VIRUS EVOLUTION

Virus Evolution, 2025, **11(1)**, veaf039
DOI: https://doi.org/10.1093/ve/veaf039
Advance Access Publication 27 May 2025
Research Article

Discovery of influenza-like virus clades in invertebrates and the evolutionary history and host-shifting events of Orthomyxoviridae in metazoans

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Abstract

Epidemics are often initiated by emerging and re-emerging infectious diseases caused by viruses of animal origin. It is thus important to identify the reservoirs of potentially zoonotic viruses and understand the dynamics of their host shifts. The flu viruses belong to the virus family Orthomyxoviridae, which also contains Isavirus, Quaranjavirus, and Thogotovirus. Many members of this virus family are known to be pathogenic to humans. For initial surveillance of animal-originated or zoonotic Orthomyxoviridae, unclassified viruses were screened by the use of high-throughput transcriptomes as a data source because of their wide species and lineage coverage. We identified 96 novel or unclassified Orthomyxoviridae members with the discovery of three new lineages of the virus, possibly new genera, one sister to Influenza + Thogotovirus, one to Influenza + Thogotovirus + Quaranjavirus, and another one to all orthomyxoviruses except Isavirus. Throughout the evolution of Orthomyxoviridae, there might be multiple host-shifting incidences, shifting between six different animal host phyla. The most common host shifts seemed to be between Arthropoda and Chordata; however, further evidence would be needed to fully support this statement. Nonetheless, Orthomyxoviridae viruses can infect a wide range of animal phyla, while some members hold a higher risk of shifting back to Chordates and humans that warrants surveillance.

Keywords: influenza-like; evolution; invertebrates; Orthomyxoviridae; host-shifting; Thogotovirus; Quaranjavirus; Isavirus; influenza

Introduction

Most, if not all, emerging and re-emerging infectious diseases, including SARS, MERS, and influenzas, are associated with viruses of zoonotic origins, i.e. they are transmitted from animals to humans (McArthur 2019, Zhu et al. 2020). During the initial outbreak of SARS-CoV-2, the early detection, diagnosis, and treatment strategies were based on the lessons learned from previously known coronaviruses (Guo et al. 2020), while the origin of SARS-CoV-2 was identified swiftly thanks to the previous large-scale coronavirus screenings from animals over the past two decades (Zhou et al. 2020). This indicates the importance of screening novel virus lineages from animals. A virus group that is well-known for repeatedly jumping from animals to humans is 'Influenza', which includes swine flu and avian flu (Dhama et al. 2012, Tanner et al. 2015), and it has already caused six pandemics in the last 140 years (Potter 2001). All influenza viruses belong to the virus family Orthomyxoviridae (Dowdle et al. 1975), which consists of three genera other than Influenza, namely, Isavirus, Quaranjavirus, and Thogotovirus. Both 'Influenza' and 'Isavirus' are hosted only in vertebrates, while Isavirus is infamous for traumatizing the aquaculture industry by infecting farmed fishes (Rimstad and Markussen 2020). For quaranjaviruses and thogotoviruses, invertebrates are their 'reservoirs' or 'natural hosts'. However, both of these viruses are able to cross species barriers and cause diseases in humans (Taylor et al. 1966, Kosoy et al. 2015, Savage et al. 2018, Mourya et al. 2019), as well as other vertebrates such as marsupials (Da Silva et al. 2005), ducks (Kessell et al. 2012),

Received: July 15, 2024. **Revised:** April 10, 2025. **Accepted:** May 8, 2025

and sheep (Lledo et al. 2020), and are capable of inducing pathological conditions and cytokine responses, similar to highly virulent influenza (Li et al. 2008). Despite the capability of these Orthomyxoviridae members to cause multiple epidemics through various independent animal-to-human jumps, most studies have focused on influenza only. Limited studies are focusing on the other three genera (Da Silva et al. 2005, Briese et al. 2014, Contreras-Gutierrez et al. 2017, Cholleti et al. 2018, Pettersson et al. 2020). Moreover, there has been no systematic study on the entire family, nor a literature review available. Therefore, most members of the Orthomyxoviridae family and their evolutionary histories are poorly documented.

This study aims to screen and understand potential emerging infectious viruses and novel members from the Orthomyxoviridae of zoonotic origins. Here, we identified unclassified virus species from the emerging infectious virus family—Orthomyxoviridae, from different animal hosts and revealed their evolutionary history and host-shift dynamics by analysing high-throughput RNA data with broad lineage coverage.

