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Contents

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Contents

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Peer Reviewer of *World Journal of Gastrointestinal Oncology*, Lie Zheng, Director, Professor, Department of Gastroenterology, Shaanxi Provincial Hospital of Traditional Chinese Medicine, Xi'an 730000, Shaanxi Province, China. xinliwen696@126.com

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EDITORIAL

Hepatitis B virus genotypes in precision medicine of hepatitis B-related hepatocellular carcinoma: Where we are now

Caecilia H C Sukowati, Sri Jayanti, Turyadi Turyadi, David H Muljono, Claudio Tiribelli

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Caecilia H C Sukowati, Sri Jayanti, Turyadi Turyadi, Eijkman Research Center for Molecular Biology, Research Organization for Health, National Research and Innovation Agency of Indonesia, Jakarta 10340, Indonesia

Caecilia H C Sukowati, Claudio Tiribelli, Liver Cancer Unit, Fondazione Italiana Fegato ONLUS, Trieste 34149, Italy

David H Muljono, Faculty of Medicine, Hasanuddin University, Makassar 90245, South Sulawesi, Indonesia

David H Muljono, Faculty of Medicine and Health, University of Sydney, Sydney 2050, Australia

Corresponding author: Caecilia H C Sukowati, PhD, Senior Scientist, Liver Cancer Unit, Fondazione Italiana Fegato ONLUS, AREA Science Park Campus Basovizza, SS14, km 163.5, Trieste 34149, Italy. caecilia.sukowati@fegato.it

Abstract

Hepatitis B virus (HBV) infection is a major player in chronic hepatitis B that may lead to the development of hepatocellular carcinoma (HCC). HBV genetics are diverse where it is classified into at least 9 genotypes (A to I) and 1 putative genotype (J), each with specific geographical distribution and possible different clinical outcomes in the patient. This diversity may be associated with the precision medicine for HBV-related HCC and the success of therapeutical approaches against HCC, related to different pathogenicity of the virus and host response. This Editorial discusses recent updates on whether the classification of HBV genetic diversity is still valid in terms of viral oncogenicity to the HCC and its precision medicine, in addition to the recent advances in cellular and molecular biology technologies.

Key Words: Hepatitis B virus; Hepatocellular carcinoma; Genotypes; Pathogenesis; Precision medicine

Core Tip: This article discusses recent updates on the classification of hepatitis B virus (HBV) based on its genetic diversity (genotype) and its relationship with current data in HBV pathogenicity, hepatocellular carcinoma (HCC), and HCC treatment.

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INTRODUCTION

Hepatitis B virus (HBV) infection is a major player in chronic hepatitis B, liver fibrosis and cirrhosis, and finally in the development of hepatocellular carcinoma (HCC). Data from World Health Organization fact sheet estimated that in 2019 around 300 million people were living with chronic hepatitis B (CHB) infection with 1.5 million new infections each year. HBV infection led to an estimated 820000 deaths, mostly from liver cirrhosis and HCC[1], accounting for around 50% of HCC cases globally[2]. Even though highly effective vaccination against hepatitis B is available and even mandatory in many countries, chronic HBV infection remains the major cause of mortality[3].

The pathogenesis of HBV in triggering sequent liver damage occurs in an indirect mechanism related to necro-inflammation and immunological response of the host, leading to liver fibrosis and cirrhosis. However, being a DNA virus, HBV can directly cause oncogenic transformation where HBV DNA fragments might integrate into human DNA at the early steps of clonal tumor expansion. This integration may induce host genomic instability and insertional mutagenesis of diverse oncogenes[4], as we previously reviewed[5].

On the other hand, HCC itself, within the same patient and among patients, is very heterogeneous in terms of natural history, molecular classification, histology, and cellular profile. This influences disease progression, classification of the disease, prognosis, and cellular natural susceptibility to drugs[6]. This is associated with the success of cancer therapy. In this era of precision medicine, therapeutical approaches for HBV-related HCC can also be influenced by the genomic heterogeneity of the HBV. This Editorial discusses recent updates on whether the classification of HBV genetic diversity is still valid in terms of viral pathogenicity to the HCC and its treatment.

HBV GENOTYPES

HBV belongs to the *Hepadnaviridae* family with around 3.2 kilobases of compact and partially double-stranded genome. HBV genome consists of four overlapping open reading frames in the HBV genome: P, S, C, and X, each encodes for different protein(s) important in viral replication and pathogenesis[7]. In various aspects, HBV is unique including its genetic material, genome organization, genome replication, and genetic control[8].

