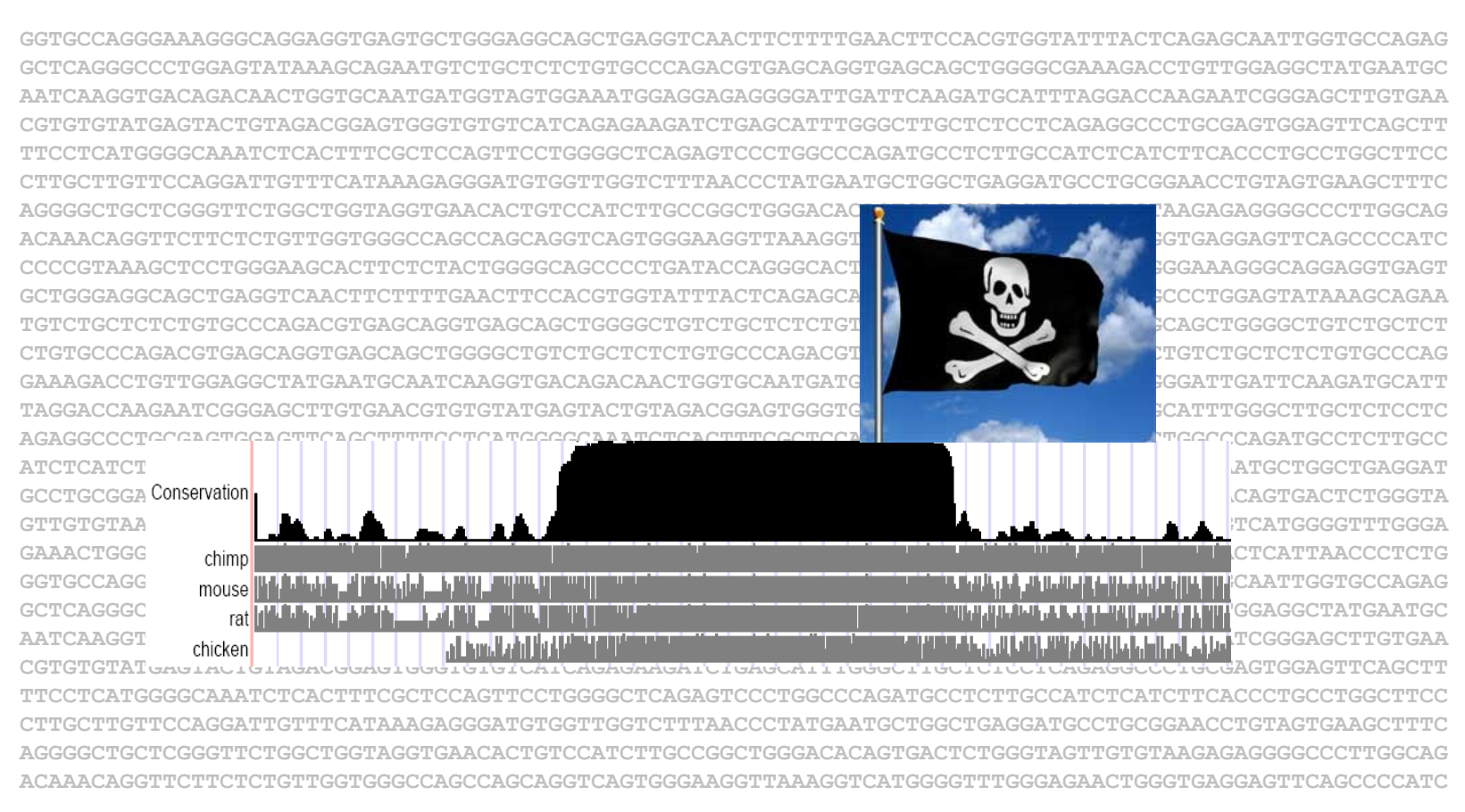
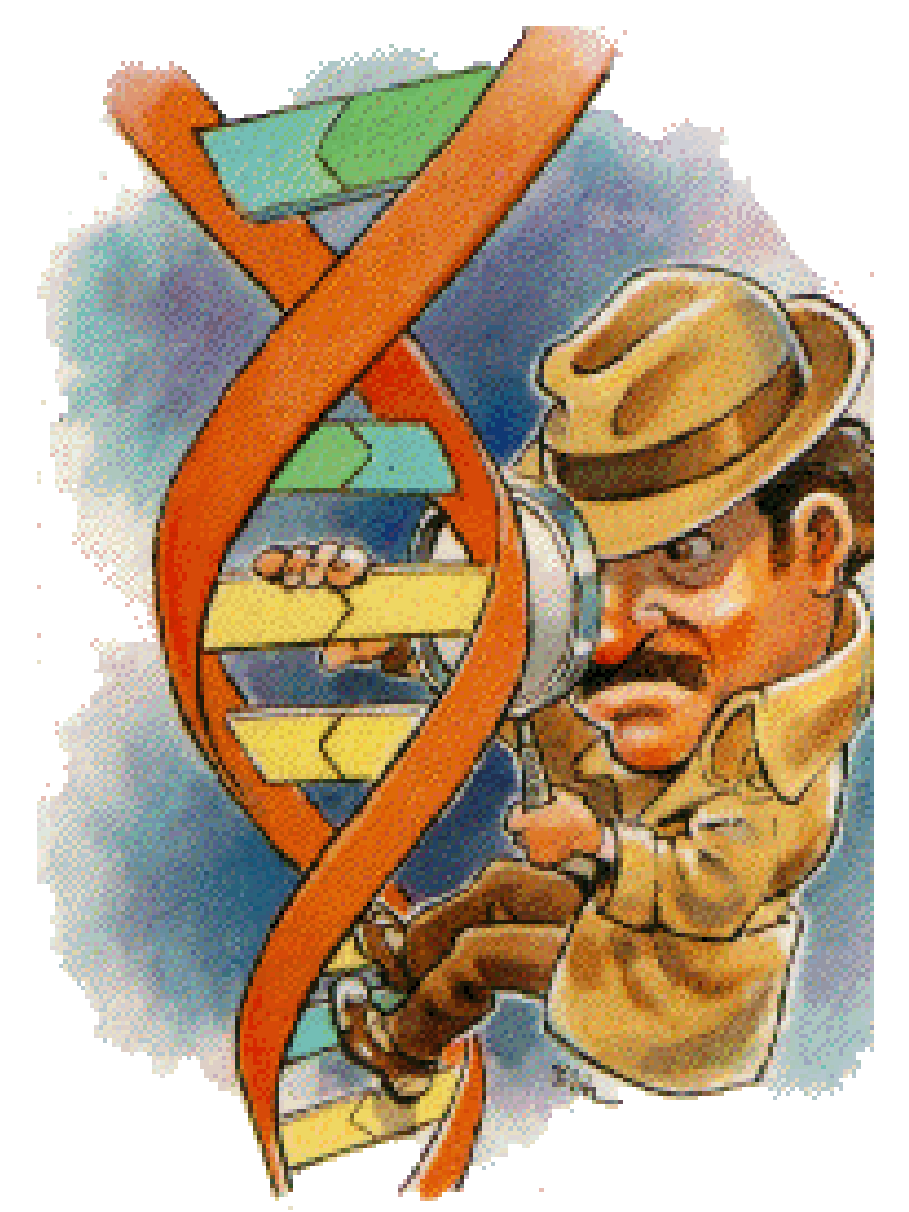


