The landscape of fitness effects of putatively functional noncoding mutations in humans

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Sep.26st, 2024, ZJU

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The journey: Natural selection and human diseases

赵烨

李正和

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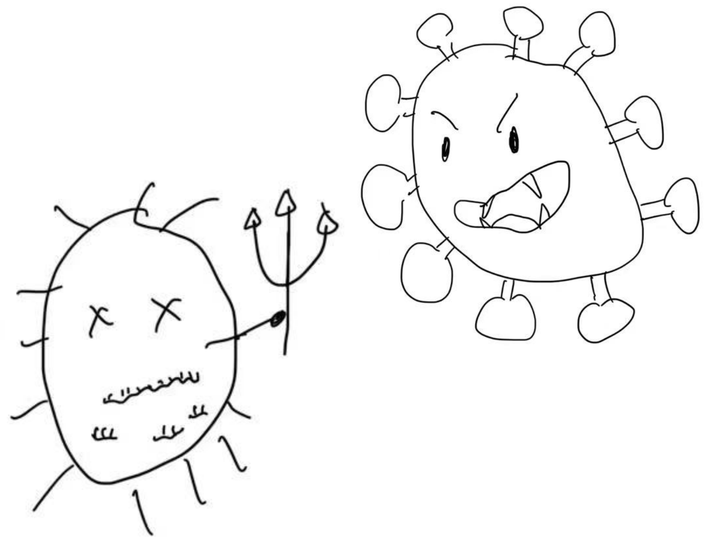

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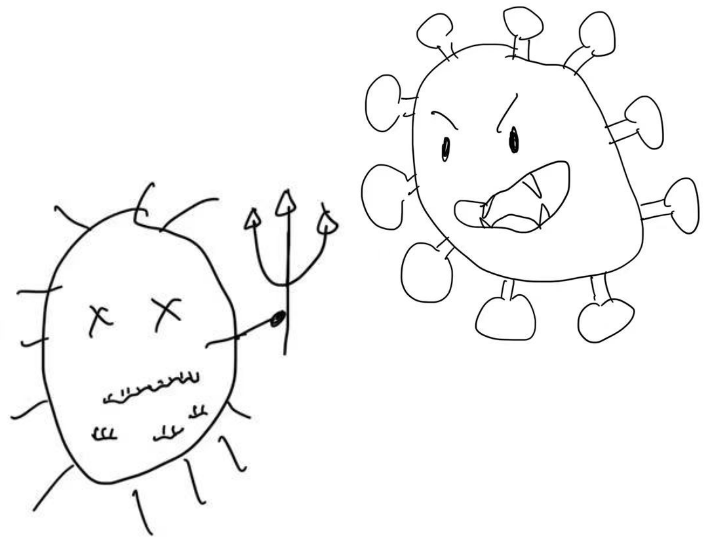

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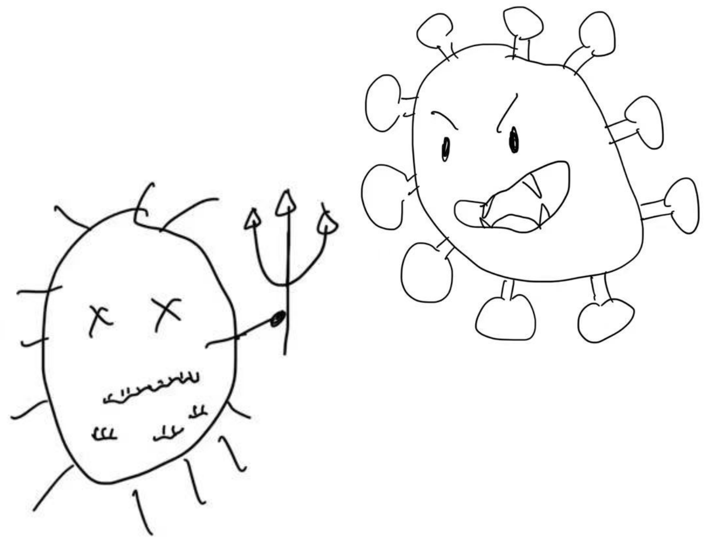

