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Getah Virus: From Molecular Evolution to Prevention and Control Strategies

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ABSTRACT

Getah virus (GETV) is an arbovirus belonging to the genus Alphavirus within the family Togaviridae. Since its initial isolation in Malaysia in 1955, GETV has expanded from its original confinement in the island regions of the South Pacific to cover a broad geographical range extending up to 60°N latitude. GETV is a single-stranded, positive-sense RNA virus primarily transmitted by mosquitoes. Studies indicate that the spread of GETV across Eurasia has been increasing. The range of infected animal species has expanded from horses and pigs to include cattle, blue foxes, and red pandas, resulting in significant economic losses to the livestock industry. Although there have been no confirmed reports of GETV causing human disease, antibodies against GETV have been detected in the serum of healthy individuals in several countries, suggesting a potential public health risk. This review provides a systematic overview of the epidemiological characteristics, molecular biology, and public health implications of GETV, with an emphasis on its potential threat to both animal and human health. The spatial and temporal distribution patterns, molecular genetic evolution, clinical implications, public health significance, and future research directions of GETV are discussed in detail.

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Key Words: Getah Virus; Geographic Distribution; Genetic Structure; Diagnosis; Prevention

Abbreviations: GETV, Getah virus; NT, Neutralization Test; CFT, Complement Fixation Test; HIT, Haemagglutination Inhibition Tes; ELISA, Enzyme-linked Immunosorbent Assay; RT-PCR, Reverse Transcription-Polymerase Chain Reaction.

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Gene structure and replication

GETV, like most other members of the genus Alphavirus, has spherical particles with a diameter of about 50-70 nm, vesicle membranes and fibrils under electron microscopic observation[1]. Its genome is a single-stranded positive stranded RNA with a total length of about 11.7-12.0 kb, with a 5' end cap structure (m7Gppp) and a 3' end poly-A tail, including a 5' untranslated region (5' UTR), an open reading frame (ORF) and a 3' untranslated region (3' UTR). Among them, ORF is divided into the 5' end of the leading region and the 3' end of the structural protein region, and the leading region encodes four non-structural proteins, nsP1-nsP4, which are responsible for viral replication, transcription, and immune escape[2].

The structural protein region encodes five structural proteins (C, E3, E2, 6K and E1) that are involved in virus assembly, receptor binding and membrane fusion[3,4] . Among them, E2 proteins are the main functional proteins for infecting host cells, initiating diseases and triggering immune responses[5,6]. Getah viruses have a highly conserved genetic structure and are very similar in sequence to the homologous sindbis virus and Semliki Forest virus. However, there will be slight differences in genome length and nucleotide sequence differences at certain sites in the non-coding or coding regions, and these features provide an important basis for relevant antiviral research and vaccine development.

In terms of genome replication, GETV is a positive-stranded RNA that can be directly recognised as an mRNA by host ribosomes, translating non-structural protein precursors from the 5' end. Non-structural proteins assemble into a replication complex that uses positive-stranded RNA as a template to synthesise negative-stranded RNA intermediates. Negative-stranded RNA is then used as a template to synthesise new positive-stranded genomic RNA and subgenomic RNA.

Subgenomic RNA is translated to generate structural protein precursors, which are cleaved and assembled into nucleocapsids, and envelope glycoproteins are inserted into the host cell membrane to release viral particles in an outgrowth manner[7].

Geographical distribution and host range

Since its first isolation in 1955, GETV has been widely distributed in 13 countries in Asia, Europe and Oceania[6], including Vietnam, Thailand, Cambodia and other countries of the Central and Southern Peninsula in Asia, Malaysia and the Philippines in Southeast Asia, India and Sri Lanka in the South Asian subcontinent, as well as Japan, South Korea, Mongolia, China, Russia and Australia. The virus has become an emerging mosquito-borne arbovirus in Eurasia[8].

GETV was first isolated in Hainan in China in 1964, and has now expanded to 16 provinces[9,10]. As of 2025, the distribution of GETV in China has significantly expanded, and the coverage has expanded from the southern provinces in the early days to many regions of the country, showing a clear trend of northward expansion.

GETV was first isolated from Culex tritaeniorhynchus in Shixian County, Hebei Province, in 2002, which was the first time GETV was isolated in the northern region of China. In addition, serological surveys of swine herds in Heilongjiang and Shandong showed an increasing trend of antibody positivity, which suggests that the virus has developed endemic transmission in some northern regions. Swine farms in the central and southwestern regions, such as Hunan, Hubei, Sichuan, and Yunnan provinces, have repeatedly reported GETV infections resulting in sow abortions and piglet deaths during 2022-2024.

The host range of GETV spans both arthropods and vertebrates, forming a complex transmission cycle. Early on, GETV was mainly isolated from four species of Culex mosquitoes[11], whereas by 2022 it had been detected in eight species of mosquitoes from four genera as well as midges, mainly Culex, Anopheles, Armigeres and Armigeres, with Culex tritaeniorhynchus being the main vector in East Asia. In addition, midges have also been shown to carry GETV, and Culex spp are widely distributed in nature, and their role as hosts of the virus provides an important biologic vector base for the spread of GETV.