# Dispensability of Mammalian DNA

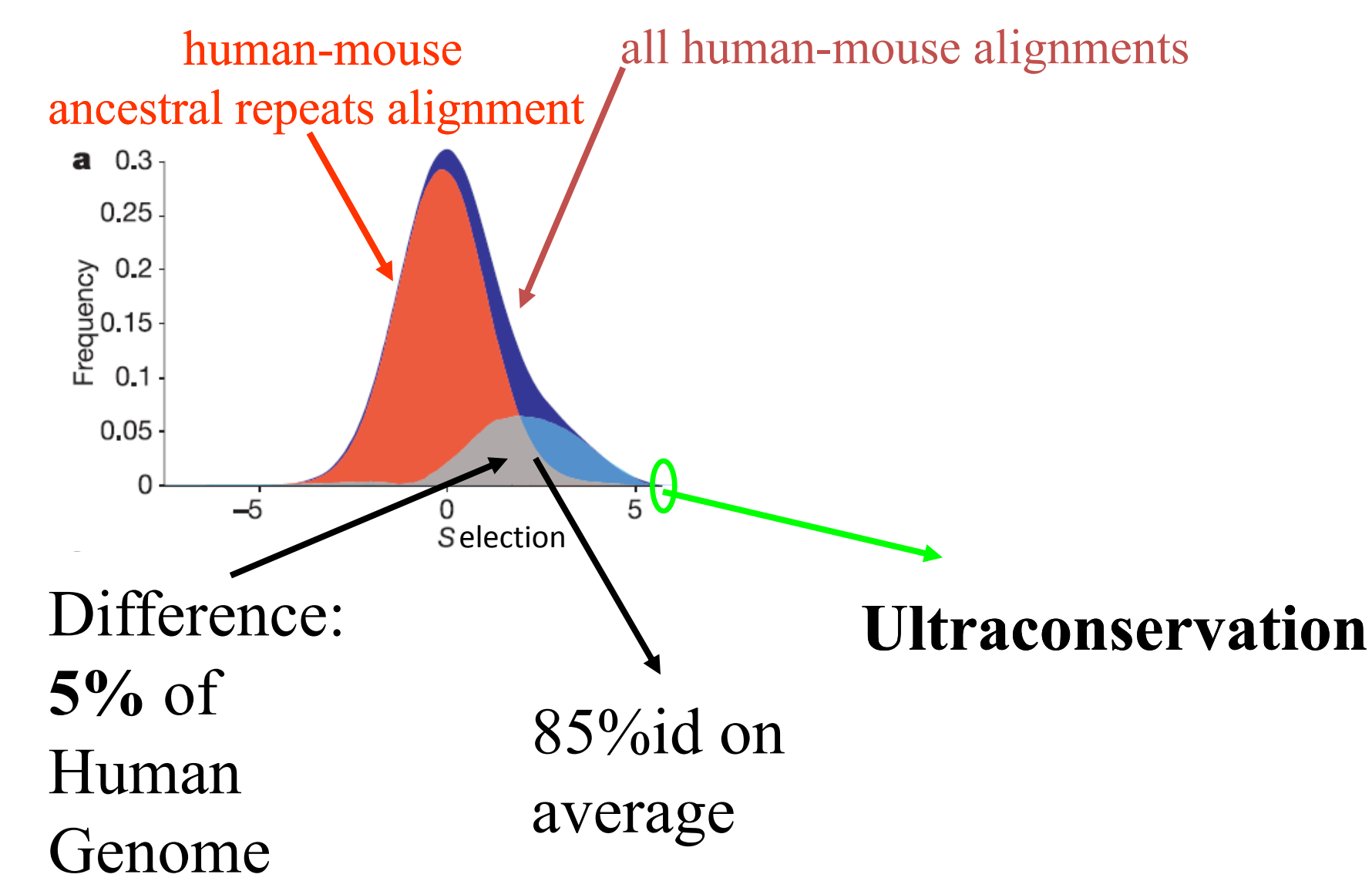
Cory McLean<sup>1</sup> and Gill Bejerano<sup>1,2</sup>

<sup>1</sup>Dept. of Computer Science and <sup>2</sup>Dept. of Developmental Biology, Stanford University, Stanford, CA 94305