Materials and methods

Data collection

The PB1 protein, which exhibits RNA-dependent polymerase activity, is the most conserved in Orthomyxoviridae (Chu et al. 2012), and is thus suitable for evolutionary analyses of viruses, which generally have high substitution rates. All 3813 transcriptomes covering 2827 metazoan species from the Transcriptome Shotgun Assembly (TSA) Database (Sayers et al. 2019) downloaded in July 2021 were used for analyses. These RNA sequences were matched with PB1 protein sequences of known Orthomyxoviridae downloaded from the NCBI virus database in July 2021 (Sayers et al. 2019) by BLASTx and the matched proteins were verified again by tBLASTn searches as the queries back to the transcribed sequences (Gertz et al. 2006) with the expected threshold of 0.05 using BLOSUM62. Subsequently, 113 transcribed RNA sequences related to the Orthomyxoviridae PB1 gene were identified from 96 species. At the time, these sequences had not been reported as belonging to any known viruses, as confirmed by cross-checking with the virus database (see Supplementary Table S1). The taxonomy of the 96 host species was identified by the NCBI Taxonomy tool (Schoch et al. 2020). The RNA sequences were translated to protein sequences using Clustal X (Larkin et al. 2007) in their correct reading frames. These protein sequences were then compared against all known Orthomyxoviridae proteins (excluding influenza viruses) in NCBI using BLAST. This search identified 380 Orthomyxoviridae PB1 sequences. To reduce redundancy, we applied cd-hit with a 99% identity threshold, resulting in 192 representative sequences. Those with amino acid (AA) sequences shorter than 520 were removed and the resulting sequences were combined with PB1 sequences from Influenza A–D viruses and Thogotovirus thogotoense to create the final PB1 reference set for subsequent phylogenetic analyses. For the detection of additional orthomyxoviral proteins beyond PB1 in these host species, a reference set of 73 orthomyxoviral proteins beyond PB1 including hemagglutinins, glycoproteins, PAs, PB2s, nucleoproteins, and hypothetical proteins (Supplementary File S1) downloaded from NCBI Identical Protein Groups was compared against the host species' transcriptomes in TSA using tBLASTn and the results were summarized in (Supplementary File S2) and the species with additional orthomyxoviral proteins were marked with blue bars in Fig. 1.

Phylogenetic analysis

The protein sequences were aligned using MAFFT (Katoh and Standley 2013), along with other reference Orthomyxoviridae PB1 proteins. After comparing with known complete PB1 protein sequences (~700 AAs long), 47 newly identified Orthomyxoviridae PB1 proteins with relatively high protein completeness (with at least 520 aligned AAs) were retained for phylogenetic analyses with known Orthomyxoviridae PB1 proteins and Tilapia lake virus (an Amnoonviridae virus from fish) PB1 protein as outgroup (Supplementary File S3) (Fig. 1), since Amnoonviridae is considered as a sister clade to Orthomyxoviridae (Turnbull et al. 2020; Arragain et al. 2023). The known Orthomyxoviridae reference members were used to position the lineage of the new viruses.

The alignments were untrimmed (Supplementary File S3), and the best substitution model was identified using ModelTest implemented in IQ-Tree 2 (Minh et al. 2020). Maximum likelihood phylogenetic reconstruction was performed along with the SH test and 1000 ultrafast bootstrap replicates using the same software. Host information was extracted from NCBI virus, while the host association was coded into seven categories: Chordata, Xenacoelomorpha, Arthropoda, Mollusca, Cnidaria, Ctenophora, and Environment/Unknown.

