A novel hepatitis E virus-like agent in wild Norway rats (*Rattus norvegicus*) from Germany

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Hepatitis E represents a rare human disease in developed countries. This disease is characterized by a self-limiting jaundice of varying severity and often accompanied by unspecific symptoms like fever, headache and pain of the upper abdomen. Autochthonous cases in Europe are caused by hepatitis E virus (HEV) genotype 3, which is most likely transmitted to humans from domestic pigs, wild boar or deer. Multiple reports on the detection of HEV-specific antibodies in rats suggested the presence of an HEV-related agent; however, infectious virus or a viral genome could not be demonstrated in these rodents so far. Recently, a nested broad-spectrum RT-PCR protocol was developed capable of detecting different HEV genotypes including those derived from wild boar and chicken. Using this novel assay, an initial screening of 30 fecal samples of wild Norway rats (Rattus norvegicus) from Hamburg (Germany) resulted in the detection of two sequences with similarities to human, mammalian and avian HEV. Investigation of liver tissue samples from additional rats from Hamburg resulted in the assessment of the complete nucleotide sequence showing a typical genome organization of HEV. Additional molecular and serological studies of Norway rats from Berlin and Stuttgart indicated a broad geographical distribution of this novel virus. Phylogenetic analyses of partial and complete genome sequences suggest this virus as separate HEV genotype tentatively designated as rat HEV. Moreover, the phylogenetic analyses of rat HEV sequences from different geographical origin demonstrated a geographical clustering suggesting an isolated long-term evolution of the different strains. Virus particles with morphology reminiscent of HEV could be demonstrated by immune electron microscopy in a fecal sample from an infected rat. Real-time RT-PCR and immunohistochemistry investigations of different tissue samples indicate the hepatotropism of the virus. Future investigations are dedicated to characterize the molecular evolution and host adaptation of the virus, to assess its zoonotic potential and to study its possible application in an animal model for human hepatitis E.

Keywords: hepatitis E virus, phylogeny, Rattus norvegicus, RT-PCR