ARTICLE @ VIROLOGY

Molecular Epidemiology and Genetic Characteristics of Rabies Virus in China

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ABSTRACT

Background Rabies virus (RABV) causes a lethal zoonosis with near-100% case-fatality. China carries complex RABV genetic diversity across distinct phylogeographic patterns, yet a synthesis of molecular epidemiological evidence is lacking.

Objective To delineate the genetic structure, lineage displacement, and transmission dynamics of major RABV clades in China, and to assess the public health significance of emerging bat-associated lyssaviruses.

Methods Published molecular epidemiological studies were synthesized. Phylogenetic analyses of N and G genes were used to infer clade distribution, host associations, and evolutionary trends.

Results RABV in China comprises Asian-lineage subclades SEA1–SEA5, together with Cosmopolitan CA1 and Arctic-like AL2. SEA1 is widespread; SEA2/SEA5 cluster in South and East China, with SEA5 endemic to Taiwan; SEA3 occurs in Yunnan, Guangxi, and Southeast Asia; CA1/AL2 are confined to northern steppe-type zones. Domestic circulation dominates, with limited cross-border importation. Ferret badgers (Melogale moschata) show a marked SEA2-to-SEA1 lineage shift, signaling incipient reservoir establishment. Bat lyssaviruses IRKV and TWBLV have been identified; their spillover potential and vaccine cross-protection remain uncertain.

Conclusion Geographical barriers, population density, and transport networks shape RABV genetic structure in China. Wildlife reservoir emergence and bat lyssavirus discovery pose new challenges to the 2030 elimination target. Enhanced surveillance, whole-genome analysis, and vaccine cross-protection studies are needed.

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Introduction

Rabies is a zoonotic acute infectious disease of the central nervous system caused by rabies virus (RABV). Once clinical symptoms develop, the case-fatality rate is nearly 100%, making it one of the deadliest infectious diseases globally[1,2]. According to estimates by the World Health Organization (WHO), approximately 59,000 people die from rabies worldwide each year, of whom about 40% are children under 15 years of age, and more than 95% of human deaths result from bites by dogs carrying RABV[3,4]. Rabies is distributed across all continents except Antarctica, with the heaviest burden falling on developing countries in Asia and Africa[5]. In response to this serious public health challenge, WHO, in collaboration with the World Organisation for Animal Health (WOAH) and the Food and Agriculture Organization of the United Nations (FAO), jointly launched the global strategic plan Zero by 30: The Global Strategic Plan to End Human Deaths from Dog-Mediated Rabies by 2030 in 2015, aiming to achieve zero human deaths from dog-mediated rabies by 2030 through comprehensive measures including large-scale dog vaccination, post-exposure prophylaxis (PEP), and public education[6,7].

RABV belongs to the family Rhabdoviridae, genus Lyssavirus, and is a single-stranded negative-sense RNA virus. Its genome is approximately 12 kb in length and sequentially encodes five structural proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and large polymerase (L)[8,9]. Among these, the N and G genes have become the most commonly used molecular markers in molecular epidemiological research due to their high genetic stability and species specificity[9,10]. Based on phylogenetic analyses of the N and G genes, global RABV has been divided into several major phylogenetic clades or lineages, and RABV from different geographical regions exhibits significant genetic diversity and geographical clustering[10,11]. This genetic structure not only reflects the long evolutionary history of the virus in specific hosts and geographical ranges, but also provides important molecular evidence for tracing viral transmission routes, assessing cross-border transmission risks, and formulating regional prevention and control strategies[11,12].

China was once one of the countries with the heaviest rabies burden globally, with an average of more than 7,000 reported cases per year in the 1980s[13]. Since the beginning of the 21st century, with the strengthening of dog management policies, the increased coverage of human rabies vaccines, and the gradual improvement of post-exposure prophylaxis systems, the incidence of human rabies in China has shown a significant downward trend[13,14]. However, due to China's vast territory, large population base, numerous dogs, and significant differences in vaccination coverage between urban and rural areas, the situation of rabies prevention and control remains severe[14,15]. Molecular epidemiological studies have shown that RABV circulating in China has a complex genetic structure and distinct geographical distribution characteristics, mainly involving the SEA1, SEA2, SEA3, and SEA5 subclades of the Asian lineage, as well as the CA1 subclade of the Cosmopolitan lineage and the AL2 subclade of the Arctic-like lineage[16,17]. The geographical distribution of these subclades is closely related to China's topography, population density, economic activity, and transportation networks, reflecting the physical and ecological barriers that may exist to gene flow[17,18]. In addition, apart from dog-origin RABV, rabies-related lyssaviruses such as Irkut virus (IRKV) and Taiwan bat lyssavirus (TWBLV) have been successively identified in Chinese bat populations in recent years, and their public health significance has attracted increasing attention[18,19].

Given the complexity of RABV genetic diversity in China and its critical role in rabies prevention and control, systematically reviewing and summarizing the molecular epidemiological characteristics and genetic evolutionary patterns of RABV in China is of important scientific value and practical significance for understanding viral transmission dynamics, assessing cross-border importation risks, optimizing vaccine strain selection, and supporting the achievement of the Zero by 30 strategic goal. Therefore, this review aims to comprehensively review and systematically analyze the molecular epidemiological characteristics, geographical distribution patterns, transmission dynamics, and genetic evolutionary patterns of the major evolutionary clades of RABV in China, while also summarizing research progress on rabies-related viruses carried by bats in China, in order to provide a scientific basis for precise rabies prevention and control and elimination strategies in China and East Asia.

