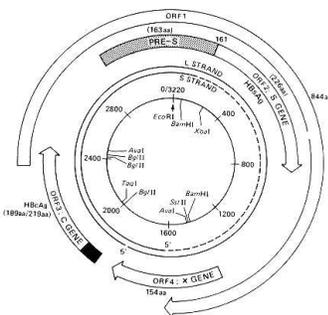


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### Current Understanding of the Hepatitis B Virus and Its Genotypes

What is hepatitis B? Hepatitis B is one of the five hepatitis infections and is the world's most common serious viral infection of the liver and is caused by the hepatitis B virus (HBV). Hepatitis B is an infection that can prematurely lead to liver cancer and liver disease. Every year, approximately 700,000 people die of hepatitis B-related liver cancer or disease. According to the World Health Organization, it is believed that one-third of the world's population has been infected with hepatitis B at some point in their lives. Within that amount, it is predicted that five percent contract chronic hepatitis B, a condition that leads to more serious health-related problems like hepatocellular carcinoma (HCC), liver cirrhosis, and polyarteritis nodosa (Hoofnagle). Because of the virus' widespread effect on a global scale, ongoing research on the epidemiology and genomics of the hepatitis B virus will eventually provide what scientists and researchers need to clearly understand the virus and how it works, paving the way for innovative ideas on how to deal with the various forms hepatitis B virus.



The genome of the hepatitis B virus is composed of circular DNA, as shown in Figure 1. This DNA, however, is unusual in that it is partially double stranded. As a result, the full-length strand is usually made up of around 3,200 base pairs while the shorter strand is composed of around 1,700 to 2,800 base pairs

**Figure 1:** Genome of the hepatitis B virus (Hunt). Its genome consists of four overlapping open reading frames: polymerase, precore/core (pc/core), envelope (preS1/S2/S genes) and the X gene

(Szmaragd). The first open reading frame (ORF) is responsible for encoding the various forms of the hepatitis B surface proteins and contains three start codons. The core open reading frame is responsible for the secretion of HBeAg, the hepatitis B e antigen, and contains two initiation regions. The third open reading frame is responsible for encoding the viral polymerase to which the end of the full-length strand is linked. The last open reading frame is “x,” whose function is still being confirmed, but is believed to be a transcriptional transactivator, which is a stimulator to replicate the genetic components of a virus (Baron).

Not only is the hepatitis B virus’s genome unusual, but so is its replication mechanism. The hepatitis B virus’s replication mechanism is odd because it uses the virally-encoded DNA polymerase, also known as reverse transcriptase (Hunt). The hepatitis B virus is unique in this sense because it is one of the few non-retroviral viruses that include reverse transcriptase in its replication mechanism. The virus also uses an RNA intermediate during its course of replication. This, combined with the fact that the hepatitis B virus lacks a proofreading mechanism, causes the virus’ replication to be very inefficient and error-prone, resulting in high genetic variability (Datta). Because of the extreme overlapping open frames of the virus, errors

are difficult to fix. The errors in the transcription process results in the relatively high rate of mutations (mostly insertions, deletions, and point mutations) while replicating, giving the virus the ability to develop resistance to antiviral treatment (Highleyman).

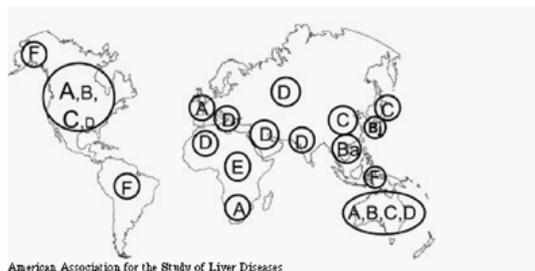
HBV genotype	Distribution
A	Brazil, Central Africa, India, Northwestern Europe, Poland, Spain, Tunisia, USA
B	China, Hong Kong, Indonesia, Japan, Philippines, Southeast Asia, Taiwan, Thailand, Vietnam
C	Australia, Brazil, China, Far East Asia, Hong Kong, Indonesia, India, Japan, Korea, Polynesia, Soloman islands, Thailand, Taiwan, USA, Vietnam
D	Afghanistan, Albania, Brazil, Czech, Iran, India, Mediterranean area, Middle East, Russia, Spain, Soloman islands, Tunisia, Turkey, USA
E	Tunisia, West Africa
F	Argentina, Alaska, Bolivia, Brazil, Central and South America, Polynesia, Venezuela
G	France, Germany, USA
H	Central and South America, Mexico

**Figure 2:** HBV Genotype Distribution

The rapid and high mutation rates associated with the hepatitis B virus has given the virus the ability to evolve and change throughout an individual and a population of people. As a result, through numerous studies of the HBV sequence in infected individuals of different

populations, the virus has been classified into eight different genotypes, as shown in Figure 2 (Szmaragd). Each genotype was categorized because of its greater than eight percent divergence from the complete HBV genome. In addition, some genotypes have subgenotypes that correlate with ethnicity. Even though all of the genotypes contained a divergence from the complete HBV genome of more than eight percent, the genotypes themselves are different from one another. Some genotypes and subgenotypes, like subgenotype Ba, are recombinations of other known genotypes. Others genotypes have enough differences that they are categorized as new and different genotypes. As a result, the eight genotypes were classified based on order of documentation and ordered from genotype A through H, with some having subgenotypes (like genotype B and its subgenotypes Ba and Bj) (Hou). Through previous studies, it has been suggested that these eight genotypes for the hepatitis B virus came about through recombination (Devesa).

