

# Introduction to Concepts ‘Genomics of Disease in Wildlife’

GDW 2017  
Colorado State University

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# Genomics Unites Human Biomedicine and Wildlife Research

## Biomedical Advances in Humans

Computer Technology

Whole Genome Annotation

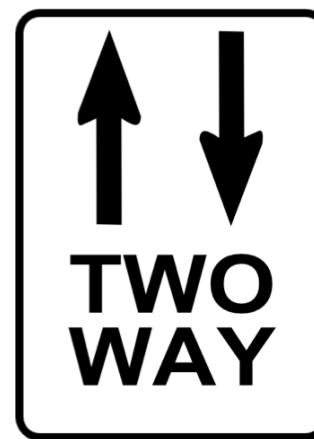
Bioinformatic Tools

Next Gen Sequencing

Transcriptomics, Proteomics

Individualized Medicine

Natural Experiment: Wildlife



Speciation

Biodiversity & Systematics

Population Genetics & Phylogeography

Genome Evolution

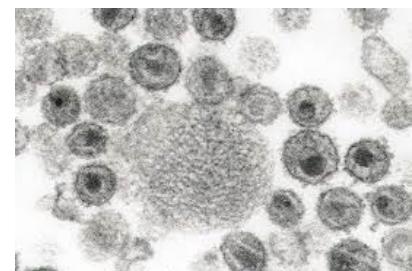
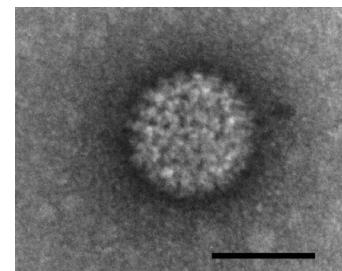
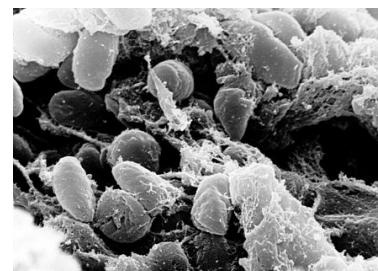
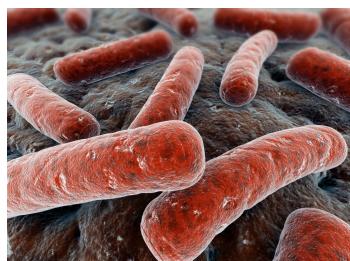
Adaptation & Selection

# Emergence Of Disease In Wild Species

- Why bother?
  - Zoonotic pathogens are responsible for ~58% human disease
  - Monitoring wildlife in natural settings rare & expensive
  - Pathogen outbreak often undetected until noticeable morbidity (rate of incidence) or mortality (death)
  - Host immune genomics reflects selective filters and/or adaptations of survivors to previous outbreaks of disease
- What species?
  - Are some species more susceptible or more resistant?
  - Are some species more likely to be reservoir hosts?
  - Genomic methods identify the molecular basis of the evolutionary arms race between host and pathogen.
  - Are lessons to be learned from wildlife that can be applied to human disease outbreaks?
  - Are lessons to be learned from humans that can be applied to wildlife disease outbreaks?

# DNA Sequencing of Pathogens

- Genome organization, structure and function
- Estimation of pattern and rate of mutation within each pathogen gene
- Estimation of genetic diversity within the pathogen
- Identification of emergent strain
- Geographic and evolutionary origin of emergent strain(s)
- Patterns of global transmission
- Co-evolution and adaptation
- Selection
- Fitness traits-replication rate, transmissibility, immune recognition
- Intra-host diversification and horizontal gene transfer among strains
- Vaccine and drug therapy development



# DNA Sequencing of Host Species

- Evolutionary history of species
- Population structure and phylogeography
- Historic and ongoing patterns of migration
- Genetic diversity
- Inbreeding
- Endangered or relic species, subspecies and populations
- Identification of genes involved in disease resistance and progression
- Predictive effects of pathogen emergence in naïve host populations

# Design Concepts Incorporating NGS Data

- Essential Hypothesis-Driven design will optimize NGS data
- Establish Clear Objectives
- Survey Existing Genomic Resources
- Estimate Sample Size necessary to achieve objectives
- Establish a Realistic Collection Strategy:
  - Disease event, timeline,
  - Patterns of transmission and dissemination,
  - Host specificity,
  - Opportunistic, constant surveillance,
  - Wild or managed populations
- Assess Availability, Quantity, and Quality of Biological Specimens
- Identify Computational resources to analyze large datasets
- Establish a genomic workflow for data assessment, analyses and interpretation
- Establish a realistic budget

# GDW 2017 Host-Pathogen DataSets

## {external hard drive as Geneious projects}

### **Host**

Felidae

Mammals  
(Carnivores, cetaceans)

Mammals  
(Rodents, Carnivores, Human)

Birds  
(Outbreaks in mammals & humans)

