruses have opened a new window into this area, especially HBV. But why?

It is of interest that the prevalence of HBV genotypes throughout the world is clearly linked to migration. For example, the ancestors of Eskimos migrated from South East (SE) Asia to the North and passed through the Behring channel to Alaska, which partially explains why there was as high a prevalence of hepatitis B surface antigen (HBsAg) positivity in this area as in SE Asia (1).

Second, in some studies (2-5) from South America, genotypes E and A, which are the dominant types in Africans, were found in an area with genotype F/H dominance. They derived from those with African descent who came into South

America during the slave trading period a few hundred years ago. In our own research (6) in the Pacific region (which is an endemic area with genotype C dominance) we compared HBV surface and core genes with the ones from SE Asian patients and from international databases. The gradient of nucleotide and amino acid variations from west to east in our study were most consistent with the hypothesis of migration of Polynesian people from Southern China through Melanesia and Fiji and their radiation across the Pacific to fill the Polynesian triangle in different times. We also found an interesting association that supported the immigration history of SE Asian ancestors southwards and their colonization in the Pacific islands.

D is the most prevalent and the most distributed genotype. It is found in Western populations, the Indian subcontinent, The Middle East and North of Africa. Genotype D contains 4 subgroups (D1 to D4) and 2 subtypes (ayw2 and ayw3). We have collected all the available data from India (7-18), Bangladesh (Jazayeri, unpublished), Turkey (19-33), Pakistan (34-39), and Iran (40-48). We considered the relationship between the potential genotypes in these countries and their evolution.

We considered the samples from East to West. Our unpublished data on 66 Bangladeshi isolates revealed 4 genotypes (A, B, C and D) with genotype D predominant. In India, genotype D was dominant (67%), but there were other genotypes: A

(22%), C (8 %) and recombination (3%).

In Pakistanis 62 % were genotype D, A (14%), C (6 %), other genotypes (4%) and recombination (10%). However, in Turkey, authors found genotype D as the dominant genotype (87%), 1.3% for both genotypes A and C and recombination 12%. In Iran, interestingly, no other genotype than D has been found.

Why, from west to east, is homogeneity in HBV genotypes lost?

According to archaeological and anthropological findings, the ancestors of Caucasians (Arians) firstly colonized to the North of the Caspian Sea. Because of difficulties in agriculture and climate change, they migrated in three directions: one group moved west towards Europe, another group moved south to Iran (and established the ancient Persian Empire) and the last group migrated to India.

It might be that those people who acquired the virus with the genotype D before their migration, then transmitted the virus generation by generation after their migration. This is why the dominant genotype in India, Iran and most part of the Europe is D.

Why, is there a heterogeneous pattern in the east and a homogenous pattern in the West?

It is likely that selection of HBV genotypes A to H had been occurring in different parts of the world (perhaps related to immune pressure based largely on human leukocyte antigens [HLA] types). After colonization of infected people with certain genotypes, their importation to this area from intermixing of people. Further evolution occurred, giving some of these sequences a distinctive motif, and some genetic recombination between genotypes also occurred, which led to the heterogenous pattern in parts of this area (like Bangladesh, India and Pakistan). In some areas, isolation of people in the absence of intermixing with other genotypes led to a homologous pattern (like Iran and Turkey).

Due to lack of reliable data from other genotype D-dominant countries in The Middle East and North Africa, the analysis of whole data regarding genotype D evolution in the world is not conclusive. In addition, the sample size in some studies from such countries is quite small.

Future studies are needed to carry out work on the prevalence of HBV genotypes in the neighboring countries of this region and comparing

data to the European sequences which might lead to a more precise conclusion.