Based on genome-wide sequence divergence of at least 7.5%, HBV is classified into nine genotypes (A–I) and one putative genotype (J). Except for genotypes E, G, and putative J, all HBV genotypes are also further subdivided into subgenotypes, with DNA divergence between 4 and 7.5%[9,10]. Among these, genotypes A to E account for about 96.2% of all global chronic hepatitis B[11], thus the main genotypes found in HCC.

HBV genotypes are related to geographic distributions, ethno-geographic ranges, population migration, and HBV evolution[12]. Genotype A (HBV/A), divided into subgenotypes A1 to A8, is distributed in northern and northwestern Europe, South Africa, and Brazil, and includes. HBV/B, divided into subgenotypes B1 to B10, is found primarily in Asia and the Arctic. HBV/C, composed of subgenotypes C1 to C17, is primarily distributed in the Pacific islands, and HBV/D, consisting of D1 to D12, is widely distributed in the Mediterranean, India, and Russia. HBV/E and HBV/F are distributed in the African continent, where E is restricted to West and Central Africa while F is mainly distributed all over Africa and includes subgenotypes F1 to F6. HBV/G is widespread in Europe, America, Africa, and Asia. HBV/H is mainly distributed in America. HBV/I is mainly distributed in Asia, Vietnam, Laos, southwestern China, and eastern India, and includes subgenotypes I1 to I3. HBV/J was recently found in Japan[10,13].

HBV GENOTYPES AND PATHOGENESIS TO HCC

Following the classification of HBV genotypes, studies to understand the association between HBV genotypes and the progression of chronic liver diseases, especially for HCC, have also been attempted. Since HCC development is complex involving long-term progression, the results, as expected, are varied. In addition, HBV genotypes are also linked with core and basal core promoter (BCP) mutations. It was shown that the core promoter and BCP A1762T/G1764A mutation usually occurs nearly 10 years before the identification of HCC and may be an early episode of hepatocarcinogenesis[14].

For the last 2 decades, various studies have been performed in several regions, especially in China, India, and Alaska, showing in particular the association between HBV genotypes and HCC occurrence. One of the earliest studies showed

that from 154 HCC case patients, followed in 14 years from around 4800 HBV carriers in Taiwan, HBV/C was associated with an increased risk of HCC compared with other HBV/A and HBV/B (adjusted OR = 5.11), strongly associated with higher plasma HBV DNA levels[15]. This study on the risk of HBV/C was then confirmed by several other reports in Asian populations, including in mainland China, Vietnam, and Japan, also in the last five years[16-21]. However, a study in China showed that a heterozygous mutation status of reverse transcriptase rt169/rt180 was associated with the increased risk of HCC, regardless of HBV genotypes[22].

In the Alaskan population, several studies showed that the HCC risk was higher for HBV/F, followed by HBV/C and HBV/A, compared to HBV/B and HBV/D[23,24]. In the Indian population, however, HBV/D was the predominant genotype associated with HCC cases[25], even though another study showed that patients with HBV/A and HBV/D showed similarities in clinical, histological severity, and therapeutic responses[26]. A study in Africa showed that carriers of HBV/A1 and HBV/E display unique clinical features. Even though HBV/E-infected individuals had high HBV viral loads, and transmitted HBV perinatally, HBV/A1-infected individuals with low viral loads and horizontal transmission, exhibited a higher extent of liver damage and a higher risk of developing HCC[27].

Here, we need to emphasize, that the above studies were majorly country-based, analyzing the predominant genotypes that exist within countries, thus limiting a direct comparison comprising a larger number of samples with all (or almost all genotypes) from a wider geographical area. However, as previously demonstrated by Wong *et al*[28], a meta-analysis study analyzing 43 studies with a total of 14545 patients with HBV genotypes of A to H, still showed that HBV/C was associated with a higher risk of HCC as compared with other major HBV genotypes A, B, and D. This partially explains the higher risk of HCC in patients from Southeast Asia, where HBV/C is predominant. The patient was infected with HBV/C, often at higher risk for more active liver disease and cirrhosis[28].

PRECISION MEDICINE FOR HBV-RELATED HCC

Patients with distinct HBV genotypes experienced varying prognosis, immune responses, and clinical symptoms, consequently influencing hepatitis B e antigen (HBeAg) seroconversion, hepatitis B surface antigen (HBsAg) seroclearance, and resistance to antiviral drugs[13,29]. Connections have been noted between the risk of HCC in youth and HBV/B, as well as, in later stages of life, with genotype C. Even specifically, associations have been observed among subgenotypes and HCC risk with subgenotype Ba in younger individuals and subgenotype Ce in those at a more advanced age[30].