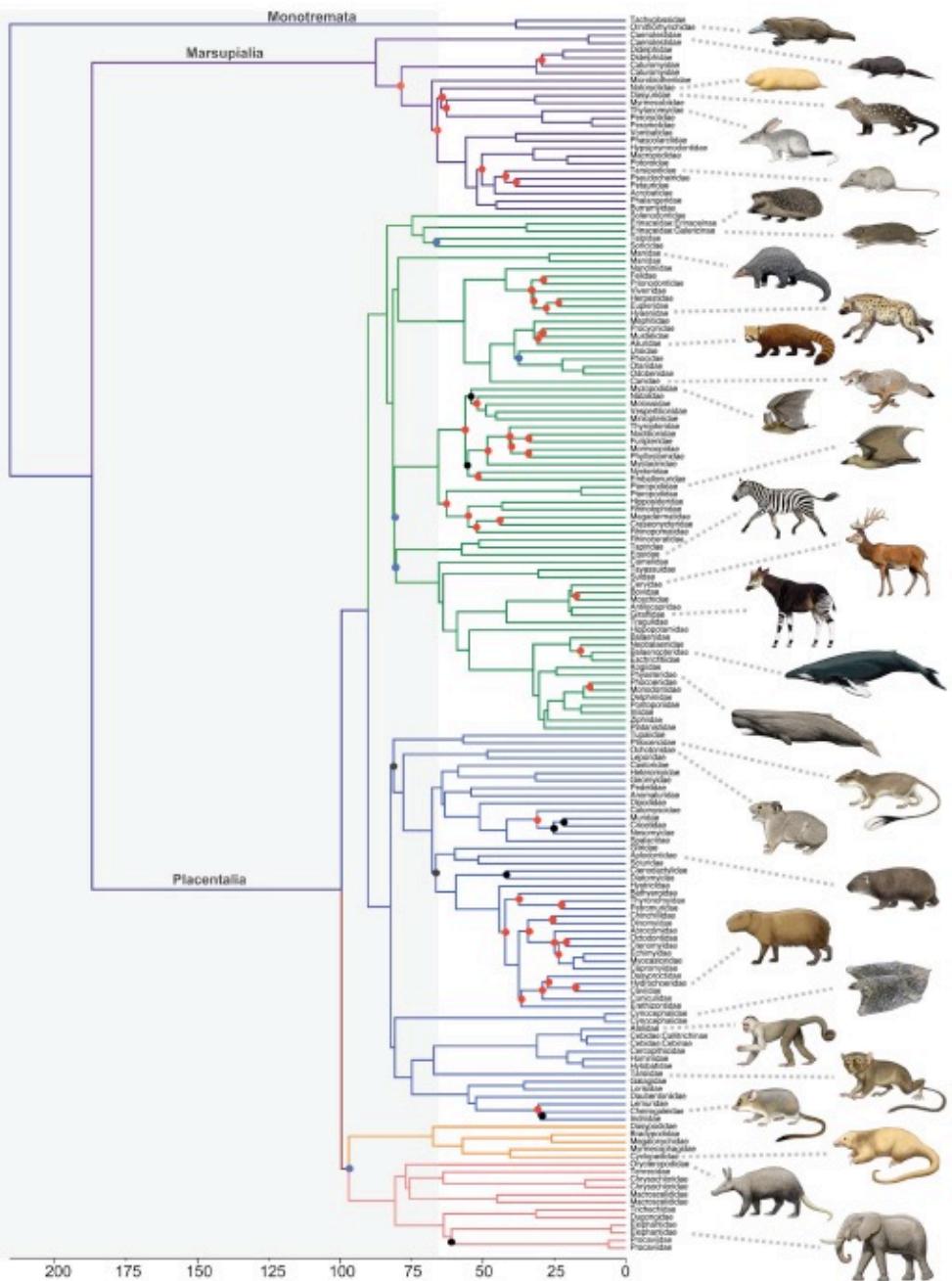
### **Pathogen**

Feline Immunodeficiency Virus

Morbillivirus (Paramyxoviridae)  
Canine Distemper virus  
Dolphin Morbillivirus

Yersinia pestis (sylvatic plague)

Chlamydia psittaci (chlamydiosis)

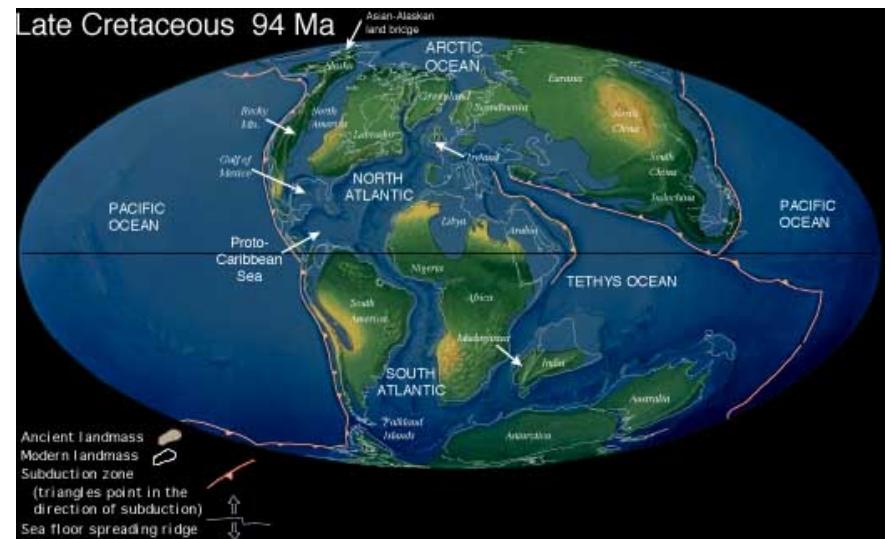


# Mammalian Evolution

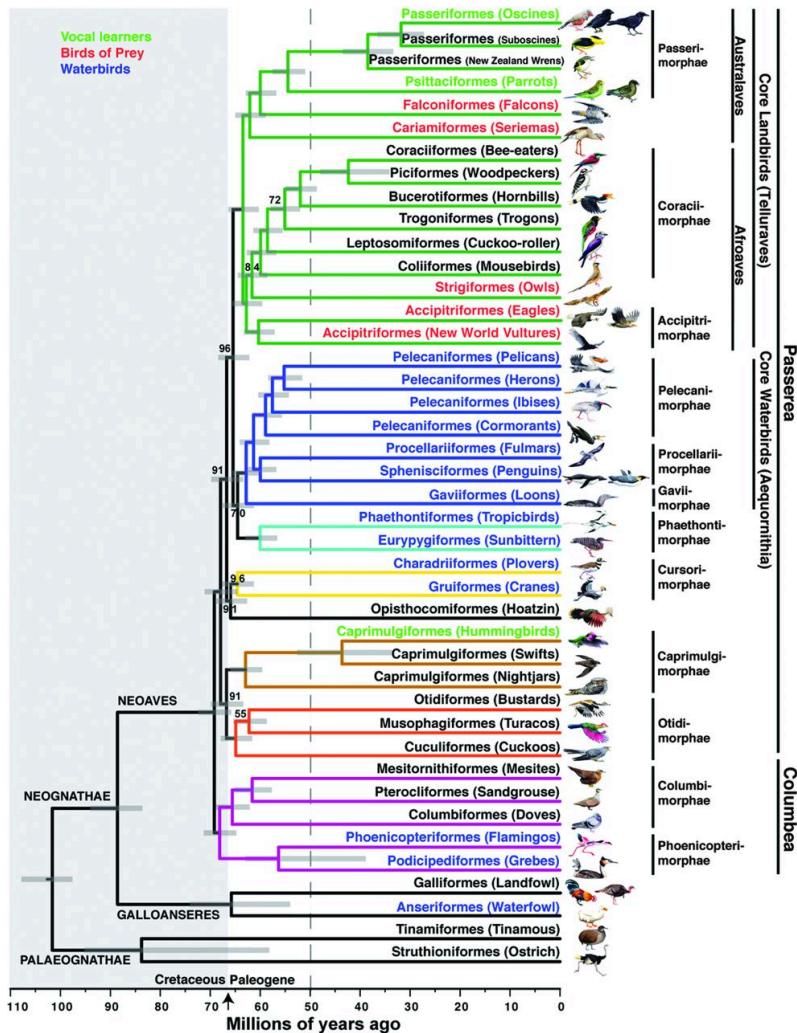
*Ancestor of Eutherian (placental) Mammals arose ~100 MYA*