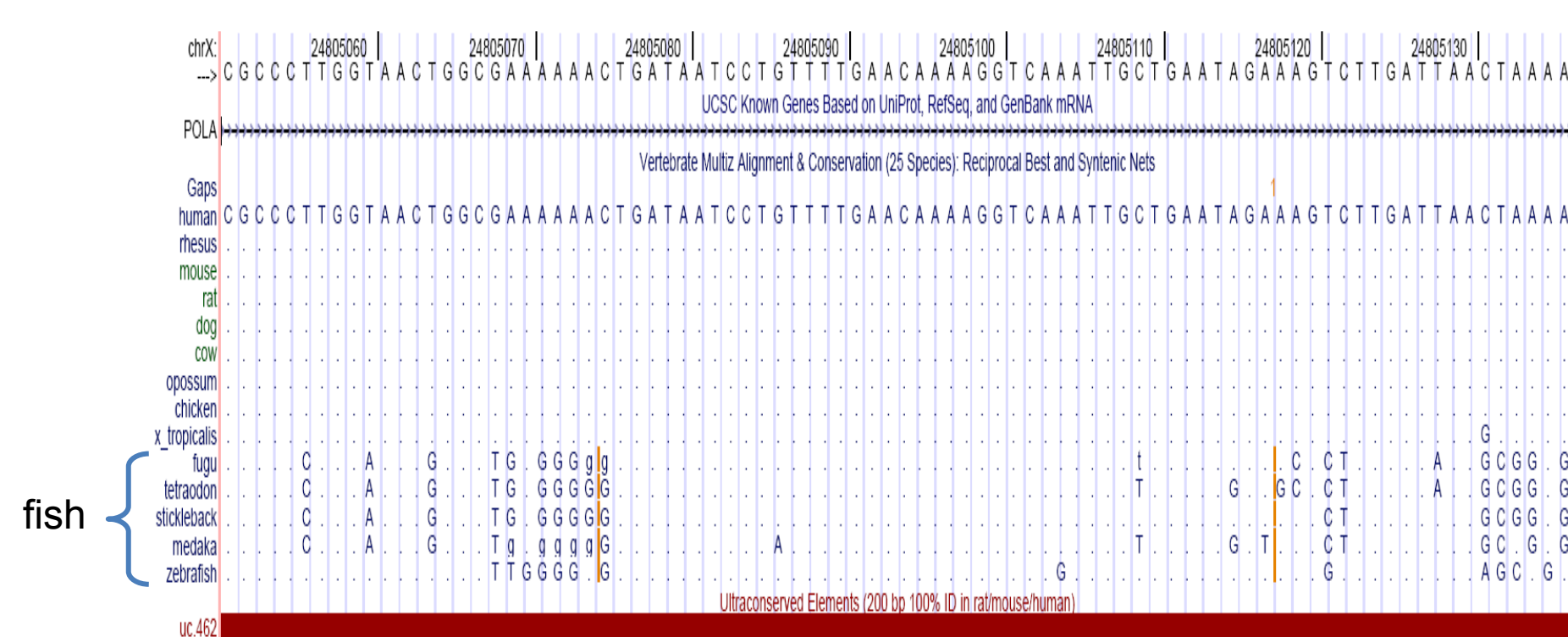


## Introduction

Conserved elements in the Human Genome<sup>1</sup>

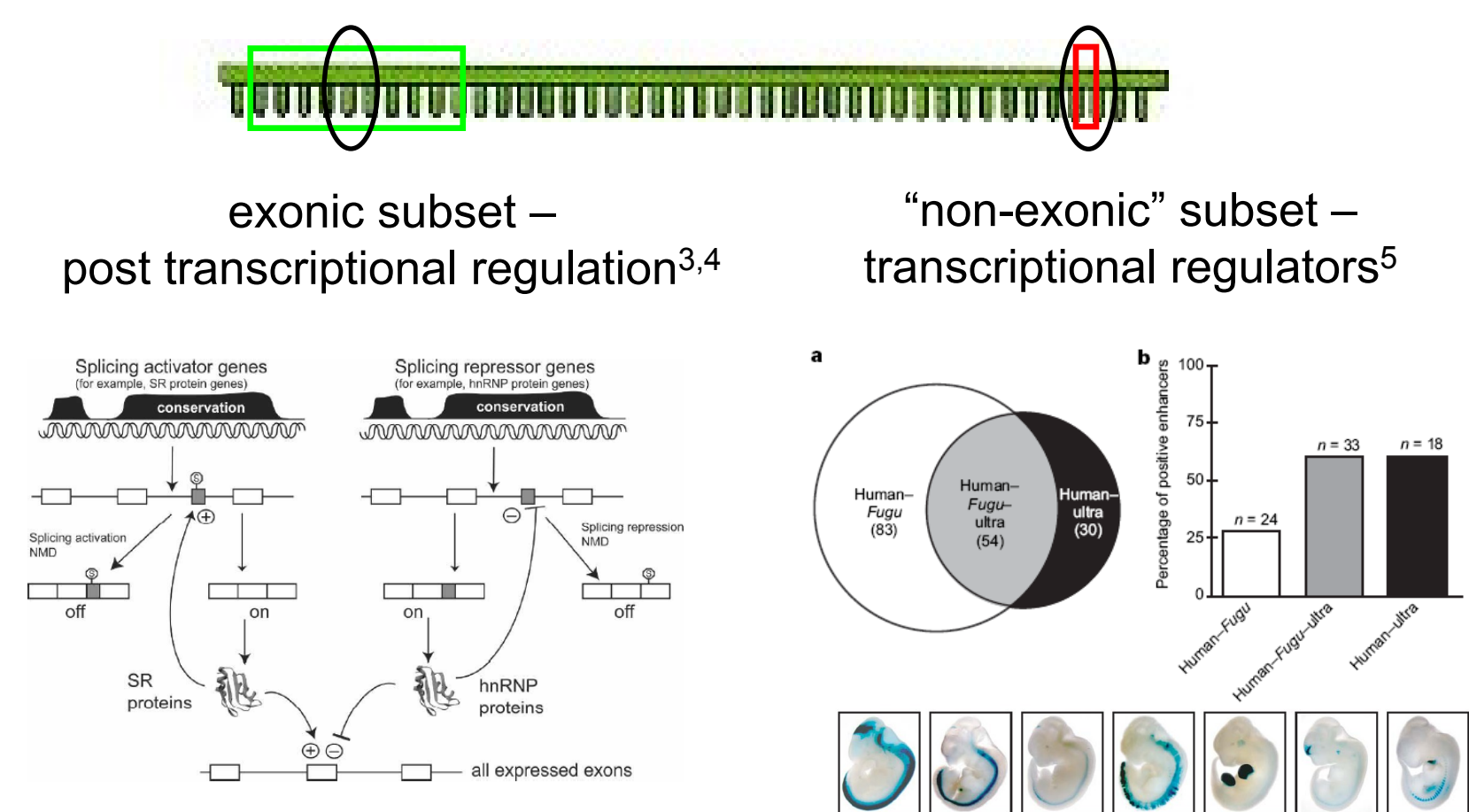


Ultraconserved Elements<sup>2</sup> ("ultras")

