

Perspectives in Comparative Genomics and Evolution

Elinor K. Karlsson, PhD

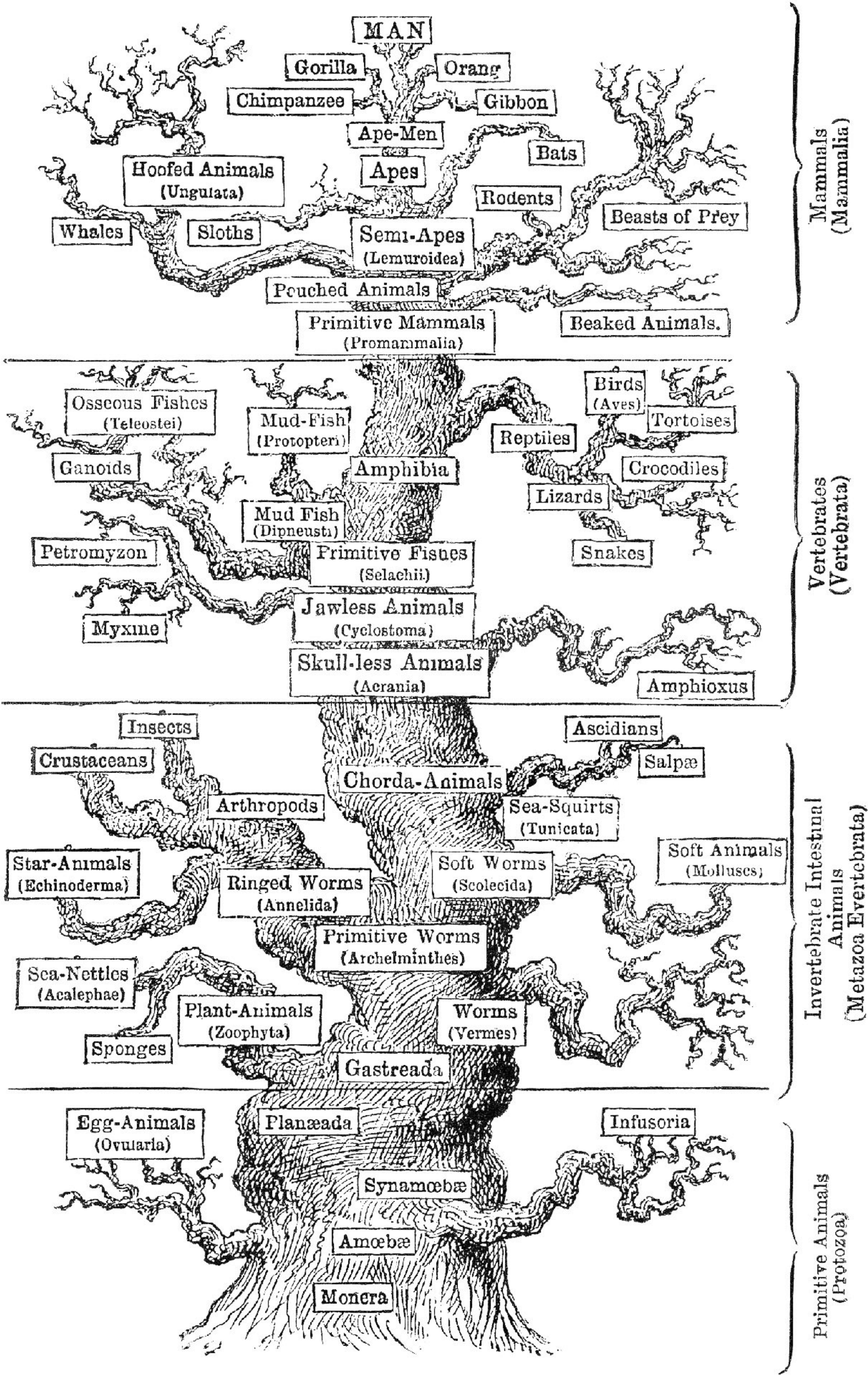
University of Massachusetts Medical School

Broad Institute of MIT and Harvard

Charles Darwin, "Principle of divergence, transitional organs, instincts" (unpublished; 1839-1872)

Comparative Genomics:

Study of the entire tree of life, from microbes to humans, both extinct and extant, and the evolutionary processes that shape this diversity



Haeckel, Ernst. The evolution of man. 1897.