To date, the sole recourse to prevent or delay the onset of HCC in individuals with CHB is antiviral therapy. Interferon-alpha (IFN-α) and nucleosides/nucleotide analogues [NUCs, *e.g*. entecavir (ETV), tenofovir (TDF)] are the treatment modalities currently available for chronic HBV infection[31,32]. Nevertheless, it is important to note that treatment responses can vary among different HBV genotypes.

HBV/B and HBV/E were categorized as strong responders for IFN-α and NUCs meanwhile HBV/C and HBV/D were weak responders for both therapeutic approaches[33]. HBV/A patients showed better virological responses after IFN-α treatment with 62.5% of HBV DNA reduction compared to HBV/B, HBV/C, and HBV/E. Furthermore, the rates of HBsAg clearance following IFN-α treatment exhibited variability across genotypes. Notably, HBV/A and HBV/B demonstrated clearance rates at 22% and 33%, respectively, surpassing HBV/C and HBV/E at 0%[34]. Meanwhile, the pegylated IFN (peg-IFN) treatment still showed good treatment response among CHB children with HBV/C by giving 67% of HBeAg seroconversion[35], which is twice higher than adults[36], indicating the use of peg-IFN was still effective for children with chronic HBV/C infection. Meanwhile, treatment responses also manifested in the utilization of different NUCs among West African patients with CHB. In a comprehensive 5-year cohort study involving CHB patients with genotype E, it was observed that TDF demonstrates superior suppression of HBsAg and HBV DNA compared to ETV [34].

As the efficacy of currently available treatment varies among the genotypes, several novel therapies have emerged to tackle the issue. Genotype-specific effects were evident in the current utilization of a therapeutic vaccine called NASVAC containing HBsAg and hepatitis B core antigen (HBcAg) from HBV/A. In clinical trials, NASVAC demonstrated superior efficacy compared to Peg-IFN in reducing HBV DNA levels. This effect was particularly pronounced among CHB patients with HBV/D, as opposed to those with HBV/A and HBV/C[37]. In the HBV genotype humanized model, the use of core protein allosteric modulators efficiently inhibited HBeAg secretion for HBV/A, HBV/B, HBV/D, and HBV/E compared to ETV. However, it did not demonstrate significant advantages over ETV in suppressing HBV DNA[38].

PERSPECTIVE IN MOLECULAR AND CELLULAR BIOTECHNOLOGY

Advances in biotechnology and molecular biology continue to elucidate further characterization of both the pathogen (HBV) and the host (human liver cells). A robust approach to studying the pathogenicity and searching for treatment related to HBV genotypes is by taking advantage of *in vitro* and *in vivo* manipulation of the virus, as well as in animal models.

To understand how each genotype may act differently, several recent studies by the group of Zhang *et al*[39] successfully produced stable cell lines producing high titers of HBV genotype A2, B2, C1, E, F1b, and H by transfecting plasmids in permissive HepG2 cells. They showed differences in genotype-associated variations in viral antigen production, infection kinetics, and responses to human IFN-α treatment[39]. This study was then followed by a deeper analysis of the replicative capacity of infectious patient-derived HBV clones covering genotypes A to E. All clones

produced viral particles, and they were infectious in HepG2-sodium taurocholate co-transporting polypeptide (NTCP) cells, primary human hepatocytes, and human chimeric mice. However, among genotypes, HBV/D exhibited higher infectivity than other genotypes in vitro, although it was comparable to HBV/A and HBV/B *in vivo*. Together with HBV/A, HBV/D also induced more pronounced intrahepatic and proinflammatory cytokine responses leading to a rapid clearance[38]. Previously, it was shown that HBV/C could generate more reactive oxygen species and DNA double-strand breaks than HBV/D in Huh7 and HepG2[40].

Liu *et al*[38] have demonstrated how HBV genotypes affect host immune responses by using human-derived HBV genotype clones transfected in hepatic cell lines as well as *in vivo* (chimeric mice). Mice exposed to HBV/A and HBV/D exhibit a more noticeable inflammatory reaction, by increasing proinflammatory cytokines (IFN-γ, tumor necrosis factor-α, interleukin-6) and chemokines (CCL2 and CXCL10), in comparison to HBV/B, HBV/C, and HBV/E[38].

The pan-D-subgenotypes reverse transcriptase inhibitor had also been identified as a potent anti-HBV agent, demonstrating consistent inhibitory effects across various HBV/D-subgenotypes in vitro. This suggested the possibility of further optimization, making it a promising drug candidate for treating HBV/D-infected patients, regardless of the specific D-subgenotypes[41].

