

# Shrew-borne Thottapalayam Virus: An Indian Perspective

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## Abstract

In 1964, a field study yielded the isolation of Thottapalayam virus (TPMV). This was first report of presence of this virus from Asian house shrew (*Suncus murinus*) in Tamil Nadu state of India. TPMV has been an exception to all other known Hantaviruses (HTNV), since rest of the HTNV has been associated with the Muridae rodents. This covers over 700 species of rodents. The presence of this virus has been reported from India, Nepal, Vietnam, and China and possibility of discovering in other countries exists. In the last few years, studies have discovered many shrew-borne HTNV from across the globe. Direct relevance of human health and this virus could not be established till now. Discovery of novel TPMV from shrew has suggested that this reservoir also can participate in maintaining this virus in nature and perhaps in its transmission. Unlike other human pathogenic HTNV, the public health importance of TPMV is still unknown. This article focuses on the present information regarding epidemiology, genome analysis, reservoir host, possible human infection of TPMV and need for active surveillance in India.

**Keywords:** Thottapalayam virus; Hanta virus; Shrew

## Introduction

Thottapalayam virus (TPMV) is a member of Hantaviruses (HTNV), which belongs to *Bunyaviridae* family. It was firstly isolated from the house shrew *Suncus murinus* from South India in the year 1964 [1]. Considering its serological relatedness to other HTNV's, it was placed under the genus *Hantavirus* [2]. The electron microscopic study revealed the structural resemblance of TPMV particles with Hantaviruses (HTNV), which was further, corroborated by cross-reactivity of TPMV,

infected cells with a known Hantavirus antibody in an immune fluorescence study [3].

*Bunyaviridae* family cover a large number of viruses in four genera which are responsible for causing human diseases and show a range of clinical symptoms from mild to severe form. These infections are commonly reported in Asia and Europe in humans and recognized in two syndromes i.e. hemorrhagic fever with renal syndrome (HFRS) and Hantavirus pulmonary syndrome (HPS). The very common HTNV causing HFRS are Hantaan virus, Puumala, Dobrava virus and Seoul virus. Globally, rodents and other insectivorous small mammals are known to be the vectors of HTNV's. Thus, viruses in this genus have appeared to be evolved with their reservoir hosts [4,5]. HTNV usually does not cause an illness to their animal hosts, whereas, consequences of infection in human depends upon the infecting virus. Although a number of HTNV have a tendency to be associated with asymptomatic infections/mild disease, but few of them cause case fatality rates higher than 50%. Although in the shrew, TPMV cause transient viremia and virus is shredded through oropharyngeal secretions. However, virus is excreted in urine and feces. Its persistence in tissues (lung) has also been noticed [6]. The house shrew naturally harbors this virus and it is suspected that due to close sharing habits with other domestic rodents, the spillover to other rodent reservoir host is possible.

TPM is a tripartite, single-stranded negative sense RNA and each genomic segment has the exclusive alike 3'-terminal sequence of AUCAUCAUCUG [7]. Serological association of TPMV, when compared with other Hantaviruses using cross plaque-reduction assay (PRNT) and ELISA, it was found that the TPMV doesn't neutralize with other Hantaviruses. TPMV genomic sequences are considered as a divergent member in genus Hantavirus. The TPM virus nucleotide sequences have similarity with known Hantaviruses by 53-56%, 51-52%, and 62-63% for the nucleocapsid (S), glycoprotein (M) and RNA dependent RNA polymerase (L) segments, respectively. The amino acid difference while comparing with other Hantaviruses and TPMV was very high, with 50.8-54.5%, 54.9-57.2%, and 37.6-38.9% for the S, M and L segments proteins [8]. Phylogenetic analysis using the N protein-encoding S

segment, suggested that TPMV is an out-group in Hantaviruses thus forming separate clade, which is established in parallel to the evolution of murid, arvicolid, and sigmodontine rodents [9]. A recent study conducted in Nepal showed clustering of TPMV in a specific pattern of geographical specific from tissues of the lung house shrews, which was earlier, observed in the rodent- and sorcid-borne viruses. This conclusion was drawn based on S, M & L gene segments of Hantavirus. These results further verify that the house shrew is the reservoir of TPMV and propose an established virus-host association. Comparison of these viruses shows approximately 80% nt and >94% aa sequence correspondence to prototype TPMV [10]. Recently, TPMV was also discovered and reported in China, Nepal, and Vietnam [4,10,11] and is deliberated to have had an early evolutionary deviation from rodent-borne hantavirus [8,9]. Hunting of Zoonosis causing diseases led to discovery of further Hantavirus in bats from African region.