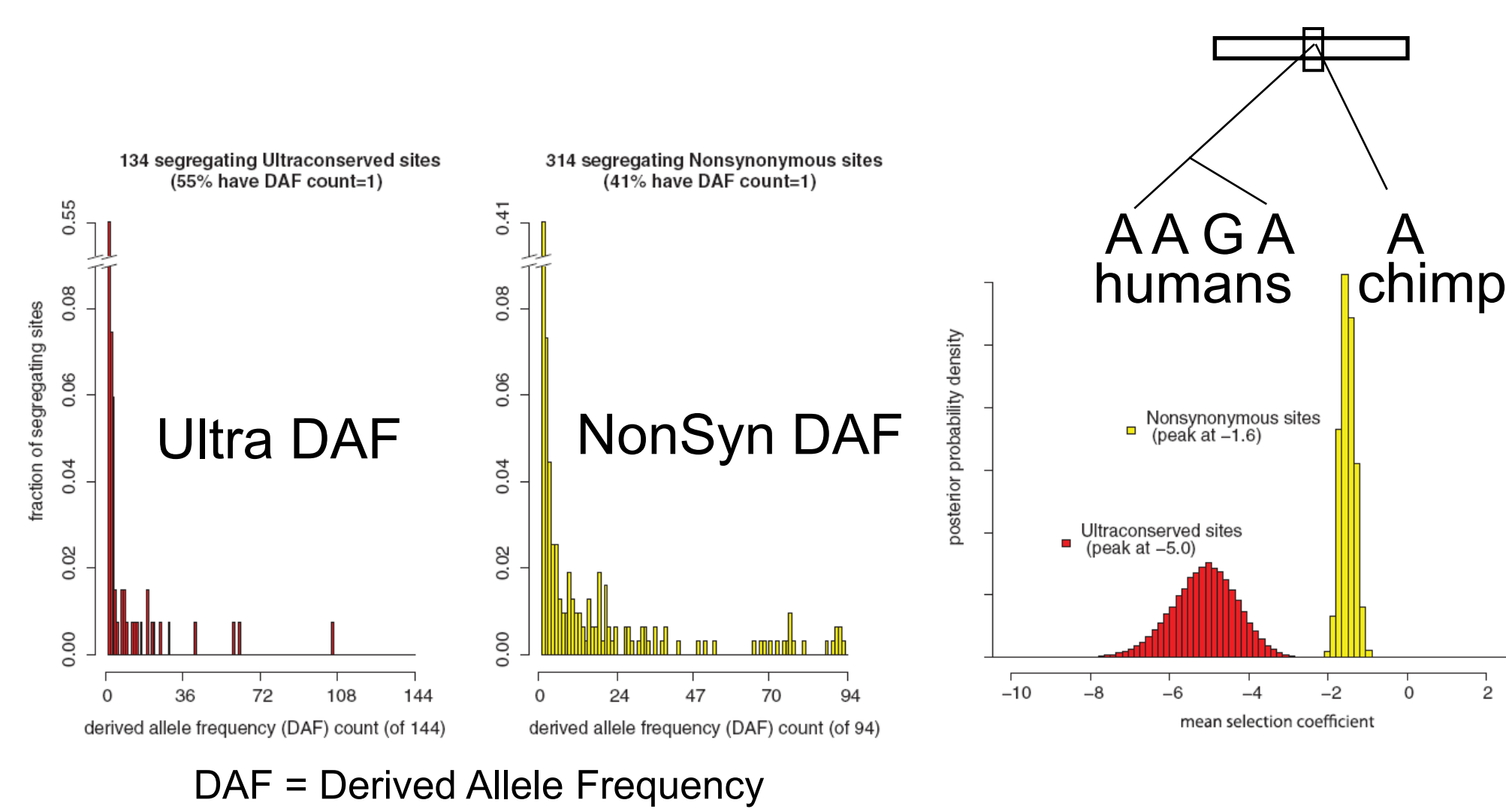


481 elements perfectly conserved (100%id) over 200bp or more between human, mouse and rat.