*KTR (Cretaceous Terrestrial Revolution)  
80-82 MYA*

*KPg (Cretaceous Paleogene mass extinction)  
65.5 MYA*



**Fig. 1 Genome-scale phylogeny of birds.**



Project design 48 species representing all major lineages of birds

Developed orthologs from comparison of human, finch and chicken.

8251 protein coding exons  
2516 intron gene set  
3679 UCE locus set

### Major insights:

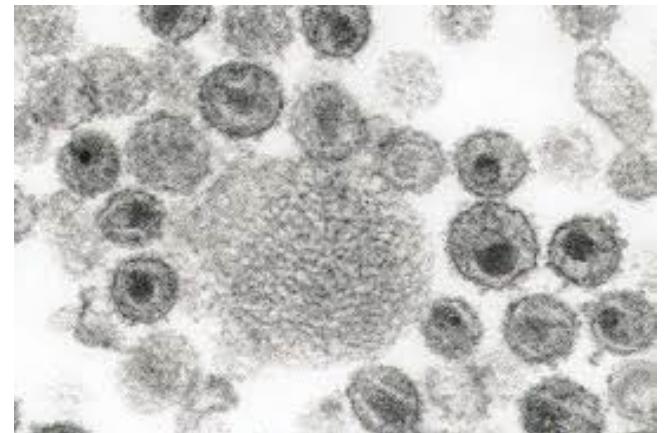
- 1) Genome size and conservation of structure
- 2) Convergent evolution of vocal learners
- 3) Evolution of genes related to flight, diet, reproduction, and vision