The available data propose that TPMV is non-pathogenic in human because it uses  $\beta$ -1 rather than  $\beta$ -3 integrin, which is the main receptor on platelets and endothelial cells accountable for vascular leakage and hemorrhage linked with Hanta cases [12]. Few reports have suggested the presence of IgG antibodies against HTNV in the sera from humans in southern India [6,13], but proof for HTNV disease in India is still missing. No study could co-relate accurately the presence of Hantavirus in the sick patient and its association in India. Due to lack of virus isolation or sequences from claimed cases, the question still remains same this virus is present in India or not. On the other hand, house shrews are house dwelling and normally living in close proximity to human and the possibility always exists to get TPMV infection in humans by urine or excreta of the animal. Presence of this virus infection has been shown in a Laotian immigrant with a febrile illness [14]. This further suggests that there is need to have the proper study to understand the existence of TPMV in the domestic rodent hosts. The discovery of viruses in insectivores suggests that they may have a significant role in the Zoonosis.

Hantaviruses have unusually different degree of pathogenicity as far as humans are concerned. Many viruses harbored by Arvicolid rodents, appear to be virulent (such as PHV). Preliminary studies indicate that TPMV might be non-pathogenic. Recently, studies have shown many TPMV like viruses in Nepal, China, and Thailand, which suggests a virus-host relationship between TPMV and shrews. TPMV can't be cultured using *in vitro* methods; since, it doesn't show any cytopathic effects. Due to this, it has been difficult studying the virus properties and its detection from the collected samples. To solve this problem a serological assay was developed using recombinant TPMV protein [14]. The serological assay developed was quite useful for the virus detection studies but the cross-reactivity posed a problem. Now, newer molecular techniques are available, which targets the TPMV S and L gene. This has made it easier to detect the presence of TPMV in the samples.

Murid rodents from subfamilies the *Muridinae*, *Arvicolinae* and *Sigmodontinae* carry almost all the Hantaviruses. Hemorrhagic fever with renal syndrome (HFRS) has been shown to be associated with Hantaan, Seoul and Puumala viruses infection by these subfamily rodents while Hantavirus Pulmonary Syndrome (HPS) is associated with Sigmodontinae-associated Hantaviruses (Sin Nombre and Andes viruses) [15,16]. Humans get infected by inhaling aerosolized secreta or excreta of chronically infected rodents. The prototype virus of HF with renal syndrome has been associated with house shrew, greater white-toothed shrew (*Crociduraruscula*) as well as Chinese mole shrew (*Anourosorex squamipes*). This suggests that a number of species of shrews can be incidental hosts of these viruses. Shrews are found in woodlands and grasslands and widely dispersed small mammal species. They make nests underground or under dense vegetation but sometimes occupy burrows of other small mammals.

## Conclusion

Murid rodents carry almost all the HTNV. These insect eating small mammals are smaller than many rodent species. The probability of contact between humans and these shrew species or excretions may be too low for virus transmission. Thus, due to the lack of identified infection or outbreak, this zoonotic infection might go unrecognized. Inhalation of aerosolized secretions may infect humans *via* excreta from chronically infected rodents. Keeping in the view, the earlier published reports and unpublished data suggesting the presence of HTNV cross-reacting antibodies emphasizes on the need to explore possibilities to determine the existence of HTNV.

Based on the little available information, it appears that this virus may not have potential to cause outbreak or epidemic. However, the human infections originating from rural settings where human-rodents interface is likely to be much closer and diagnosis could not be provided particularly in the cases of acute febrile illness undifferentiated febrile illness and viral hemorrhagic fevers involving renal or respiratory failure should be screened for TPMV. This necessitates to look into the undiagnosed human samples for TPMV, particularly when the samples are from rural areas where human-rodents interface is likely to be more closer.

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