Endless Forms Most Complicated

10-14 million species today

~4 billion years of evolution

Genotype x phenotype x individual x
species

Perspectives in Comparative Genomics Meeting

Humans

Traditional models

Non-traditional models

Veterinary models

Agricultural species

Natural models



NHGRI



National Institute of
Food and Agriculture

- Joint sponsored
- Goal: Accelerate scientific and medical breakthroughs that improve human health
- Identify key challenges & opportunities in comparative genomics - and propose ways forward

My perspective

Dogs as natural model for disease and behavior



Join the world's largest pet citizen science project

Together, we can discover new ways to help pets and their people live happier, healthier lives.

[Learn More](#)

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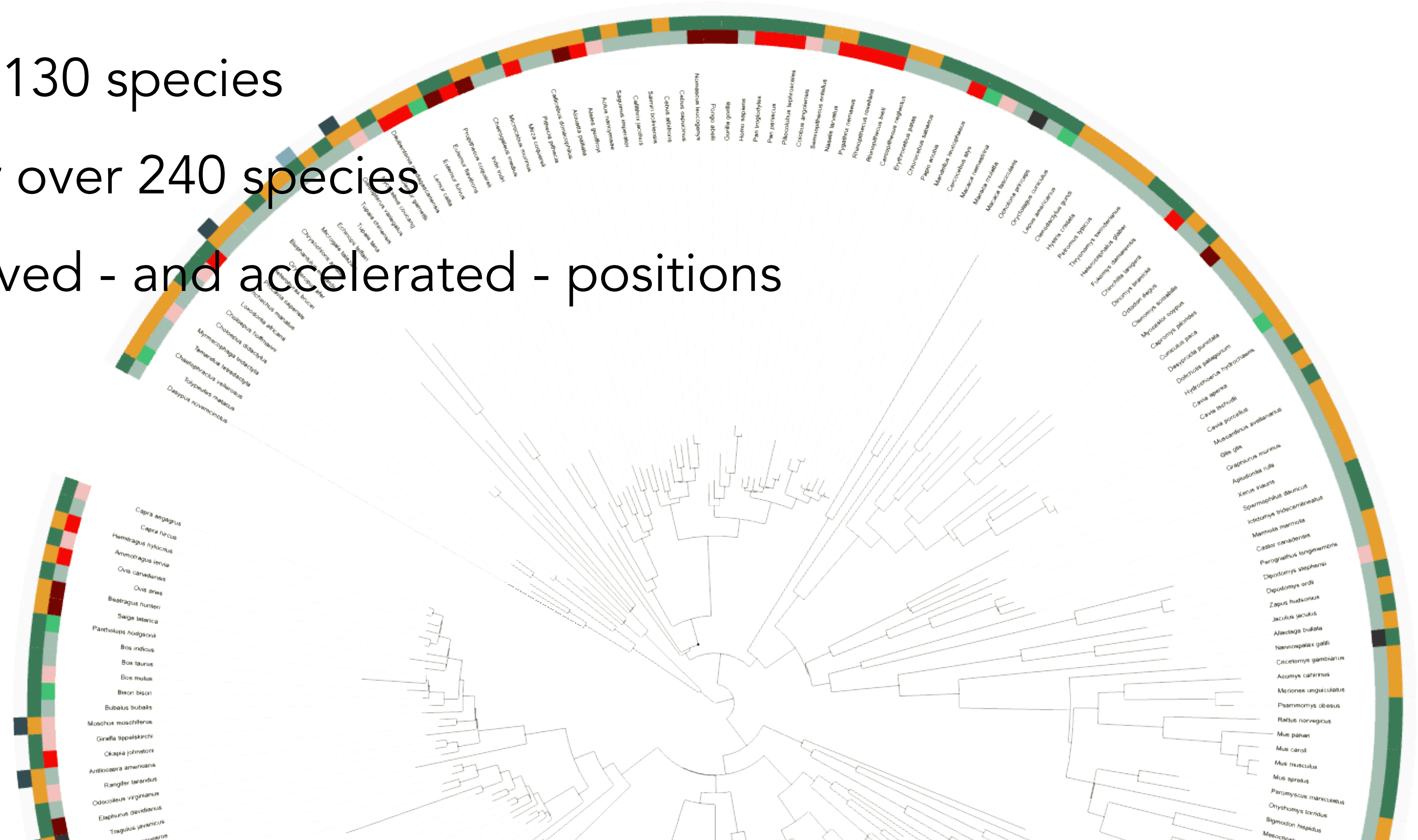
My perspective