Recently, an RNA interference therapy also emerged for CHB. VIR-2218 is an experimental N-acetylgalactosamine–conjugated RNA interference therapeutic to treat chronic HBV infection. The treatment targets a region in the HBV genome common to all viral transcripts, making it effective against HBV genotypes A to J[42]. In participants with CHB infection, VIR-2218 demonstrated dose-dependent decreases in HBsAg levels. Nonetheless, none of the participants exhibited serum HBsAg loss or hepatitis B surface antibody seroconversion[43].

CONCLUSION

To conclude, as previously documented, HBV is an ancient virus with deep ancestry where its diversity is generated by features of the unique viral replication cycle as well as by cellular host factors[44]. Thus, besides the variation of the HBV genome itself, the clinical outcome of developing HCC can be influenced by the genetic background of the host. Human genetic polymorphisms that are associated with HBV clearance and persistent infection were reviewed previously[45]. Since the discovery of NTCP, as the cellular receptor for HBV entry into host hepatocytes[46], several recent studies also showed that the NTCP S267F variant exhibited protective effects against HBV was associated with a reduced risk of LC and HCC[47,48].

Until now, even though the association between HBV genotypes, pathogenicity, and precision medicine for HCC is still debatable, the variability of treatment responses tends to emphasize the significance of HBV genotypes in clinical outcomes. We consider that HBV genotype might be put into account as one of the different factors to predict the outcome of the disease. This can also be an additional information in determining the choice of treatment when possible. However, the implication of this approach for a widely used practice is still challenged by the limitation of facilities, the cost of HBV genotyping, and the high cost of treatment, especially in low-middle-income countries.

FOOTNOTES

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ORCID number: Caecilia H C Sukowati 0000-0001-9699-7578; Sri Jayanti 0000-0003-4554-504X; Turyadi Turyadi 0000-0002-1388-4920; David H Muljono 0000-0002-5542-106X; Claudio Tiribelli 0000-0001-6596-7595.

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REFERENCES

1 **Tu T**, Block JM, Wang S, Cohen C, Douglas MW. The Lived Experience of Chronic Hepatitis B: A Broader View of Its Impacts and Why We Need a Cure. *Viruses* 2020; **12** [PMID: 32392763 DOI: 10.3390/v12050515]

2 **Llovet JM**, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, Lencioni R, Koike K, Zucman-Rossi J, Finn RS. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2021; **7**: 6 [PMID: 33479224 DOI: 10.1038/s41572-020-00240-3]

3 **Zhou K**, Dodge JL, Grab J, Poltavskiy E, Terrault NA. Mortality in adults with chronic hepatitis B infection in the United States: a population-based study. *Aliment Pharmacol Ther* 2020; **52**: 382-389 [PMID: 32432816 DOI: 10.1111/apt.15803]

4 **Levrero M**, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. *J Hepatol* 2016; **64**: S84-S101 [PMID: 27084040 DOI: 10.1016/j.jhep.2016.02.021]

5 **Sukowati CH**, El-Khobar KE, Ie SI, Anfuso B, Muljono DH, Tiribelli C. Significance of hepatitis virus infection in the oncogenic initiation of hepatocellular carcinoma. *World J Gastroenterol* 2016; **22**: 1497-1512 [PMID: 26819517 DOI: 10.3748/wjg.v22.i4.1497]

6 **Cabral LKD**, Tiribelli C, Sukowati CHC. Sorafenib Resistance in Hepatocellular Carcinoma: The Relevance of Genetic Heterogeneity. *Cancers (Basel)* 2020; **12** [PMID: 32549224 DOI: 10.3390/cancers12061576]

7 **Geng M**, Xin X, Bi LQ, Zhou LT, Liu XH. Molecular mechanism of hepatitis B virus X protein function in hepatocarcinogenesis. *World J Gastroenterol* 2015; **21**: 10732-10738 [PMID: 26478665 DOI: 10.3748/wjg.v21.i38.10732]

8 **Datta S**, Chatterjee S, Veer V, Chakravarty R. Molecular biology of the hepatitis B virus for clinicians. *J Clin Exp Hepatol* 2012; **2**: 353-365 [PMID: 25755457 DOI: 10.1016/j.jceh.2012.10.003]

9 **Toyé RM**, Loureiro CL, Jaspe RC, Zoulim F, Pujol FH, Chemin I. The Hepatitis B Virus Genotypes E to J: The Overlooked Genotypes. *Microorganisms* 2023; **11** [PMID: 37630468 DOI: 10.3390/microorganisms11081908]