Erich D. Jarvis et al. Science 2014;346:1320-1331

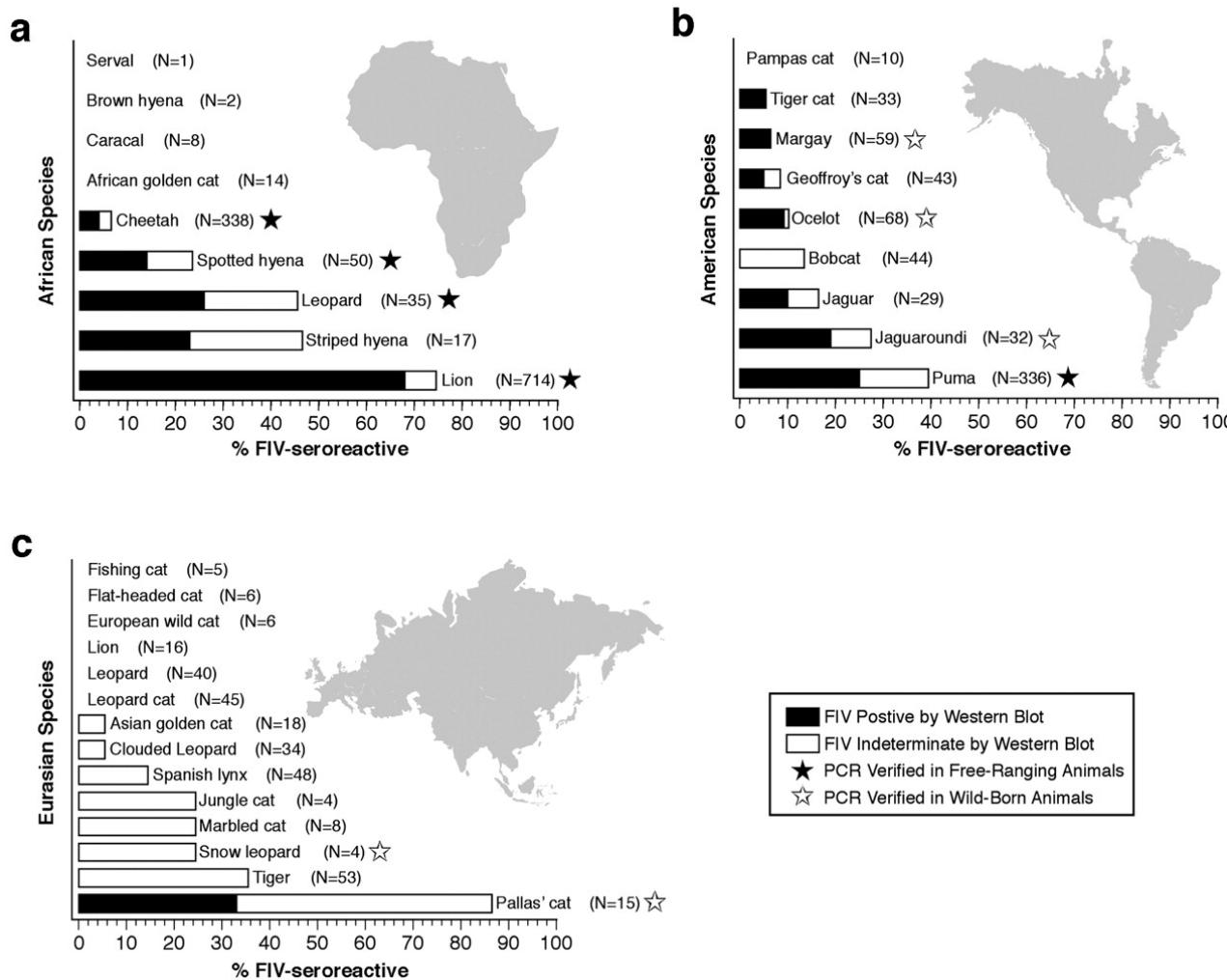


# Pathogen: Feline Immunodeficiency Virus

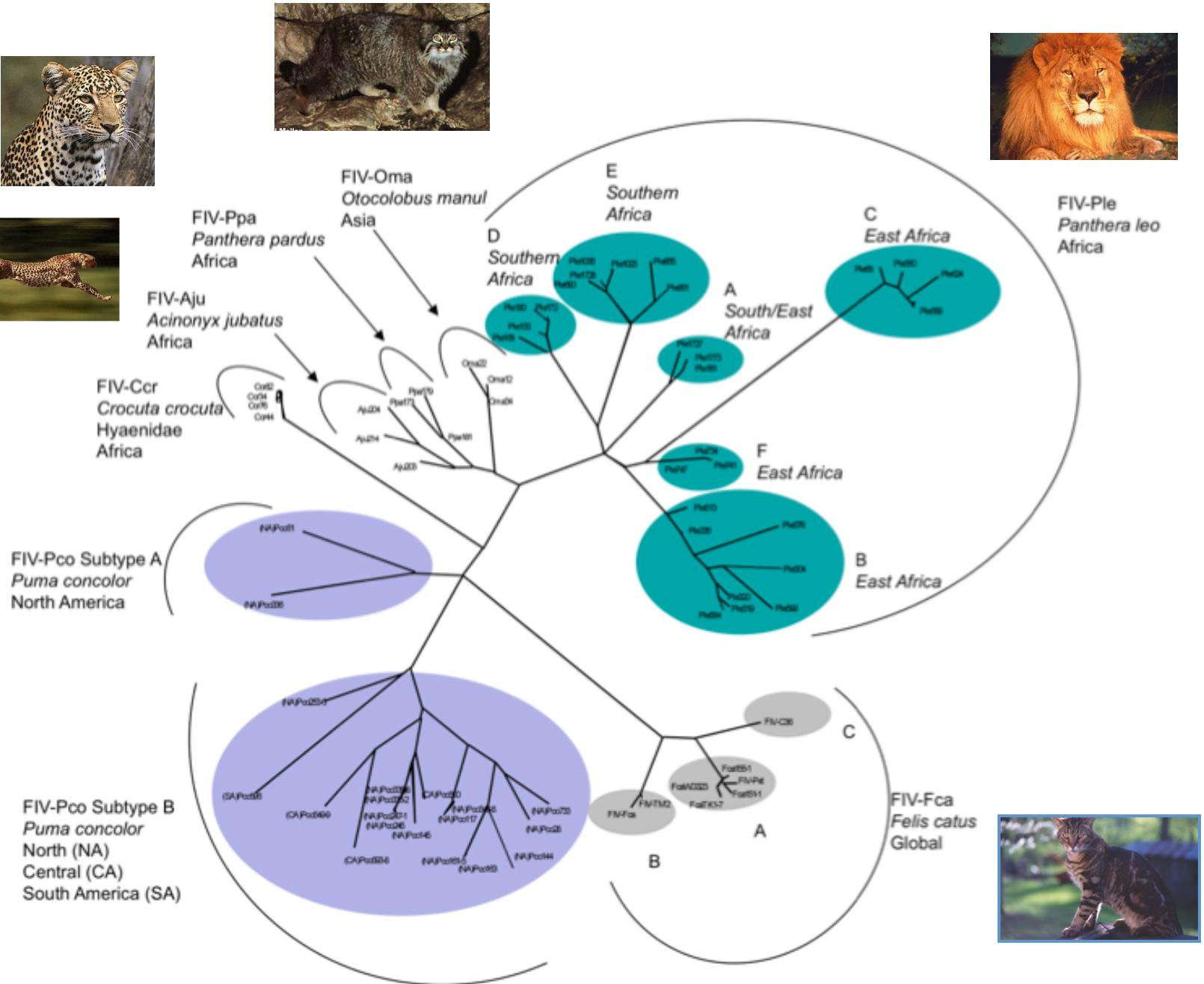
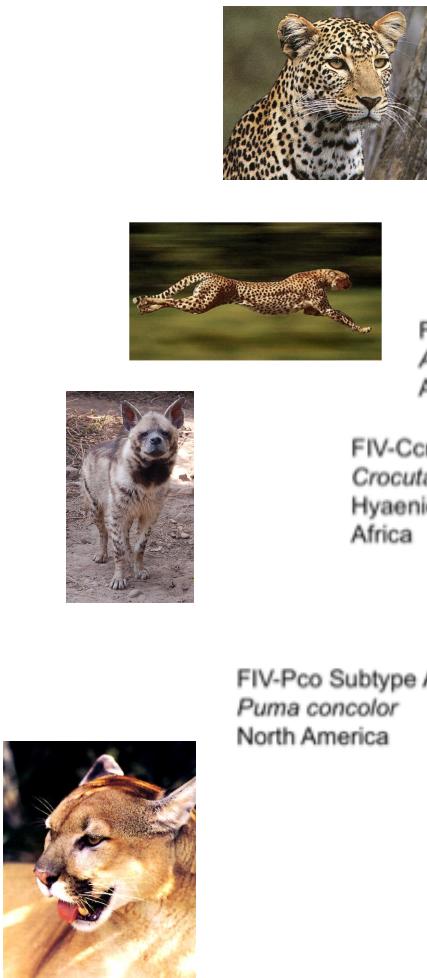
- Feline Immunodeficiency Virus (FIV) was first discovered 25 years ago as a cat lentivirus with structural, genomic, and pathogenic parallels to HIV.
- Infected domestic cats develop symptoms of immune depletion:
  - including a precipitous drop in CD4 bearing T-lymphocytes,
  - neutropenia, lymphadenopathy and
  - susceptibility to normally harmless bacteria, fungal lesions, wasting, and rare cancers
- FIV is endemic in feral cat populations and has diverged into several phylogenetic clade types across the world.



