Hepatitis B Virus and Its Genotypes: New development in Japan

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Hepatitis B virus (HBV) is a major public health problem, causing persistent infection in approximately 420 million people in the world. Recently, it was confirmed that HBV occurs in several genotypes with rather distinct geographical distribution. Here I summarize how this discovery changed the concept of acute hepatitis B in Japan.

In 1988, many researchers including our group conducted a molecular evolutionary analysis, which enabled the quantitative estimation of nucleotide sequence variations using all the known nucleotide sequences of hepadnavirus. We found that the mutation rate of HBV DNA was approximately 10,000 times as high as that of human genes and proposed that HBV could be classified into groups according to the nucleotide sequences (genotypes).[1] Currently, the presence of 10 genotypes, from A to J, has been confirmed globally.[2]

We collected approximately 3,000 specimens from all over the world to examine the global geographical distribution of HBV genotypes. The analysis revealed regional disparities; A and D genotypes being predominant in both Europe and North America, B and C in East Asia, D in North Africa, E in West Africa, and F and H in Latin America. This presumably reflects the adaptation of HBV to the evolutionary history of humans—that is, as human ancestors parted from chimpanzees and began evolving into *Homo sapiens* about 5 million years ago and dispersed to various parts of the world over the period of 200 thousand years, HBV also adapted to the environment of various regions around the globe. As a result, the difference in the nucleotide sequences among HBV genotypes has grown to more than 8.0%. This is considerably larger than the 0.3% difference among human individuals or the 1.2% difference between humans and chimpanzees in comparison.

On the other hand, clinical disparities of HBV infections among regions have long been recognized, even before the discovery of HBV genotypes. For example, HBV infections in Asia are transmitted mainly through mother-to-child infection, which frequently become chronic and develop into liver cancer. In Europe and North America, HBV typically spread as a sexually transmitted disease (STD) among adults, in which about 10% of the cases become chronic but rarely progress to liver cancer. On the other hand, childhood HBV infection predominates in Africa, which is highly likely to become chronic, and cases of liver cancer at younger ages are common. These differences in clinical picture had been explained by the difference in host immune competence among Caucasoid, Negroid, and Mongoloid races. However, the above-mentioned discovery of the 8% difference in the nucleotide sequence among HBV genotypes supports the idea that genotypes themselves are responsible for these clinical differences.

Japan is faced with the ever-increasing impacts of globalization. As many as 20 million Japanese people travel abroad each year, while 7 million people visit Japan from overseas. As a result,

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infections with uncommon genotypes of HBV are now being found in Japan, indicating the spread of genotypes that are not native to the country.[3] Even if only 10% of such people are to develop chronic conditions, they could serve as the core for the spread of foreign HBV genotypes in Japan. In fact, a case of HBV infection has been reported that was passed from a foreign female to a Japanese male and then to a Japanese female. A national survey has also revealed an increase of a genotype commonly seen in Europe and North America.[4]

These facts underscore the limitations of the current HBV infection control measures in Japan, which focus on mother-to-child infection, and indicate the need of HBV vaccination of all newborns. We must also begin to recognize HBV infection as an STD in this country as well, and consider starting universal vaccination for all babies and juveniles against HBV.

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