10 **Kramvis A**. Genotypes and genetic variability of hepatitis B virus. *Intervirology* 2014; **57**: 141-150 [PMID: 25034481 DOI: 10.1159/000360947]

11 **Velkov S**, Ott JJ, Protzer U, Michler T. The Global Hepatitis B Virus Genotype Distribution Approximated from Available Genotyping Data. *Genes (Basel)* 2018; **9** [PMID: 30326600 DOI: 10.3390/genes9100495]

12 **Kocher A**, Papac L, Barquera R, Key FM, Spyrou MA, Hübler R, Rohrlach AB, Aron F, Stahl R, Wissgott A, van Bömmel F, Pfefferkorn M, Mittnik A, Villalba-Mouco V, Neumann GU, Rivollat M, van de Loosdrecht MS, Majander K, Tukhbatova RI, Musralina L, Ghalichi A, Penske S, Sabin S, Michel M, Gretzinger J, Nelson EA, Ferraz T, Nägele K, Parker C, Keller M, Guevara EK, Feldman M, Eisenmann S, Skourtanioti E, Giffin K, Gnecchi-Ruscone GA, Friederich S, Schimmenti V, Khartanovich V, Karapetian MK, Chaplygin MS, Kufterin VV, Khokhlov AA, Chizhevsky AA, Stashenkov DA, Kochkina AF, Tejedor-Rodríguez C, de Lagrán ÍG, Arcusa-Magallón H, Garrido-Pena R, Royo-Guillén JI, Nováček J, Rottier S, Kacki S, Saintot S, Kaverzneva E, Belinskiy AB, Velemínský P, Limburský P, Kostka M, Loe L, Popescu E, Clarke R, Lyons A, Mortimer R, Sajantila A, de Armas YC, Hernandez Godoy ST, Hernández-Zaragoza DI, Pearson J, Binder D, Lefranc P, Kantorovich AR, Maslov VE, Lai L, Zoledziewska M, Beckett JF, Langová M, Danielisová A, Ingman T, Atiénzar GG, de Miguel Ibáñez MP, Romero A, Sperduti A, Beckett S, Salter SJ, Zilivinskaya ED, Vasil'ev DV, von Heyking K, Burger RL, Salazar LC, Amkreutz L, Navruzbekov M, Rosenstock E, Alonso-Fernández C, Slavchev V, Kalmykov AA, Atabiev BC, Batieva E, Calmet MA, Llamas B, Schultz M, Krauß R, Jiménez-Echevarría J, Francken M, Shnaider S, de Knijff P, Altena E, Van de Vijver K, Fehren-Schmitz L, Tung TA, Lösch S, Dobrovolskaya M, Makarov N, Read C, Van Twest M, Sagona C, Ramsl PC, Akar M, Yener KA, Ballestero EC, Cucca F, Mazzarello V, Utrilla P, Rademaker K, Fernández-Domínguez E, Baird D, Semal P, Márquez-Morfín L, Roksandic M, Steiner H, Salazar-García DC, Shishlina N, Erdal YS, Hallgren F, Boyadzhiev Y, Boyadzhiev K, Küßner M, Sayer D, Onkamo P, Skeates R, Rojo-Guerra M, Buzhilova A, Khussainova E, Djansugurova LB, Beisenov AZ, Samashev Z, Massy K, Mannino M, Moiseyev V, Mannermaa K, Balanovsky O, Deguilloux MF, Reinhold S, Hansen S, Kitov EP, Dobeš M, Ernée M, Meller H, Alt KW, Prüfer K, Warinner C, Schiffels S, Stockhammer PW, Bos K, Posth C, Herbig A, Haak W, Krause J, Kühnert D. Ten millennia of hepatitis B virus evolution. *Science* 2021; **374**: 182-188 [PMID: 34618559 DOI: 10.1126/science.abi5658]

13 **Chen J**, Li L, Yin Q, Shen T. A review of epidemiology and clinical relevance of Hepatitis B virus genotypes and subgenotypes. *Clin Res Hepatol Gastroenterol* 2023; **47**: 102180 [PMID: 37479136 DOI: 10.1016/j.clinre.2023.102180]

14 **Kumar R**. Review on hepatitis B virus precore/core promoter mutations and their correlation with genotypes and liver disease severity. *World J Hepatol* 2022; **14**: 708-718 [PMID: 35646275 DOI: 10.4254/wjh.v14.i4.708]

