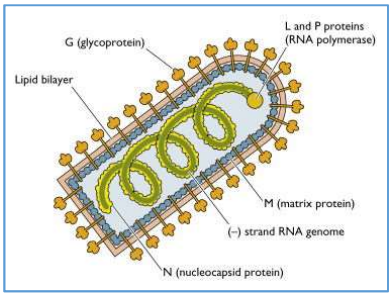
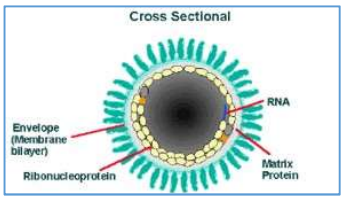
Rhabdoviridae family



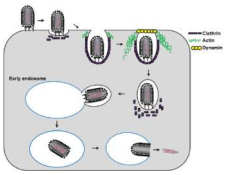
Rod shaped negative sense non segmented single stranded RNA viruses which encodes five viral proteins. Four major genera infect humans – Lyssavirus, Vesiculovirus, Ephemerovirus, Novirhabdovirus.

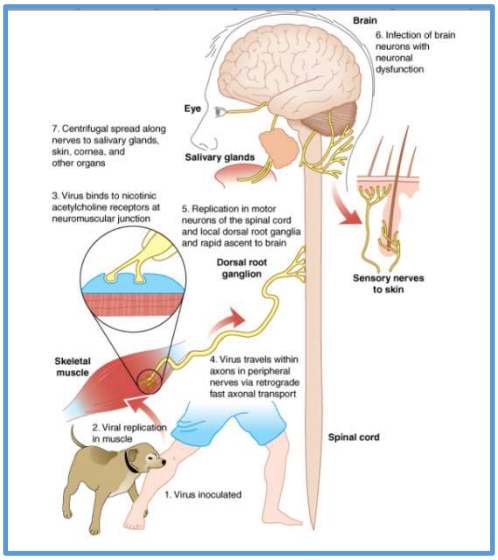
Within Lyssavirus genus multiple genotypes including – *Rabies virus* [1], Lagos bat virus [2], *Mokola virus* [3], *Duvenhage virus* [4], *European bat lyssavirus 1* [5], and *EBLV- 2* [6], ***Australian bat lyssavirus [7]***, *Irkut virus[*8], Aravan virus [9], Khujand virus [10], West Caucasian bat virus [11], Shimoni virus [12]. Also split into 3 phylogroups based in genetic, immunological and pathogenic characteristics.



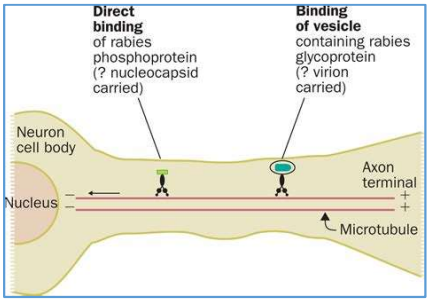
Bullet shaped, length of 180nm, diameter 75um. Helical nucleocapsid 30-35 coils, enclosed in a lipoprotein envelope 7.5-10nm thick, with 'Glycoprotein spikes' (G protein). These cover the entire virion except the blunt end. The genome encodes five genes, N, P, M, G and L. G-protein associate into trimers on the virion surface and is involved in cellular reception and is the antigen that induced virus neutralising antibodies. Variability in this protein is responsible for serotypic differences among lyssaviruses. One mutation in position 333 of G protein can disrupt virulence.

Attachment can be through either a ganglioside or CD56 – a neuronal adhesion molecule in rabies – but unclear in ABLV. In muscles rabies binds to nicotinic Acetylcholine receptor (nAch). Once bound to one of these it internalises (via Clathrin-mediated endocytosis CME) and then fuses with lysosome, allowing the nucelocapsid to escape into the cytosol – this is triggered by a low pH.





