

# Reconstructing the evolutionary origins and phylogeography of hantaviruses

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**Rodents have long been recognized as the principal reservoirs of hantaviruses. However, with the discovery of genetically distinct and phylogenetically divergent lineages of hantaviruses in multiple species of shrews, moles, and insectivorous bats from widely separated geographic regions, a far more complex landscape of hantavirus host distribution, evolution, and phylogeography is emerging. Detailed phylogenetic analyses, based on partial and full-length genomes of previously described rodent-borne hantaviruses and newly detected non-rodent-borne hantaviruses, indicate an Asian origin and support the emerging concept that ancestral non-rodent mammals may have served as the hosts of primordial hantaviruses.**

## A new frontier

Guided by decades-old historical accounts associating hantaviruses (family *Bunyaviridae*, genus *Hantavirus*) with shrews [1–4] and moles [5], and empowered by molecular technology and the generosity of museum curators and field mammalogists who willingly granted access to their archival tissue collections, opportunistic investigations have resulted in the identification of genetically distinct and phylogenetically divergent lineages of hantaviruses in multiple species of shrews and moles (order Eulipotyphla, families Soricidae and Talpidae) [6–27] and insectivorous bats (order Chiroptera; see [Glossary](#)) [28–32] from widely separated geographic regions. These newfound hantaviruses broaden our knowledge about their reservoir host distribution significantly beyond that of rodents (order Rodentia, families Muridae and Cricetidae). In addition, the discovery of genetically distinct eulipotyphla- and chiroptera-associated hantaviruses enriches our understanding about their evolutionary origins and indicates that their phylogeography is far more complex and ancient than

originally contemplated. As such, an emerging new frontier in hantavirus research is now focused on filling major gaps in our understanding about the ecology, host diversity, transmission dynamics, and pathogenic potential of these previously unrecognized, still-orphan hantaviruses, before the next new disease outbreak is documented.

## Early history of hantavirus discovery and epidemic activity

The seminal discovery of Hantaan virus (HTNV), as the etiologic agent and prototype virus of hemorrhagic fever with renal syndrome (HFRS), in a Korean striped field mouse (*Apodemus agrarius corea*) trapped in 1976 [33], serves as a milestone in modern-day hantavirology. The isolation of HTNV has made possible the identification of multiple other HFRS-causing hantaviruses, including Puumala virus (PUUV) in the bank vole (*Myodes glareolus*) [34], Seoul virus (SEOV) in the Norway rat (*Rattus norvegicus*) [35], and Dobrava virus (DOBV) in the yellow-necked mouse (*Apodemus flavicollis*) [36]. Although HFRS has been recognized for more than 1000 years [37], and hantaviruses themselves may have existed for thousands [38] to tens of millions [39–43] of years, renewed attention to these once exotic rodent-borne viruses was prompted by a terrifying outbreak of a rapidly progressive, frequently fatal respiratory disease, now known as hantavirus cardiopulmonary syndrome (HCPS), caused by Sin Nombre virus (SNV) transmitted by the deer mouse (*Peromyscus maniculatus*) in southwestern USA in 1993 [44–47]. HFRS- and HCPS-causing hantaviruses are harbored by different lineages of rodent subfamilies in the Old and New Worlds, respectively. However, the two clinical syndromes represent a spectrum of disease such that HFRS cases commonly have cardiopulmonary features and HCPS cases frequently exhibit renal insufficiency or dysfunction [48,49].

## Evolutionary lessons from rodent reservoirs

To date, rodents have been the only reservoir hosts associated with pathogenic hantaviruses. Therefore, historically,

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Keywords: hantavirus; Eulipotyphla; Chiroptera; evolution; host-switching.

0966-842X/

© 2014 Published by Elsevier Ltd. <http://dx.doi.org/10.1016/j.tim.2014.04.008>

## Glossary

**Chiroptera:** an order of placental mammals, the bats. They are grouped in the Laurasiatheria lineage together with Eulipotyphla and some other mammalian orders that do not include Rodentia.

**Co-divergence or co-speciation:** terms used to refer to the reciprocal differentiation or speciation of interacting taxa, presumably in response to evolutionary pressures exerted by one on the other and vice versa. In the strictest sense, this would involve 'one-for-one' changes in taxon pairs and occur on similar timescales.

**Eulipotyphla:** an order of placental mammals that includes most taxa formerly in Insectivora (dissolved when it was shown to be polyphyletic), such as the families Soricidae (true shrews) and Talpidae (moles and shrew moles). Used here in place of Soricomorpha to refer to soricids and talpids because Soricomorpha is paraphyletic: Soricidae are more closely related to the family Erinaceidae (which includes hedgehogs) than Talpidae.

**Genetic drift:** the fixation of genotypes through random processes, tending to build-up over time and differentiate populations isolated from gene flow. Noted to be an important mechanism of evolution in hantaviruses that are largely isolated in specific hosts.

**Gene flow:** the movement of genetic forms into new populations, such as those formerly isolated by geography, or even by host type.

**Host-switching or host capture:** the stable establishment of a parasite into a new and distinct host species.

**Monophyletic:** a evolutionary term used in phylogenetics to refer to a group of taxa that includes an ancestral species and all its descendants. See also paraphyletic and polyphyletic.