15 **Yu MW**, Yeh SH, Chen PJ, Liaw YF, Lin CL, Liu CJ, Shih WL, Kao JH, Chen DS, Chen CJ. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. *J Natl Cancer Inst* 2005; **97**: 265-272 [PMID: 15713961 DOI: 10.1093/jnci/dji043]

16 **Chan HL**, Tse CH, Mo F, Koh J, Wong VW, Wong GL, Lam Chan S, Yeo W, Sung JJ, Mok TS. High viral load and hepatitis B virus subgenotype ce are associated with increased risk of hepatocellular carcinoma. *J Clin Oncol* 2008; **26**: 177-182 [PMID: 18182659 DOI: 10.1200/JCO.2007.13.2043]

17 **Yin J**, Zhang H, He Y, Xie J, Liu S, Chang W, Tan X, Gu C, Lu W, Wang H, Bi S, Cui F, Liang X, Schaefer S, Cao G. Distribution and hepatocellular carcinoma-related viral properties of hepatitis B virus genotypes in Mainland China: a community-based study. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 777-786 [PMID: 20160279 DOI: 10.1158/1055-9965.EPI-09-1001]

18 **Yin J**, Zhang H, Li C, Gao C, He Y, Zhai Y, Zhang P, Xu L, Tan X, Chen J, Cheng S, Schaefer S, Cao G. Role of hepatitis B virus genotype mixture, subgenotypes C2 and B2 on hepatocellular carcinoma: compared with chronic hepatitis B and asymptomatic carrier state in the same area. *Carcinogenesis* 2008; **29**: 1685-1691 [PMID: 18192693 DOI: 10.1093/carcin/bgm301]

19 **Chan HL**, Tsang SW, Liew CT, Tse CH, Wong ML, Ching JY, Leung NW, Tam JS, Sung JJ. Viral genotype and hepatitis B virus DNA levels are correlated with histological liver damage in HBeAg-negative chronic hepatitis B virus infection. *Am J Gastroenterol* 2002; **97**: 406-412 [PMID: 11866280 DOI: 10.1111/j.1572-0241.2002.05478.x]

20 **Hoan NX**, Hoechel M, Tomazatos A, Anh CX, Pallerla SR, Linh LTK, Binh MT, Sy BT, Toan NL, Wedemeyer H, Bock CT, Kremsner PG, Meyer CG, Song LH, Velavan TP. Predominance of HBV Genotype B and HDV Genotype 1 in Vietnamese Patients with Chronic Hepatitis. *Viruses* 2021; **13** [PMID: 33671832 DOI: 10.3390/v13020346]

21 **Mahmood S**, Niiyama G, Kamei A, Izumi A, Nakata K, Ikeda H, Suehiro M, Kawanaka M, Togawa K, Yamada G. Influence of viral load and genotype in the progression of Hepatitis B-associated liver cirrhosis to hepatocellular carcinoma. *Liver Int* 2005; **25**: 220-225 [PMID: 15780042 DOI: 10.1111/j.1478-3231.2005.01077.x]

22 **Wang W**, Shu Y, Bao H, Zhao W, Wang W, Wang Q, Lei X, Cui D, Yan Z. Genotypes and Hot Spot Mutations of Hepatitis B Virus in Northwest Chinese Population and Its Correlation with Diseases Progression. *Biomed Res Int* 2019; **2019**: 3890962 [PMID: 31886206 DOI: 10.1155/2019/3890962]

23 **Livingston SE**, Simonetti JP, McMahon BJ, Bulkow LR, Hurlburt KJ, Homan CE, Snowball MM, Cagle HH, Williams JL, Chulanov VP. Hepatitis B virus genotypes in Alaska Native people with hepatocellular carcinoma: preponderance of genotype F. *J Infect Dis* 2007; **195**: 5-11 [PMID: 17152003 DOI: 10.1086/509894]

24 **McMahon BJ**, Bruden D, Bruce MG, Livingston S, Christensen C, Homan C, Hennessy TW, Williams J, Sullivan D, Rosen HR, Gretch D. Adverse outcomes in Alaska natives who recovered from or have chronic hepatitis C infection. *Gastroenterology* 2010; **138**: 922-31.e1 [PMID: 19909749 DOI: 10.1053/j.gastro.2009.10.056]

25 **Asim M**, Malik A, Sarma MP, Polipalli SK, Begum N, Ahmad I, Khan LA, Husain SA, Akhtar N, Husain S, Thayumanavan L, Singla R, Kar P. Hepatitis B virus BCP, Precore/core, X gene mutations/genotypes and the risk of hepatocellular carcinoma in India. *J Med Virol* 2010; **82**: 1115-1125 [PMID: 20513073 DOI: 10.1002/jmv.21774]