Molecular Epidemiological Characteristics of Major Evolutionary Clades of Dog-Origin Rabies Virus in China

Globally, based on phylogenetic analysis of the nucleoprotein (N) gene, rabies virus (RABV) has been divided into several major geographical evolutionary clades, including the African lineage, Cosmopolitan lineage, Arctic-related lineage, Asian lineage, and Indian subcontinent lineage[19]. In China, RABV mainly involves the SEA1, SEA2, SEA3, and SEA5 subclades of the Asian lineage, as well as the CA1 subclade of the Cosmopolitan lineage and the AL2 subclade of the Arctic-like lineage[20-22] (SEA4 is distributed in the Philippines[23]) (Figure 1). Among these, the Asian lineage is the predominant RABV strain circulating in China. The main transmission vector of RABV in China is dogs. Through long-term transmission and evolution, the virus has spread to wild animals such as ferret badgers, foxes, and raccoon dogs, as well as large domestic animals such as cattle, camels, and sheep, forming distinct geographical distribution characteristics. Studies have confirmed[24] that each RABV subclade in China has a specific geographical distribution pattern (Figure 2), reflecting the physical barriers that may exist to gene flow. Phylogeographic analysis shows that viral movement between different geographical locations is relatively limited[25]. Domestic circulation dominates viral transmission, and the introduction of RABV from Southeast Asia into southern China is the only cross-border importation route with adequate theoretical support[25]. Based on phylogenetic studies focusing on viruses isolated from specific regions[26-28], RABV in China has shown a trend of spreading from eastern and southern regions to western and northern regions[29]. This pattern may be closely related to the gradual development of transportation networks, which increase the opportunities for rabid dogs to move or be transported between different regions. In addition, although human rabies in China is mostly transmitted by dogs, there are also sporadic cases of transmission by other wild animals, such as ferret badgers and bats, which also exhibit significant geographical characteristics. This section will systematically discuss the molecular epidemiology and genetic characteristics of rabies virus in China, and explore the genetic diversity, spatiotemporal distribution patterns, and transmission routes of different viral subclades.

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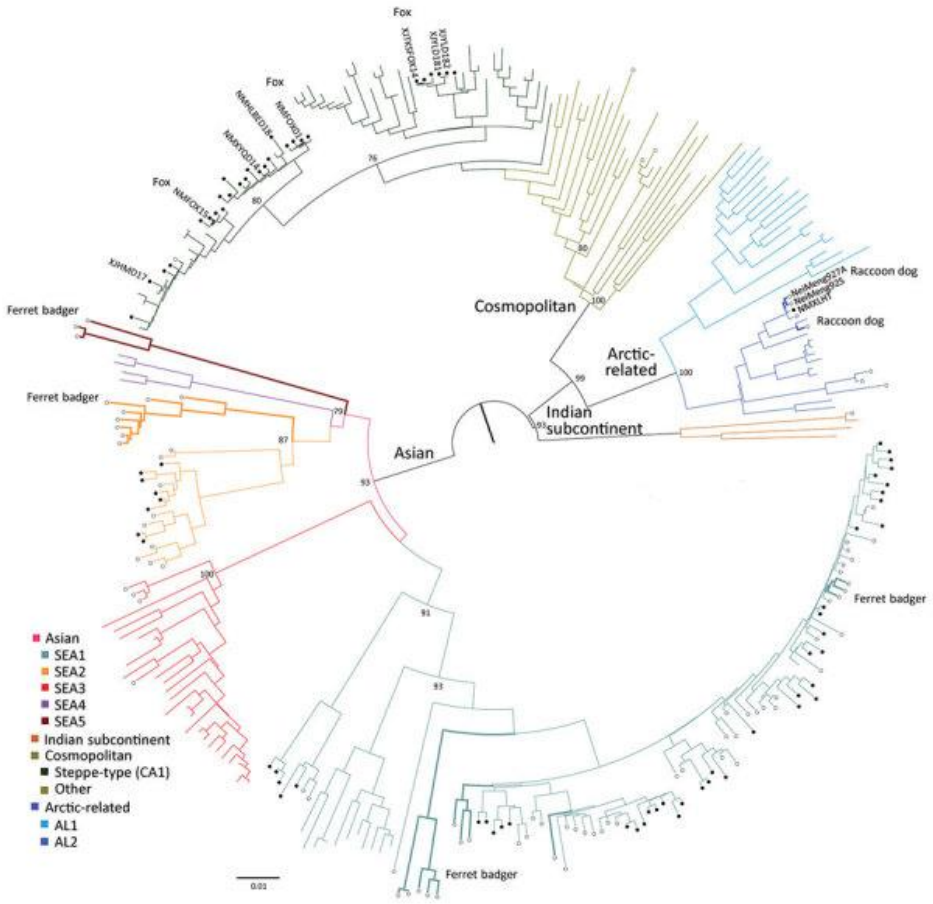

Figure 1 Phylogeny of full rabies virus nucleoprotein sequences in China[23]

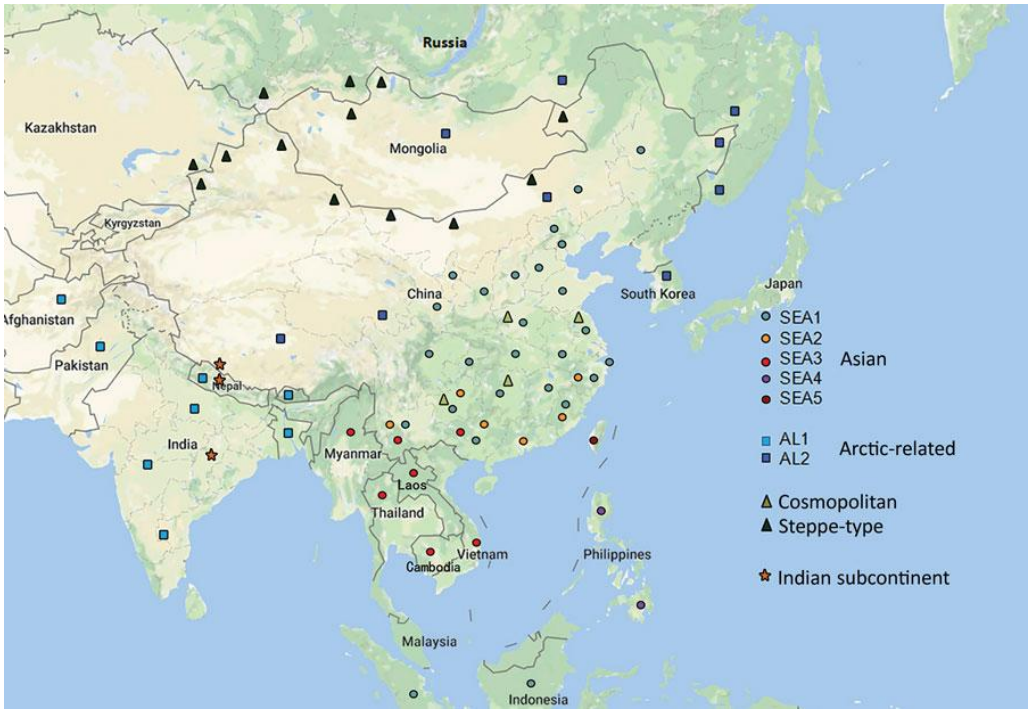

Figure 2. Geographic distribution of rabies virus clades and subclades in China and neighboring countries[23]