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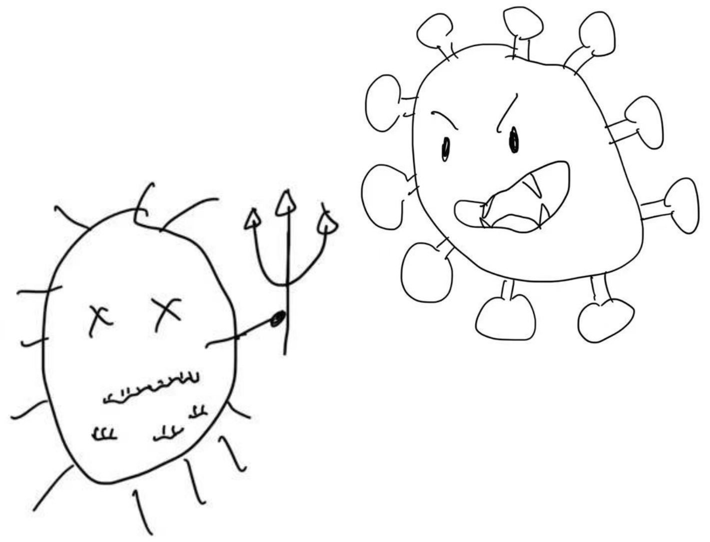

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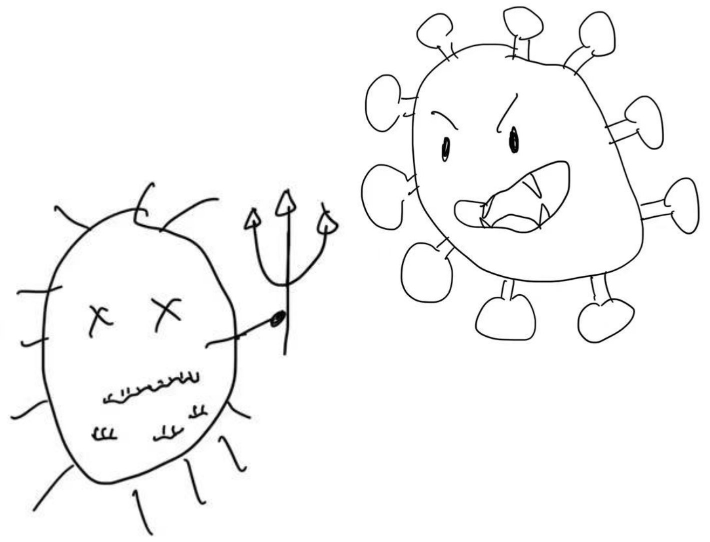

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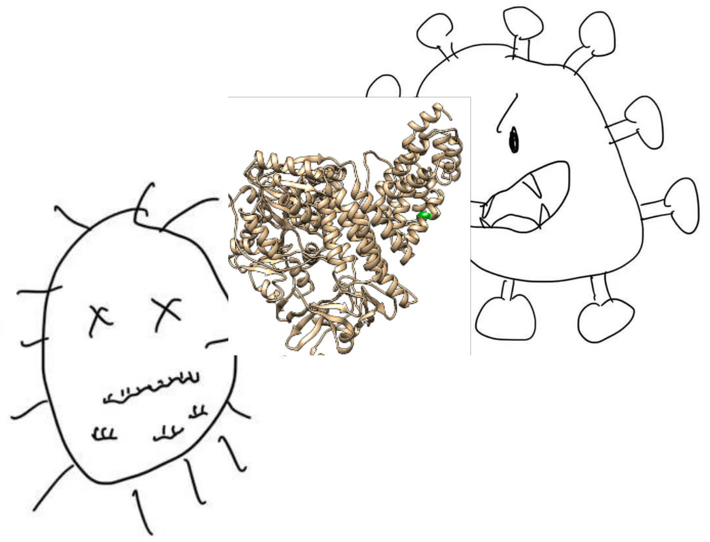