Additionally, studies have also shown that a strong association exists between HBV genotypes and their distinct geographic distributions (Hou). Figure 3 shows a map of the geographic distribution of HBV genotypes around the world. HBV genotypes A and D are most common to Europe, Russia, North Africa, and India. Genotypes B and C are more common to both East and Southeast Asia and Australia. On the other hand, genotypes F, G, and H are predominantly found, but not exclusive to, Central and South America (Pas). Unlike the other geographic locations, North America displays a wide and varied mixture of HBV genotypes,



**Figure 1.** Geographic distribution of hepatitis B virus genotypes.

**Figure 3:** Geographic Distribution Map of HBV Genotypes Worldwide

including genotypes A, B, C, and D. The distribution of HBV genotypes around the world

reflects and displays the general pattern of human immigration and colonization (Campos). This is a possible explanation behind the diverse range of HBV genotypes in the United States and why the genotype found in North Africa is the same as the genotype found in Europe. Even though a correlation is seen between the genotype and its geographic distribution, researchers are still trying to discover the scientific reason behind the distribution and why some genotypes are more common in an area than others.

Though studies are still being conducted in conjunction with the hepatitis B virus, many correlations have already been discovered between the various genotypes of HBV and clinical outcomes and manifestations of the viral infection. A 14-year study done in Taiwan showed that HBV genotype C was associated with a higher risk of hepatocellular carcinoma relative to the other genotypes. Various studies have shown that chronic hepatitis B is more likely to be serious in individuals with HBV genotype C than in individuals with HBV genotype. Another study between HBV genotype B and C gave data that suggested that more serious liver diseases are seen in individuals with genotype C, while genotype B correlated to development of hepatocellular carcinoma in non-cirrhotic patients. Furthermore, studies in Europe have shown that most HBV genotype A patients develop chronic hepatitis B, while those with genotype D develop only acute hepatitis B (Liu).

Despite the efforts to learn more about the different genotypes of the hepatitis B virus, scientific studies have just shown associations between clinical manifestations and the different HBV genotypes. Most of the studies performed have not given definitive and conclusive scientific results for why there are different genotypes, how they are distributed, and what the clinical differences between the genotypes are. Also, many studies involving HBV genotypes B and C were done in Asia, where those genotypes predominantly occur in the population.

Therefore, the results obtained from these studies have yet to be confirmed in other countries with HBV genotypes B and C. The lack of data pertaining to the hepatitis B virus in developing regions, like many regions of Africa, has created an unfilled gap in information that is still incomplete. Additionally, genotype distribution will continue to change over time, as the human population continues with its patterns of population migration into other regions (Fung). As a result, further testing of hypotheses and associations must be performed in order to acquire a better understanding between the HBV genotypes and their clinical manifestations.

The lack of conclusiveness of studies trying to correlate HBV genotypes and clinical manifestations has resulted in limited cures for the hepatitis B virus, especially for those patients who develop chronic hepatitis B. No effective cures have been found for chronic hepatitis B. However, there are five drugs that have been approved for treatment of chronic hepatitis B. These drugs include standard interferon (IFN)  $\alpha$ , lamivudine, adefovir dipivoxil, pegylated IFN- $\alpha$  2a and entecavir (Liu). Recent studies are pointing to a possible correlation between specific HBV genotypes and the progression of hepatitis B in patients.

At this point in time, research is still being done for the hepatitis B virus. Developments are still being made for the correlation between the HBV genotypes, hepatitis B epidemiology, and the geographic distribution of the virus. Differences are present in the medical and virological characteristics of the different genotypes of HBV, but scientific evidence for why and how that might affect different ethnicities and populations of people is still being sought. Once loose ends are tied in the HBV genotype research, more conclusive evidence regarding the HBV genotypes will allow for scientists and researchers to create drugs specific to individual genotypes. In doing so, the drugs will have specificity to the certain genotype that it is supposed to work on. In addition, making specific drugs to deal with each genotype will allow for a more

cost-efficient approach to treating patients. This way, patients can avoid the adverse effects that come hand in hand with possibly ineffective treatments used as a broad blanket to cover all HBV genotypes (Liu).

Thorough understanding of the factors behind the mutations and genotypes of the hepatitis B virus will allow for a more efficient approach for early diagnosis of the infection, as well as a more effective treatment. It will give important information dealing with the pathogenicity of the virus and its response to different types of therapy. Though the research for hepatitis B and its causative virus is still in its preliminary stages and is still inconclusive in many aspects, researchers and scientists are on a promising path leading to a better understanding of the hepatitis B virus. Continued research will lead to a clearer understanding of the structure, mutation, genotypes, and distribution of the virus. With further research, in time, effective treatments for the hepatitis B virus and its various genotypes will surface, leading to better methods for dealing with the more serious health problems that arise from hepatitis B infection.

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