GETV has a wide variety of vertebrate hosts, including not only common domestic animals such as pigs, horses and cattle, but also wildlife such as foxes and red pandas[12,13]. In the case of domestic animals, for example, animals such as pigs and horses may become intermediate hosts for the virus to circulate and proliferate in nature after being infected with GETV, and the discovery of wildlife hosts has further broadened knowledge of the ecological chain of transmission of the virus.

Molecular genetic evolution

Phylogenetic analyses based on the E2 gene sequence showed[14] that GETV can be clearly divided into four independent evolutionary clusters (GI-IV)[15]. The specific characteristics of each cluster are as follows:

The GI evolutionary group is highly specific and currently contains only the virulent strain MM2021 isolated from Malaysia in 1955[16] . From the time dimension, this strain was isolated at an early age, and its gene sequences form independent branches in the evolutionary tree, which are distinctly genetically different from other groups of viruses, and may represent an evolutionary branch of an earlier virus in a specific geographic region.

The GII group is represented by the SAGV strain isolated from Japan in 1956, and the group contains several other viral strains with similar genetic characteristics. Virus isolation times in cluster GII are similar to those in cluster GI, but geographically more oriented towards East Asia, The conserved regions in their gene sequences contrast with the GI population, reflecting the divergence in evolutionary pathways of viruses from different geographic regions.

As the largest evolutionary branch of GETV, group GIII occupies 90% of all current isolates. Its distinctive features are its wide distribution and prominent pathogenicity[16]. Isolations of this group of viruses have been recorded from several regions from tropical to temperate zones, with a host range covering mosquitoes, domestic animals and wildlife, which is closely related to their strong environmental adaptability. Studies have shown that group GIII viruses are significantly more pathogenic to animal hosts (e.g., pigs, horses, etc.) than other groups, and some strains can trigger clinical symptoms such as fever and inflammatory reactions in the host, making them a key target for epidemiological surveillance at present.

The GIV cluster is considered to be the youngest evolving cluster in GETV, and its gene sequences show clear recent evolutionary features. This cluster contains strains isolated from several geographic regions, including Thailand, Yunnan, China, and Russia, and spans a wide range of geographic distributions. Notably, some strains of the GIV group have mutations in the antigenic epitope region of the E2 gene[15], a genetic variation that may be associated with their enhanced ability to transmit across hosts and provide a new entry point for the study of the evolutionary dynamics of the virus.

Phylogenetic analyses showed that the most recent common ancestor (tMRCA) of GETV dates back to ca. 1880 (95% HPD: 1799-1943), with an evolutionary rate of ca. 3.27×10^{-4} substitutions/site/year, which is comparable to that of other metaviruses such as Rose River virus)[17]. Eight positive selection sites were identified in the E2 protein, including Glu4, Lys36, His86, and Glu323[18], of which the His86Tyr mutation is located in Heparin sulfate binding site, which may enhance the adhesion of the virus to host cells. Glu323 is located on the surface of the viral envelope and may affect antibody recognition and immune escape. Notably, group GIII viruses have characteristic mutations in the region of the nonstructural protein nsP3 (e.g., Pro1234Ser), which correlate with elevated replication efficiency of the viruses in mosquito vectors and may be the molecular basis for their geographic expansion. In addition, polymorphisms in lysine (Lys253) and arginine (Arg253) at position 253 of the E2 protein were found in Chinese isolates, the

former being associated with high pathogenicity in pigs.

Pathogenicity

1. Animal infections

GETV is an important arboviral pathogen capable of infecting a wide range of vertebrates and there is significant variability in infection within animal populations. The first outbreak of equine infection occurred in the Kanto region of Japan in 1978, with horses showing signs of fever, rash and limb oedema for 1-4 days[19,20]. A few developed conjunctivitis or swollen joints, and most of the sick horses recovered on their own within a week, with no fatal cases. Higher rates of GETV antibody positivity in horse herds were detected in Xinjiang in 2019 - 2020, and strains with unique molecular characteristics were also isolated.

The infection appeared in pigs in Japan in 1985, when 8 out of 12 piglets produced by a sow showed signs of depression, tremors and yellow-brown diarrhoea 2 days after birth, followed by death within 3-5 days after birth. The remaining four piglets showed hypoplasia[8], which is the first evidence that porcine GETV is pathogenic. The 2017 outbreak in Hunan, China, in which about 200 piglets died and more than 150 pregnant sows aborted, resulting in severe economic losses, was the first report of a large-scale outbreak caused by GETV in a pig population in China. Newborn piglets show depression, tremors and yellow-brown diarrhoea and often die within 3-5 days. The infection of pregnant sows can lead to abortion, stillbirth or mummification of the foetus.