26 **Madan K**, Batra Y, Sreenivas V, Mizokami M, Tanaka Y, Chalamalasetty SB, Panda SK, Acharya SK. HBV genotypes in India: do they influence disease severity? *Hepatol Res* 2009; **39**: 157-163 [PMID: 19208036 DOI: 10.1111/j.1872-034X.2008.00417.x]

27 **Maepa MB**, Ely A, Kramvis A, Bloom K, Naidoo K, Simani OE, Maponga TG, Arbuthnot P. Hepatitis B Virus Research in South Africa. *Viruses* 2022; **14** [PMID: 36146747 DOI: 10.3390/v14091939]

28 **Wong GL**, Chan HL, Yiu KK, Lai JW, Chan VK, Cheung KK, Wong EW, Wong VW. Meta-analysis: The association of hepatitis B virus genotypes and hepatocellular carcinoma. *Aliment Pharmacol Ther* 2013; **37**: 517-526 [PMID: 23305043 DOI: 10.1111/apt.12207]

29 **Athamneh RY**, Arıkan A, Sayan M, Mahafzah A, Sallam M. Variable Proportions of Phylogenetic Clustering and Low Levels of Antiviral Drug Resistance among the Major HBV Sub-Genotypes in the Middle East and North Africa. *Pathogens* 2021; **10** [PMID: 34684283 DOI: 10.3390/pathogens10101333]

30 **Fernandes da Silva C**, Keeshan A, Cooper C. Hepatitis B virus genotypes influence clinical outcomes: A review. *Can Liver J* 2023; **6**: 347-352 [PMID: 38020195 DOI: 10.3138/canlivj-2023-0003]

31 **Kim SW**, Yoon JS, Lee M, Cho Y. Toward a complete cure for chronic hepatitis B: Novel therapeutic targets for hepatitis B virus. *Clin Mol Hepatol* 2022; **28**: 17-30 [PMID: 34281294 DOI: 10.3350/cmh.2021.0093]

32 **European Association for the Study of the Liver**. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]

33 **Duraisamy GS**, Bhosale D, Lipenská I, Huvarova I, Růžek D, Windisch MP, Miller AD. Advanced Therapeutics, Vaccinations, and Precision Medicine in the Treatment and Management of Chronic Hepatitis B Viral Infections; Where Are We and Where Are We Going? *Viruses* 2020; **12** [PMID: 32906840 DOI: 10.3390/v12090998]

34 **Boglione L**, D'Avolio A, Cariti G, Milia MG, Simiele M, De Nicolò A, Ghisetti V, Di Perri G. Sequential therapy with entecavir and PEG-INF in patients affected by chronic hepatitis B and high levels of HBV-DNA with non-D genotypes. *J Viral Hepat* 2013; **20**: e11-e19 [PMID: 23490378 DOI: 10.1111/jvh.12018]

35 **Komatsu H**, Inui A, Yoshio S, Kanto T, Umetsu S, Tsunoda T, Fujisawa T. High Dose of Pegylated Interferon for the Treatment of Chronic Hepatitis B in Children Infected With Genotype C. *JPGN Rep* 2020; **1**: e005 [PMID: 37206604 DOI: 10.1097/PG9.0000000000000005]

36 **Lau GK**, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, Gane E, Fried MW, Chow WC, Paik SW, Chang WY, Berg T, Flisiak R, McCloud P, Pluck N; Peginterferon Alfa-2a HBeAg-Positive Chronic Hepatitis B Study Group. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005; **352**: 2682-2695 [PMID: 15987917 DOI: 10.1056/NEJMoa043470]

37 **Al-Mahtab M**, Akbar SMF, Yoshida O, Aguilar JC, Guillen G, Hiasa Y. Antiviral Response across Genotypes after Treatment of Chronic Hepatitis B Patients with the Therapeutic Vaccine NASVAC or Pegylated Interferon. *Vaccines (Basel)* 2023; **11** [PMID: 37243066 DOI: 10.3390/vaccines11050962]

38 **Liu Y**, Park D, Cafiero TR, Bram Y, Chandar V, Tseng A, Gertje HP, Crossland NA, Su L, Schwartz RE, Ploss A. Molecular clones of genetically distinct hepatitis B virus genotypes reveal distinct host and drug treatment responses. *JHEP Rep* 2022; **4**: 100535 [PMID: 36035359 DOI: 10.1016/j.jhepr.2022.100535]

