

Bat Lyssaviruses in Europe

Subjects: Zoology

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Bat lyssaviruses have become the topic of intensive molecular and epidemiological investigations. Since ancient times, rhabdoviruses have caused fatal encephalitis in humans which has led to research into effective strategies for their eradication.

Keywords: lyssavirus phylogroups ; Chiroptera ; evolution

1. Introduction

The Order Chiroptera has a Laurasiatherian origin ("laurasian beasts"), evolved between 50 and 70 million years ago (MYA), and has undergone rapid diversification ^{[1][2]}. Due to their capabilities of self-powered flight and echolocation, bats ^[3] comprise over 20%, or more than 1460 species, of all modern mammals and are globally distributed, with the exception of the extreme polar regions ^[4]. They have many characteristics that differentiate them from other mammalian species, such as their unique physiology ^{[5][6]}, metabolism ^[7], and immune system ^{[2][8][9]}. These features make them a suitable reservoir for viral zoonoses ^{[4][10][11]} and more than 200 viruses have been isolated from or detected in bats ^{[12][13][14]}. The order comprises 45 species in Europe ^[15] from two superfamilies, the Rhinolophoidea and Vespertilionoidea ^[16], representing a natural reservoir of RNA-viruses.

Viruses from 11 families have been isolated on the continent ^[17] and bat lyssaviruses in Europe (family *Rhabdoviridae*) have been the subject of detailed reviews ^{[18][19][20][21]}. Lyssaviruses are a genus of negative-sense single-strand RNA viruses in the family *Rhabdoviridae*, subfamily *Alpharhabdovirinae*. Notably, they are members of the order *Mononegavirales*, which includes other prominent zoonotic pathogens such as filoviruses (Ebola, Marburg, etc.) and the neurotropic *Bornaviridae* ^[22]. Based on genetic divergence, lyssaviruses are classified into 21 different viral species. Recently, several putative new lyssaviruses were published ^{[23][24][25][26]}. Apart from the Mokola virus (MOKV) and Ikoma lyssavirus (IKOV), which have rodents and African civets as a reservoir, respectively ^{[25][27][28]}, the rest of the lyssaviruses can be transmitted by Chiroptera ^{[27][29]}. According to the most recent ICTV report ^[24], lyssavirus names are provided here followed by the traditional abbreviations used to identify their isolates: rabies virus (RABV), Aravan virus (ARAV), Australian bat lyssavirus (ABLV), Bokeloh bat lyssavirus (BBLV), Duvenhage virus (DUVV), European bat lyssavirus 1 (EBLV-1), European bat lyssavirus 2 (EBLV-2), Gannoruwa bat lyssavirus (GBLV), Ikoma lyssavirus (IKOV), Irkut virus (IRKV), Khujand virus (KHUV), Lagos bat virus (LBV), Lleida bat lyssavirus (LLEBV), Mokola virus (MOKV), Shimoni bat virus (SHIBV), Kotalahti bat lyssavirus (KBLV), Divača bat lyssavirus (DBLV), West Caucasian bat virus (WCBV), Matlo bat lyssavirus (MBLV), and Lyssavirus *Formosa*, which includes Taiwan bat lyssavirus 1 (TWBLV-1) and Taiwan bat lyssavirus 2 (TWBLV-2) ^{[21][24][30][31][32][33][34][35]}. In fact, KBLV and MBLV are only tentative lyssaviruses.

2. Origin, Evolution, and Geographic Distribution of Bat Lyssaviruses

Despite the greater diversity of African lyssaviruses ^[36], Hayman et al. ^[37] assumed that they have a Palearctic origin and challenged "Out of Africa" hypothesis. The Lyssaviruses' most recent common ancestor (MRCA) evolved from an insect rhabdovirus between 7000 and 11,000 years ago ^{[30][38][39]} which was transmitted to representatives of the order Chiroptera and spread globally ^{[38][40]}. According to Rupprecht et al. ^[30], Africa is the most likely home to the ancestors of taxa within the Genus *Lyssavirus*, family *Rhabdoviridae*. A large number of different lyssaviruses co-evolved with bats as ultimate reservoirs over millions of years. On the other hand, Velasco-Villa et al. ^[41] argue that in the Western Hemisphere before the arrival of the first European colonizers, rabies virus was present only in bats and so-called mesocarnivores (canids, raccoons, skunks, etc.). It is assumed that all mammals are susceptible to infection with the rabies virus. However, it is most possible that lyssaviruses will never be eradicated due to their presence in chiropteran hosts.