1 Subclade SEA1: The Most Widely Distributed RABV Lineage in China

The SEA1 subclade of RABV has the most significant impact, being distributed across most provinces in China, except Xinjiang and Inner Mongolia. Due to the higher population density, more intensive economic activity, and greater interpersonal contact in mainland China compared with the northwestern and northern border regions, while the border regions such as Xinjiang and Inner Mongolia are sparsely populated, vast in territory, and have limited contact with inland areas, RABV transmission between these regions is restricted to some extent. It should be noted that the main transmission vector of SEA1 is dogs, but a clear lineage shift phenomenon has been observed in isolates from ferret badgers. Early isolates from ferret badgers almost all belonged to the SEA2 subclade[30]; however, since 2014, all RABVs isolated from ferret badgers in Jiangxi have been classified into the SEA1 subclade, which is currently the predominant subclade transmitted by dogs. This subclade contains two sub-lineages, SEA1a and SEA1b, with N-gene nucleotide similarities of 94%-98% between them. The N-gene similarity between SEA1-type and SEA2-type ferret badger RABVs is approximately 88%. Studies have shown that ferret badger-associated SEA1 is rapidly replacing the related SEA2 subclade and has become dominant in rabies epidemics transmitted by ferret badgers[31] (Figure 3). In addition, because ferret badger-associated SEA1 RABVs show certain differences from dog-associated SEA1, ferret badger-associated SEA1 may become a major independent branch in the phylogenetic tree. The independent rabies epidemic occurring in ferret badgers indicates that the persistent transmission chain of rabies in ferret badgers appears to occur 3 to 5 years or longer after the transmission of dog rabies. Therefore, as the impact of dog rabies persists, the threat posed by ferret badger transmission to humans has become complex and serious.

2 Subclades SEA2 and SEA5: South China, East China, and Taiwan

The SEA2 and SEA5 subclades mainly affect parts of South China and East China. Notably, the SEA5 subclade is endemic to Taiwan and is transmitted among ferret badgers. These viruses share a common ancestor with the SEA2 subclade viruses mainly isolated from southeastern China, reflecting the impact of geographical barriers on gene flow. Taiwan is geographically separated from mainland China by the Taiwan Strait. After 1949, Taiwan and mainland China were artificially separated, and the movement of people and goods was almost completely interrupted. Therefore, the Taiwan Strait has acted as a barrier to gene flow, which may be the main reason for the relative homogeneity of RABV strains in Taiwan. Phylogenetic trees show that RABV strains from Taiwan share high homology with those from southeastern China across the Taiwan Strait. Taiwan is divided into eastern and western parts by the Central Mountain Range, which may be one of the main geographical factors for the division of rabies populations in Taiwan into two lineages. This observation is consistent with previous reports[32,33]. The ancestors of the Taiwan-specific lineages SEA5a and SEA5b appeared around 1956 and 1941, respectively, dates close to the year of artificial separation between mainland China and Taiwan (1949). All virus isolates of the SEA5 subclade are from ferret badgers, and it has been reported that the N gene of ferret badger-associated RABV evolves faster than that of other dog-associated RABV subgroups[24] (Figure 4).

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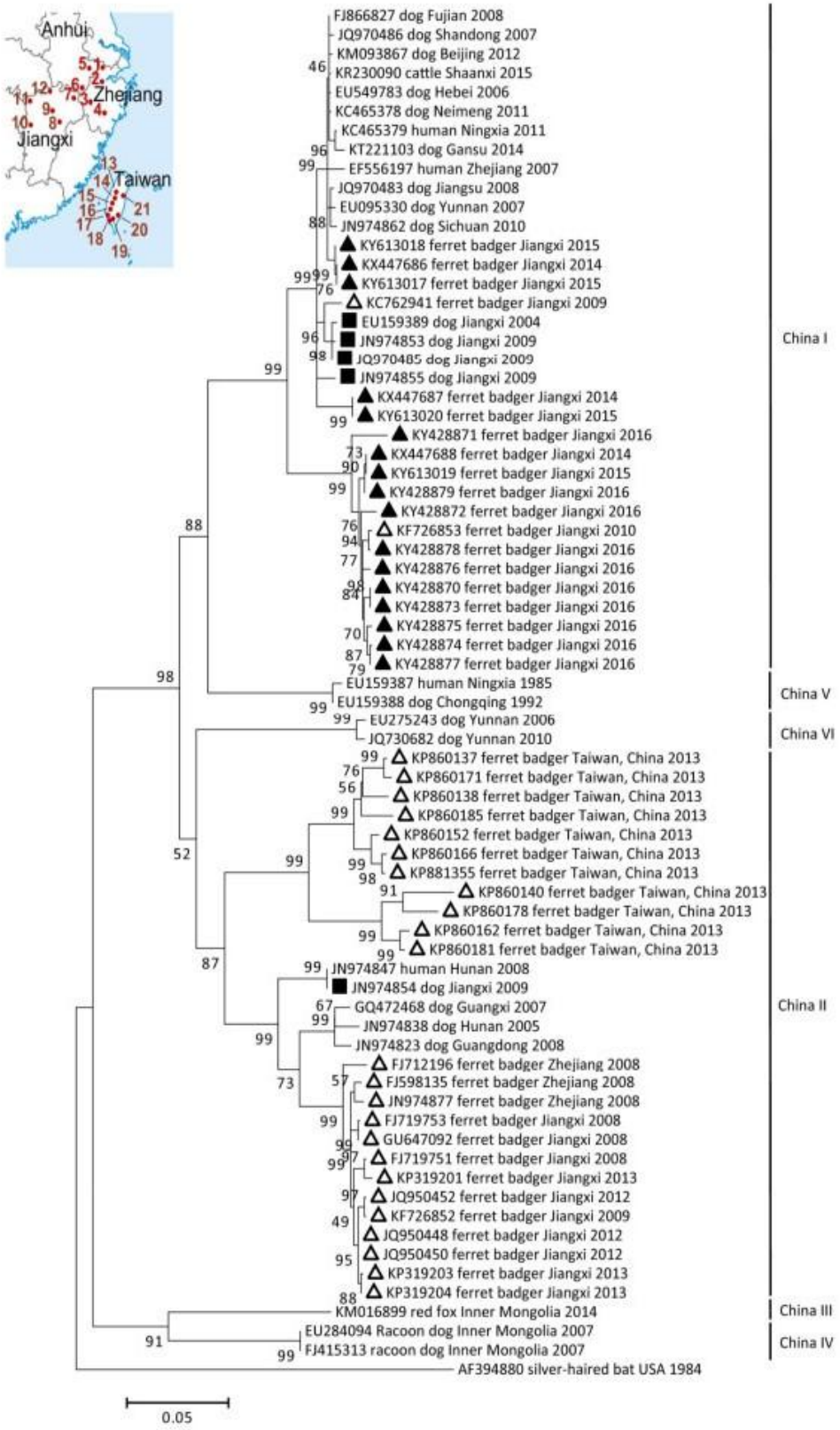