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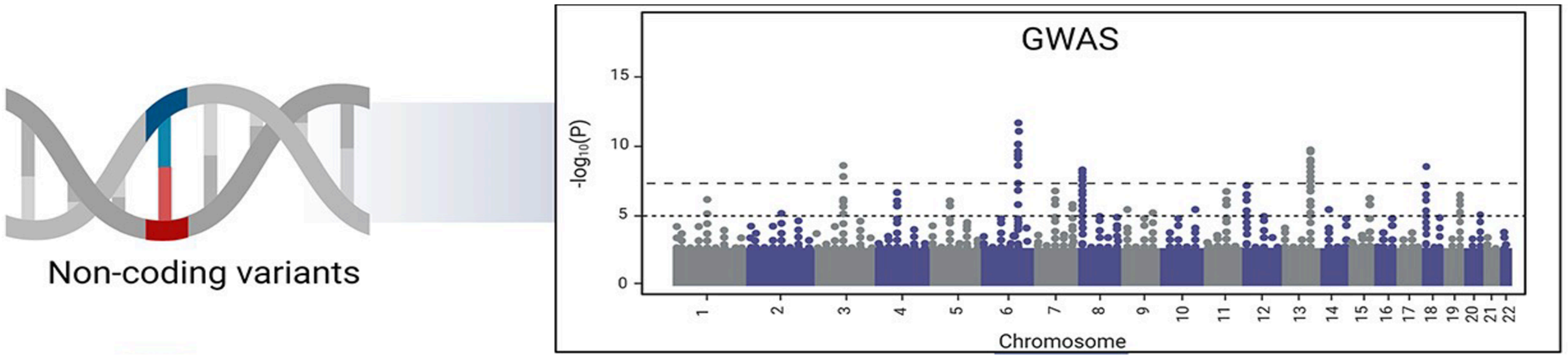
- What about complex diseases?

Disease associated non-coding variants

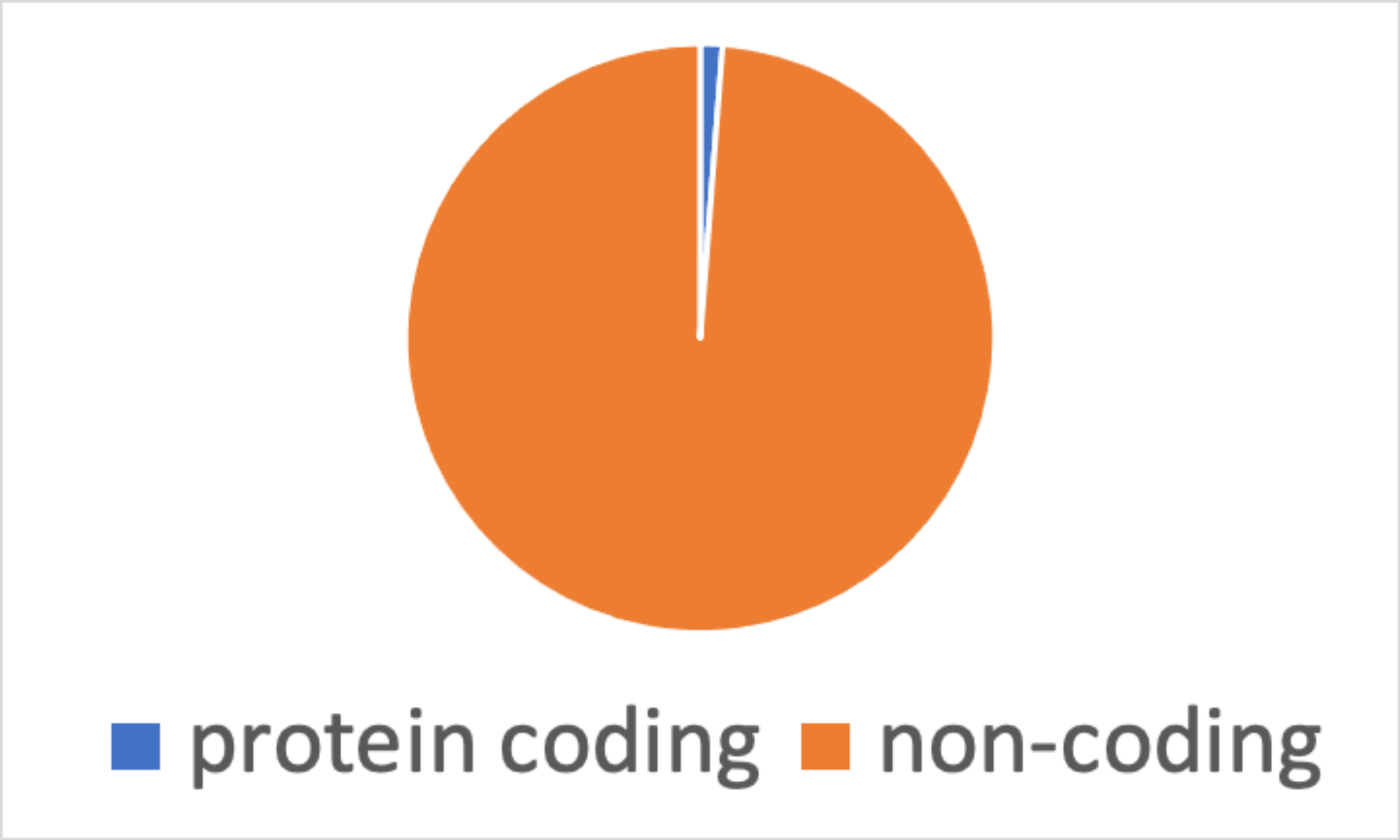
Most variants, including most of the functional ones that contribute to disease risk, are not in protein-coding regions.



