ICTV Virus Taxonomy Profile: *Hepeviridae*

Michael A. Purdy, 1,* Tim J. Harrison, 2 S. Jameel, 3 X-J. Meng, 4 H. Okamoto, 5 W. H. M. Van der Poel, 6 Donald B. Smith 7 and ICTV Report Consortium

**Abstract**

The family *Hepeviridae* includes enterically transmitted small non-enveloped positive-sense RNA viruses. It includes the genera *Piscihepevirus*, whose members infect fish, and *Orthohepevirus*, whose members infect mammals and birds. Members of the genus *Orthohepevirus* include hepatitis E virus, which is responsible for self-limiting acute hepatitis in humans and several mammalian species; the infection may become chronic in immunocompromised individuals. Extrahepatic manifestations of Guillain–Barré syndrome, neuralgic amyotrophy, glomerulonephritis and pancreatitis have been described in humans. Avian hepatitis E virus causes hepatitis–splenomegaly syndrome in chickens. This is a summary of the International Committee on Taxonomy of Viruses (ICTV) Report on the taxonomy of the *Hepeviridae*, which is available at [www.ictv.global/report/hepeviridae](http://www.ictv.global/report/hepeviridae).

**Table 1.** Characteristics of the family *Hepeviridae*

<table>
<thead>
<tr>
<th>Typical member:</th>
<th>human hepatitis E virus Burma (M73218), species <em>Orthohepevirus</em> A, genus <em>Orthohepevirus</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virion</strong></td>
<td>Non-enveloped, 27–34 nm diameter with a single capsid protein</td>
</tr>
<tr>
<td><strong>Genome</strong></td>
<td>6.4–7.2 kb capped positive-sense monopartite RNA containing three ORFs</td>
</tr>
<tr>
<td><strong>Replication</strong></td>
<td>Occurs in association with the host endoplasmic reticulum</td>
</tr>
<tr>
<td><strong>Translation</strong></td>
<td>From genomic (ORF1) and a subgenomic (ORF2 and ORF3) capped mRNA</td>
</tr>
<tr>
<td><strong>Host range</strong></td>
<td>Mammals (<em>Orthohepevirus</em> A, C and D), birds (<em>Orthohepevirus</em> B) and trout (<em>Piscihepevirus</em>)</td>
</tr>
<tr>
<td><strong>Taxonomy</strong></td>
<td>Two genera</td>
</tr>
</tbody>
</table>

**VIRION**

The virions of human hepatitis E virus are icosahedral, non-enveloped, spherical particles with a diameter of approximately 27–34 nm (Table 1, Fig. 1). The capsid is formed by capsomers consisting of homodimers of a single capsid protein, forming the virus shell. Each capsid protein contains three linear domains forming distinct structural elements: S (the continuous capsid), P1 (three-fold protrusions) and P2 (two-fold spikes). Neutralizing epitopes have been found in the P2 domain. Each domain contains a putative polysaccharide-binding site that may interact with cellular receptors. Native T=3 capsids contain flat dimers, with less curvature than those of T=1 virus-like particles [1].

![Fig. 1. Negative contrast electron micrograph of human hepatitis E virus virions from a case stool collected in Nepal. (A) virion and (B) empty capsid. The bar represents 100 nm (photograph from M. Purdy).](image-url)
overlaps ORF1. The 5’ non-coding regions: ORF2 overlaps ORF3 but neither
like supergroup
the first ORF (ORF1) have limited similarity with the
HUD, Hepeviridae unique domain, also called the Z domain [7]; PP, a
hypervariable polyproline region that is dispensable for virus infectiv-
ity; Macro, macro domain; Hel, helicase; and RdRP, RNA-dependent
polymerase [7, 8]. ORF2 encodes a capsid protein and is followed
by a short 3’ NCR. ORF3 overlaps ORF2 in a different reading frame
and encodes a small phosphoprotein with a multi-functional C-termi-
nal region. The scale is in bases.

