CHAPTER 1

Genotype of Hepatitis Delta Virus

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Classification of HDV Genotype

Hepatitis delta virus (HDV) is a defective virus that requires hepatitis B virus (HBV) surface antigen for virion assembly and infection,[1] and contains a negative single stranded circular RNA genome of 1.7 kilobases.[2,3] HDV is classified into three genotypes (genotype I, II and III) based on genetic sequence analysis (Fig. 1).[4] Genotype II shows approximately 75% homology to genotype I, and genotype III shares about 60 to 65% homology with genotype I and II. There are many variants within each genotype. Especially, HDV genotype II is further divided into two types (i.e., IIa and IIb), with 77% nucleotide homology between the complete sequences of genotype IIa and IIb.[5] The nucleotide homology between genotype IIb and IIb-M, the newly identified IIb variant, is 88-90%.[6] Similarly, IIa variant was recently found in Siberia (IIa-Yakutia), which in comparison with IIa shows a similar degree of genetic differences.[7] These genotypes show different geographical distributions and clinical pictures, which is thought to be caused by functional differences of genotype-specific sequences of HDV-RNA as well as HDAg protein.

Geographical Distribution of HDV Genotype

Genotype I has been identified in most areas of the world and represented by many different isolates (Fig. 1).[8] Genotype II is confined to East Asia (mainly Siberia, Japan, and Taiwan),[9] in contrast to the ubiquitous global distribution of genotype I. Genotype IIb was first identified in Taiwan,[5] and was subsequently reported among patients from the Miyako Islands,[10] one of the nearest Japanese islands to Taiwan. Recently, a new genetic variant of HDV genotype IIb (IIb-M) was identified.[6] Genotype III is isolated to the northern part of South America, and is closely associated with fulminant hepatitis.[4]

Clinical Significance of HDV Genotype

HDV genotypes are known to affect the pathogenesis and diverse clinical pictures of HDV infection.[4,7,9] Genotype I causes hepatic diseases ranging from mild to severe, often with the aggressive hepatitis and frequently associated with liver cirrhosis (LC) and hepatocellular carcinoma (HCC). On the other hand, genotype II is generally associated with a more favorable outcome than genotype I.[9] A IIa variant recently reported in Yakutia, Siberia, Russia also causes

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Hepatitis Delta Virus, edited by Hiroshi Handa and Yuki Yamaguchi.

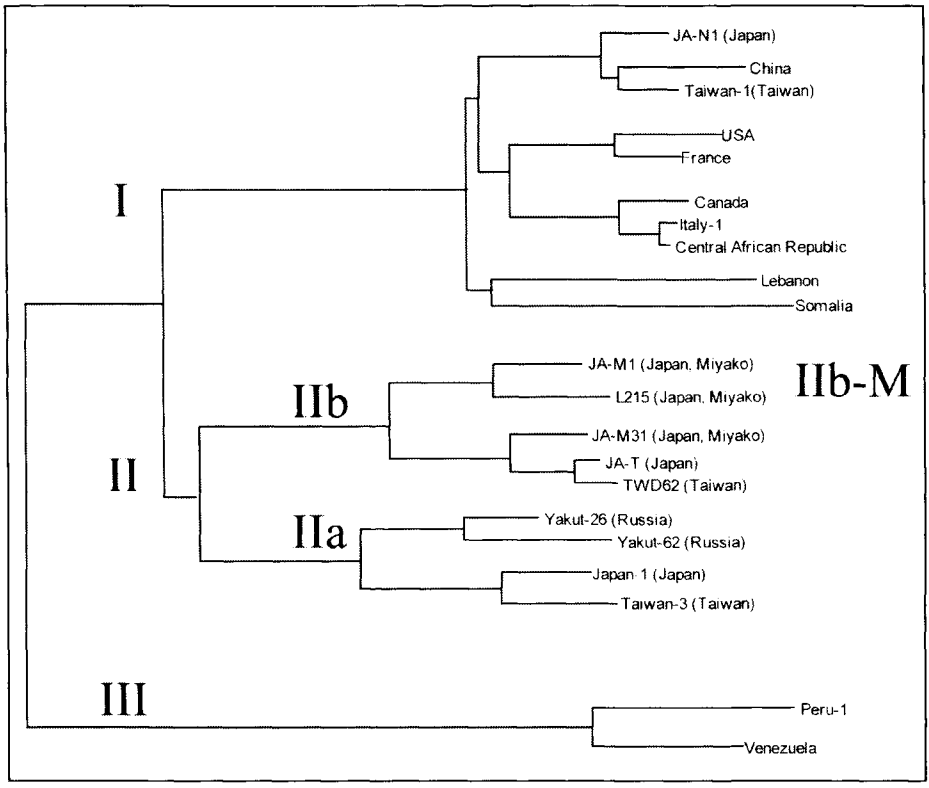

Figure 1. Phylogenetic tree analysis of HDV isolates. Sources of isolates are as follows: TWD62 (AF018077), Taiwan-3 (U19598), Taiwan-1 (M92448), Yakut-26 (AJ309879), Yakut-62 (AJ309880), Japan-1 (X60193), Lebanon (M84917), Somalia (U81988), China (X77627), USA (M28267), France (D01075), Italy-1 (X04451), Canada (AF098261), Central African Republic (AJ000558), Peru-1 (L22063), Venezuela (AB037948), JA-M1 (AF309420), JA-M31(AB118841), JA-T (AB118847) were sequenced in this study. (GenBank accession number).

a severe hepatitis comparable to genotype I in this cohort.[7] Genotype III is associated with fulminant hepatitis.[4] These findings strongly suggest that the genetic structure of HDV can profoundly influence the pathogenesis of liver injury in HDV infection.

In Japan, chronic HDV infection is endemic in the Miyako Islands where genotype IIb and IIb-M are found, and their clinical pictures differed despite relatively uniform clinical backgrounds including virological factors of HBV.[10,11] Most of the patients with chronic HDV genotype IIb infection were asymptomatic carrier (ASC) or chronic hepatitis (CH) and none were at the liver cirrhosis (LC) or hepatocellular carcinoma (HCC) stage. In contrast, about half of patients with genotype IIb-M were in the CH and LC stages, respectively, and none of them were ASC.[6] These findings indicate that patients with genotype IIb-M are more likely to progress to LC and HCC than those with genotype IIb, and that differences in HDV genotype could cause the different clinical pictures observed in this population.

In general, the genetic structure responsible for clinical features could not be readily determined because the genetic differences between the different genotypes are too diverse as seen in Figure 2. In contrast, despite the different clinical pictures between IIb and IIb-M, the genetic differences are small enough to enable the definition of the genetic features of HDV pathogenesis