Once inside the muscle it replicates in muscle cells/spindle subsequently infects the nerve that innervates the spindle and moves centrally along the axon. Replication doesn't occur in glial cells only neurons. Virus is present in dorsal root ganglia within 60-72 hrs. Natural rabies virus requires replication at the periphery before effect central spread. Therefore timely administration of RIG and active immunization can prevent spread. Once inside the nerves treatment probably does very little to prevent subsequent replication and spread. The axon movement requires interaction between cytoplasmic dyein light chain with the rabies virus. Once in the spinal cord it infects virtually every nerve cell in the spinal cord. Once in the CNS virus spread to the rest of the body via egress down peripheral nerves. The high concentration in saliva is from shedding of mucosal nerve terminals but also from direct replication in salivary glands.



Viral particles inactivated by UV, desiccation, formalin, phenol, detergents, and pH <3 or >11.

Australian bat lyssavirus - endemic within Australian bat populations. Was found after investigating the Hendra virus deaths. Initially in retrospective samples from black flying foxes that had died in 1996 found a unique virus of the Lyssavirus genus. Subsequently the second variant (clade) was found in the Yellow bellied sheath tail bat. It is clear now that two distinct variants (clades) circulate. One in frugivorous bats (genus *Pteropus*) and the other in insectivorous microbats (genus *Saccolaimus*). 3 human deaths the last in 2013 (all in Qld). 2 horse deaths also in 2013. ABLV appears to use a different endocytic pathway and is genetically most closely related to European bat lyssavirus-1. ? questions over terrestrial ABLV unanswered.

> **Oct 1996** – 39yo female Rockhampton. Bat carer (Yellow tailed), but also cared for dogs, cats, cockatoos. Pain and numbness in her left arm → 2-3days later developed dizziness, vomiting,

headache and fever. Admitted to hospital but by d8 developed diplopia, cerebellar signs, slurred speech and difficulty swallowing. Progressed to weakness in all limbs and bilateral facial palsy. GCS became fluctuant. D11 unresponsive. CSF positive for anti-lyssavirus Ab, and PCR positive.

Nov 1998 – 37o female Mackay. 5d hx of fever, and left should pain. Difficulty swallowing. Unable to fully open mouth, and drooling. Throat exam caused spasmodic attempts to swallow. 12hr rapidly deteriorated with increased agitation, and more frequent muscle spasms. Then revealed had a history of bat bite (Aug 1996). D2 unable to communicate and needed ventilation. PCR saliva positive at d2. Post mortem Virus isolated from brain, and spinal cord tissue. Sequencing found the Pteropus variant.

Feb 2013 – 8yo boy from Long Island. Scratched by a bat while playing tennis but didn't tell parents. 2 months later admitted to Brisbane hospital with convulsions abdominal pain and fever. Progressive CNS decline and d28 died.

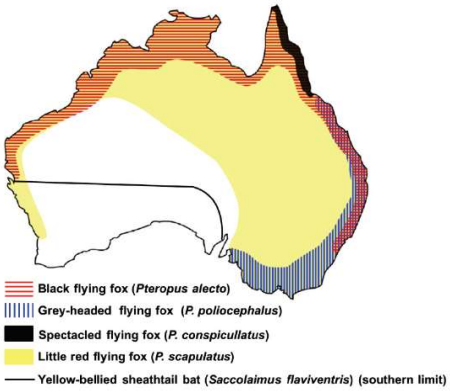
ABLV has been isolated from all four species of flying foxes found on mainland Australia

The black flying fox, the grey headed flying fox, the little red flying fox, and the spectacled flying fox.




ABLV also isolated from a single species of Microchiroptera, the yellow-bellied sheath tail bat but there are antibodies in 5 of the other 6 on mainland Australia. The consensus is that all Australian bat species are considered as potential host reservoirs of ABLV.

Figure 1. Distribution of ABLV host reservoir species. Adapted from [12–14].



Diagnosis

Radiology	NAAT Assay	Other
T2 midbrain, hypothal, brainstem +/- deep + subcortical white matter	**real time-PCR** (saliva, throat, skin, CSF) Then conventional PCR for confirmation (Skin RT-PCR sensitivity 98% specificity 98.3%) 3 x saliva specimens >95%*	**Serology** – EIA IgG (immune status) [<0.5 IU/mL] Rapid fluorescent focus inhibition test (**RFFIT**) and convalescent (serum). **CSF antibody** diagnostic direct IFA – lyssavirus Ag **skin biopsy** (nape full thickness) **brain biopsy** (brain stem, cerebellum, hippocampus) **Histopath** – Negri bodies