GENOME

Viral genomes are positive-sense monopartite RNA of about
6.4 to 7.2 kb, with three ORFs flanked by short 5’- and 3’-termi-
non-coding regions; ORF2 overlaps ORF3 but neither
overlaps ORF1. The 5’-end is m’G-capped and the 3’-end is
polyadenylated (Fig. 2). Non-structural proteins encoded by
the first ORF (ORF1) have limited similarity with the ‘alpha-
like supergroup’ of viruses and contain domains consistent
with a methyltransferase, papain-like cysteine protease,
macro domain, RNA helicase and RNA-dependent RNA
polymerase [2]. Some of these properties have been con-
firmed experimentally. It remains unclear whether the
ORF1-encoded activities function as a single protein with
multiple functional domains or as individually cleaved
smaller proteins. Virions are constructed from a capsid
protein encoded by ORF2 that may be proteolytically processed.
A small immunoreactive protein (12.5 kDa) encoded by the
third ORF (ORF3) has been shown to exhibit multiple func-
tions associated with virion morphogenesis, egress and viral
pathogenesis. The capsid and ORF3 proteins are translated
from a subgenomic RNA that is generated from the genome.
Although human hepatitis E viruses are shed into faeces as
non-enveloped virions, they appear to be released into the
bloodstream as membrane-associated virions [3].

REPLICATION

The replication of human hepatitis E virus is not well under-
stood. The viral RNA-dependent RNA polymerase associ-
ates with the host endoplasmic reticulum through residues
encoding a predicted transmembrane domain in order to
begin replicating the viral genome. It appears that replica-
tion involves temporal separation and alternating cycles of
positive- and negative-sense RNAs to produce capsid, ORF3
protein, ORF1 polypeptide and new genomes, resulting in
the generation of progeny virions [2, 4].

TAXONOMY

Orthohepevirus. Members of this genus infect a wide range
of mammals, including humans, domestic and wild swine,
der, sheep, rabbits, camels, mongooses, (Orthohepevirus A
members), rats, ferrets, shrews, bandicoots, mink (Orthohe-
pevirus C members), bats (Orthohepevirus D members), and
birds (Orthohepevirus B members) [5]. Unclassified viruses
have been detected in moose and foxes, and in droppings
from little egrets and kestrels. Human hepatitis E virus can
cause self-limiting acute hepatitis in humans and is trans-
mittted by contaminated water or the consumption of
undercooked or raw meat and dairy and other products
from infected animals. Human hepatitis E virus is the lead-
ing cause of acute hepatitis in developing countries [6].

Piscihepevirus. This genus includes a single species whose
typical isolate, cutthroat trout virus, infects trout, although
its pathogenicity and full host range are unknown [5].

RESOURCES

Full ICTV Online (10th) Report: www.ictv.global/report/
hepeviridae.

Funding information
Production of this summary, the online chapter and associated resour-
ceses was funded by a grant from the Wellcome Trust (WT108418AA).

Acknowledgements
Members of the ICTV Report Consortium are Elliot J. Lefkowitz,
Andrew J. Davison, Stuart G. Siddell, Peter Simmonds, Michael J.
Adams, Donald B. Smith, Richard J. Orton and Nick J. Knowles.

Conflicts of interest
The authors declare that there are no conflicts of interest.

References
4. Varma SP, Kumar A, Kapur N, Durgapal H, Acharya SK et al. Hepa-
titis E virus replication involves alternating negative- and positive-
6. Khuroo MS. Discovery of hepatitis E: the epidemic non-A, non-B hep-
7. Kelly AG, Netzel NE, White PA. Ancient recombination events and
8. Koonin EV, Gorbalenya AE, Purdy MA, Rozanov MN, Reyes GR et al.
Computer-assisted assignment of functional domains in the non-
structural polyprotein of hepatitis E virus: delineation of an addi-