Hepatitis Delta Virus

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PREFACE

Since its discovery in 1979, HDV has occupied a unique position in virus taxonomy. It does not belong to any of the established viral family but constitutes its own genus, deltavirus, whereas it does have significant similarity to viroids, subviral agents of higher plants. HDV RNA genome is smaller than any known animal virus genome, so small that it encodes only a single protein. Therefore, its propagation is largely dependent on factors supplied by host and another virus, hepatitis B virus (HBV). For example, HDV makes use of HBV’s surface antigens for envelope proteins. HDV replicates through RNA-dependent RNA synthesis by cellular DNA-dependent RNA polymerase(s). RNA editing by cellular enzyme(s) and RNA cleavage by viral ribozymes are also involved in the viral life cycle. From a medical point of view, patients infected with both HBV and HDV tend to develop more severe clinical symptoms than those infected with HBV alone. All these features make HDV unique and attractive, and its research over the last two decades has resulted in a number of findings that have wide implications beyond the immediate subject.

This book concisely describes various aspects of HDV, from basics to cutting-edge research, from medicine to molecular virology and biology. Chapters were written by internationally renowned scientists. We want to take this opportunity to thank all the authors who generously contributed. We hope their conscientious efforts will have made this book useful to broad readers for many years to come. We would also like to acknowledge the expert assistance of Cynthia Conomos and Sara Lord at Landes Bioscience.

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CHAPTER 1

Genotype of Hepatitis Delta Virus

Nobuyuki Enomoto,* Hideki Watanabe, Kazuyoshi Nagayama, Tsuyoshi Yamashiro and Mamoru Watanabe

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,10 and was subsequently reported among patients from the Miyako Islands,11 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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a severe hepatitis comparable to genotype I in this cohort. Genotype III is associated with fulminant hepatitis. 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. 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. 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.

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**Figure 1. Phylogenetic tree analysis of HDV isolates.** Sources of isolates are as follows: TW562 (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).
and replication in vivo. Thus, a detailed comparative analysis of HDV genomes between genotype IIb and IIb-M provided a unique opportunity to define the critical genetic features of HDV which determine liver injury. As described later, HDV genotype IIb-M has specific genetic structures in the RNA editing site and the packaging signal sequence of HDAg which could potentially influence the efficiency of HDV replication. The observed correlation between HDV genetic structure and clinical characteristics suggests a critical role of variations in the RNA editing site and packaging signal of the HDAg gene in determining the diversity of clinical outcomes, even among patients infected with the same genotype of HDV.

**Virological Significance of HDV Genotype**

Among different HDV genotypes, the difference is highest in the hypervariable region (nt 1598-657) and moderately high in HDAg (nt 957-1597), whereas the autocatalytic regions coding ribozyme activity are well conserved (Fig. 2, Table 1). The hypervariable region is markedly variable even within the same genotype, supporting the notion that this region does not have any relevant biological function aside from the formation of the rod structure of HDV RNA required for RNA synthesis by RNA polymerase II. On the other hand, the requirement for strict secondary or tertiary structure of the autocatalytic domain seems to be so crucial for full activity of ribozyme needed for rolling-circle mechanism of HDV replication.