The 200 Mammals Project: resolving conservation to single bases

New genomes for 130 species

Align genomes for over 240 species

Find highly conserved - and accelerated - positions



Genome sequencing consortia

Genome 10K

200 Mammals Project (now Zoonomia)

Earth Biogenome Project

Vertebrate Genomes Project

Bird 10K

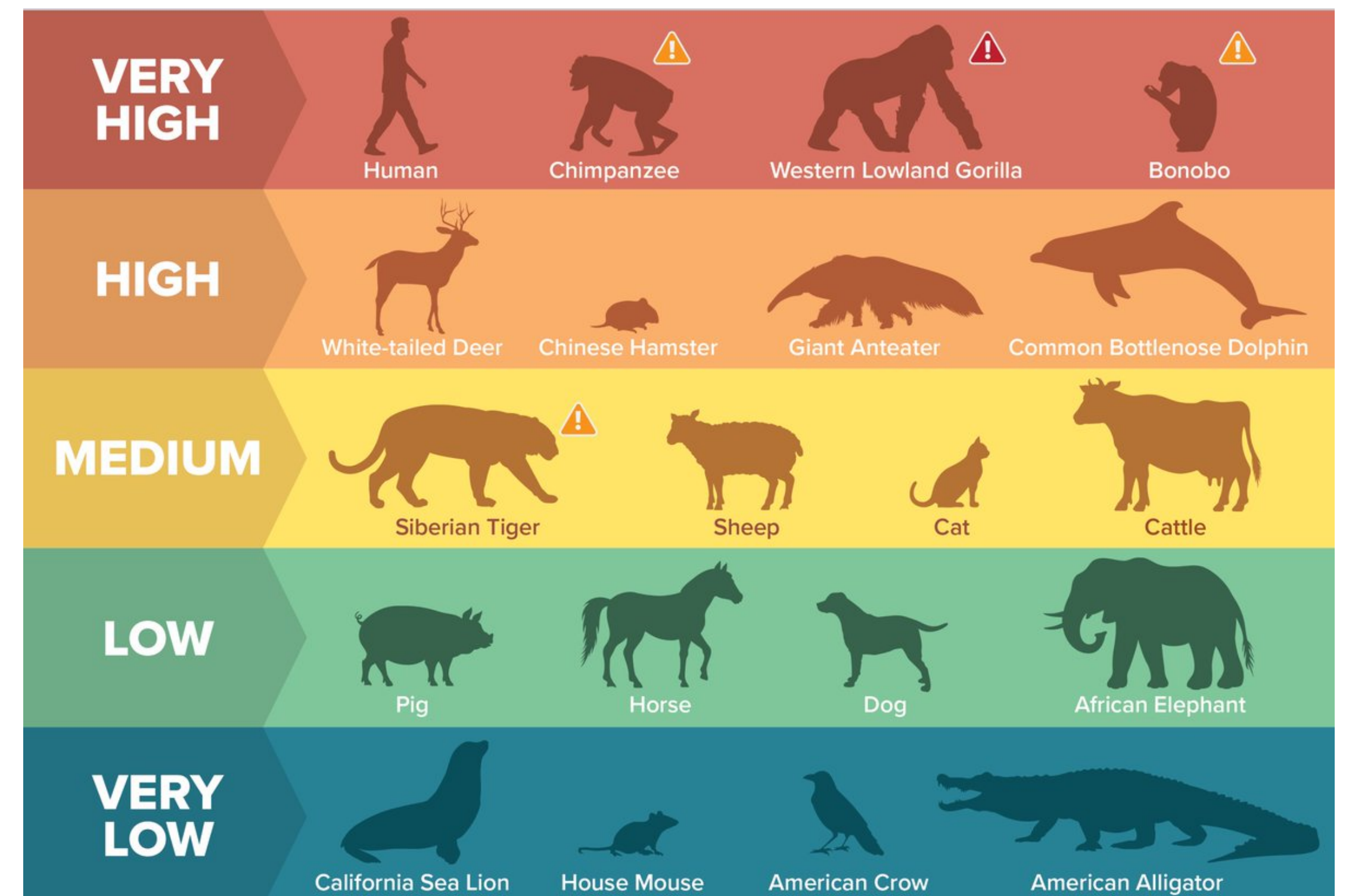
Bat 1K

DNA Zoo

PNAS Proceedings of the National Academy of Sciences of the United States of America

Broad host range of SARS-CoV-2 predicted by comparative and structural analysis of ACE2 in vertebrates

Joana Damas^{a,1}, Graham M. Hughes^{b,1}, Kathleen C. Keough^{c,d,1}, Corrie A. Painter^{e,1}, Nicole S. Persky^{f,1}, Marco Corbo^a, Michael Hiller^{g,h,i}, Klaus-Peter Koepfli^j, Andreas R. Pfenning^k, Huabin Zhao^{l,m}, Diane P. Genereuxⁿ, Ross Swoffordⁿ, Katherine S. Pollard^{d,o,p}, Oliver A. Ryder^{q,r}, Martin T. Nweeia^{s,t,u}, Kerstin Lindblad-Toh^{n,v}, Emma C. Teeling^b, Elinor K. Karlsson^{n,w,x}, and Harris A. Lewin^{a,y,z,2}



