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Eastern Equine Encephalitis Virus

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Summary

Eastern equine encephalitis virus (EEEV) is a mosquito-borne virus capable of causing large outbreaks of encephalitis in humans and horses. In North America, EEEV infection has a very high mortality rate in humans, and survivors often suffer severe neurological sequelae. Interestingly, EEEV infections from South American isolates are generally subclinical. Although EEEV is divided into two antigenic varieties and four lineages, only eleven isolates have been sequenced and eight of these are from the North American variety (Lineage I). Most sequenced strains were collected from mosquitoes and only one human isolate has been sequenced. EEEV isolates exist from a variety of hosts, vectors, years, and geographical locations and efforts should focus on sequencing strains that represent this diversity.

Ecology and epidemiology

EEEV is transmitted by mosquitoes and is capable of causing outbreaks of encephalitis in humans and horses. Although human infection with EEEV is a relatively rare occurrence, the case fatality rate ranges from 30 % to almost 80% [1, 2]. Additionally, survivors of the disease may experience serious sequelae such as mental retardation, convulsions, and paralysis [1]. Although infection with North American strains may cause high mortality in humans and equines, South American strains are seldom associated with human disease and sporadic outbreaks have been limited to horses [3]. Other species of animals are also susceptible to infection with EEEV including sheep, pigs, deer, dogs, rodents, bats, and marsupials, as well as a wide variety of birds [2]. Reptiles and amphibians have also tested seropositive for EEEV infection.

EEEV is endemic to South, Central, and North America. EEEV transmission occurs in focal, well-defined regions of North America where it occurs in hardwood swamp habitats, and this limits the occurrence of cases in horses and humans (Figure 1). North American subtype also occurs in the Caribbean, where its presence is due to migration of the avian hosts.

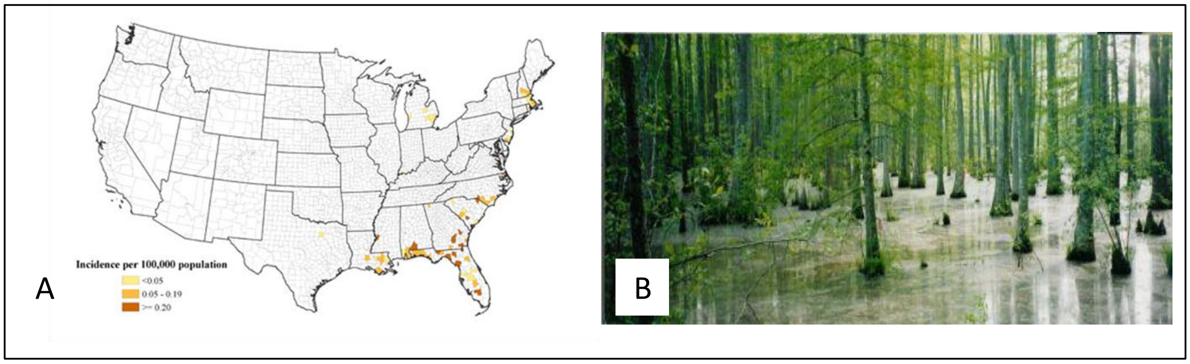

Figure 1. EEEV distribution and associated habitat in Northern America. EEEV is endemic to the eastern United States (A) where it cycle among mosquitoes and birds in hardwood swamps (B).

Passerine birds (i.e. perching songbirds) serve as the host for EEEV, and *Culiseta melanura*, an ornithophilic mosquito (a species of mosquito that feeds primarily on birds), serves as the principal vector of EEEV in North America. Non-avian species such as humans and horses may become infected with EEEV by species of mosquitoes that feed on both birds and mammals ("bridge vectors"). In North America the mosquito-bird transmission cycle of EEEV is seasonal with activity being limited to summer and early fall in temperate regions. It is unclear how EEEV is maintained in temperate regions as there is no evidence of dormancy in infected mosquito eggs [4]. The life cycle of South American strains is less well understood but may involve small mammals, birds, and possibly reptiles. *Culex* (*Melanoconion*) spp. serve as the primary mosquito vector for South American strains [5].

Viral taxonomy and genome diversity

EEEV is a member of the *Togaviridae* family, *Alphavirus* genus. The genomes are approximately 11.4 kb in length and consist of single-stranded, positive sense RNA. EEEV strains are divided into two antigenic varieties (North American and South American) and further divided into four lineages based on genetic sequence. Lineage I is present in the eastern United States, Canada, and the Caribbean. Lineages II-IV are found in South and Central America with Lineage II endemic to Brazil, Guatemala and Peru, Lineage III endemic to Argentina, Brazil, Columbia, Ecuador, Guiana, Panama, Peru, Trinidad and Venezuela, and Lineage IV represented by a single isolate from Brazil [4, 6] (Figure 2).