# Prevalence and distribution of FIV seroreactivity in free-ranging and captive but wild-born animals.



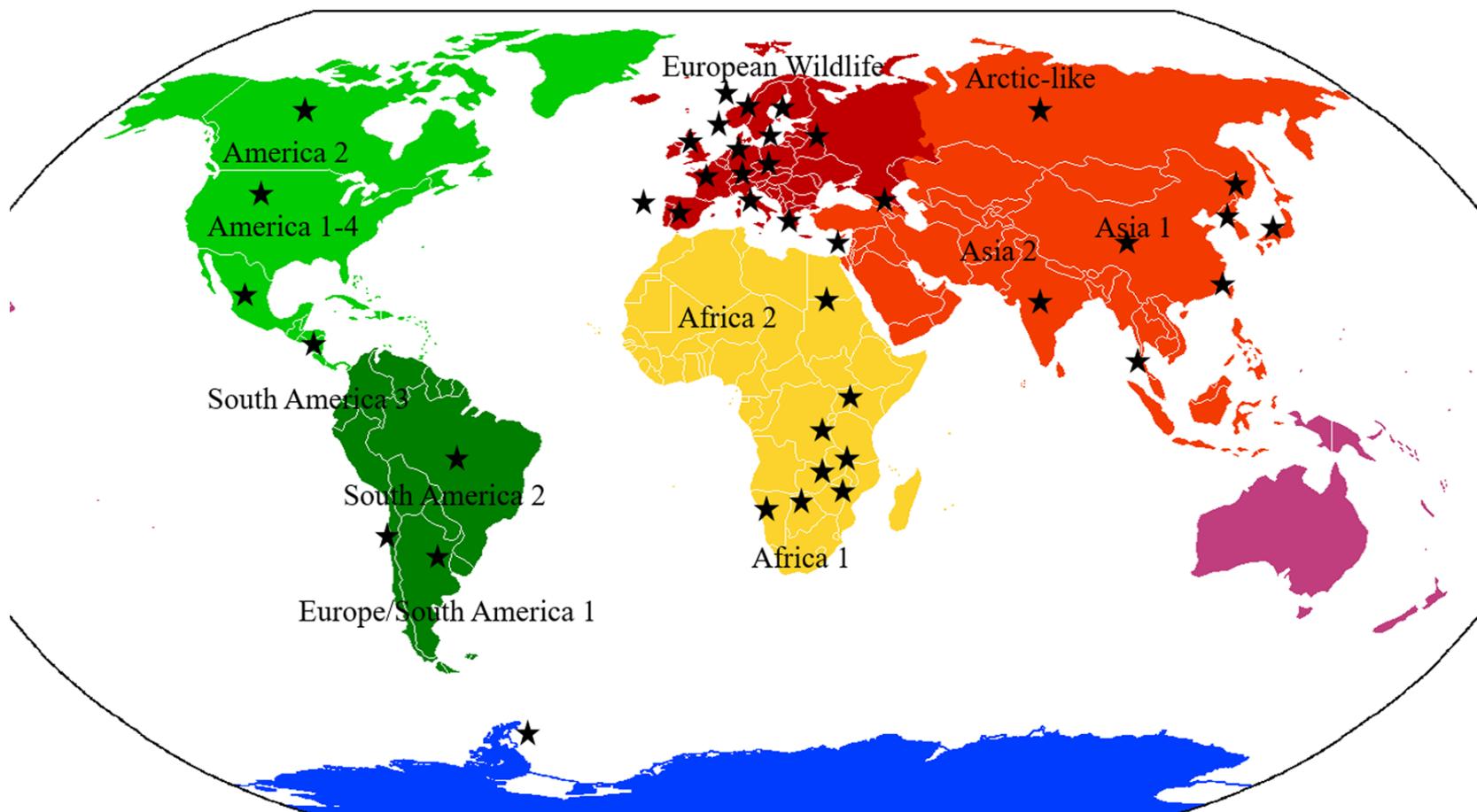
Troyer J L et al. J. Virol. 2005;79:8282-8294



# Canine Distemper Virus Emergence in Wildlife

- CDV is a *Morbillivirus* [Measles, phocine distemper, cetacean morbillivirus, peste des petits ruminants, rinderpest (eradicated)] within the family *Paramyxoviridae*.
- RNA virus with unsegmented genome, linear negative sense, single-stranded.
- Growing concern as found in increasing numbers of non-canine species in the wild and in managed populations
- Global patterns of prevalence
- Highly contagious with high morbidity and mortality
- Jumps between species with emergent and re-emergent pattern
- Genome ~ 15,000 bp encodes 6 structural genes and 2 virulence factor genes