Figure 3 Maximum likelihood phylogenetic tree based on the complete nucleoprotein gene of rabies viruses isolated from China[31]

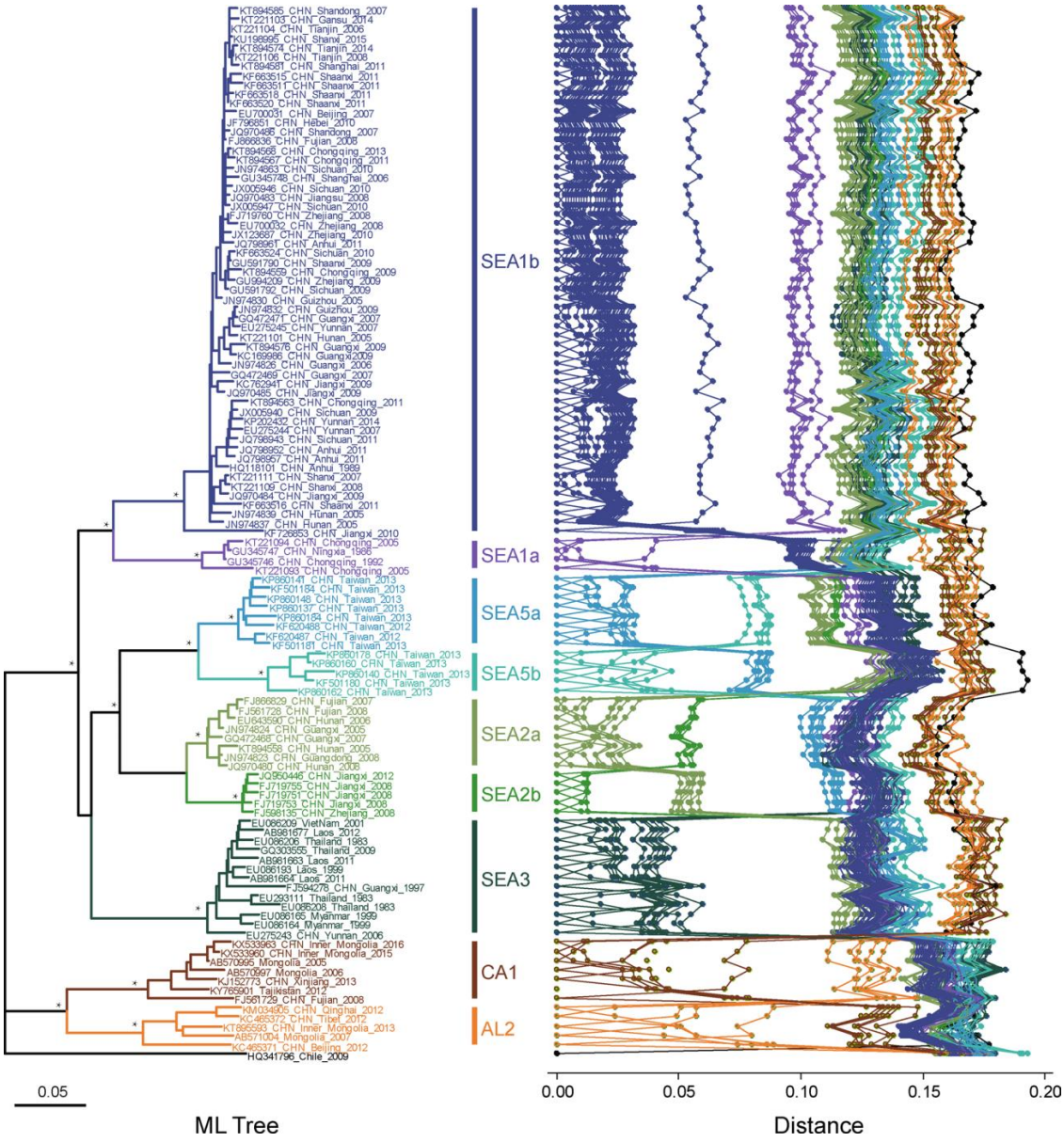

Figure 4 Phylogenetic and distance analysis of RABV nucleoprotein sequences in China[24]

3 Subclade SEA3: Southwest Border and Southeast Asian Connection

The SEA3 subclade is distributed in the two southwestern border provinces of Yunnan and Guangxi, as well as in China's Southeast Asian neighbors Myanmar, Laos, Thailand, and Vietnam, reflecting the close epidemiological links between these regions. Yunnan and Guangxi share certain cultural similarities with neighboring Southeast Asian countries and have maintained close exchanges since ancient times. Some scholars believe that Yunnan is an important geographical area for the domestic spread and outward expansion of RABV[34]. Evolutionary reconstruction results indicate that since 2000, the re-emergent RABV lineages in Yunnan have contained representatives of the three major Southeast Asian subclades SEA1-3, but the SEA3 subclade has not been detected after 2010, and only one SEA2 subclade was found in Yunnan in 2011[34]. It is speculated that due to possible random changes or differences in adaptation to the epidemiological environment of Yunnan, the YN-B and YN-C strains could not maintain persistent transmission chains, which may have led to SEA1 outcompeting the SEA2 and SEA3 subclades[25](Figure 5).