Results and discussion

Phylogenetic relationships within Orthomyxoviridae

To assess how Orthomyxoviridae dispersed in metazoans, we analysed 3813 transcriptomes covering 2827 metazoan species from the TSA Database (Sayers et al. 2019). Subsequently, 113 transcribed RNA sequences from 96 species were identified to be related to Orthomyxoviridae PB1 genes (RNA-directed RNA polymerase catalytic subunit) (Supplementary Table S1), and many of them were unclassified before. PB1 sequences of known Orthomyxoviridae members were incorporated in phylogenetic analyses to infer the affinity and potential classification of the identified viruses (Fig. 1) (Supplementary File S3). We found three new lineages of the virus, possibly new genera: Clade α is sister to Influenza + Thogotovirus, Clade β is sister to Influenza + Thogotovirus + Quaranjavirus, while Clade γ is sister to all other Orthomyxoviridae clades except Isavirus (Fig. 1). These viruses were identified from several metazoan lineages, including Mollusca (shellfish) and some of the basal lineages, i.e. Ctenophora (commonly known as comb jellies), Cnidaria (composed of jellyfishes, hydras, and corals), Isopoda (an ancient Crustacea lineage), and Xenacoelomorpha (specifically *Symsagittifera roscoffensis*, which is the only animal capable of photosynthesis) (Olendraite et al. 2023). Cnidaria and Ctenophora are two of the most primitive metazoan lineages that have been proposed to be the sister group of all other animals (bilaterians) and are very important for studying the early evolution of animals and the origin of multicellular organisms (Rytkonen 2018, Daley and Antcliffe 2019, Nielsen 2019). In addition, we identified new viruses belonging to Thogotovirus and Quaranjavirus. These viruses constitute a basal assemblage concerning all the other members of Orthomyxoviridae excluding the Isavirus that cluster as a clade, denoted as Clade 1 hereafter (Fig. 1).

The occurrence of Orthomyxoviridae in multiple ancient metazoan lineages might indicate ancestral orthomyxovirids' abilities to infect and co-exist with multiple ancient Metazoan lineages, or there might be frequent host-shift events that occurred throughout the co-evolution of animals and Orthomyxoviridae.

Figure 1. Maximum likelihood phylogeny of Orthomyxoviridae based on PB1. Branches and tips are coloured by viral genus. GenBank accession numbers and virus names are labelled at the tips. Node support values are indicated by coloured circles. Host information for each virus is displayed on the right, alongside a phylogenetic tree of the six host phyla analysed (top right). For newly discovered Orthomyxoviridae members, a bar following the virus name indicates cases where multiple orthomyxoviral proteins were identified in the host transcriptome.

Furthermore, apart from the newly identified viruses that belonged to the named genera of Orthomyxoviridae, several novel (or unclassified) viruses were found to cluster together and form completely new clades that warrant research attention. In short, Orthomyxoviridae are widely dispersed across diverse metazoans, including ancient animal lineages.

Host associations

Emerging infectious diseases are often characterized by viral host-switching events (Geoghegan et al. 2017), which entail strong and stringent adaptive evolution of the viruses as they colonize a new niche (Simmonds et al. 2019). Understanding how viruses overcome ecological and genetic barriers during host shifts is of paramount importance in disease control. By inferring from the phylogenetic tree, the ancestor of orthomyxovirids was more likely to infest Chordates originally, as the most basal genus—the isaviruses—and the outgroup—Tilapia lake virus—are all Chordates infesting (Fig. 1). Therefore, there could be several host-shifting events from Chordates to arthropods, Ctenophora, Cnidaria, Xenacoelomorpha, and Mollusca in Clade 1. Furthermore, inferring from the host associations of arboviruses in Thogotovirus and Quaranjavirus (Clades 1A and 1B), there might have been 18 possible instances of host-shifting from arthropods back to Chordates in these arboviruses. Hence, based on these inferences, host-shiftings between Arthropoda and Chordata were probably the most frequent, and the Orthomyxoviridae virus can invade diverse metazoan hosts.

As discussed above, the derived Clade 1 (all orthomyxoviruses except Isavirus) in the phylogenetic tree shows a higher frequency of possible host shifts across phyla (Fig. 1) and invaded a broader taxonomic spectrum of hosts. It harbours clades of zoonotic viruses with insect hosts, such as Dhori thogotovirus, Quaranfil quaranjavirus, and Thogoto thogotovirus. Many of these viruses are so-called arboviruses, which are viruses that can be transmitted to vertebrates by arthropod species such as ticks and mosquitoes (Shope and Meegan 1997). These viruses have been reported to be capable of replicating in both vertebrate and arthropod cells (Mária et al. 2018). The ancestor of Clade 1 was inferred to have infested Chordates originally, hence it might have evolved the ability to frequent host shifts in Clade 1, and the ability could be attributed to (i) rapid protein evolution (Jayaraman et al. 2022) that enables the virus to quickly adapt to new hosts. Or (ii) as the sister clade of the Orthomyxoviridae—the Amnoonviridae (Turnbull et al. 2020, Arragain et al. 2023)—and the more basal Orthomyxoviridae—the Isavirus—were both infesting fishes as their natural host, it is reasonable to hypothesize that the ancestor of all Orthomyxoviridae was infesting fishes originally too. The high mobility and wide distribution of Chordates across biomes and fishes across oceans, rivers, and the globe might have facilitated the physical dispersal of the virus across taxonomic groups, especially when Isopoda, Ctenophora, Cnidaria, and Mollusca are also aquatic creatures. The two hypotheses are not mutually exclusive, as the two mechanisms might have occurred simultaneously or sequentially with positive feedback. Such mechanisms, particularly protein evolution, warrant empirical tests. In this regard, the fast-evolving antigen of influenza A (Morens and Taubenberger 2019), which belongs to Clade 1, might lend support to the first hypothesis. As Orthomyxoviridae possibly originated from Chordates, several genus members of Thogotovirus and Quaranjavirus which are all from two clades denoted as Clades 1A and 1B (Fig. 1) which infest Arthropoda primarily have regained their ability to infect Chordates again, such as Araguari virus in marsupial (Da Silva et al. 2005), Oz virus in various mammals including humans (Tran et al. 2022), as well as Quaranfil quaranjavirus (Presti et al. 2009), Bourbon virus (Kosoy et al. 2015), Dhori thogotovirus, and Thogoto thogotovirus in humans (Lledo et al. 2020) as being arboviruses. This suggests members from Clades 1A and 1B can hold a higher risk of shifting back to infecting Chordates, including humans, which warrants attention and further surveillance for being new arboviruses.