References

1. McMahon BJ, Lanier AP, Wainwright RB. Hepatitis B and hepatocellular carcinoma in Eskimo/Inuit population. *Int J Circumpolar Health*. 1998;**57** Suppl 1:414-9.
2. 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**(12):1689-92.
3. Mathet VL, Cuestas ML, Ruiz V, et al. Detection of hepatitis B virus (HBV) genotype E carried--even in the presence of high titers of anti-HBs antibodies--by an Argentinean patient of African descent who had received vaccination against HBV. *J Clin Microbiol*. 2006;**44**(9):3435-9.
4. Campos RH, Mbayed VA, Pineiro YLFG. Molecular epidemiology of hepatitis B virus in Latin America. *J Clin Virol*. 2005;**34** Suppl 2:S8-S13.
5. Motta-Castro AR, Martins RM, Yoshida CF, et al. Hepatitis B virus infection in isolated Afro-Brazilian communities. *J Med Virol*. 2005;**77**(2):188-93.
6. Jazayeri MS, Basuni AA, Cooksley G, Locarnini S, Carman WF. Hepatitis B virus genotypes, core gene variability and ethnicity in the Pacific region. *J Hepatol*. 2004;**41**(1):139-46.
7. Biswas A, Chandra PK, Datta S, et al. Frequency and distribution of hepatitis B virus genotypes among eastern Indian voluntary blood donors: Association with precore and basal core promoter mutations. *Hepatol Res*. 2009;**39**(1):53-9.
8. Borkakoty BJ, Mahanta J, Biswas D. Circulating genotypes of hepatitis B virus in Arunachal Pradesh. *Indian J Med Res*. 2008;**127**(1):65-70.
9. Banerjee A, Chandra PK, Datta S, et al. Frequency and significance of hepatitis B virus surface gene variant circulating among 'antiHBc only' individuals in Eastern India. *J Clin Virol*. 2007;**40**(4):312-7.
10. Chauhan R, Kazim SN, Kumar M, Bhattacharjee J, Krishnamoorthy N, Sarin SK. Identification and characterization of genotype A and D recombinant hepatitis B virus from Indian chronic HBV isolates. *World J Gastroenterol*. 2008;**14**(40):6228-36.
11. Chauhan R, Kazim SN, Bhattacharjee J, Sakhuja P, Sarin SK. Basal core promoter, precore region mutations of HBV and their association with e antigen, genotype, and severity of liver disease in patients with chronic hepatitis B in India. *J Med Virol*. 2006;**78**(8):1047-54.
12. Vivekanandan P, Bissett S, Ijaz S, et al. Correlation between hepatitis B genotypes, 1896 precore mutation, virus loads and liver dysfunction in an Indian population. *Indian J Gastroenterol*. 2008;**27**(4):142-7.
13. Chandra PK, Banerjee A, Datta S, Chakravarty R. G1862T mutation among hepatitis B virus-infected individuals: association with viral genotypes and disease outcome in Kolkata, Eastern India. *Intervirology*. 2007;**50**(3):173-80.
14. Kar P, Polipalli SK, Chattopadhyay S, et al. Prevalence of hepatitis B virus genotype D in precore mutants among chronic liver disease patients from New Delhi, India. *Dig Dis Sci*. 2007;**52**(2):565-9.
15. Thakur V, Sarin SK, Rehman S, Guptan RC, Kazim SN, Kumar S. Role of HBV genotype in predicting response to lamivudine therapy in patients with chronic hepatitis B. *Indian J Gastroenterol*. 2005;**24**(1):12-5.