Matt Verdolivo/UC Davis

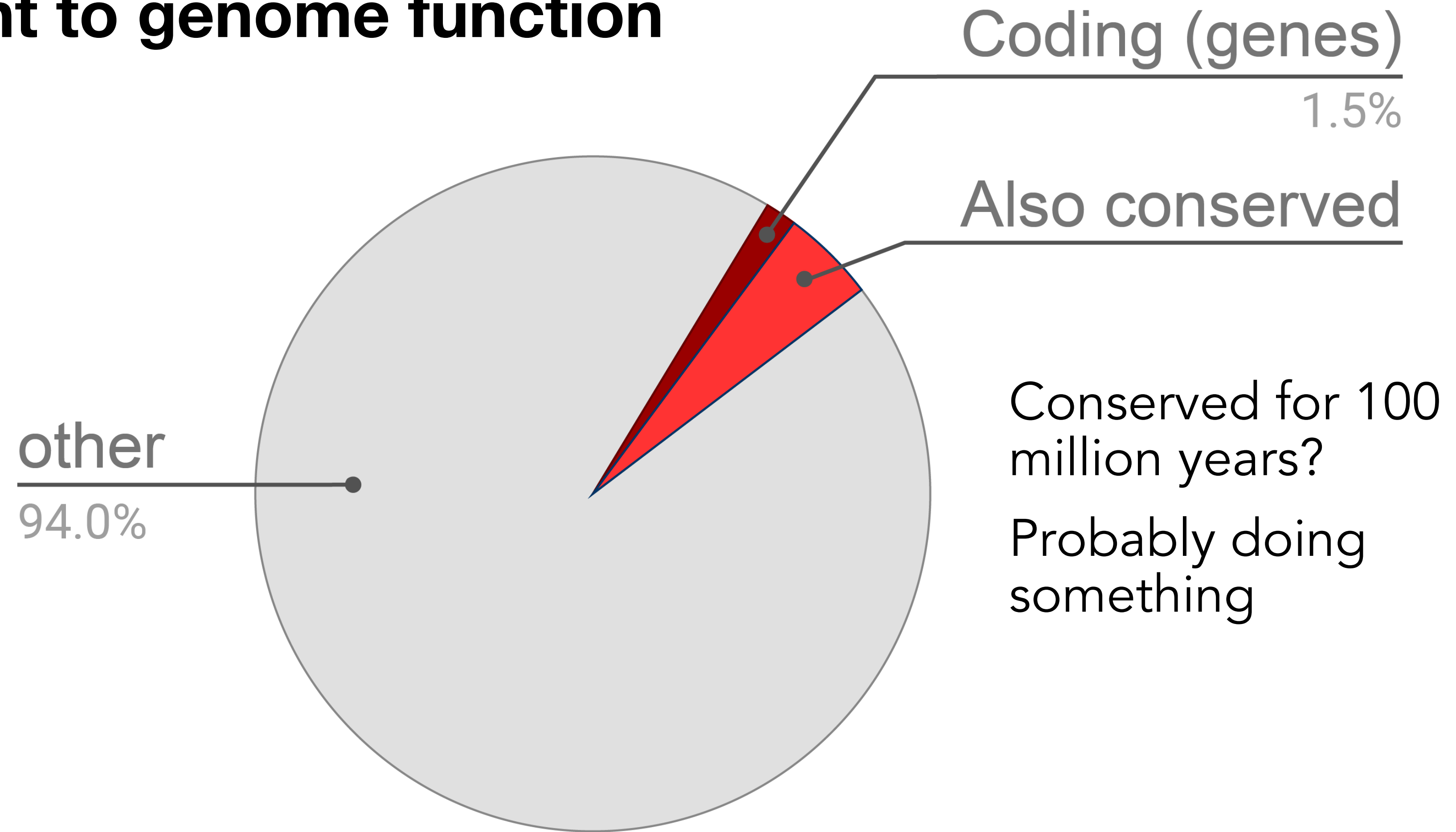
Why Comparative Genomics?