Lyssaviruses have undergone purifying selection followed by a neutral evolution of the viral genomes ^[42]. The low rate of nonsynonymous evolution of lyssaviruses is probably the result of constraints imposed by the need to replicate in multiple

cell types (muscle, peripheral and central nervous systems, and salivary glands) within the host, which in turn boosts cross-species transmission (e.g., different groups of mammals), or because viral proteins are not subject to immune selection, which means existing lyssaviruses are well adapted to their reservoir [43][44].

The host switching of the classic rabies lyssavirus (RABV) from bats to other mammals is estimated to have occurred 800 to 1400 years ago, which does not explain the timing of the oldest putative human rabies cases, estimated to have circulated 4000 years ago in ancient Mesopotamia [45][46]. A possible explanation is that the Mesopotamian RABV lineage disappeared as a consequence of genetic drift (loss of polymorphism) or its high fatality rates [45]. According to Rupprecht et al. [47] and Badrane et al. [48], bats are the primary evolutionary host of rabies viruses as a reservoir of all existing lyssaviruses except MOKV and IKOV, whereas other mammals and humans only maintain several lineages of RABV, including the extinct Mesopotamian strain [30][45][49].

In Europe, bat lyssaviruses (**Figure 1**) were detected in the United Kingdom, the Netherlands, Finland, Denmark, Poland, Czech Republic, Germany, Switzerland, France, Spain, Hungary, Italy, Slovenia, Croatia, Bulgaria, Ukraine, and Russia [19][21][35][50][51][52][53]. During the last two decades, previously unknown lyssaviruses were isolated as follows: WCBV in 2002 on the European side of the Caucasus Mts. [54], BBLV in 2010 from Germany [55], LLEBV in 2011 from Spain [56], KBLV in 2017 from Finland [23], and DBLV in 2014 from Slovenia [35].

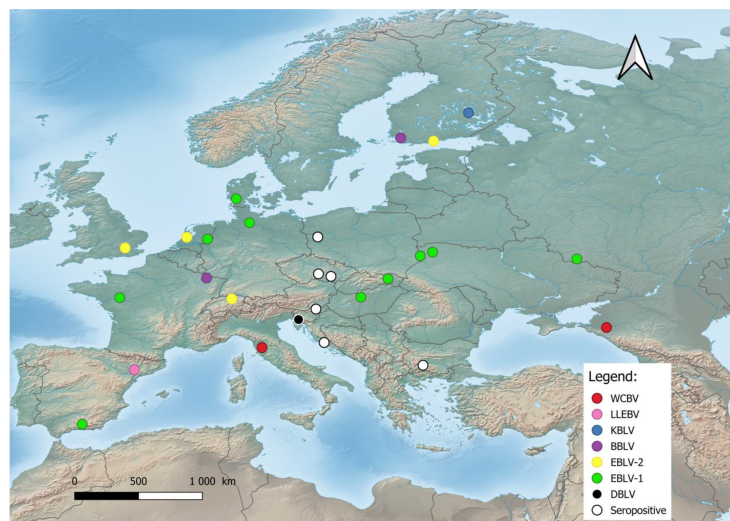


Figure 1. Distribution of bat lyssaviruses in Europe. Abbreviations used: WCBV—West Caucasian bat lyssavirus; LLEBV—Lleida bat lyssavirus; KBLV—Kotalahti bat lyssavirus; BBLV—Bokeloh bat lyssavirus; EBLV-1—European bat lyssavirus 1; EBLV-2—European bat lyssavirus 2; DBLV—Divača bat lyssavirus, Seropositive—Seropositive Blood samples.

The most frequent lineages are EBLV-1, first reported in 1955 from Germany, and EBLV-2, isolated in 1985 in Switzerland [49][50]. EBLV-1 is exclusively detected in Serotine bats (*Eptesicus serotinus*), while EBLV-2 is mainly found in Daubenton's bats (*Myotis daubentonii*). EBLV-1 is present in two forms: EBLV-1a and EBLV-1b. EBLV-1a displays a wide geographical distribution between France and Russia with phylogenetic homogeneity—an indication of extensive dispersal by bats [20][57]. Recent research has shown that EBLV-1 is associated with the bat *E. serotinus* of the mountainous parts of Southern Europe, such as the French Alps or the Iberian Peninsula [58]. EBLV-1 demonstrates the risk of spillover because of its host's close phylogenetic relation with a different bat, the *E. isabellinus*. The phylogenetic analysis of nine EBLV-1 strains of *E. serotinus* distributed in the south of the Pyrenees revealed that two of them are closely related to EBLV-1a sequences from Southern France, i.e., this group expanded to Northern Spain. The results of the conducted research give the authors reason to assume the expansion of the EBLV-1a subtype across southern France, with a very recent arrival to the Iberian Peninsula, i.e., a current southwards dissemination [50]. In contrast, EBLV-1b is distributed between Spain and Poland with a well-defined geographic structure, indicating restricted contact between bat populations [20][50]. Therefore EBLV-1b had the potential to spread southwards according to the *E. isabellinus* distribution. The lineage of EBLV-1 is presumed to have arisen 500 to 750 years ago and has a relatively recent origin [57]. Conversely, the lineage of EBLV-2 is dated to more than 8000 years ago, with current establishment in Europe within the last 2000 years. [59]. EBLV-2 has been reported in Western Europe and is also represented by two forms: EBLV-2a and EBLV-2b [51][60]. The first occurs in the United Kingdom, Netherlands, Germany, Switzerland, and Denmark, while the second includes the Finnish EBLV-2 strains and a strain from Switzerland [59], where the divergence of the Finnish strains from the Swiss strain occurred within the last 200 years [59].