# Prevalence of CDV in non-dog species



Martinez-Gutierrez and Ruiz-Saenz BMC  
Veterinary Research (2016) 12:78

**Table 1** Orders, Families and Species that CDV can infect naturally and/or experimentally

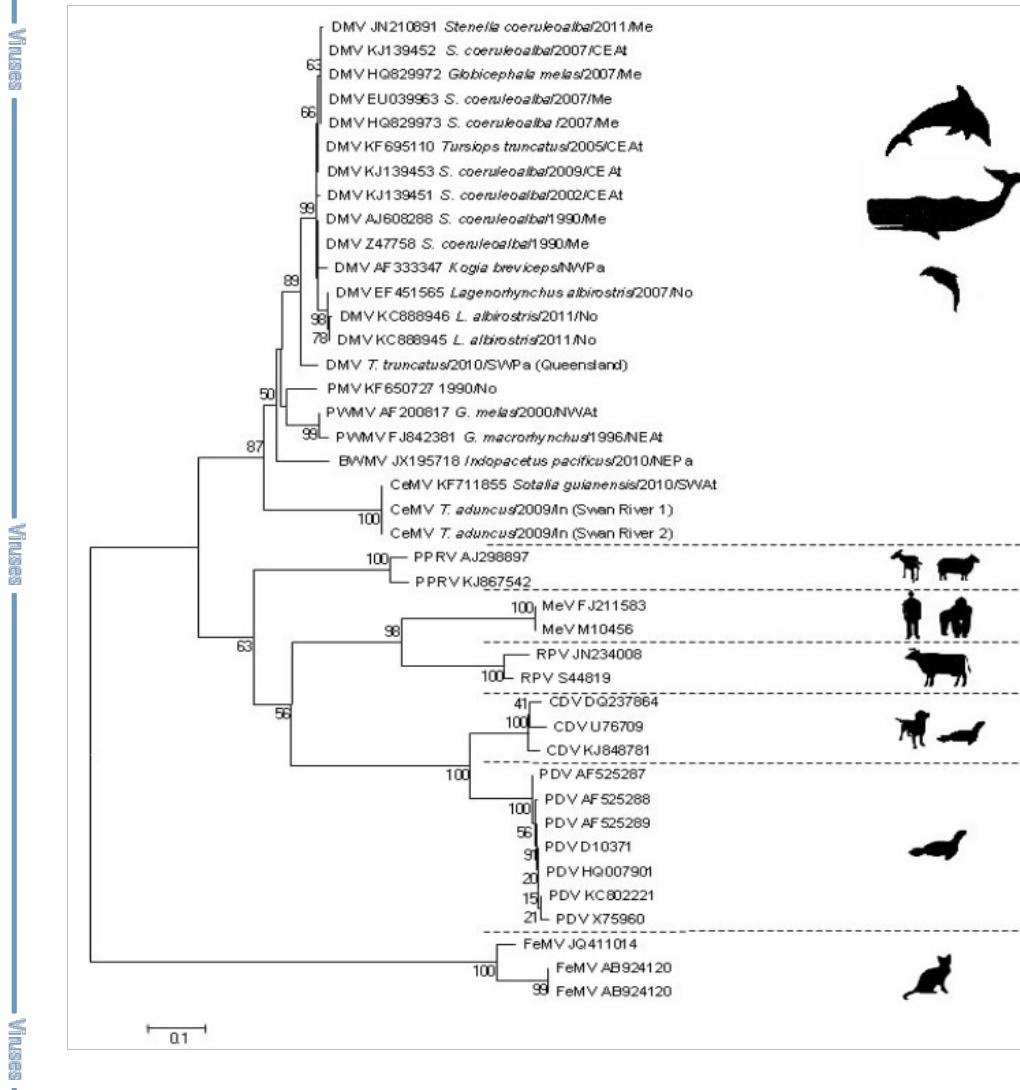
Order	Family	Number of records (% of total)	Number of studies reporting clinical signs in infected animals (%)	Species
Carnivora	Canidae	82 (30.0)	27/82 (32.9)	<i>Canis adustus, Canis aureus, Canis latrans, Canis lupus, Canis lupus baileyi, Canis lupus dingo, Canis lupus signatus, Canis mesomelas, Cerdocyon thous, Chrysocyon brachyurus, Lycalopex culpaeus, Lycalopex griseus, Lycalopex gymnocercus, Lycalopex vetulus, Lycaon pictus, Nyctereutes procyonoides, Nyctereutes procyonoides viverrinus, Urocyon littoralis catalinae, Vulpes chama, Vulpes lagopus, Vulpes macrotis mutica, Vulpes velox, Vulpes vulpes, Vulpes zerda</i>
	Felidae	49 (17.9)	24/49 (48.9)	<i>Acinonyx jubatus, Felis lynx, Felis silvestris, Felis silvestris catus, Leopardus geoffroyi, Leopardus pardalis, Lynx Canadensis, Lynx lynx, Lynx pardinus, Lynx rufus, Panthera leo, Panthera leo persica, Panthera onca, Panthera pardus, Panthera pardus japonensis, Panthera tigris, Panthera tigris altaica, Panthera tigris tigris, Panthera uncia, Puma concolor</i>
	Mustelidae	43 (15.7)	23/43 (67.4)	<i>Enhydra lutris kenyoni, Galictis vittata, Galictis cuja, Gulo gulo, Lontra Canadensis, Martes foina, Martes martes, Martes melampus, Martes pennanti, Meles meles, Melogale moschata subaustraliaca, Mustela erminea, Mustela itatsi sibirica, Mustela luteola, Mustela nigripes, Mustela nivalis, Mustela putorius, Mustela putorius furo, Mustela vison, Neovison vison, Taxidea taxus</i>
	Procyonidae	18 (6.5)	9/18 (50.0)	<i>Nasua nasua, Potos flavus, Procyon lotor, Procyon pygmaeus</i>
	Ursidae	13 (4.7)	2/13 (15.3)	<i>Ailuropoda melanoleuca, Ursus americanus, Ursus americanus floridanus, Ursus arctos, Ursus arctos horribilis, Ursus arctos marsicanus, Ursus maritimus, Ursus thibetanus</i>
	Phocidae	12 (4.4)	8/12 (66.6)	<i>Halichoerus grypus, Hydrurga leptonyx, Lobodon carcinophagus, Phoca caspica, Phoca sibirica, Phoca vitulina, Pusa caspica</i>
	Viverridae	9 (3.2)	9/9 (100)	<i>Arctictis binturong, Gennetta gennetta, Paguma larvata, Paradoxurus hermaphroditus, Viverricula indica</i>
	Hyaenidae	6 (2.2)	2/6 (33.3)	<i>Crocuta crocuta, Hyaena hyaena</i>
	Ailuridae	3 (1.1)	2/3 (66.6)	<i>Ailurus fulgens</i>
	Mephitidae	2 (0.7)	2/2 (100)	<i>Mephitis mephitis</i>
Rodentia	Odobenidae	1 (0.4)	0/1 (0)	<i>Odobenus rosmarus</i>
	Otariidae	1 (0.4)	1/1 (100)	<i>Zalophus californianus</i>
	Muridae	10 (3.6)	10/10 (100)	<i>Mus musculus<sup>a</sup></i>
	Cricetidae	7 (2.5)	7/7 (100)	<i>Mesocricetus auratus<sup>a</sup></i>
	Sciuridae	1 (0.4)	1/1 (100)	<i>Marmota caudata</i>
	Caviidae	1 (0.4)	1/1 (100)	<i>Cavia porcellus<sup>a</sup></i>
	Primates	7 (2.5)	7/7 (100)	<i>Macaca fascicularis, Macaca fuscata, Macaca mulatta</i>
	Cebidae	1 (0.4)	1/1 (100)	<i>Saimiri sciureus<sup>a</sup></i>
	Artiodactyla	2 (0.7)	0/2 (0)	<i>Sus scrofa domestica<sup>a</sup>, Sus scrofa</i>
	Tayassuidae	2 (0.7)	0/2 (0)	<i>Tayassu tajacu</i>
Proboscidea	Cervidae	1 (0.4)	0/1 (0)	<i>Cervus nippon</i>
	Elephantidae	1 (0.4)	0/1 (0)	<i>Elphas maximus</i>
		272 (100)	141/272 (51.8)	