1. Human medicine
2. Genomic innovation
3. Agriculture and environment

Human medicine

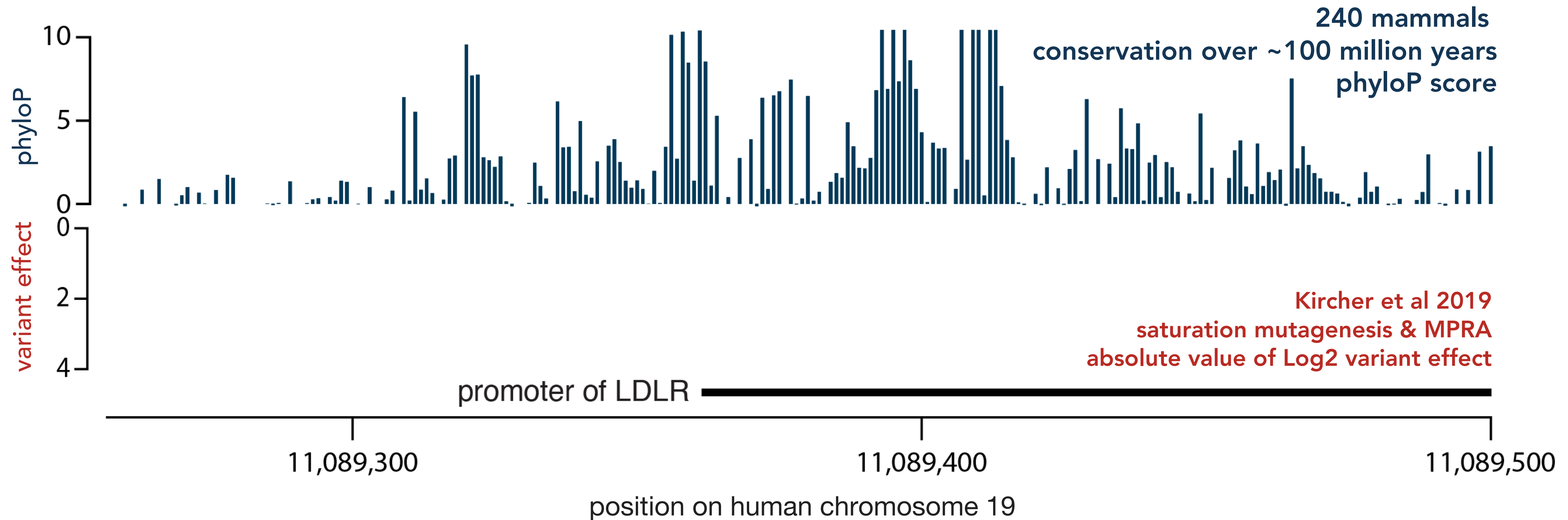
Genetic variant to genome function



	# samples	Branch length	Expected number of false positives
29 Mammals Project	29	4.9	22,995,049
200 Mammals Project	241	16.6	191

	# samples	Branch length	Expected number of false positives
29 Mammals Project	29	4.9	22,995,049
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gnomAD v3	71,702	0.17	2,604,359,690

Conservation & functional scores in promoter of LDLR



Human medicine

1. Variant to function