16. Thakur V, Guptan RC, Kazim SN, Malhotra V, Sarin SK. Profile, spectrum and significance of HBV genotypes in chronic liver disease patients in the Indian subcontinent. *J Gastroenterol Hepatol*. 2002;17(2):165-70.
17. Thippavazzula R, Mogili C, Chandra M, Khaja MN, Habeeb MA, Habibullah CM. Prevalent HBV genotypes and subtypes in a South Indian population. *J Clin Virol*. 2006;37(1):58-64.
18. Jazayeri M, Basuni AA, Sran N, et al. HBV core sequence: definition of genotype-specific variability and correlation with geographical origin. *J Viral Hepat*. 2004;11(6):488-501.
19. Bozdayi G, Turkyilmaz AR, Idilman R, et al. Complete genome sequence and phylogenetic analysis of hepatitis B virus isolated from Turkish patients with chronic HBV infection. *J Med Virol*. 2005;76(4):476-81.
20. Bozdayi AM, Aslan N, Bozdayi G, et al. Molecular epidemiology of hepatitis B, C and D viruses in Turkish patients. *Arch Virol*. 2004;149(11):2115-29.
21. Bozdayi AM, Bozkaya H, Turkyilmaz AR, et al. Nucleotide divergences in the core promoter and precore region of genotype D hepatitis B virus in patients with persistently elevated or normal ALT levels. *J Clin Virol*. 2001;21(1):91-101.
22. Bozdayi AM, Uzunalimoglu O, Turkyilmaz AR, et al. YSD: a novel mutation in HBV DNA polymerase confers clinical resistance to lamivudine. *J Viral Hepat*. 2003;10(4):256-65.
23. Kaya S, Cetin ES, Aridogan BC, Onal S, Demirci M. Distribution of hepatitis B virus (HBV) genotypes among HBV carriers in Isparta. *Iran Biomed J*. 2007;11(1):59-63.
24. Sertoz RY, Erensoy S, Pas S, Ozacar T, Niesters H. Restriction fragment length polymorphism analysis and direct sequencing for determination of HBV genotypes in a Turkish population. *New Microbiol*. 2008;31(2):189-94.
25. Ozaslan M, Ozaslan E, Barsgan A, Koruk M. Mutations in the S gene region of hepatitis B virus genotype D in Turkish patients. *J Genet*. 2007;86(3):195-201.
26. Ozgenc O, Ozacar T, Erensoy S, et al. Clinical significance of basal core promoter and precore mutations in chronic hepatitis B. *Hepatogastroenterology*. 2007;54(80):2319-23.
27. Sayiner AA, Ozcan A, Sengonul A. Naturally occurring MHR variants in Turkish patients infected with hepatitis B virus. *J Med Virol*. 2008;80(3):405-10.
28. Senturk H, Tahan V, Canbakan B, et al. Chronic hepatitis C responds poorly to combination therapy in chronic hepatitis B carriers. *Neth J Med*. 2008;66(5):191-5.
29. Aksoy A, Ozdarendeli A. [Genotyping of hepatitis B virus by restriction enzyme analysis]. *Mikrobiyol Bul*. 2006;40(3):215-23.
30. Leblebicioglu H, Eroglu C. Acute hepatitis B virus infection in Turkey: epidemiology and genotype distribution. *Clinical Microbiology & Infection*. 2004;10(6):537-41.
31. Eroglu C, Leblebicioglu H, Gunaydin M, et al. Distinguishing hepatitis B virus (HBV) genotype D from non-D by a simple PCR. *J Virol Methods*. 2004;119(2):183-7.
32. Serin MS, Akkiz H, Abayli B, Oksuz M, Aslan G, Emekdas G. Genotyping of hepatitis B virus isolated from chronic hepatitis B patients in the south of Turkey by DNA cycle-sequencing method. *Diagn Microbiol Infect Dis*. 2005;53(1):57-60.
33. Sunbul M, Leblebicioglu H. Distribution of hepatitis B virus genotypes in patients with chronic hepatitis B in Turkey. *World J Gastroenterol*. 2005;11(13):1976-80.
34. Baig S, Siddiqui AA, Chakravarty R, Moatter T, Unnissa T, Nazr ul H. Phylogenetic analysis of hepatitis B virus in Pakistan. *J Coll Physicians Surg Pak*. 2008;18(11):688-94.
35. Baig S, Siddiqui AA, Ahmed W, Qureshi H, Arif A. The association of complex liver disorders with HBV genotypes prevalent in Pakistan. *Virol J*. 2007;4:128.
36. Alam MM, Zaidi SZ, Shaukat S, et al. Common genotypes of Hepatitis B virus prevalent in injecting drug abusers (addicts) of North West Frontier Province of Pakistan. *Virol J*. 2007;4:63.
37. Alam MM, Zaidi SZ, Malik SA, et al. Molecular epidemiology of Hepatitis B virus genotypes in Pakistan. *BMC Infect Dis*. 2007;7:115.
38. Abbas Z, Muzaffar R, Siddiqui A, Naqvi SA, Rizvi SA. Genetic variability in the precore and core promoter regions of hepatitis B virus strains in Karachi. *BMC Gastroenterol*. 2006;6:20.
39. Idrees M, Khan S, Riazuddin S. Common genotypes of hepatitis B virus. *J Coll Physicians Surg Pak*. 2004;14(6):344-7.
40. Mohebbi SR, Amini-Bavil-Olyae S, Zali N, et al. Molecular epidemiology of hepatitis B virus in Iran. *Clin Microbiol Infect*. 2008;14(9):858-66.
41. Bahramali G, Sadeghizadeh M, Amini-Bavil-Olyae S, et al. Clinical, virologic and phylogenetic features of hepatitis B infection in Iranian patients. *World J Gastroenterol*. 2008;14(35):5448-53.
42. Mojiri A, Behzad-Behbahani A, Saberifirozi M, et al. Hepatitis B virus genotypes in southwest Iran: molecular, serological and clinical outcomes. *World J Gastroenterol*. 2008;14(10):1510-3.
43. Alavian SM, Keyvani H, Rezai M, Ashayeri N, Sadeghi HM. Preliminary report of hepatitis B virus genotype prevalence in Iran. *World J Gastroenterol*. 2006;12(32):5211-3.
44. Amini-Bavil-Olyae S, Sarrami-Forooshani R, Adeli A, et al. Complete genomic sequence and phylogenetic relatedness of hepatitis B virus isolates from Iran. *J Med Virol*. 2005;76(3):318-26.
45. Amini-Bavil-Olyae S, Sarrami-Forooshani R, Mahboudi F, et al. Genotype characterization and phylogenetic analysis of hepatitis B virus isolates from Iranian patients. *J Med Virol*. 2005;75(2):227-34.
46. Goodarzi Z, Malekzadeh R, Montazeri G, et al. Phylogenetic Analysis of HBV Based on PreS Region in Iranian Hepatocellular Carcinoma Patients. *Hep Mon*. 2007;7(4):201-5.
47. Mohamadkhani A, Poustchi H, Montazeri Gh E, Malekzadeh R. Clinical significance of precore and core promoter mutations in genotype D hepatitis B-related chronic liver disease. *Govaresh*. 2007;12:36-42.
48. Veazjalali M, Norder H, Magnus L, Jazayeri SM, Alavian SM, Mokhtari Azad T. A new core promoter mutation and premature stop codon in the S gene in HBV strains from Iranian patients with cirrhosis. *J Viral Hepat*. In Press.