3. Phylogeny of Bat Lyssaviruses

Based on the sequence analysis of the lyssavirus N gene, serologic cross-reactivity and pathogenicity bat lyssaviruses are divided into two phylogroups [48][61][62][63], <https://ictv.global/report/chapter/rhabdoviridae/rhabdoviridae/lyssavirus> and an unresolved but widely adopted third phylogroup [64][65], <https://www.who-rabies-bulletin.org/site-page/classification> which might contain some of the most divergent lyssaviruses (**Figure 2**). European viruses are included in Phylogroups I and group of lyssaviruses, which are highly divergent. Phylogroup II is discussed only as a potential scenario for cross-species bat transmission.

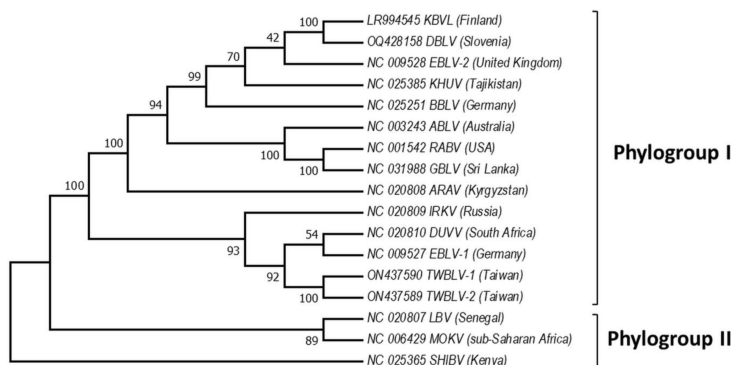


Figure 2. Phylogeny of bat lyssaviruses. The N + P + M + G + L coding regions of representative reference sequences of lyssaviruses used in the analysis were derived from Genbank. The evolutionary history was inferred by using the Maximum Likelihood method and General Time Reversible model. There were a total of 568 positions in the final dataset. Evolutionary analyses were conducted in MEGA X. Virus names are: RABV—rabies virus, ARAV—Aravan virus, ABLV—Australian bat lyssavirus, BBLV—Bokeloh bat lyssavirus, DUVV—Duvenhage virus, EBLV-1—European bat lyssavirus 1, EBLV-2—European bat lyssavirus 2, GBLV—Gannoruwa bat lyssavirus, IKOV—Ikoma virus, IRKV—Irkut virus, KHUV—Khujand virus, LBV—Lagos bat virus, MOKV—Mokola virus, SHIBV—Shimoni bat virus, KBVL—Kotalahti bat lyssavirus, DBLV—Divača bat lyssavirus, TWBLV-1—Taiwan bat lyssavirus 1, and TWBLV-2—Taiwan bat lyssavirus 2.