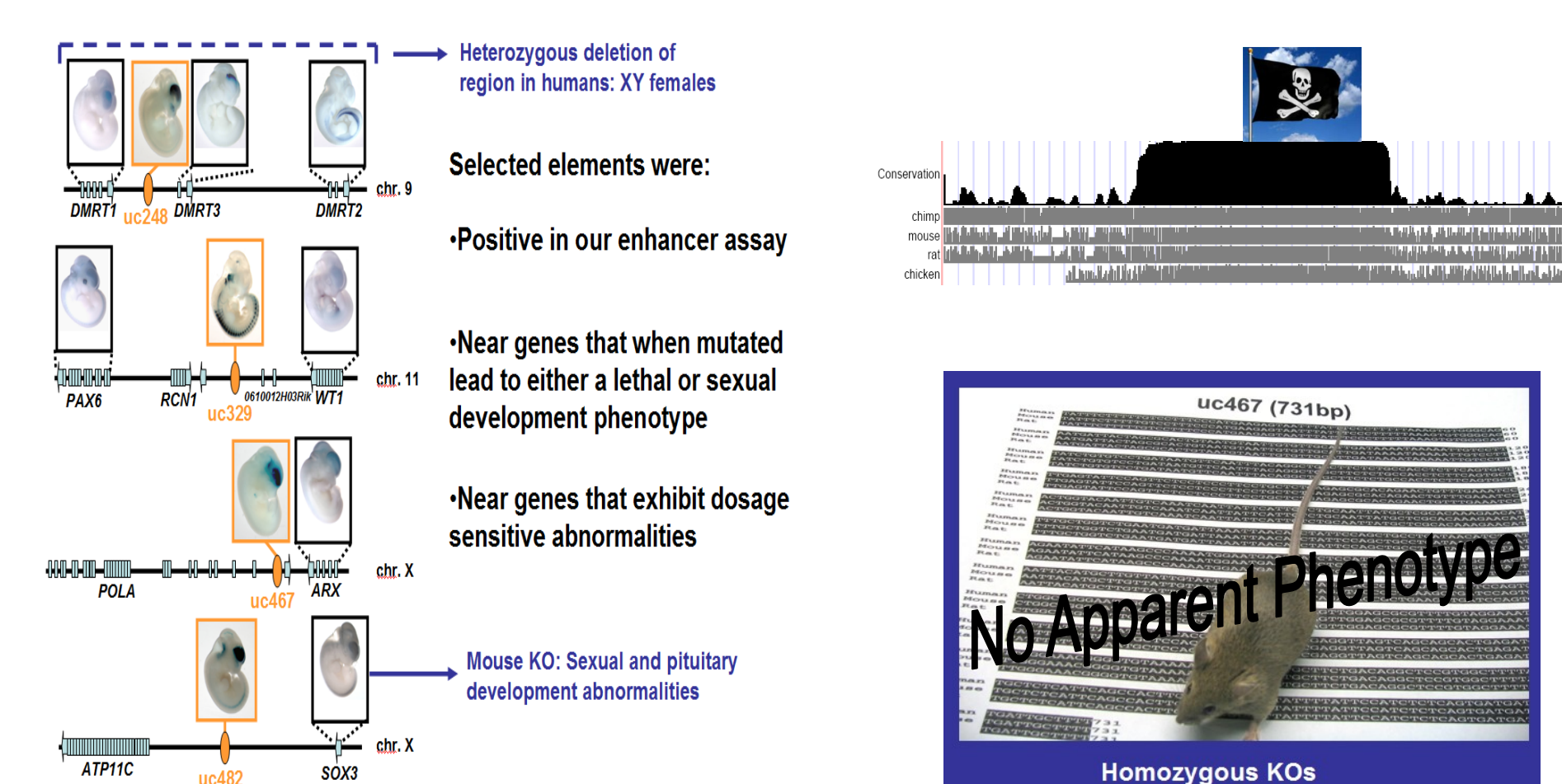
Ultras are Functional



Ultras under *Strong* Human Selection<sup>6</sup>

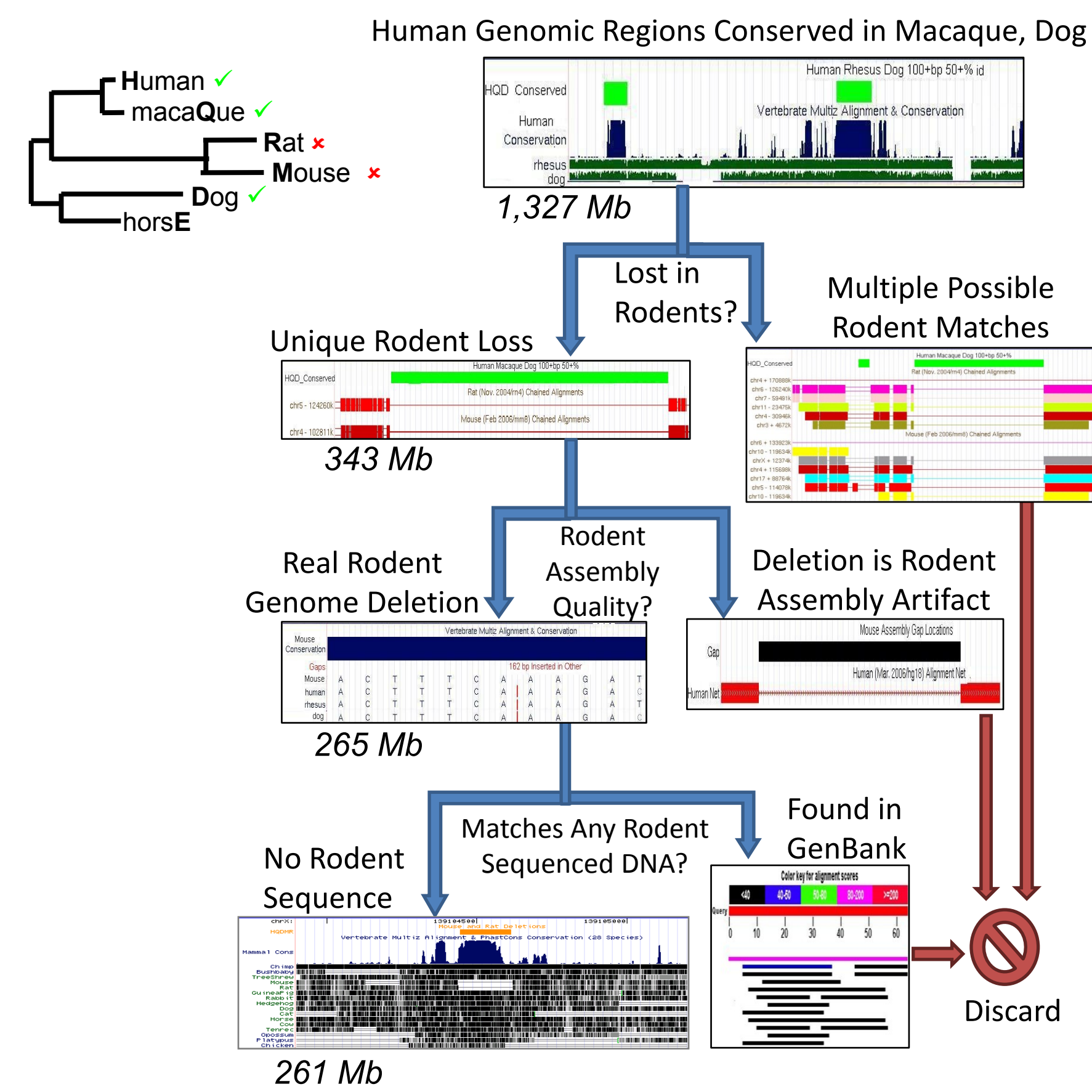


Touch an Ultra And You – DIY<sup>7</sup>



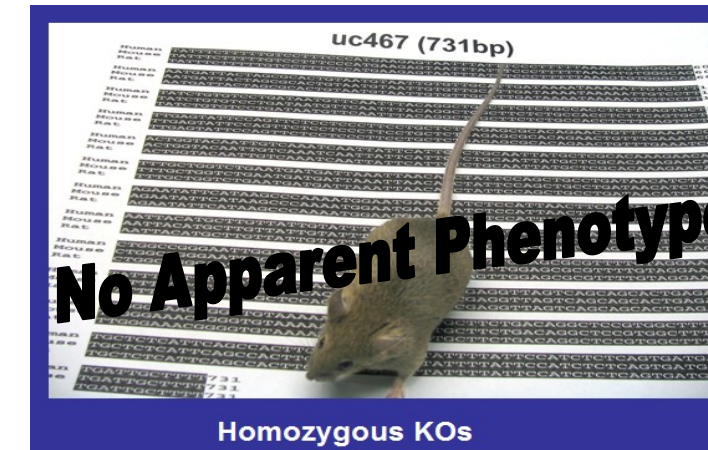
## Evolutionary Analysis

Computational Pipeline to Discover Rodent-specific Losses



Ultras are Fiercely Retained through *Evolution*

Ultras are >350 fold more persistent than neutral DNA (25% rodent deleted)



100%id primates-dog: 2,264,330bp  
rodents deleted: 1,447bp (0.064%)

Genomic deletion evolutionarily doomed

$$\Pr(\text{fixation} \mid N_e, s) = \frac{1 - e^{-s}}{1 - e^{-2N_e s}}$$

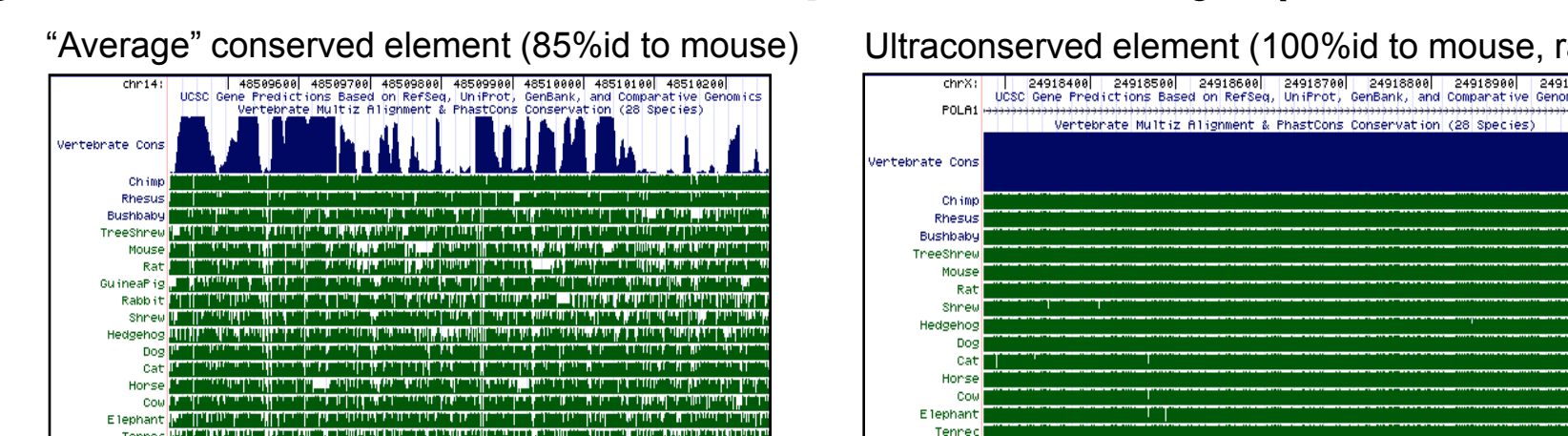
$N_e$ : Effective population size  
 $s$ : Selective (dis)advantage

Why do ultra knockouts lack a phenotype?

1. Phenotype not manifested under laboratory conditions
2. Fitness loss too small to detect (e.g. 1% magnitude) but evolutionarily disfavored

Corroborating evidence found in proteins: 12% of genes (510 of 4,234) with knockout results reported have experiment with no phenotype, including ancient genes *Gli1*, *Hoxa7*, *Dach2*, *Pbx2*. Likely a (potentially large) underestimate<sup>8</sup>.

Is functional density (conservation %id) a good measure of dispensability (deletions)?