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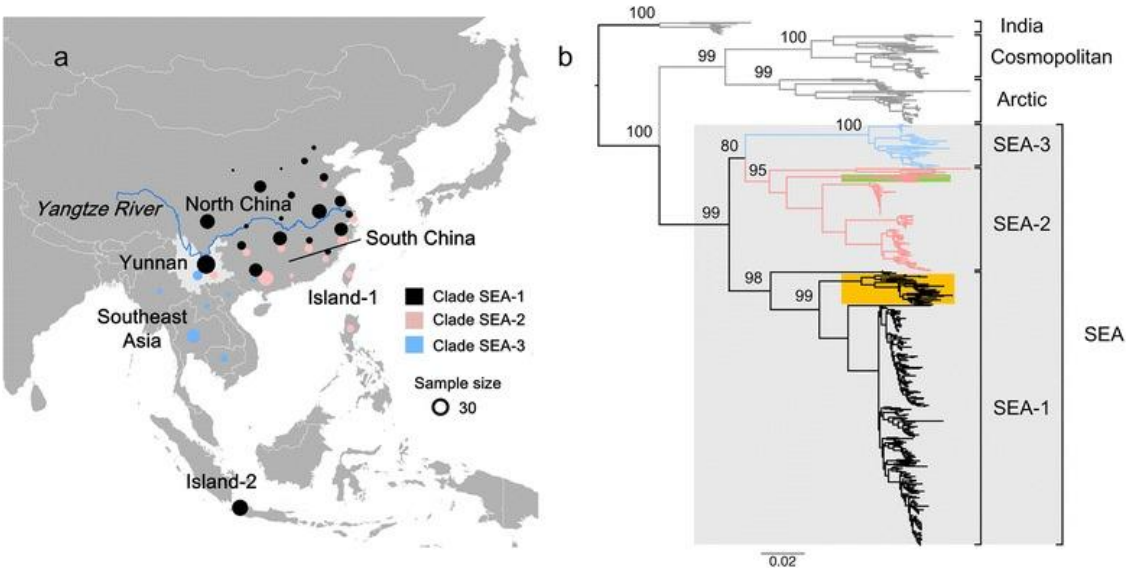

Figure 5 Phylogeny of Southeast Asian RABV N gene[25]

4 Subclades CA1 and AL2: Northwest and North China

The CA1 and AL2 lineages mainly affect Northwest and North China[35,36]. The CA1 subclade mainly affects Inner Mongolia and its surrounding areas, including Mongolia, Xinjiang, and neighboring countries such as Tajikistan. The AL2 subclade mainly affects Qinghai and Tibet, which are adjacent to Xinjiang. Studies have confirmed that the CA1 and AL2 subclades are grassland-type subclades transmitted by foxes. The areas affected by the CA1 and AL2 subclades are the most sparsely populated regions in China, and low population density and limited economic activity may restrict viral transmission. Notably, the CA1 subgroup includes a sequence from Fujian Province in southeastern China, indicating that the virus has undergone long-distance transmission.

5 Indian Subcontinent Lineage: Cross-Border Importation Risk

In addition, the Indian subcontinent lineage had not been identified in China until 2017, when the first human rabies case caused by this lineage was discovered in a border area of Tibet near Nepal. This human case was caused by a bite from a local stray dog and is the only Indian subcontinent lineage RABV confirmed in China to date. This finding suggests that with the increase in cross-border movement of people and animals, China faces a potential risk of importation of novel RABV lineages, and enhanced rabies surveillance and early warning in border areas is needed.

Research Progress on the Molecular Epidemiology of Bat-Origin Rabies-Related Viruses in China

Members of the order Chiroptera are natural hosts of rabies virus and play an important role in the transmission of rabies to animals and humans. Because China is a country with a serious rabies epidemic, confirming the background incidence of rabies-related viruses carried by bats is an important public health issue. Due to the considerable challenges of studying viruses carried by bats, early China lacked research reports in this area. In recent years, with increased attention to wildlife and the development of new technologies, scholars have conducted in-depth and systematic studies on rabies-related viruses carried by bats in China, with research focus shifting

from sero-epidemiology to molecular epidemiology.

1 Early Sero-Epidemiological Studies

Systematic research on rabies-related viruses carried by bats in China started relatively late. In a study on the seroprevalence of rabies virus in bat samples collected from Yunnan, Guangxi, Guangdong, and Hainan provinces between 2005 and 2006[37], 685 bat samples from 8 species in 4 families were tested using the fluorescent antibody virus neutralization test (FAVN test) and the indirect fluorescent antibody test (iFAT). The results showed that seropositive samples were detected only from three bat species (Rousettus leschenaulti, Rhinolophus blythi, and Rhinolophus ferrumequinum), with a seroprevalence of 2.2% (15/685). Among these, 13 samples (12 fruit bats and 1 insectivorous bat) were positive by iFAT, and 2 insectivorous bats were weakly positive by FAVN. These results indicate that bats may play a role in the ecology of rabies virus in China. This study was the first report of rabies seroprevalence in bats in China. Due to technical limitations, the study was confined to serological research.

2 N Gene Study of RABV in Bats from Guangxi

In a serological and genetic study of rabies virus conducted on 2,969 bats of 6 species collected from different regions of southern Guangxi between 2003 and 2008[38], the positive rate of rabies virus N gene was 2.86%, showing a band-like geographical distribution pattern extending from the southwest to the northeast of Guangxi Province. However, when these positive samples were further studied using anti-N protein monoclonal antibodies for rabies and related viruses, no antigen-positive samples were found. Sequencing of a 260-nucleotide fragment of the N gene (positions 574-833) of the viral isolates showed nucleotide homologies of 86.9%-99.6%. Phylogenetic analysis indicated that all these viruses were highly homologous with locally circulating RABV, and some strains were highly homologous with the production strains of currently used human rabies vaccines, but showed no homology with bat viruses isolated from other parts of the world.