2. Best model organism
3. Source / reservoir for zoonotic diseases
4. *and more ...*



Why Comparative Genomics?



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- 2. Genomic innovation**
3. Agriculture and environment

Genomic Innovation

Hibernation



Credit: A. Hindle

Prior to hibernation: obese and insulin resistant

While hibernating for 6-9 months

- sedentary and no food intake
- synapses lose connectivity
- experience repeated ischemia/reperfusion events

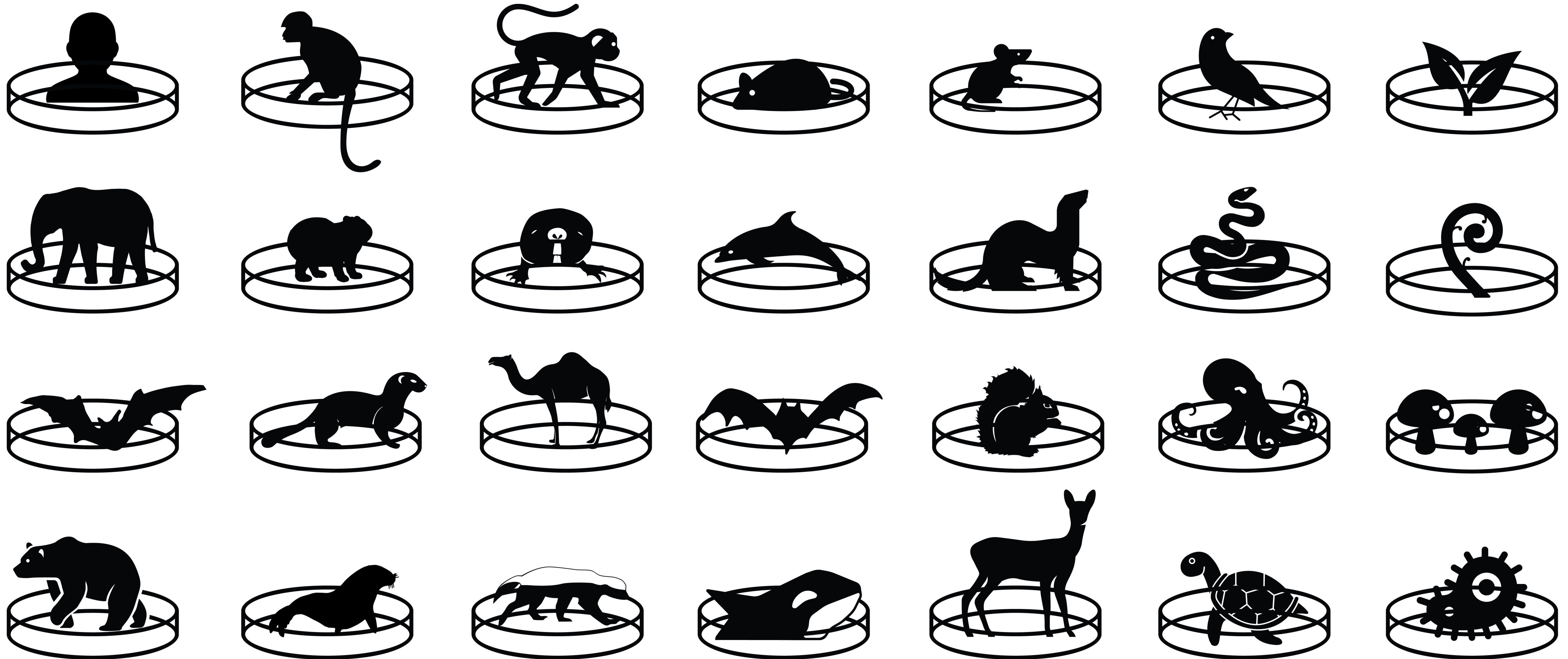
How do they do this? Can we replicate it in humans?