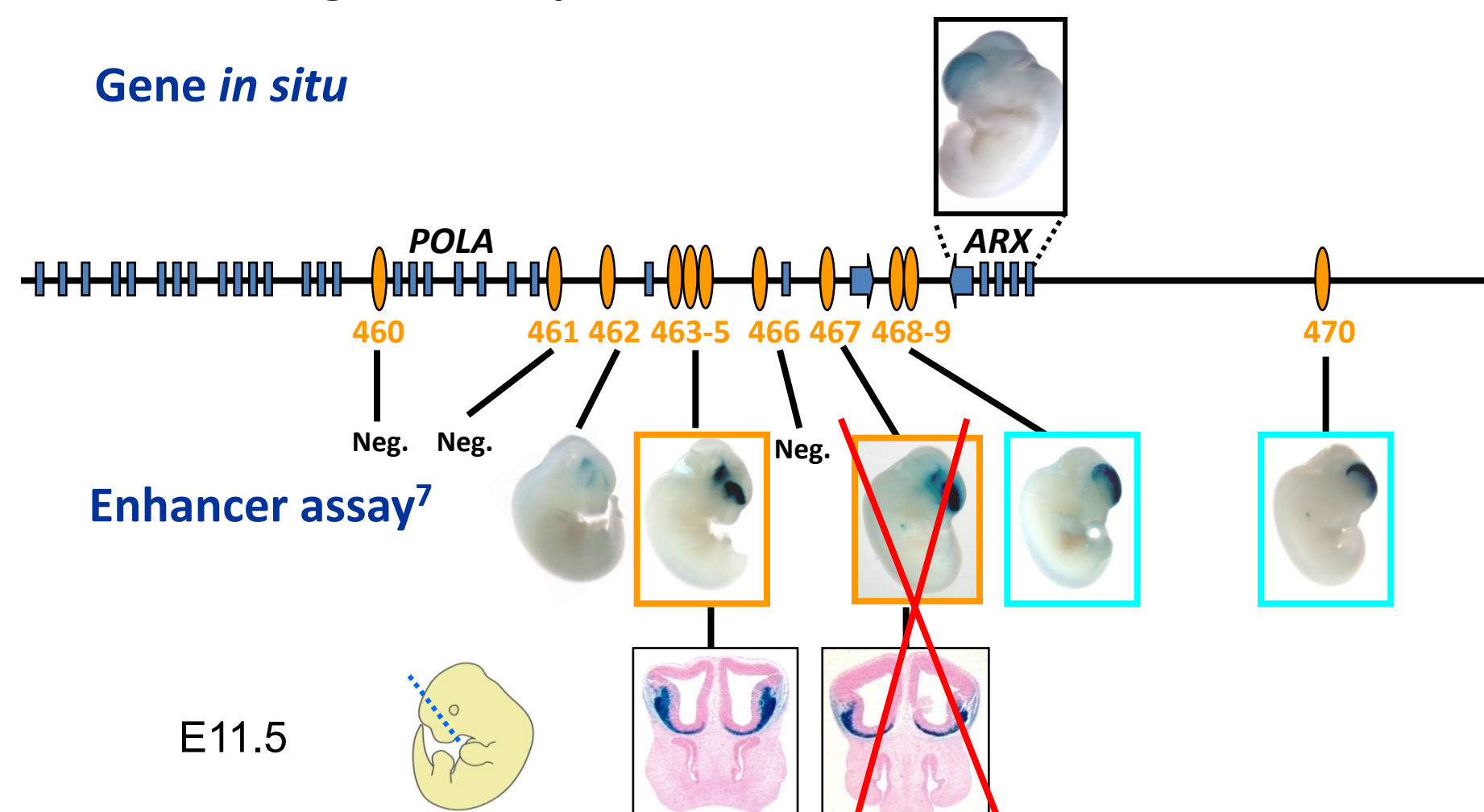
Which one is more likely to be lost throughout evolution?

In protein context, Allan Wilson et. al.<sup>9</sup> postulated (1977)

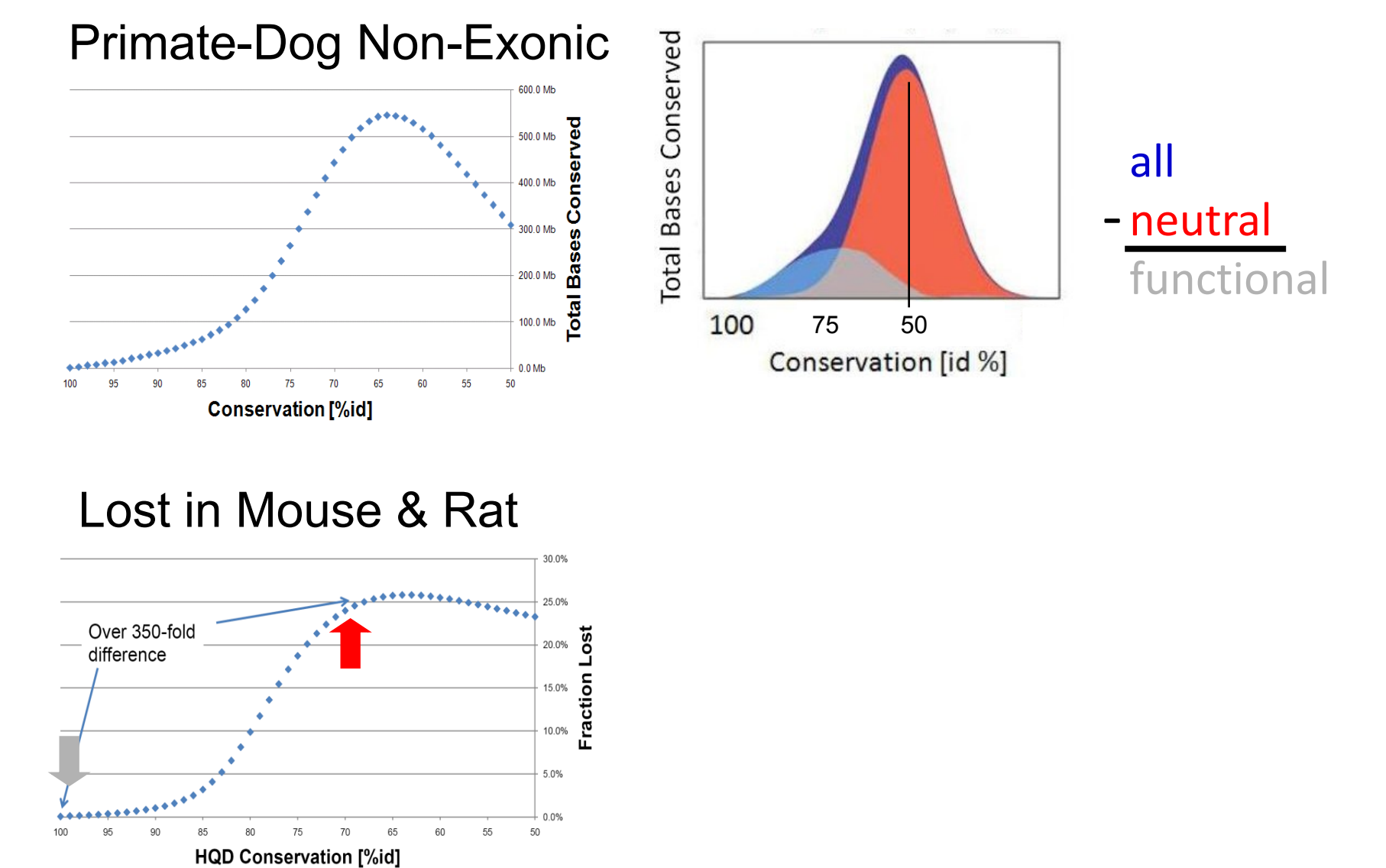
constraint  $\propto$  functional density  $\times$  functional importance