**Natural selection:** the differential representation of types in future generations caused by fitness differences (where fitness is the ability to reproduce, or survive to reproduce). Negative selection results in proportionally fewer individuals of a given type in subsequent generations and ultimately leads to the disappearance of that type, whereas positive selection results in an increase in the proportion of individuals of a given type in future generations and can ultimately lead to the fixation of that type to 100%.

**Paraphyletic:** a evolutionary term used in phylogenetics to refer to a group of taxa that includes an ancestral species and most of its descendants minus a monophyletic group. See also monophyletic and polyphyletic.

**Polyphyletic:** a evolutionary term used in phylogenetics to refer to groups of taxa that do not exclusively share a common ancestor. See also monophyletic and paraphyletic.

**Reassortment:** an exchange of segment(s) between parental viruses. A potentially important source of innovation for segmented viruses, particular hantaviruses show evidence of reassortment. For example, AZGV, RKPV, and LXV all show incongruities in terms of their phylogenetic positions across S, M, and L segments, suggesting that these segments have different evolutionary histories.

**Recombination:** the recombining of genetic material from two 'parental' viruses. Because the hantavirus genome is separated into three segments, we use 'recombination' here to refer specifically to rearrangement of the genomic material between parental viruses within a given segment. AZGV, RKPV, and RPLV represent recombinants for the S segment: weak bootstrap support values reflect uncertainty in their evolutionary histories.

**Rodentia:** an order of placental mammals, the rodents, that includes several families discussed here, such as Muridae (Old World mice, rats, and gerbils) and Cricetidae (New World mice and rats, hamsters, voles, lemmings). Rodentia falls into the lineage Euarchontoglires, as opposed to the group Laurasiatheria that includes shrews, moles (Eulipotyphla), and bats (Chiroptera).

rodents have been an important focus of hantavirus surveillance and research. The breadth of rodent taxa harboring hantaviruses spans two families (Muridae and Cricetidae) and four subfamilies within the suborder Myomorpha of the order Rodentia, and includes mice, rats, lemmings and voles (Table S1 in the supplementary material online; representative human cases are included). Generally, each rodent host species has its own hantavirus species [43], although in some cases various hantavirus genotypes have been described from multiple closely related host species (e.g., [50]). Overall, the rodent-borne hantaviruses can be divided into two major lineages: a highly diverse lineage distributed in New World mice and rats, lemmings, and voles (Cricetidae subfamilies Arvicolinae, Neotominae, and Sigmodontinae), and another distinct, less diverse lineage distributed in Old World mice and rats (Muridae subfamily Murinae) that is sister to a highly

diverse and globally distributed lineage of soricid and talpid-borne hantaviruses (Figure 1). Thus, within the rodent-borne lineages, hantaviruses are geographically structured in distribution similar to their host subfamilies, the Old World Murinae, New World Neotominae and Sigmodontinae, and northern hemisphere Arvicolinae. The average sequence divergences at the amino acid level of 26% for the small genomic segment (S), 29% for the medium segment (M), and 23% for the large segment (L) among the rodent-borne hantaviruses represented in Table S1 are substantial and may reflect a high degree of host specialization.

In many instances the relatedness among host taxa and the relatedness among their hantaviruses correspond [43], with the most notable exception being the lack of support for monophyly of the rodent-borne hantaviruses in light of their relationships with those found in shrews, moles, and bats [12,31,51]. That each species of rodent hosts a specific hantavirus, or in some cases a few closely related hantaviruses, and the phylogenetic congruency between host and virus within many rodent lineages, has led to the perception that hantaviruses are a model of host–parasite coevolution in the strictest meaning, that of co-divergence. The timing of hantavirus divergence remains a still-unanswered question (Box 1). However, mounting phylogenetic evidence from the recently described hantaviruses across a range of other mammalian hosts confirms that rodent-borne hantaviruses are polyphyletic. That is, they do not form a single lineage, but one that probably involved one or more exchanges of ancestral viruses with other mammals, such as shrews, moles, and/or bats [12,31], or their common ancestor. Evolutionary forces have continued to shape hantavirus diversification in the different host groups and geographic settings.

## New hosts discovered, redefining hantavirus evolutionary trajectories and origins

Although not recognized at the time, Thottapalayam virus (TPMV), a once unclassified virus isolated from an Asian house shrew (*Suncus murinus*) captured in southern India in 1964 [1], was technically the first hantavirus. However, even after TPMV was shown to be a hantavirus [3] it was assumed to represent a spillover event from a rodent host. Shrews and moles were generally ignored in the ecology and evolution of hantaviruses despite the finding of HFRS antigens or antibodies in the Eurasian common shrew (*Sorex araneus*), Eurasian pygmy shrew (*Sorex minutus*), Eurasian water shrew (*Neomys fodiens*), European mole (*Talpa europaea*), Chinese mole shrew (*Anourosorex squamipes*), and northern short-tailed shrew (*Blarina brevicauda*) [2,4,5,52,53]. Each of these species, and many other species of shrews and moles, representing five subfamilies and two families of Eulipotyphla, have been shown to host hantaviruses (Table S1) whose genetic diversity far surpasses that of hantaviruses carried by rodents [6–27]. In addition, highly divergent lineages of hantaviruses have been identified in seven species of insectivorous bats, including the banana pipistrelle (*Neoromicia nanus*) in Côte d'Ivoire [28,32], hairy slit-faced bat (*Nycteris hispida*) in Sierra Leone [29], Pomona roundleaf bat (*Hipposideros pomona*) in Vietnam [30,32], and Japanese house bat

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