FAUNA BIO

Genomic Innovation

What else can other species do?



Why Comparative Genomics?



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Agriculture and biodiversity conservation



Fir0002/Flagstaffotos

**Genetic selection for
food production**



David Monniaux

**Find protective
adaptations in wild
populations**



Revive & Restore / Scott Stine

**Restore diversity from
frozen cell cultures
thru IVF**



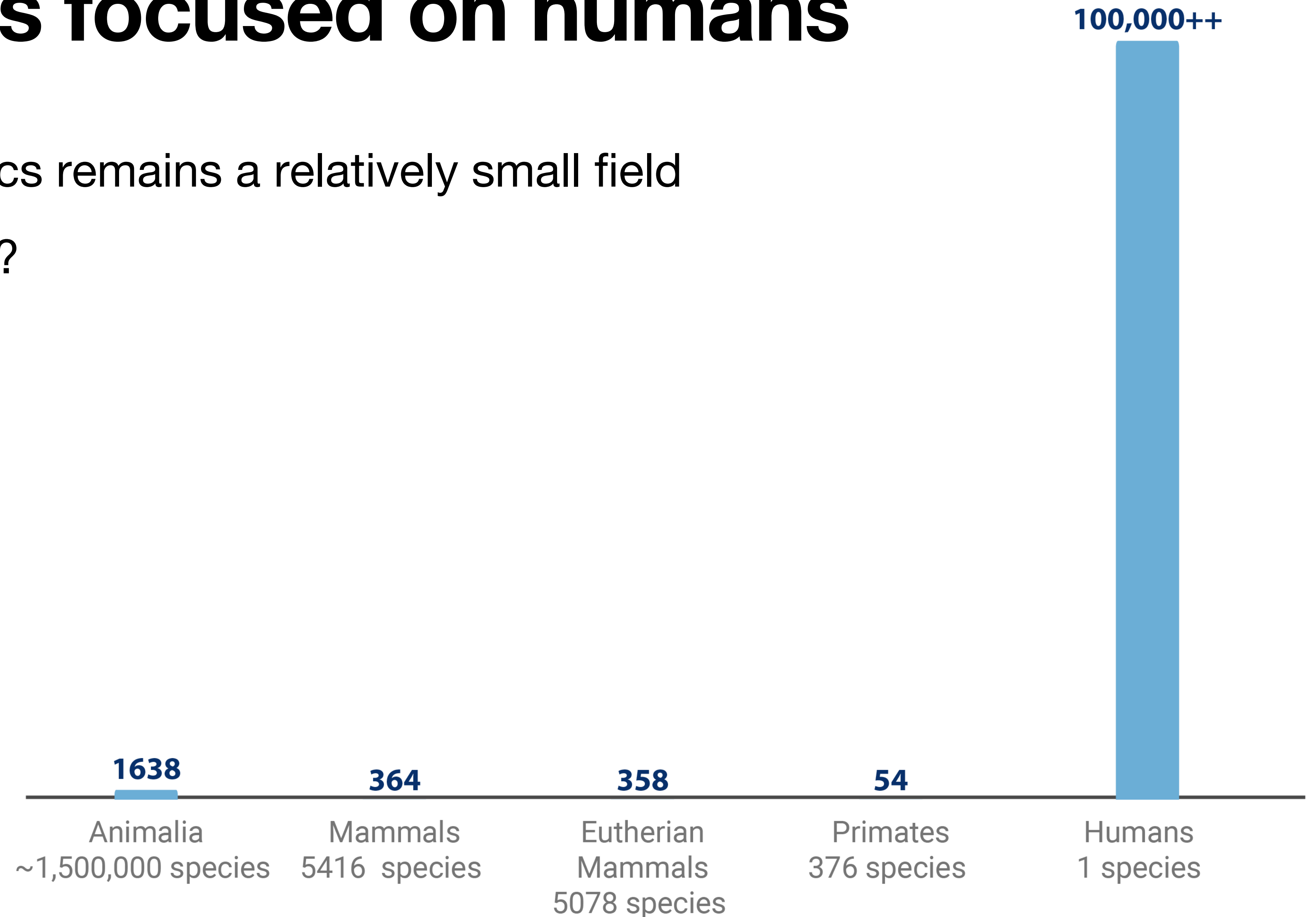
USFWS Mountain-Prairie

**Retain diversity in
critically endangered
populations**

Genomics is focused on humans

Comparative genomics remains a relatively small field

What are we missing?



Challenge #1: Technical

Comparative genomics is inherently cross-disciplinary

The problem: lack of integration limits value of data

No universal standards for genomic data or phenotype data

Projects with many diverse species don't have an obvious "home"

Complexity of problems challenge available computational infrastructure and software

Way forward: leverage advances in human genomics

Build a "library for life" that integrates genomic & phenotype resources, provides universal standards, and expands computational infrastructure

Develop software for comparing multidimensional data within and between species, temporal-spatial scales, and environments

Support systems / browsers and robust data sharing requirements for comparative genomics

Challenge #2: Interpersonal

Comparative genomics needs worldwide area of study and use

The problem:

Acute shortages of skilled computational scientists.

Data management, ownership and sharing challenges

Focus on species that are easy-to-access at cost of diversity

Way forward: collaboration

Provide training opportunities in computational sciences

