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Hepatitis Delta Virus Genetic Variability: From Genotypes I, II, III to Eight Major Clades?

P. Dény (✉)

Service de Bactériologie, Virologie, Hygiène, Laboratoire Associé au Centre National de Référence des hépatites B et C, Hôpital Avicenne, Assistance Publique – Hôpitaux de Paris, Université Paris 13, EA3406, 93009 Bobigny Cedex, France
paul.deny@avc.ap-hop-paris.fr

Abstract Hepatitis D virus (HDV) is a satellite of hepatitis B virus (HBV) for transmission and propagation, and infects nearly 20 million people worldwide. The HDV genome is composed of a compact circular single-stranded negative RNA genome with extensive intramolecular complementarity. Along with epidemiological, geographic distribution and pathological patterns, the variability of HDV has been limited to three genotypes and two subtypes that have been characterized to date. Recently, extensive phylogenetic reconstructions based on the delta antigen gene and full-length genome sequence data, have shown a wide and probably ancient radiation of African lineages, suggesting that the genetic variability of HDV is much more complex than previously thought. Indeed, sequences previously affiliated with genotype IIb should now be considered as belonging to clade 4 (HDV-4) and African HDV sequences segregate within four additional clades: HDV-5, HDV-6, HDV-7 and HDV-8. These results bring the geographic distribution of HDV closer to the genetic variability of its helper HBV.

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Viral Genetics of HBV and HDV

Despite an effective vaccine, infection with hepatitis B virus (HBV) is mainly transmitted through the mother-to-neonate route in endemic countries. In most cases, chronic infection results and the transmission will therefore occur from generation to generation. HBV could be considered as an indirect marker of population migration. Transmitted from the mother, it might be considered as an alternate to mitochondrial DNA (mtDNA) (Ingman et al. 2000). MtDNA analyses indicate that around 59,000–100,000 years before present, earth colonization might have occurred from Africa to the Middle East, Asia then to Australia, Europe and to Americas. Several hypothesis have been proposed to link the HBV to human evolution and dispersal around the globe (reviewed in Simmonds 2001). (1) The existence of *Hepadnaviridae* in other primates, mammals and birds makes possible a co-speciation of HBVs during evolution. (2) The higher divergence of the South American HBV genotype F strains (HBV/F) could have given rise to HBV spreading from this area to the rest of the world during the slave trade. (3) The existence of primate-specific strains might also explain a cross species contamination such as in HIV. These hypotheses are not necessarily mutually exclusive, and each could contribute, in part, to the present day distribution of HBV among humans around the world. Regardless of the origin and evolution of HBV, nucleotide similarity approaches and evolutionary reconstructions indicate the existence of at least eight HBV genotypes (labelled HBV/A to HBV/H), the existence of many subtypes and specific gene phylogenies identify recombinant forms (Norder et al. 2004).

Hepatitis delta virus (HDV) was identified in 1977 as a foreign antigen in the serum and the liver of Italian patients infected with HBV (Rizzetto et al. 1977). The origin of HDV remains difficult to understand and the age of the HDV–HBV association needs to be clarified. This viral-like agent has been classified as a satellite of HBV, being dependant on HBV for virion assembly and propagation (Sureau et al. 1993), but not for HDV–RNA replication. The HDV genome is a circular single-stranded RNA of 1672–1697 bases with extensive intramolecular complementarity (Wang et al. 1986; Radjef et al. 2004). Part of the HDV genome might share historical homology with viroids or plant virus satellite RNA sequences (Elena et al. 1991). Interestingly, a pseudoknot ribozyme is evidenced in both genomic and antigenomic RNA strands, corresponding to the best conserved parts of the genome. However, due to a low degree of similarity between viroids and the HDV genome, this ancestral viroid affiliation is disputed (Jenkins et al. 2000). Furthermore, viroids are not known to code any protein, while HDV does. A double rolling circle model