In addition, cattle become infected with fever, loss of appetite and depression. Wild animals infected with GETV also show appropriate symptoms. Infection in blue foxes manifests as fever, anorexia, depression, and neurological symptoms[13], and in red pandas, the infection can even be fatal. GETV-specific antibodies were detected in serum samples from chickens, ducks, goats, and birds[21].

2. Human infection risk analysis

Data from serological surveys show evidence of latent infection of GETV in populations from different regions. GETV-specific IgM and IgG antibodies are present in some of the patients with unexplained fever[22], but no clinical cases have been reported. Although there have been no clear reports of GETV directly causing clinical disease in humans, given the pathogenic manifestations triggered by the virus in animals such as horses and pigs, health surveillance of animal practitioners (especially equine and swine farm workers) is important.

Diagnosis

Diagnostic methods for GETV are divided into two main categories: serological and pathogenic tests. Among them, serological tests are mainly used to determine infection

by detecting specific antibodies, which mainly include neutralization test (NT), complement Fixation test (CFT), haemag--glutination inhibition test (HIT) and ELISA.

Among them, indirect ELISA with recombinant E2 protein as antigen is currently the most commonly used method[23], which has a sensitivity of 96.7% and specificity of 98.3% for detecting antibodies, and is suitable for mass screening. The p62-E1 protein ELISA developed by a Chinese team further improved the sensitivity of the assay (up to 1:12800 dilution)[24] .

Additionally, pathogen detection is used to determine infection directly by detecting viral nucleic acids or particles and includes reverse transcription-polymerase chain reaction (RT-PCR) and virus isolation and culture. Among them, RT-PCR is aimed at targeting the conserved C gene or NSP3 region, with detection sensitivity up to 10^3TCID50/ml for acute phase samples (e.g. blood, tissue).

The selection of assays should be tailored to specific objectives. For rapid clinical screening purposes, high-throughput methods such as ELISA or HIT are preferred for mass screening applications. When confirmatory diagnosis and scientific research are required, a combination of RT-PCR and Neutralization Testing (NT) can be employed to enhance diagnostic precision. For viral traceability studies, comprehensive approaches including virus isolation and culture, coupled with genetic sequencing, are recommended to analyze viral variations and reconstruct transmission chains.

Prevention, control and vaccine development

Enclosed management of susceptible animals, such as pigs and horses, to avoid contact with mosquito-breeding environm--ents; regular cleaning of barns to reduce the spread of the virus in the animal population[25].

Measures such as insecticide spraying and removal of breeding sites, targeting the main vectors such as Culex mosquitoes, have reduced the incidence of outbreaks by 70% when implemented in Japanese stables. Enforcement of closed management and cutting off contact between mosquito vectors and their hosts at morbid farms are key measures to control outbreaks.

Vaccines currently available include inactivated, subunit and live vaccines. An inactivated formaldehyde vaccine (MI-110) developed in Japan provided 85% protection in horses, but required annual summer booster immunisation and had reduced protection against emerging group GIII strains[26].

Recombinant subunit vaccines based on the structural domain of the E2 protein have induced neutralising antibody titres up to 1:640 in mouse models and are currently being tested in swine[18].

Challenges and prospects

Current GETV research faces multiple challenges: in human infection risk assessment, although there is serological evidence of human exposure, there is a lack of systematic studies of clinical cases, and there is a need to establish a sentinel surveillance network to assess cross-species pathogenic potential.

Geographically, it has spread from the tropics to the temperate and boreal zones as a result of ecological changes and animal migrations, with positive samples from several temperate rangelands and signs of spread on the fringes of the boreal zone. The host range has expanded from domestic animals such as horses and pigs to cattle and foxes.

Because the symptoms of infection are similar to those of other viral diseases, there are problems of missed diagnosis and misdiagnosis due to a lack of diagnostic awareness, as well as a lack of uniform statistical standards and monitoring systems, making it difficult to accurately estimate the economic burden on the livestock industry.

In the future, prevention and control work can be advanced in four core directions: strengthening surveillance, optimising vaccines, conducting research on mechan--isms, and conducting risk assessments.

Conclusions

GETV, an emerging zoonotic virus, has shown significant geographic expansion over the past 20 years. Group GIII GETV has become the dominant prevalent strain, causing severe economic losses to the livestock industry. Although the risk of human infection is not yet clear, the detection of antibodies in healthy populations suggests the need for increased health surveillance of relevant practitioners. Vaccine research and development, especially the construction of a live attenuated vaccine platform, has provided new ideas for the prevention and control of GETV and related alphaviruses.

Future global collaboration focusing on human infection mechanisms, virus-vector--host interactions and novel prevention and control strategies will be needed to address this arbovirus challenge.

Contribution statement

Yaqing Guo and Xinrong Wang: data curation, writing- original draft preparation.conceptualization, methodology. *Xiaodong Sun:* visualization, software, validation. *Xinbei Li:* methodology, investigation. *Hao Xu*： software, validation. Project administration. *Guoyu Niu:* writing--reviewing and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

All data included in this study are available upon request by contact with the corresponding author.

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