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Genetics of Rabies: Virus Evolution and Host Interaction

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Abstract:

Rabies is a zoonotic, progressive, and fatal neurological disease caused by the Rabies lyssavirus. As an RNA virus, the rabies virus exhibits a high mutation rate during replication, making it prone to genetic changes. Advances in rabies virus genetics are enhancing our understanding of its key evolutionary mechanisms. Due to its rapid evolution, the virus can diversify quickly, resulting in substantial genetic variation among different strains. Phylogenetic analyses of rabies virus sequences have revealed that specific viral lineages are often associated with particular host species. Identifying the genetic factors, such as distinct proteins or nucleotide sequences, that enable the virus to evade the host immune response is crucial for understanding its adaptability and pathogenicity of the chapter, highlighting the key points and findings.

Keywords: Genome, RNA virus, zoonotic, evolution, host interaction

Introduction:

Rabies is a zoonotic, fatal and progressive neurological disease caused by the Rabies Lyssavirus. The word "Rabies" is derived from the Latin word 'rabere' meaning 'to rage' or 'to be mad' reflecting the neuropsychiatric manifestations of the disease. As the name suggests the individual suffering from this disease shows extreme agitation, aggression, confusion, and hydrophobia (fear of water) and finally leading to death. These symptoms often give the impression of madness. According to WHO, the human rabies vaccination is administered annually to more than 29 million people worldwide, mostly as post-exposure prophylaxis (PEP) following an animal bite or scratch. But still the number of deaths due to rabies is very high with an estimated 59,000 human deaths every year in over 150 countries, with 95% of the cases occurring in Asia and Africa.

As an RNA virus, the rabies virus is highly prone to developing mutations during the normal replication process, closely monitoring the genetic evolution of circulating virus strains is of unquestionable importance for the development of vaccines and therapeutics. Furthermore, Genomic data enable high-resolution phylogenetic analysis of rabies virus samples, allowing researchers to track transmission pathways and patterns of spread with exceptional detail across both temporal and spatial scales. This provides valuable insights for improving rabies control and management strategies.

Genetic Structure and Characteristics:

Rabies virus is an unsegmented negative strand RNA virus having a bullet-like shape, with a diameter of 75 nm and a length of 100–300 nm depending on the strain. Unsegmented negative strand RNA viruses are grouped into two families, Rhabdoviridae and Paramyxoviridae. Rabies virus and rabies related virus belongs to the Lyssavirus genus of the Rhabdoviridae family. In the rabies virion two structural and functional units can be distinguished (a) the host derived lipidic envelope, that contains the transmembrane glycoprotein G, the major viral antigen and the M2 protein that is located on the inner side and (b) the nucleocapsid core, that is transcriptionally active and is composed of all the necessary elements for the viral transcription (Tordo et al., 1988).

The single-stranded negative-sense RNA genome of the rabies virus is 11.9 kb in size and contains five genes (N, P, M, G, and L genes) which encodes five proteins in the order nucleoprotein (N), phosphoprotein (P or NS), matrix protein (M), glycoprotein (G) and large protein or RNA-dependent RNA transcriptase (L) (Park et al., 2005). Single-point amino acid mutations promote changes of antigenicity and infectivity (Cai et al. 2022). Research on genetics of rabies virus is deepening our understanding of key evolutionary processes, including the molecular basis of host adaptation and the emergence of the virus in new host species (Brunker et al., 2018).

Genetic Evolution of Rabies Virus:

The high mutation and substitution rate of the rabies virus, as an RNA virus, leads to the rapid emergence and fixation of new genetic variations within the population, often occurring within months or years. Because of this accelerated evolutionary process, the rabies virus can quickly diversify, leading to significant genetic variation among different strains. This genetic variability is a key factor contributing to the observed differences in virulence and pathogenicity across various rabies virus strains, affecting how aggressively the virus infects hosts and how the disease progresses. In a study, it was found that epidemiological separation between reservoirs is also a reason for neutral genetic differentiation and it sets the stage for purifying selection to maintain adaptive changes (Bourhy et al., 2008). On another analysis, a large set of viruses were sampled from bats, which confirmed that rabies virus from those species that have similar behavioral traits tend to associate together phylogenetically (Davis et al., 2006). Strong evidence suggests that rabies virus initially emerged in bats before switching hosts and eventually giving rise to the widespread form of canine rabies found around the world. Understanding viral transmission dynamics from genetic data generally relies on principles from phylogenetics and population genetics, while also connecting the evolution of the pathogen to patterns of infection and transmission.

Combining genetic data with environmental variables and population dynamics in phylogeographic frameworks provides a way to measure how various factors affect the transmission patterns driving the spread of rabies both within and between countries (Dellicour et al., 2019).

Host Genetics and Susceptibility to Rabies:

Phylogenetic analyses of rabies virus sequences have shown that specific rabies virus lineages are linked to particular host species. Rabies virus proteins engage with host proteins in multiple ways to support viral replication. They use both direct and indirect strategies to inhibit innate immune responses, thereby weakening the host's defense mechanisms and promoting more efficient viral replication. Rabies shows the 'viral heterogeneity' which is represented by the nucleotide sequence variation of the viral RNA, due to which a heterogeneous population of viruses remain within single individual. Mice were infected with two different rabies virus variants, one originating from dogs and the other from bats. It was found that each variant activated distinct patterns of immune-related gene expression. Notably, the dog-derived variant prompted a stronger activation of host immune defense genes compared to the bat-derived variant (Appolinário et al., 2022). It suggests that different rabies virus variants vary in how quickly and intensely they stimulate immune responses in the brain, which can influence how fast the disease develops, how severe it becomes, or how long the incubation period lasts. Also, changes in the viral glycoprotein that impact its ability to bind to host cell receptors can influence how effectively the virus enters nerve cells. This, in turn, can affect the incubation period, the extent of viral spread, and its ability to invade the nervous system. A well-known example is the G333 mutation (Khalifa et al., 2021).

Implications of Genetic Insights for Rabies Control:

A modern technique, Reverse genetics is used to investigate the functions of specific genes by directly altering their sequences and examining the resulting phenotypic changes. This approach serves as a valuable tool for molecular studies of RNA viruses and is widely applied in rabies virus research, for production of vaccines as well as for use in gene therapy. The use of next-generation sequencing (NGS) to examine lyssavirus host shift events is increasingly common; however, leveraging the depth of sequencing data to explore viral heterogeneity remains a largely unexplored area of research. Gene therapy can eliminate rabies from the infected neurons by using rAAV-N796 and also CRISPR/Cas9 system in combination with the MMEJ-based method may also be used to fight the rabies virus (Nelwan et al., 2018). Genetic signatures (like codon usage bias, adaptation signals) give clues about virus adaptation to different hosts. Recognizing the genetic elements, such as specific proteins or sequences that enable the virus to evade the host immune response is crucial for predicting potential vaccine failures and for guiding the development of supplementary treatments or enhanced vaccine designs.

Conclusion:

Rabies is a severe threat to public health across the world. Although vaccination has been proved to be the most effective way of pre- and post- exposure medical intervention against rabies, the human death toll due to rabies is still very high. The genetic material of the rapidly evolving rabies virus holds information about its behavior, transmission, and interaction with host organisms. Due to advancements in genetic research, scientists are able to decode the viral genome and study the host genetic factors, which have led to better understanding of the disease progress, viral spread and immune responses.

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