3 Discovery and Pathogenicity of Irkut Virus (IRKV)

In 2002 and 2010, one human rabies case related to bats was reported each in Tonghua County and Longjing City, Jilin Province. Based on these clues, Chinese scholars conducted systematic surveillance of bat rabies virus in Jilin Province to determine the public health impact, and in 2012 successfully isolated for the first time in China a rabies-related virus--Irkut virus (IRKV)--from the white-bellied tube-nosed bat (Murina leucogaster)[39]. This virus was originally isolated from the white-bellied tube-nosed bat in Eastern Siberia, Russia in 2002, and in 2007 the only confirmed case of bat rabies virus spillover infection in the Russian Far East was reported: a human death caused by a bat bite.

In a 2017 incident in Liaoning Province where a dog bit a local farmer, the dog died on the 10th day after the bite, and the injured farmer was treated with the 2-1-1 post-exposure prophylaxis (PEP) regimen, producing a high antibody titer. However, because the brain sample from the dead dog was severely decomposed, neither the rabies tissue culture infection test nor the mouse inoculation test could isolate the virus from the sample. Using reverse transcription-polymerase chain reaction (RT-PCR) to test the canine brain sample, the amplified complete N gene sequence was highly similar to the bat IRKV isolated in Jilin Province in 2012, thus confirming that the dog was infected with IRKV. In addition, studies have confirmed that IRKV has certain pathogenicity to dogs and cats. Using a large dose of 50,000 mouse LD50/dose (approximately one thousand

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times the usual live virus inoculation dose) for challenge tests, some experimental animals died (mortality rates of 1/5 for dogs and 3/5 for cats)[40]. Using direct fluorescent antibody (DFA) and reverse transcription-polymerase chain reaction (RT-PCR) to detect IRKV antigen and RNA in brain tissue and saliva specimens from dead animals, all samples from dead animals were IRKV-positive. Surviving animals remained healthy without any symptoms for 90 days after infection. At the end of the study, all surviving animals were euthanized with an overdose of sodium pentobarbital, and DFA and RT-PCR were used to detect IRKV antigen and RNA; brain and saliva samples were IRKV-negative. Based on the above cases, bat rabies virus faces the problem of adaptation to a new host when infecting a new host, i.e., when spillover spreading occurs. Based on the results of challenge tests, it can be inferred that such spillover transmission is difficult to occur under natural conditions, and the spillover transmission route from bats to dogs and then from dogs to humans cannot be established. In addition, although the bitten person developed a high level of antibodies after vaccination and was protected from rabies, it is still uncertain whether the existing vaccine provides protective efficacy against IRKV.

4 Discovery and Classification of Taiwan Bat Lyssavirus (TWBLV)

In a rabies virus surveillance study conducted on 332 bat samples from 13 species collected from different regions of Taiwan between 2014 and the end of May 2017, 2 samples tested positive for virus by direct fluorescent antibody test and reverse transcription PCR. One sample was found in Tainan City in a bat with no specific clinical symptoms but loss of appetite, which died on July 2, 2016. The other sample was a dead bat found in Yunlin County on April 12, 2017. Both bats were Japanese pipistrelles (Pipistrellus abramus)[41]. This study successfully isolated lytic virus from the brains of the 2 bats. Genome sequence analysis showed that the two strains were highly homologous and were named TWBLV. Whole-genome sequence analysis showed that TWBLV had certain differences from the other 16 known lyssaviruses (Table 1). Currently, this strain has been listed by the International Committee on Taxonomy of Viruses (ICTV) as a separate species of lyssavirus and belongs to phylogroup I.

Table 1. Comparison of gene homology between TWBLV and the typical lyssavirus[41]

Lyssavirus species (GenBank accession no.)	Identity, %					Concatenated coding genes (N+P+M+G+L)
	N	P	M	G	L	
Rabies lyssavirus (NC001542)	75.2	62.8–63.1	74.6–74.8	61.6–62.3	71.7	70.0–70.1
Lagos bat lyssavirus (NC020807)	73.5–73.7	53.8–54.1	73.6	55.0–55.6	71.3–71.4	67.8–67.9
Mokola lyssavirus (NC006429)	72.7–73.3	52.2–52.4	72.0–72.6	56.7–56.9	70.6–70.7	67.3 –67.4
Duvenhage lyssavirus (NC020810)	77.7–77.9	67.5–67.6	78.4–79.2	63.9–64.0	74.8–74.9	73.2
European bat 1 lyssavirus (NC009527)	78.8–79.4	69.6–69.7	80.9–81.1	66.1	76.7–76.8	75.1
European bat 2 lyssavirus (NC009528)	75.3–75.6	66.0–66.3	79.2–79.5	64.5–64.6	73.7	72.2–72.3
Australian bat lyssavirus (NC003243)	76.3–76.5	62.2	72.1	61.7–62.0	72.3–72.5	70.4
Aravan lyssavirus (NC020808)	76.5 –76.7	65.6–66	80.3–80.6	64.4–64.5	74.6–74.9	72.9–73.1
Khujand lyssavirus (NC025385)	74.6–74.7	67.0–67.1	78.6–78.7	64.5–64.9	74.2–74.3	72.4–72.5
Irkut lyssavirus (NC020809)	79.0–79.1	68.3–68.6	80.3	65.3–65.8	75.3–75.4	74
Irkut lyssavirus-THChina12 (JX442979)	80.5–80.6	68.7–69.0	79.8–80.0	64–64.6	75.1–75.4	74
West Caucasian bat lyssavirus (NC025377)	72.3–72.7	51.2–51.5	71.4	52.0	68.3–68.4	65–65.2
Shimoni bat lyssavirus (NC025365)	74.1–74.5	54.9–55.1	74.2–74.6	56.2–56.4	71.1–71.2	68.2
Ikoma lyssavirus (NC018629)	69.7–69.8	51.9–52.3	69.3–69.6	50.9–51.2	65.4–65.6	62.9
Bokeloh bat lyssavirus (NC025251)	75.0–75.2	66.0–66.3	78.2	64.4–64.5	74.1–74.2	72.3–72.4
Lleida bat lyssavirus (NC031955)	69.2–69.5	50.8–50.9	70.4–70.9	51.2	66.2	63.2–63.3
Gannoruwa bat lyssavirus (NC031988)	75.5–75.7	62.8–63.1	75.4–75.7	63.7–64.3	73.5–73.6	71.5–71.6

*G, glycoprotein; L, RNA-dependent RNA polymerase; M, matrix protein; N, nucleoprotein; P, phosphoprotein.