Provide trans-agency funding opportunities that encourage interdisciplinary, synergistic research — partnerships between computational scientists, field scientists, and local communities

Support projects with multi-faceted design: advance human health & support biodiversity conservation

Challenge #3: Scientific

Discovering the rules of biology across the tree of life

The problem

Some of the biggest discoveries in basic biology & medicine are from other species (e.g. CRISPR (bacteria), transposons)

Genomics is now focused primarily on humans, and research/data in other species is difficult to integrate

Way forward

Normalizing the use of any organism as a “model organism”

Developing new experimental methods for non-traditional models

Building true cross-disciplinary collaborations

Why?

- Find both what we share with other species and what makes us unique.
- Accelerate the discovery of new therapeutics for common and rare diseases
- Address the environmental impact of humans on our planet, and preserve biodiversity

Acknowledgements:

All meeting participants, and especially Shawn Burgess, Hans Cheng, Charles Danko, Clare Gill, Erich Jarvis, Klaus-Peter Koepfli, James Koltes, Eric Lyons, Lakshmi Matukumalli, Theodore Morgan, Elaine Ostrander, Oliver Ryder, Lynn M Schriml, Lorjetta Schools, Pam Soltis, Taylorlyn Stephan, Jennifer Troyer, Susan VandeWoude, Kris Wetterstrand, and Huaijun Zhou

51 *Turricula chilensis*.

52 *Pleurotoma subequalis*.

53 " *turbinellodes*.

57 *Fusus subreflexus*.

58, 59 " *Noachinus*.

60 " *Patagonicus*.

63 *Triton verruculosus*.

64 " *lanceolatus*.

65 " *patagonicus*.

70, 71 *Terebra costellata*.

72 " *patagonica*.

73 " *patagonica*.

Image credit: Charles Darwin, "The structure and distribution of coral reefs" (1842)