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Review

Genetic insights on host and hepatitis B virus in liver diseases

Hoang van Tong [a,1,*], C. Thomas Bock [b], Thirumalaisamy P. Velavan [a,1]

[a] Institute of Tropical Medicine, University of Tübingen, Tübingen, Germany
[b] Department of Infectious Diseases, Robert Koch Institute, Berlin, Germany

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ABSTRACT

Hepatitis B virus (HBV) infection is a major global health problem and many studies have underlined the importance of inter individual variability and somatic mutations during the clinical course of HBV infection. In recent years, high-throughput technologies have provided new possibilities to study the genetic basis of many diseases. We reviewed all literature available on genome-wide association studies (GWASs), whole genome, exome and RNA sequencing studies as well as studies on HBV infection and the pathogenesis of related liver disease. Many GWASs conclude that the genetic variants in the *HLA* region (*HLA-DP*, *HLA-DQ*, *HLA-DR* and *MICA*), *KIF1B*, *DEPDC5* and *PNPLA3* influence HBV infection, its clinical course and the response to hepatitis B vaccination. The next generation sequencing approach provides important clues on the mutational landscape of genes involved in signaling pathways in particular JAK/STAT, Wnt/β-catenin, p53 pathways and multiple chromatin regulator genes that significantly promote hepatocarcinogenesis. In addition, the hotspots of recurrent integrations of HBV-DNA into host chromosomes such as *hTERT*, *PDGF* receptor, *MLL* are involved in pathogenesis of hepatocellular carcinoma (HCC). Additionally, the transitions T > C/A > G, C > T/G > A, C > A/G > T and T > A/A > T remain specific for HCC induced by viral infection and the DNA methylation in the CpG island is proposed as a biomarker for HCC. We have described common mutations in the HBV genome (G1896A, rtM204V, rtM204I) which modulate the pathogenesis and carcinogenesis of the liver. Further GWASs in different ethnic groups and additional functional studies are required to warrant the significance of such defined genetic factors. Such findings continue to shape our understanding of the genetic architecture of host–virus interactions and provide new clues and directions in determining genetic markers that modulate HBV infection and related liver diseases. The studies using high-throughput technologies help identifying potential genetic threats however the utility of mutational information can be complex in predicting prognostic significance and shall pose challenges to its clinical implementation.

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* Corresponding author at: Institute of Tropical Medicine, University of Tübingen, Wilhelmstrasse, 27, 72074 Tübingen, Germany. Tel.: +49 7071 2980234; fax: +49 7071 294684.
E-mail addresses: tong.van-hoang@uni-tuebingen.de, hoangvantong@gmail.com (H.v. Tong).
[1] These authors contributed equally.

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1. Introduction

Hepatitis B virus (HBV) infection is a major global health problem and remains a leading cause of acute and chronic hepatitis B (AHB and CHB), liver cirrhosis (LC) and hepatocellular carcinoma (HCC). Globally, at least 2 billion people are infected with HBV and more than 350 million are reported to be chronic HBV carriers. An estimated 1.2 million HBV-related deaths occur annually [1]. HBV is endemic in sub-Saharan Africa, South-East Asia, and parts of America with infection rates ranging from 8% to 20% [2]. HBV infection is a well established cause of LC and approximately 70–80% of cirrhosis cases occur among HBV-related HCC patients [3,4]. Approximately 8–10% of HBeAg-negative patients progress to cirrhosis annually, compared to 2–6% of HBeAg-positive patients [5]. In addition, other vital factors including HBV-DNA levels, HBV genotypes, co-infection with hepatitis C virus (HCV) or human immunodeficiency virus (HIV) and the core promoter mutations in the HBV genome contribute to LC progression [5]. HCC is the third leading cause of cancer related deaths with more than 500,000 new cases annually diagnosed worldwide and accounts for approximately 50% of all HCC cases in childhood [3,6]. In Asia, South East-Asia and sub Saharan Africa, the higher incidence of HCC is related to the high prevalence of HBV infection. In recent years, an increasing HCC incidence is reported in several Western countries [7,8]. The risk of HCC among chronic HBV carriers is 100-fold higher compared to non-carriers and is directly proportional to the high level of HBV replication [8–10]. However, the distribution of these risk factors and its correlation with the incidence of HCC depends largely upon geographical region, ethnic descent, prolonged use of alcohol, environmental factors and various co-morbidities [10]. In addition, HCC occurs more frequently in males than in females, with increasing rates starting at the age of 20 years in high-risk countries compared to 50 years of age in low-risk countries [7].