Phylogroup I includes all these lyssaviruses RABV, ARAV, ABLV, BBLV, DUVV, EBLV-1, EBLV-2, GBLV, IRKV, KBLV, DBLV, KHUV, TWBLV-1, and TWBLV-2, whereas LBV, MOKV, and SHIBV form Phylogroup II [23][31][34][35][66][67][68][69]. Phylogenetically, the most divergent lyssaviruses LLEBV, IKOV, WCBV, and MBLV appear related [27][55][56][70]. Phylogroup I is divided into two major groups: the first includes the Palearctic lyssaviruses IRKV, EBLV-1, TWBLV-1, TWBLV-2 and African DUVV lyssaviruses and the second ARAV, BBLV, KHUV, and EBLV-2 which are also lyssaviruses with Palearctic distribution, as well as Australian—ABLV, Oriental—GBLV, and American—RABV [38]. Interestingly, EBLV-1 is most closely related to DUVV and IRKV, while EBLV-2 to KBLV, KHUV, and BBLV [30][32]. Based on the close phylogenetic relation between EBLV-1 and DUVV lyssaviruses [71], it is hypothesized that EBLV-1 originated in North Africa and spread to Europe (Iberian Peninsula) via the Strait of Gibraltar. However, Hayman et al. [13] present phylogenetic evidence based on the rabies N gene sequences that EBLV-1 and DUVV share a common ancestor with IRKV (isolate from Russia) and both have been transferred to Africa from the Palearctic region, and Europe in particular. Phylogenetic relationships in the most divergent lyssaviruses demonstrate close phylogenetic relatedness between the LLEBV virus from Spain, sub-Saharan Africa MBLV with the Eurasian WCBV and the African IKOV lyssavirus [34][37][72]. Genetically, LLEBV is more closely related to IKOV than to WCBV, in contrast with MBLV [34].

For a better understanding of lyssavirus phylogeny and their current distributions, a closer look at their bat species reservoirs is required. Generally, morphological keys such as Dietz et al. [73] are widely used for bat identification. On the other hand, morphological identification from carcasses can be limited due to the state of decomposition or nearly indistinguishable morphological features in juvenile bats and can lead to misidentifications [74]. Therefore, genetic markers are highly required due to their role for precise bat taxonomic clarification especially in cryptic species complexes, e.g., Çoraman et al. [75] and De Benedictis et al. [76]. Genomic and mitochondrial analyses have placed bats into two suborders: Yinpterochiroptera—including the five families in the superfamily Rhinolophoidea plus the flying foxes—Pteropodidae, and Yangochiroptera—including the three superfamilies: Emballonuroidea, Vespertilionoidea, and Noctilionoidae, comprising a total of 13 families. Two superfamilies (Rhinolophoidea and Vespertilionoidea) are of particular interest in Europe because their representatives are the main reservoir of lyssaviruses. The greater horseshoe bat (*Rhinolophus ferrumequinum*) (Rhinolophidae, Rhinolophoidea) and the Vespertilionoidea species Greater mouse-eared bat (*Myotis myotis*), Lesser mouse-eared bat (*M. blythii*), Natterer's bat (*M. nattereri*), Serotine bat (*Eptesicus serotinus*), Meridional serotine (*E.*

isabellinus), Common pipistrelle (*Pipistrellus pipistrellus*), Nathusius's pipistrelle (*P. nathusii*), Brown long-eared bat (*Plecotus auritus*), Common noctule (*Nyctalus noctula*), Parti-coloured bat (*Vesperilio murinus*) (Vespertilionidae), Common bent-wing bat (*Miniopterus schreibersii*) (Miniopteridae), and European free-tailed bat (*Tadarida teniotis*) (Molossidae) have all been documented as being infected by EBLV-1 [50][53][77][78][79]. The virus was also isolated from the Egyptian fruit bat (*Rousettus aegyptiacus*) (Pteropodidae) in a Dutch zoo [80]. Regardless of the high number of bat hosts recorded for EBLV-1, EBLV-2 is restricted to *Myotis daubentonii* and *M. dasycneme* [49][50][51]. KBLV was found only in *Myotis brandtii* [23], BBLV only in *M. nattereri* [81][82], and DBLV only in *M. capaccinii* [35]. For comparison, from those bat species, virus serological detection is provided on 15 bats (*R. ferrumequinum*, *B. barbastellus*, *E. serotinus*, *M. blythii*, *M. brandtii*, *M. capaccinii*, *M. myotis*, *M. nattereri*, *N. noctule*, *P. nathusii*, *P. pipistrellus*, *P. auratus*, *M. schreibersii*, *T. teniotis*, *R. aegyptiacus*), identification of viral species affiliation on 16 bats (*R. ferrumequinum*, *E. isabellinus*, *E. serotinus*, *M. brandtii*, *M. capaccinii*, *M. dasycneme*, *M. daubentonii*, *M. myotis*, *M. nattereri*, *N. noctule*, *P. nathusii*, *P. pipistrellus*, *P. auratus*, *V. murinus*, *M. schreibersii*, *R. aegyptiacus*) and both identified in 12 bat species (*R. ferrumequinum*, *E. serotinus*, *M. brandtii*, *M. capaccinii*, *M. myotis*, *M. nattereri*, *N. noctule*, *P. nathusii*, *P. pipistrellus*, *P. auritus*, *M. schreibersii*, *R. aegyptiacus*).

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