

Hepatitis B virus genotypes, mutations and the risks for hepatocellular carcinoma

Hepatitis B virus (HBV) has infected more than 400 million people worldwide. HBV infected individuals remaining at increased risk of developing end-stage liver disease including cirrhosis, hepatic failure, and hepatocellular carcinoma (HCC). HCC is the fifth most common cancer worldwide and the third most common cause of cancer mortality. The important risk factors for HCC include the presence of HBV e antigen (HBeAg), a surrogate marker of active viral replication, and the amount of hepatitis B viral load in serum. Recent studies suggest that the genetic characteristics of HBV, including HBV genotype and specific genetic mutations, are associated with the development of HCC.^{1,2}

HBV is generally classified into four serotypes or subtypes (adr, adw, ayr and ayw) based on antigenic determinants of the hepatitis B surface antigen (HBsAg). These serotypes are further classified into nine subtypes (ayw1-4, ayr, adw2, adw4, adrq+, and adr-q-).³ The prevalence of these serotypes was found to be varied in different parts of the world. HBV is classified into 8 genotypes (A-H), based on an intergroup divergence of 8% or more in the complete nucleotide sequence.³ HBV genotyping methods mainly utilize partial sequence of the HBV genome such as the pre-S or S gene. Advanced molecular biology techniques have revealed significant diversities in sequences of HBV DNA that created allelic differences among the four major HBV serotypes. These genotyping methods include direct sequencing, restriction fragment length polymorphism, line probe assay, and enzyme-linked immunoassay. Recent focus is on the clinically important differences in outcomes that are associated with the different HBV genotypes. The eight HBV genotypes display a distinct geographic distribution pattern.⁴ Genotypes A is mainly distributed in north-west Europe, North America and Central Africa. Genotype D is predominant in Southern Europe, Middle East and India. Genotype E is predominant mainly in Africa. Genotype F is distributed in individuals among American natives, Polynesia, Central and South America, and Genotype F mostly in United States, France. Genotypes B and C are the predominant HBV genotypes in Eastern Asia, including Taiwan. HBV genotype C infection has been associated with later occurring and lower rates of spontaneous clearance of HBeAg in serum compared with genotype B.^{1,2,4,5} Genotype C is additionally associated with higher levels of HBV DNA replication, more advanced liver disease in general, and a decreased rate of response to interferon therapy compared with genotype B.^{1,5,6} The high prevalence of HBV genotypes B and C among Asians raise the possibility that HBV genotype may be related to the endemicity of HBV infection. A study in Switzerland found that genotype A was more common among patients with chronic hepatitis B, whereas genotype D was more prevalent among patients with resolving acute hepatitis B suggesting that HBV genotype A was associated with a higher rate of chronic HBV infection.⁷ HBV genotypes may contribute to the wide range in prevalence of HBV infection in different parts of the world through differences in rates of replication and abilities to evade immune clearance, but studies comparing the replication capacity and immune response of the various HBV genotypes have not been performed. Studies have shown a strong relationship between HBV genotypes and mutations in the precore and core promoter regions

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that abolish or diminish the production of HBeAg.^{8,9} Thus, the most common precore mutation, a G to A substitution at nucleotide 1896 (G1896A), which creates a premature stop codon (eW28X) is found in association with HBV genotypes B, C, and D but not genotype A. This accounts for the preponderance of HBeAg-negative chronic hepatitis B in Southern Europe and Asia. The basis for the genotype dependent selection of the precore G1896A mutation is related to the need to maintain base pairing of the stem loop structure of the pregenome encapsidation sequence (ϵ).^{10,11} HBV genotypes B, C, and D frequently have a T at nucleotide 1858, which is directly opposite nucleotide 1896 in the stem of ϵ , whereas HBV genotype A usually has a C at nucleotide 1858, which forms a more stable bond with the wild type (G) rather than the variant sequence (A).¹² Yet the mechanism was explored by which HBV genotype G, which has 2 stop codons in the precore region, maintains HBeAg production.¹³ Other studies reported a correlation between HBV genotype and HBeAg clearance in Asian patients. The prevalence of HBeAg was higher in patients with genotype C compared to those with genotype B suggesting that HBeAg clearance occurred at higher rates among patients with genotype B.^{12,14} HBsAg carriers with genotype B had lower histologic activity scores.¹² The correlation between HBV genotype and liver disease has also been found in several studies such as a study in Japan found that liver dysfunction was observed less frequently in hepatitis B carriers with genotype B compared to those with genotype C.¹⁵ Two studies in Chinese patients with chronic HBV infection showed that genotype C was more prevalent in cirrhosis patients.^{1,14} Possibly a longer duration of high levels of HBV replication may contribute to more active liver disease in cirrhosis patients with HBV genotype C. A Taiwanese report showed that the rate of HBeAg loss was significantly higher in patients with genotype B compared to those with genotype C (41% vs. 15%).⁵ An interferon-therapy study showed that HBeAg-negative patients infected with HBV genotype A responded better than those with genotype D/E (70% vs. 40%).¹⁶ Our study on the prevalence and profile of chronic HBV infection and its risk factors in pregnant women in India showed that the most common HBV genotype was D (84%) followed by A+D and A (8% each). The prevalence of HBsAg positivity among asymptomatic pregnant women was 1.1% with 71% having high HBV DNA levels.¹⁷

In conclusion, growing evidences suggest that HBV genotypes may influence HBeAg seroconversion rates, patterns and rates of mutations in the precore and core promoter regions, and the severity of liver disease. Different HBV genotypes predominantly affect the disease occurrence and severity in various parts of the world. The mechanism remains unclear for the relationship between HBV genotype and mode of transmission and thus the relationship between HBV genotypes and HCC is also not clear. Further studies are needed to confirm these associations to identify the mechanisms.

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Conflicts of Interest

There is no conflict of interest.

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