5 Nationwide Retrospective Surveillance Study

Due to the considerable challenges of systematically studying rabies virus carried by bats, research progress reported in China is currently limited. Nevertheless, the fact that the positive rate of rabies-related viruses carried by bats in China is extremely low has been confirmed in studies. In a retrospective study of 1,044 brain tissue samples and 3,532 saliva samples collected from 63 different bat species in 21 provinces of China between 2006 and 2018[42], the sample collection covered 62% of bat species in China. This study selected a conserved 120-bp gene of rabies virus and used RT-qPCR techniques based on TaqMan probes and SYBR Green fluorescent dye to detect whether the above bat samples carried rabies virus, but no positive results were obtained. These results indicate that the positive detection rate of rabies virus in healthy bat populations is consistent with the approximately 0.1% positive rate reported in the literature for brain or saliva samples[43-45]. In addition, multiple lines of evidence indicate that bats are sensitive to rabies virus. Although there have been reports of asymptomatic infection in bats[46], most infected bats will develop signs of rabies (including inability to fly, abnormal behavior, and aggression) and eventually die[47,48]. Therefore, when detected bat samples are all dead samples, the proportion of positive samples is higher, and currently all newly discovered bat virus species have been detected or isolated from sick or dead bats[49].

Discussion

1 Mechanisms Underlying the Genetic Diversity and Geographical Clustering of RABV in China

This review systematically summarizes the molecular epidemiological characteristics of the major evolutionary clades of RABV in China, revealing that RABV in China exhibits significant genetic diversity and distinct geographical clustering. The SEA1, SEA2, SEA3, and SEA5 subclades of the Asian lineage dominate in China, while the CA1 subclade of the Cosmopolitan lineage and the AL2 subclade of the Arctic-like lineage form relatively independent epidemic areas in Northwest and North China[20-22]. This complex genetic pattern is the result of multiple factors acting together.

First, geographical barriers have played a key role in shaping the genetic structure of RABV in China. The Taiwan Strait, as a natural geographical barrier, has effectively blocked viral gene flow between Taiwan and mainland China, leading to the formation of a relatively independent SEA5 lineage in Taiwan[32,33]. Similarly, the vast grasslands, deserts, and high-altitude regions in western and northern China have extremely low population density and limited economic activity, restricting the transmission range of RABV and confining the CA1 and AL2 subclades mainly to Inner Mongolia, Xinjiang, Qinghai, and Tibet[24]. In contrast, the densely populated eastern and southern regions of China, with developed transportation networks and high dog mobility, provide favorable conditions for the widespread transmission of the SEA1 subclade[29].

Second, phylogeographic analysis indicates that domestic circulation of RABV dominates viral transmission in China, with limited evidence of cross-border importation[25]. The introduction of RABV from Southeast Asia into southern China is currently the only cross-border importation route with adequate theoretical support[25], which is consistent with the geographical adjacency and historical close exchanges between Yunnan, Guangxi, and Southeast Asian countries[34]. However, the discovery of a human case of the Indian subcontinent lineage RABV in a border area of Tibet in 2017 suggests that with the increase in cross-border movement of people and

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animals, the risk of importation of novel RABV lineages cannot be ignored and deserves high attention.

2 Public Health Significance of Ferret Badgers as Independent Wildlife Hosts

The increasingly prominent role of ferret badgers in the epidemiology of RABV in China is an important finding revealed by this review. The successful adaptation of the SEA1 subclade in ferret badgers and its rapid replacement of the SEA2 subclade[31] indicate that ferret badgers are no longer merely incidental hosts of RABV, but may be evolving into wildlife hosts with independent transmission capability. Detectable genetic differences have emerged between ferret badger-associated SEA1 and dog-associated SEA1, suggesting that RABV in ferret badgers may be following an independent evolutionary trajectory and could potentially form a major independent branch in the phylogenetic tree in the future.

This finding has far-reaching public health significance. On the one hand, the persistent transmission chain of rabies in ferret badgers usually occurs 3 to 5 years or longer after the transmission of dog rabies, indicating that the epidemic of rabies in ferret badgers is closely related to dog rabies, and dog vaccination remains the fundamental strategy for controlling rabies in ferret badgers. On the other hand, as wild animals, ferret badgers have wide ranges of activity and are difficult to vaccinate on a large scale. Once a stable wildlife transmission chain is formed, the complexity and difficulty of rabies control will increase substantially. Therefore, while continuing to promote dog vaccination, it is necessary to strengthen active surveillance of wild animals such as ferret badgers, assess their risk as independent hosts of RABV, and explore novel prevention and control strategies such as oral vaccines for wildlife rabies[50].

3 Isolation Evolution and Homology of RABV in Taiwan

The molecular epidemiological characteristics of RABV in Taiwan provide a unique case for understanding the impact of geographical isolation on viral evolution. The ancestors of the two Taiwan-specific lineages, SEA5a and SEA5b, are traced back to approximately 1956 and 1941, respectively[32]. These time points are highly close to the historical event of artificial separation between the two sides of the Taiwan Strait in 1949, strongly suggesting the decisive impact of geographical isolation and interruption of personnel exchanges on viral gene flow. The high homology between RABV in Taiwan and RABV in southeastern China further confirms that RABV on both sides of the strait shares a common ancestor, while the east-west orientation of the Central Mountain Range in Taiwan may be an important geographical factor for the division of rabies populations on the island into two lineages[32].

Notably, all virus isolates of the SEA5 subclade are from ferret badgers, and the evolutionary rate of their N gene is significantly higher than that of dog-associated RABV subgroups[24]. This finding suggests that host switching may be accompanied by changes in viral evolutionary rate, and that different host species may exert different selective pressures on RABV. This phenomenon not only has evolutionary biological significance, but also raises new questions for the assessment of vaccine protective efficacy--whether virus strains with faster evolutionary rates may produce antigenic variations that affect the cross-protective efficacy of existing vaccines is worthy of further study.

4 Spillover Risk and Vaccine Protective Efficacy of Bat-Origin Rabies-Related Viruses

Although research on bat-origin rabies-related viruses in China started relatively late, important progress has been made. The discoveries of IRKV and TWBLV have not only enriched the genetic

diversity of the genus Lyssavirus in East Asia, but have also sparked important discussions about the spillover risk of bat-origin viruses and their potential threats to public health safety[39,41].