The host immune response against HBV is believed to modulate HBV infection and the progression of HBV-related diseases. The interplay between HBV infection and the immune response leads to a large spectrum of pathologies, including subclinical, acute self-limiting and fulminant hepatitis, an asymptomatic carrier state, chronic hepatitis progressing to LC and the life threatening HCC. Genetic susceptibility to HBV infection and liver disease was investigated in different ethnic groups. A number of gene loci associated with HBV infection and its clinical outcome has been identified [11]. The millions of single nucleotide polymorphism (SNP) distributed throughout the human genome provide a basis to identify novel diagnostic biomarkers for many diseases [12]. Of interest, high-throughput technologies including Genome-Wide Association Studies (GWASs) and Whole Genome Sequencing (WGS) that were developed in the last decade aid in the identification of novel genetic biomarkers for a number of diseases, including HBV infection and HBV-related liver disease [11,13–15]. This review describes and discusses reported viral mutations and host genetic variation identified by high-throughput technologies in the context of HBV infection, HCC and other liver diseases, thereby providing a better understanding of viral–host genetic interaction.

2. Hepatitis B virus variants and clinical outcomes

2.1. Hepatitis B virus genome and its variability

The HBV genome is a partially circular double-stranded DNA molecule of 3.2 kb that encodes four overlapping open reading frames (ORFs), including a viral nucleocapsid protein (Hepatitis B core Antigen or core protein – HbcAg), a viral surface protein (Hepatitis B surface Antigen or S protein – HbsAg), a multi functional viral DNA polymerase (P), and the X protein (Hepatitis B X protein – HBxAg) [2,3,16,17]. The *P* gene covers approximately 80% of the viral genome and has a complete overlap of the *S* gene and a partial overlap with the *C* and the *X* genes. In addition, preCore and the Core promoter share a considerable region of the genome sequence with the *X* gene [18].

HBV is classified into eight distinct genotypes (A–H) based on at least 8% heterogeneity in the entire genome, whereas the HBV sub-genotypes are defined based on 4–8% heterogeneity [18–20]. Multiple exposure to different HBV genotypes and the recombination between different HBV genotypes during the clinical course of HBV infection results in considerable HBV genomic diversity [21,22]. The HBV genotypes are distributed with distinct geographical and ethnic patterns that allow HBV genotyping as a practical tool to trace transmission routes and to reconstruct the evolutionary history of HBV [18–20]. The HBV genotype A is distributed mostly in Northwestern Europe, North America and in Africa, whereas HBV genotypes B and C predominate in Asia. The HBV genotype D prevails in the Mediterranean region, although occurs world-wide. The HBV genotype E is found in West Africa, HBV genotypes F and H in the Americas and HBV genotype G circulates in Europe and the United States [19,23]. HBV genotypes are associated with distinct features of the clinical course of liver disease in many ethnicities. In Taiwanese patients, the HBV genotype B associates with less active disease, slower progression to LC and with a lower incidence of HCC, compared to HBV genotype C [24]. On the other hand, HBV genotype D is associated with more severe liver disease or even HCC in young patients, compared to HBV genotype A [23,25]. The geographical distribution of HBV genotypes aids in predicting the therapy response and HBV transmission patterns as well as progression of liver disease. For instance, during the HBV-interferon therapy, individuals with HBV genotypes A and B respond better to interferon than patients with HBV genotypes C and D. However, clear associations between HBV genotypes and treatment responses to lamivudine or adefovir dipivoxil in other geographical settings are not established [25].

2.2. Mutations in the hepatitis B virus genome

Mutations occur frequently in the HBV genome and numerous mutations have been shown to associate with HBV replication, pathogenesis, host immune response, antiviral drug resistance

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