39 **Zhang M**, Zhang Z, Imamura M, Osawa M, Teraoka Y, Piotrowski J, Ishida Y, Sozzi V, Revill PA, Saito T, Chayama K, Liang TJ. Infection courses, virological features and IFN-α responses of HBV genotypes in cell culture and animal models. *J Hepatol* 2021; **75**: 1335-1345 [PMID: 34363922 DOI: 10.1016/j.jhep.2021.07.030]

40 **Datta S**, Roychoudhury S, Ghosh A, Dasgupta D, Chakraborty BC, Ray S, Gupta S, Santra AK, Datta S, Das K, Dhali GK, Chowdhury A, Banerjee S. Distinct distribution pattern of hepatitis B virus genotype C and D in liver tissue and serum of dual genotype infected liver cirrhosis and hepatocellular carcinoma patients. *PLoS One* 2014; **9**: e102573 [PMID: 25032957 DOI: 10.1371/journal.pone.0102573]

41 **Khatun M**, Kumar K, Baidya A, Mondal RK, Baszczyński O, Kalčic F, Banerjee S, Dhali GK, Das K, Chowdhury A, Janeba Z, Chakrabarti S, Datta S. Variability in the Responses of Hepatitis B Virus D-Subgenotypes to Antiviral Therapy: Designing Pan-D-Subgenotypic Reverse Transcriptase Inhibitors. *J Virol* 2022; **96**: e0180021 [PMID: 34730399 DOI: 10.1128/JVI.01800-21]

42 **Gupta SV**, Fanget MC, MacLauchlin C, Clausen VA, Li J, Cloutier D, Shen L, Robbie GJ, Mogalian E. Clinical and Preclinical Single-Dose Pharmacokinetics of VIR-2218, an RNAi Therapeutic Targeting HBV Infection. *Drugs R D* 2021; **21**: 455-465 [PMID: 34741731 DOI: 10.1007/s40268-021-00369-w]

43 **Gane E**, Lim YS, Kim JB, Jadhav V, Shen L, Bakardjiev AI, Huang SA, Cathcart AL, Lempp FA, Janas MM, Cloutier DJ, Kaittanis C, Sepp-Lorenzino L, Hinkle G, Taubel J, Haslett P, Milstein S, Anglero-Rodriguez YI, Hebner CM, Pang PS, Yuen MF. Evaluation of RNAi therapeutics VIR-2218 and ALN-HBV for chronic hepatitis B: Results from randomized clinical trials. *J Hepatol* 2023; **79**: 924-932 [PMID: 37290591 DOI: 10.1016/j.jhep.2023.05.023]

44 **Revill PA**, Tu T, Netter HJ, Yuen LKW, Locarnini SA, Littlejohn M. The evolution and clinical impact of hepatitis B virus genome diversity. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 618-634 [PMID: 32467580 DOI: 10.1038/s41575-020-0296-6]

45 **Zeng Z**. Human genes involved in hepatitis B virus infection. *World J Gastroenterol* 2014; **20**: 7696-7706 [PMID: 24976707 DOI: 10.3748/wjg.v20.i24.7696]

46 **Ni Y**, Lempp FA, Mehrle S, Nkongolo S, Kaufman C, Fälth M, Stindt J, Königer C, Nassal M, Kubitz R, Sültmann H, Urban S. Hepatitis B and D viruses exploit sodium taurocholate co-transporting polypeptide for species-specific entry into hepatocytes. *Gastroenterology* 2014; **146**: 1070-1083 [PMID: 24361467 DOI: 10.1053/j.gastro.2013.12.024]

47 **Yang F**, Wu L, Xu W, Liu Y, Zhen L, Ning G, Song J, Jiao Q, Zheng Y, Chen T, Xie C, Peng L. Diverse Effects of the NTCP p.Ser267Phe Variant on Disease Progression During Chronic HBV Infection and on HBV preS1 Variability. *Front Cell Infect Microbiol* 2019; **9**: 18 [PMID: 30881922 DOI: 10.3389/fcimb.2019.00018]

48 **Binh MT**, Hoan NX, Van Tong H, Sy BT, Trung NT, Bock CT, Toan NL, Song LH, Bang MH, Meyer CG, Kremsner PG, Velavan TP. NTCP

S267F variant associates with decreased susceptibility to HBV and HDV infection and decelerated progression of related liver diseases. *Int J Infect Dis* 2019; **80**: 147-152 [PMID: 30685591 DOI: 10.1016/j.ijid.2019.01.038]

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