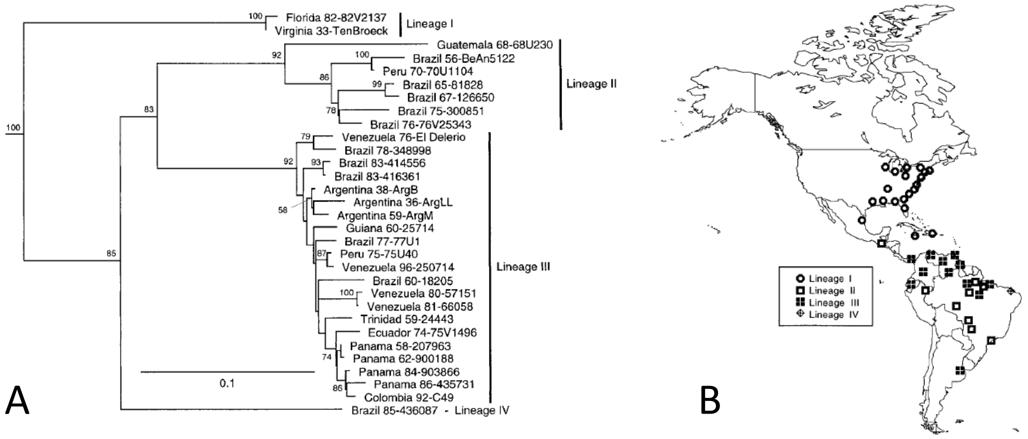

Figure 2. Phylogeny and distribution of EEEV lineages. (A) Phylogenetic tree of EEEV isolates generated from partial nsP4, E2, and 3' untranslated sequence. (B) Map showing the location of Lineage I-IV isolates [4].

North American isolates of EEEV are highly conserved and strains isolated decades apart over a wide geographical range differ in nucleotide sequence by less than 2%. Conversely, South American strains (Lineages II-IV) can differ in nucleotide sequence by up to 25% [2, 4, 7]. South American strains are 25-38% different in nucleotide sequence from North American strains [4].

Near neighbors of EEEV include Venezuelan equine encephalitis virus (VEEV) and western equine encephalitis virus (WEEV). EEEV differs in nucleotide sequence from VEEV by about 38% and from WEEV by about 50-52% [8].

Gaps in sequence data

Genome sequence is available for 11 isolates however, two of these isolates are vaccine strains that are derived from parental strains. Eight of the eleven isolates are from North America and belong to Lineage I. Only one strain from each of the other lineages has been sequenced. Finally, most sequenced strains are from mosquito hosts and were collected over 10 years ago. Therefore, temporally and geographically diverse isolates should be sequenced including isolates from humans and equines as well as endemic hosts such as rodents and birds, as they become available.

Potential sources of material

Potential sources of strains of EEEV strains and near neighbors include Scott Weaver and Bob Tesh (UTMB), Mike Turell at USAMRIID, and Aaron Brault (CDC, Ft. Collins).

References

1. Adams, A.P., et al., *Common marmosets (Callithrix jacchus) as a nonhuman primate model to assess the virulence of eastern equine encephalitis virus strains.* J Virol, 2008. **82**(18): p. 9035-42.
2. Griffin, D.E., *Alphaviruses*, in *Fields Virology*, D.M. Knipe and P.M. Howley, Editors. 2007, Lippincott Williams & Wilkins: Philadelphia, PA. p. 1023-1068.
3. Aguilar, P.V., et al., *Endemic eastern equine encephalitis in the Amazon region of Peru.* Am J Trop Med Hyg, 2007. **76**(2): p. 293-8.
4. Brault, A.C., et al., *Genetic and antigenic diversity among eastern equine encephalitis viruses from North, Central, and South America.* Am J Trop Med Hyg, 1999. **61**(4): p. 579-86.
5. Arrigo, N.C., A.P. Adams, and S.C. Weaver, *Evolutionary patterns of eastern equine encephalitis virus in North versus South America suggest ecological differences and taxonomic revision.* J Virol. **84**(2): p. 1014-25.
6. Kondig, J.P., et al., *Genetic analysis of South American eastern equine encephalomyelitis viruses isolated from mosquitoes collected in the Amazon Basin region of Peru.* Am J Trop Med Hyg, 2007. **76**(3): p. 408-16.
7. Weaver, S.C., et al., *Evolution of alphaviruses in the eastern equine encephalomyelitis complex.* J Virol, 1994. **68**(1): p. 158-69.
8. Powers, A.M., et al., *Evolutionary relationships and systematics of the alphaviruses.* J Virol, 2001. **75**(21): p. 10118-31.