Limitations

While the discoveries of new viral members and clades at the genus level in this study are significant, the possibility that some sequences derived from transcriptomes represent endogenous viral elements (EVEs) rather than exogenous viruses must be considered (Nino Barreat and Katzourakis 2024). However, EVEs typically undergo relaxed selection, leading to accelerated evolution and mutations that often result in frameshifts or degraded coding sequences. Such degradation would likely hinder robust alignment with exogenous Orthomyxoviridae members. In contrast, the sequences identified here align well with exogenous viruses, suggesting they are more likely of exogenous origin. Even if some sequences are EVEs, their high similarity to exogenous viruses implies recent integration into host genomes, as frameshifts or pseudogenization would otherwise obscure detectable AA sequence homology. This further supports the notion that the respective hosts had indeed been (recently) infected by exogenous Orthomyxoviridae. Thus, our central conclusions about Clade 1's broad host range and Clade 1A/1B's chordate invasion remain supported. Nevertheless, the detection of additional orthomyxoviral proteins (beyond PB1) in the same host species should provide stronger evidence for the presence of exogenous Orthomyxoviridae members. Therefore, we have marked host species with multiple orthomyxoviral protein detections using blue bars to highlight these higher-confidence cases in (Fig. 1) and provided the details of the additional orthomyxoviral proteins matched in different species in (Supplementary File S2).

Conclusion

Using high-throughput transcriptomes as a data source for screening zoonotic viruses possesses the advantage of broad species and lineage coverage, thus this study identified novel or unclassified Orthomyxoviridae members with the discovery of three new lineages of this family, Clade α is sister to Influenza + Thogotovirus, Clade β is sister to Influenza + Thogotovirus + Quaranjavirus, while Clade γ is sister to all other orthomyxoviruses except Isavirus (Fig. 1). While 89 viruses were identified belonging to Thogotovirus or Quaranjavirus, host shifts between Arthropoda and Chordata seemed to be the most frequent, and the Orthomyxoviridae virus can infect a variety of hosts from Chordata. As Orthomyxoviridae possibly originated from Chordates, other members from both genera of Thogotovirus and Quaranjavirus may regain their ability to infect Chordates and possibly humans in the future as new arboviruses; more studies and resources might be needed in the screening and surveillance of Orthomyxoviridae in invertebrates.

Acknowledgements

Phylogenetic analysis was performed on the Secevo HPC cluster of the School of Ecology, Shenzhen campus of Sun Yat-sen University (SYSU).

Author contributions

R.W.T.L., Z.W., and K.Y.M. contributed to the study design and analysis, wrote and revised the manuscript. J.Q., L.M.T., K.H.C., and K.W.L. revised and reviewed the manuscript.

Supplementary data

Supplementary data is available at *VEVOLU Journal* online.

Conflict of interest: None declared.

Funding

The work was supported by grants from Shenzhen Science and Technology Program (project No. 202206193000001, 20220817122-906001), the National Natural Science Foundation of China (32170655), and the Natural Science Foundation of Guangdong Province (2024A1515011210).

Data availability

The sequences that support the findings of this study are available in Supplementary File SFile 3.

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Virus Evolution, 2025, 1–6
https://doi.org/10.1093/ve/veaf039
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