<sup>a</sup>Experimental infections reported

**PMC full text:** [Viruses. 2014 Dec; 6\(12\): 5145–5181.](#)  
Published online 2014 Dec 22. doi: [10.3390/v6125145](#)  
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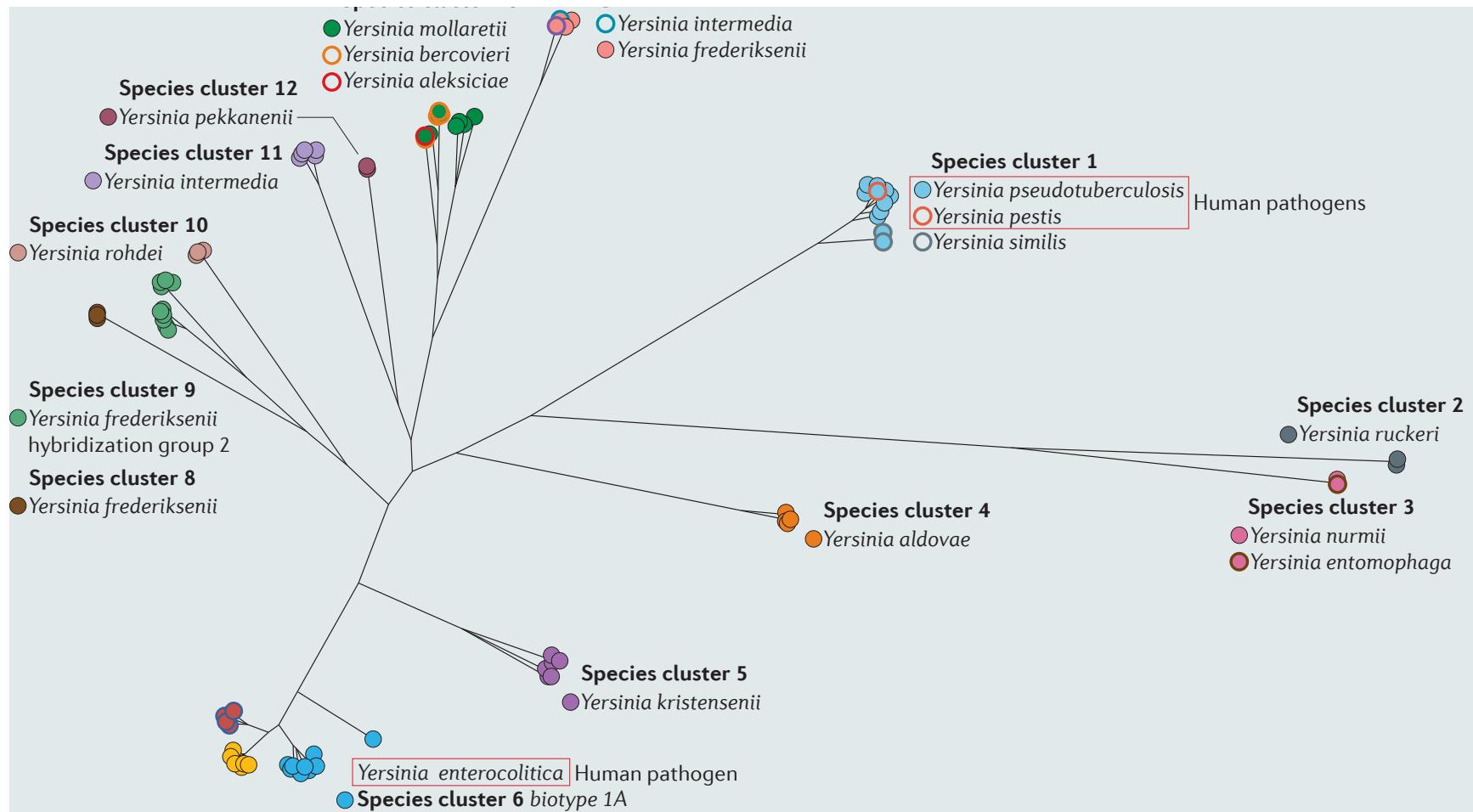
**Figure 2**



# *Yersinia pestis* and sylvatic plague in North America

- Causative agent of plague
- Introduced in 1900 to North America with rat infested steamships from affected areas with epidemics in port cities until ~1925
- Urban host species rodents with flea as vector infected rural rodents
- Sylvatic hosts include chipmunk, prairie dog, mouse, prairie vole, rabbit, squirrel
- Epizootic emergence in carnivores such as black-footed ferret, bobcat, puma, coyotes, dog and wolf, cat
- Gram negative, rod shaped coccobacillus
- Chr genome size ~ 4.6 MB. Some strains have plasmids with genome size ~ 3kb to 182 kb
- CSU Feature: Plague Expert Mike Antolin will give us a talk on *Yersinia pestis* disease ecology

# Phylogenomics of *Yersinia*



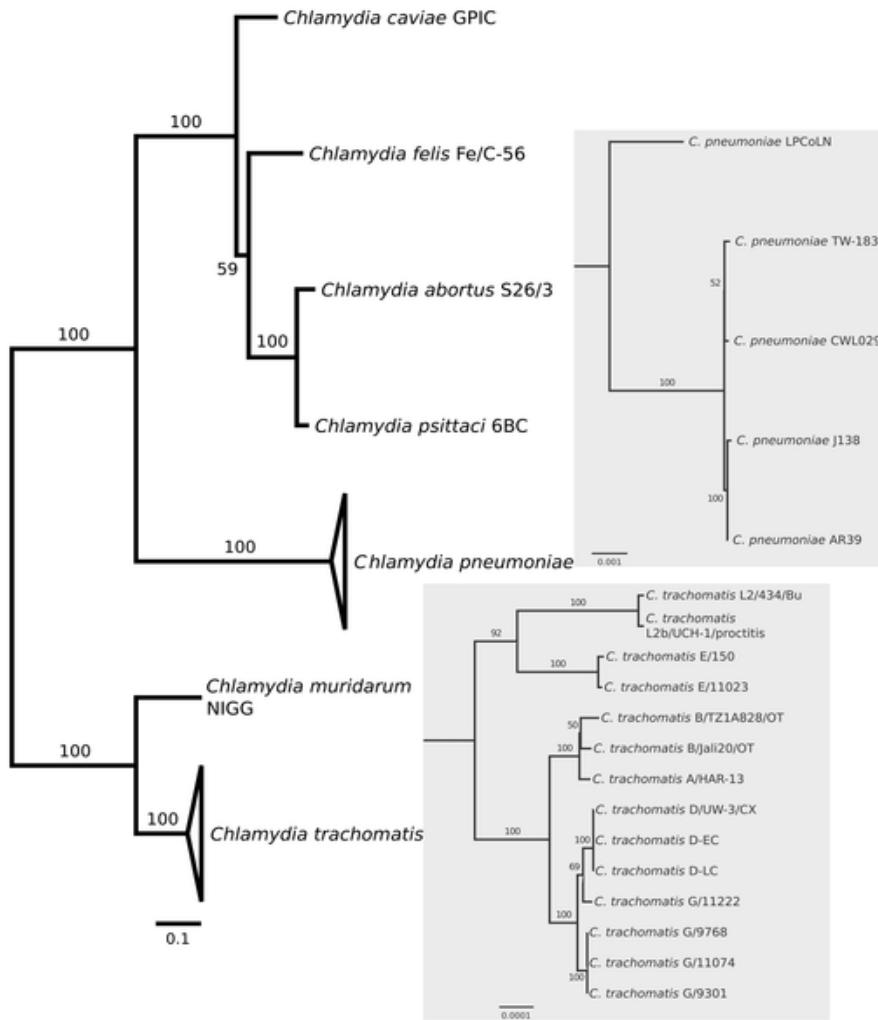
McNally A, Thomson NR, Reuter S, Wren BW.