Since proven in different organisms<sup>10</sup>

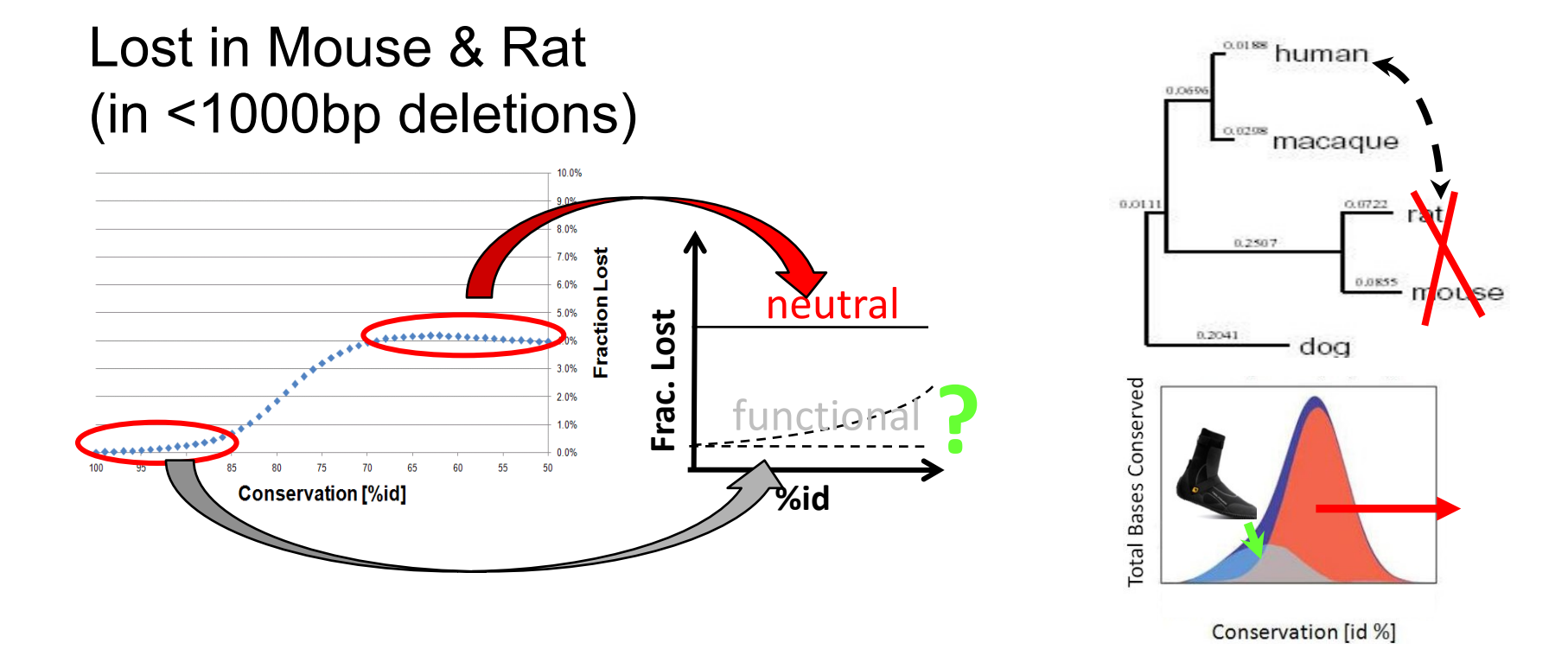
But cis-regulatory DNA seems much more redundant