Pathogenicity studies of IRKV have shown that although the virus has certain pathogenicity to dogs and cats, cross-species transmission from bats to dogs and then from dogs to humans faces numerous obstacles under natural conditions[40]. The survival of some animals in high-dose challenge tests and the rarity of natural infection cases both suggest that the adaptability of IRKV to new hosts is limited. However, the 2017 incident of a dog infected with IRKV in Liaoning Province indicates that although spillover transmission is rare, it is not impossible, and the protective efficacy of existing rabies vaccines against IRKV remains uncertain[40]. TWBLV, as a newly recognized member of the genus Lyssavirus by ICTV, has whole-genome differences from classical RABV, suggesting that existing vaccines may not provide complete protection[51].

Nationwide retrospective surveillance studies[42] have shown that the positive rate of rabies virus in healthy bat populations is extremely low (approximately 0.1%), consistent with global reports[43-45]. However, bats have high species diversity, wide distribution, and cryptic behavior, and systematic surveillance still faces enormous challenges. Currently, all newly discovered bat-origin rabies-related viruses have come from sick or dead bats[49], which means that findings based on passive surveillance may be seriously underestimated. Establishing active surveillance networks targeting bats, developing highly sensitive detection technologies, and assessing the neutralizing activity of existing vaccines against bat-origin rabies-related viruses are important directions for future research.

5 Study Limitations and Future Directions

This review is mainly based on published molecular epidemiological studies and has the following limitations. First, there is uneven spatiotemporal coverage in existing studies: research in eastern and southern regions is relatively sufficient, while sample sizes in western and northern remote areas are limited, which may affect the accurate assessment of transmission dynamics of the CA1 and AL2 subclades. Second, research on bat-origin rabies-related viruses is still insufficient, and most provinces lack systematic bat surveillance data, making it difficult to comprehensively assess the true role of bats in RABV ecology. Third, most existing studies have focused on partial fragments of the N and G genes, and whole-genome-level phylogenetic studies are relatively scarce, limiting in-depth understanding of viral evolutionary mechanisms, recombination events, and adaptive mutations.

Future research should be strengthened in the following aspects: first, expanding RABV surveillance networks in western and northern border areas, with a focus on cross-border importation risks; second, establishing a nationwide bat rabies surveillance system and combining new technologies such as metagenomics to improve detection sensitivity; third, conducting more whole-genome sequencing studies to reveal the fine evolutionary history and adaptive mechanisms of RABV; fourth, systematically assessing the protective efficacy of existing vaccines against different RABV subclades and bat-origin rabies-related viruses, to provide a basis for optimized selection of vaccine strains; fifth, strengthening host-virus interaction research to elucidate the molecular mechanisms by which wild animals such as ferret badgers serve as potential independent hosts of RABV.

6 Implications for Rabies Elimination Strategies in China

The complex genetic structure and dynamic transmission patterns of RABV in China present

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challenges for achieving the goal of Zero human deaths from dog-mediated rabies by 2030, but also point the way forward. The widespread distribution of the SEA1 subclade suggests that dog vaccination coverage needs to reach higher levels nationwide, particularly in rural and remote areas. The independent transmission chain of rabies in ferret badgers suggests that even after the elimination of dog rabies, attention must still be paid to the persistent presence and rebound risk of wildlife rabies. The existence of cross-border importation risks requires strengthening surveillance and early warning capabilities in border areas. Although the discovery of bat-origin rabies-related viruses has not yet constituted a large-scale threat, their potential challenge to the protective efficacy of existing vaccines reminds us that vaccine research and development and surveillance systems need to be capable of responding to novel viruses.

In summary, molecular epidemiological research on RABV in China has not only revealed the transmission patterns and evolutionary dynamics of the virus within China, but has also provided important scientific evidence for formulating precise and effective rabies prevention and control strategies. With the continuous advancement of molecular biology and genomics technologies, future in-depth research on the genetic diversity of RABV in China will further promote the transition of rabies from control to elimination.

Conclusion

This review systematically summarizes the molecular epidemiological characteristics and genetic patterns of the major evolutionary clades of rabies virus in China. The study reveals that RABV in China is dominated by the Asian lineage, forming a complex genetic pattern characterized by widespread distribution of SEA1, regional clustering of SEA2/SEA3/SEA5, and border confinement of CA1/AL2. Geographical barriers, population density differences, and the development of transportation networks are the core driving forces shaping this pattern. Domestic viral circulation dominates transmission, but cross-border importation risks remain a concern.

The lineage shift phenomenon observed in ferret badger-associated RABV reveals the important role of wildlife hosts in RABV evolution, and the public health risk of ferret badgers as potential independent hosts cannot be ignored. The discovery of bat-origin rabies-related viruses (IRKV and TWBLV) has expanded our understanding of the genetic diversity of the genus Lyssavirus in China, but the natural barriers to their spillover transmission and the cross-protective efficacy of existing vaccines require further in-depth study.

In summary, molecular epidemiological research on RABV in China provides important molecular evidence for understanding viral transmission patterns, assessing host switching risks, and optimizing prevention and control strategies. Under the strategic framework of Zero human deaths from dog-mediated rabies by 2030, continuously promoting high-coverage dog vaccination, strengthening active surveillance of wildlife, building border early warning systems, conducting whole-genome evolutionary studies, and assessing the potential impact of novel viruses on vaccine protection will be the key pathways to achieving the goal of rabies elimination.

Conflict of Interest

All authors declare that there are no conflicts of interest that could affect the objectivity or impartiality of the research results, writing process, or submission of this manuscript.

Author Contributions

Jia Li: Conceptualization, literature search, data curation, and drafting of the original manuscript.

Shouchun Cao and Xiaohong Wu: Research supervision, manuscript review and revision, academic content oversight, and submission decision.

All authors have read and agreed to the final manuscript content and are responsible for its academic integrity.

Data Availability Statement

All data cited in this review are derived from previously published literature and can be accessed through the respective original publications. No new original experimental data were generated in this review.

Ethical Statement

This study is a systematic review. All analyses were based on previously published literature data, and no human trials, animal experiments, or patient privacy data were involved. Therefore, ethical committee approval was not required.

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