Nat Rev Microbiol. 2016 Mar;14(3):177-90. doi: 10.1038/nrmicro.2015.29. Review.

# *Chlamydia psittaci* in Birds and Mammals

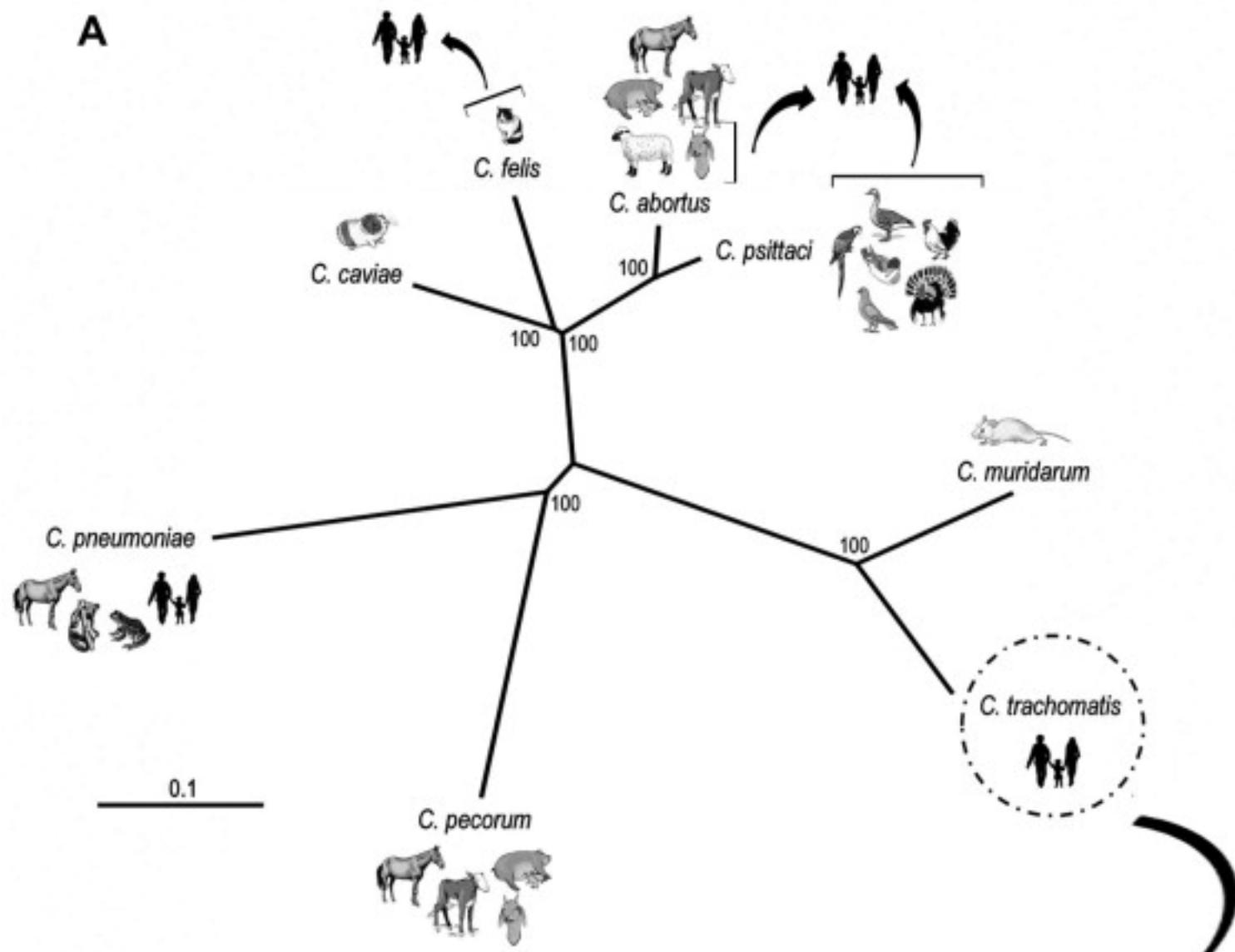
- Emergent pathogen on a global scale
- Obligate intracellular pathogen
- Recent expansion from South America into North America
- Multiple bird hosts in domestic and wild populations
- Respiratory disease in avian species and can be transmitted to humans through inhalation(psitticosis)
- Jumps into mammals (ferret, pig, cow, sheep, and human) and has a history of frequently switching hosts
- Genome ~ 1.1 Mb with a plasmid size of ~ 8 kb
- Core Genome of ~ 911 genes with rapid nucleotide evolution and high rates of recombination.

**Figure 1. Phylogenomic relationships among sequenced chlamydial genomes.**



Voigt A, Schöfl G, Saluz HP (2012) The Chlamydia psittaci Genome: A Comparative Analysis of Intracellular Pathogens. PLOS ONE 7(4): e35097. <https://doi.org/10.1371/journal.pone.0035097>

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0035097>



# Something to think about...

- ‘DataSet\_Info\_Links’
- This is a file in your hard drive that summarizes the state of NGS genomics for the host and pathogens for the course
- Can be an resource for your own research as a starting point as these NGS projects are generally accepted as good to excellent reference genomes.
- New data (BioProjects) are also in various stages of completion and can be equally useful in comparative genomics of host and pathogen.
- Projects such as Genome 10K and other new initiatives to sequence thousands of genomes within the Tree of Life are under development by SI and other collaborative institutions.