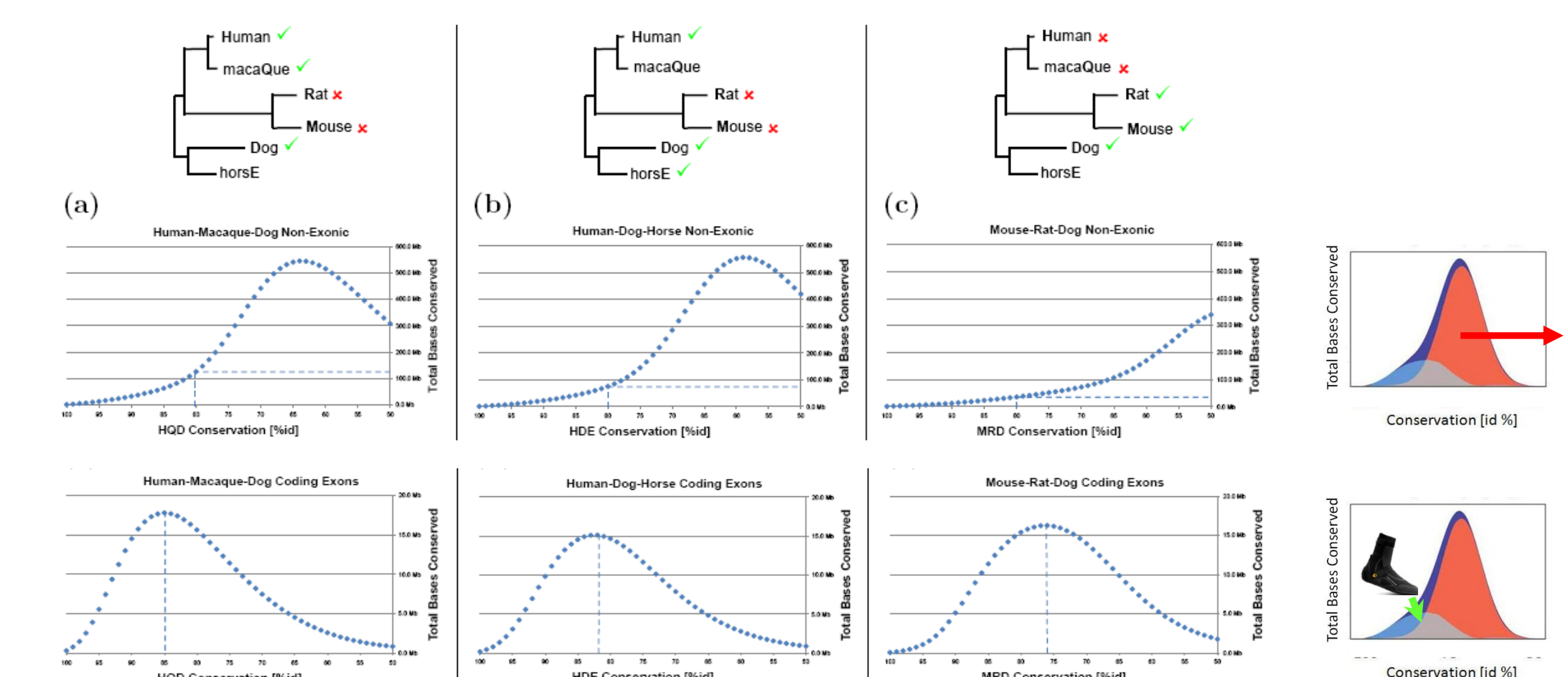
Rodent-Specific Losses



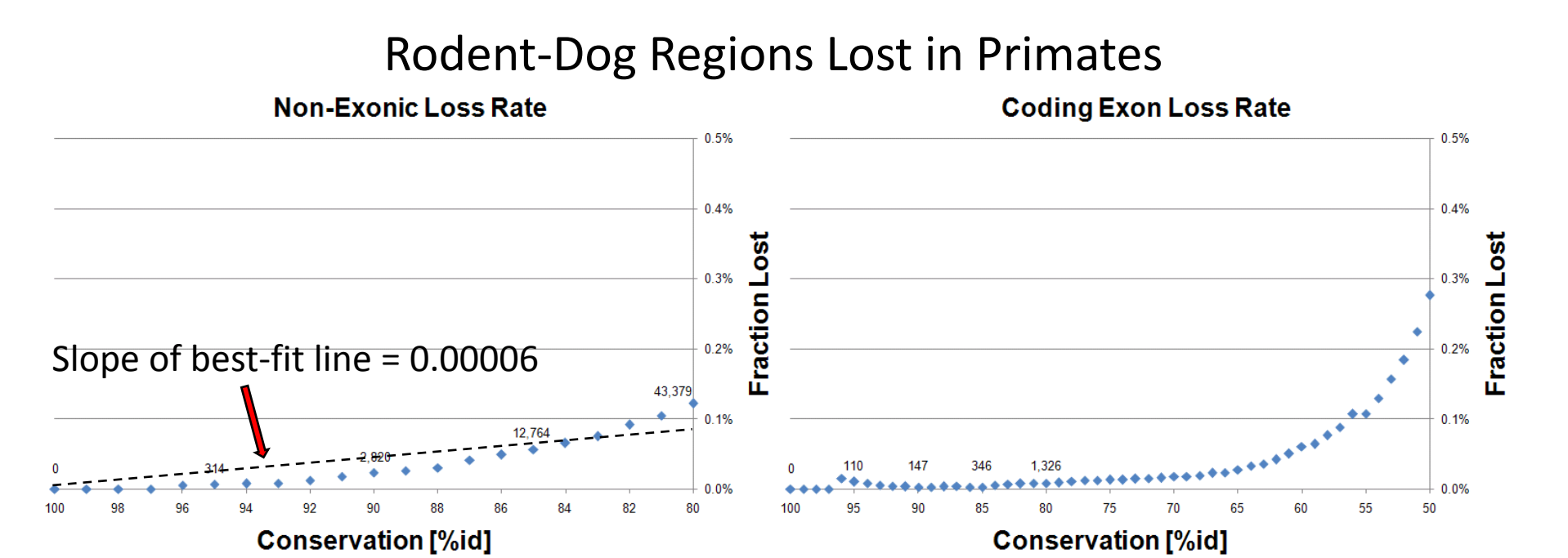
What if we could separate functional sequence from neutrally evolving sequence?



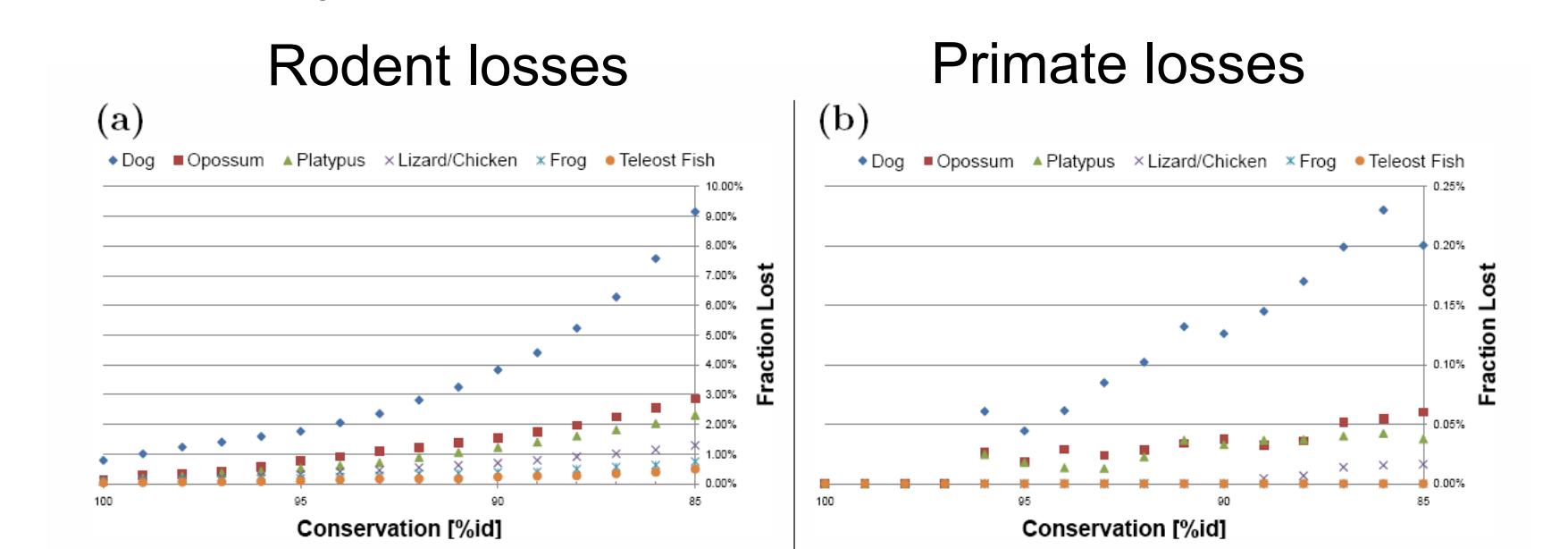
Alternate species configurations achieve desired separation



Functional DNA loss rate nearly constant regardless of conservation %id



Ancestry is a better predictor of persistence



## Summary

1. Ultraconserved elements 350-fold less likely to be lost than neutral DNA
2. Many thousands of non-coding regulatory loci under similar constraint, regardless of nucleotide conservation level
3. Ancestry information provides better predictor of indispensability than conservation %id alone

1. International Mouse Genome Sequencing Consortium, *Nature*, 2002  
 2. Bejerano et al., *Science*, 2004  
 3. Ni et al., *Genes Dev.*, 2007  
 4. Lareau et al., *Nature*, 2007  
 5. Pennacchio et al., *Nature*, 2006  
 6. Katzman et al., *Science*, 2007  
 7. Ahituv et al., *PLoS Biol.*, 2007  
 8. Barabási et al., *Brief Funct. Genomic Proteomic*, 2007  
 9. Wilson et al., *Annu. Rev. Biochem.*, 1977  
 10. Pal et al., *Nat. Rev. Genet.*, 2006