Schipper and Posthuma, 2022

Non-coding DNA

Non-coding DNA: DNA does not code for protein



The ENCODE Project Consortium, 2012

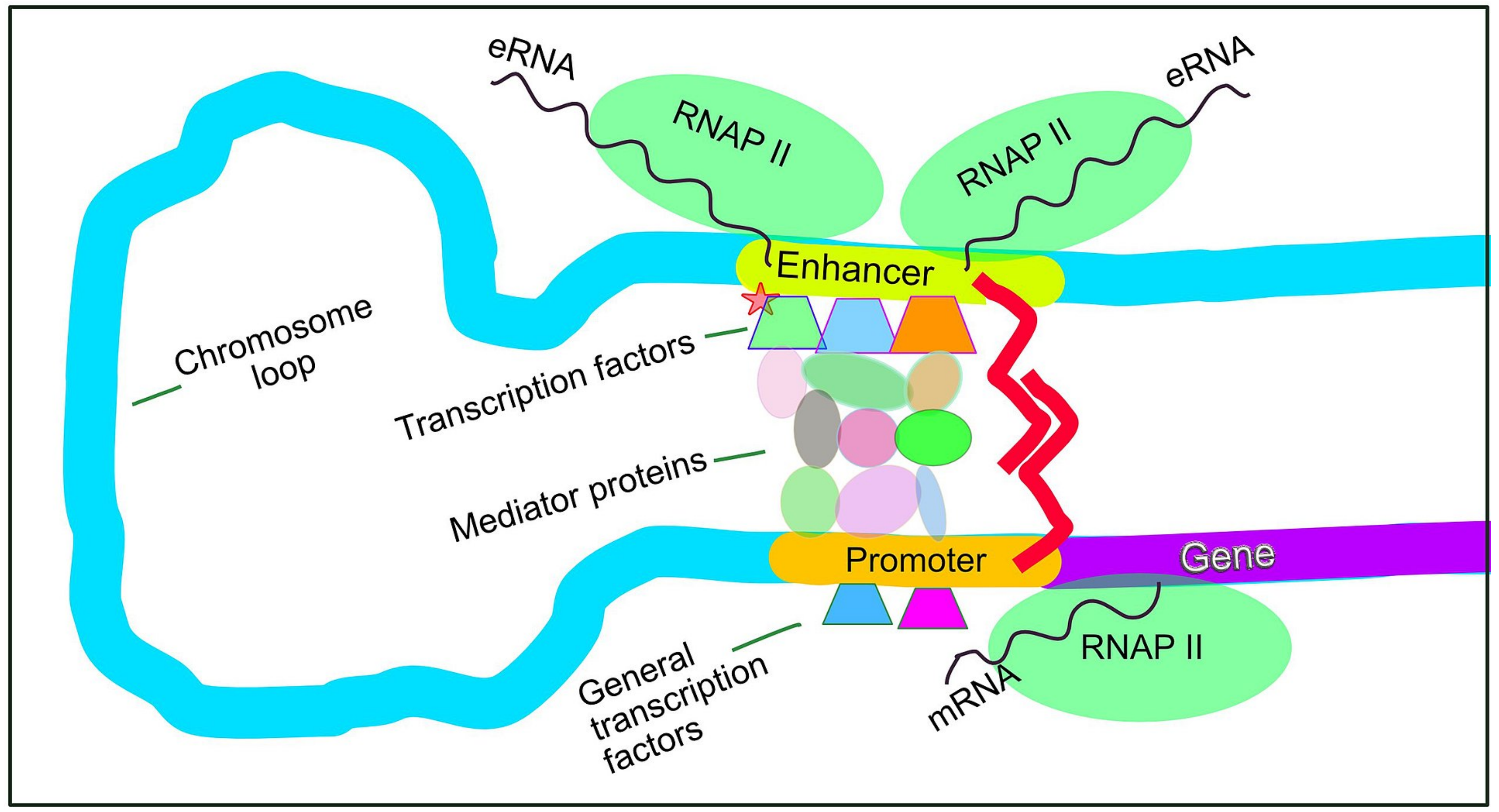
- protein coding: 1.22%
- non-coding: 98.78%

Non-coding DNA

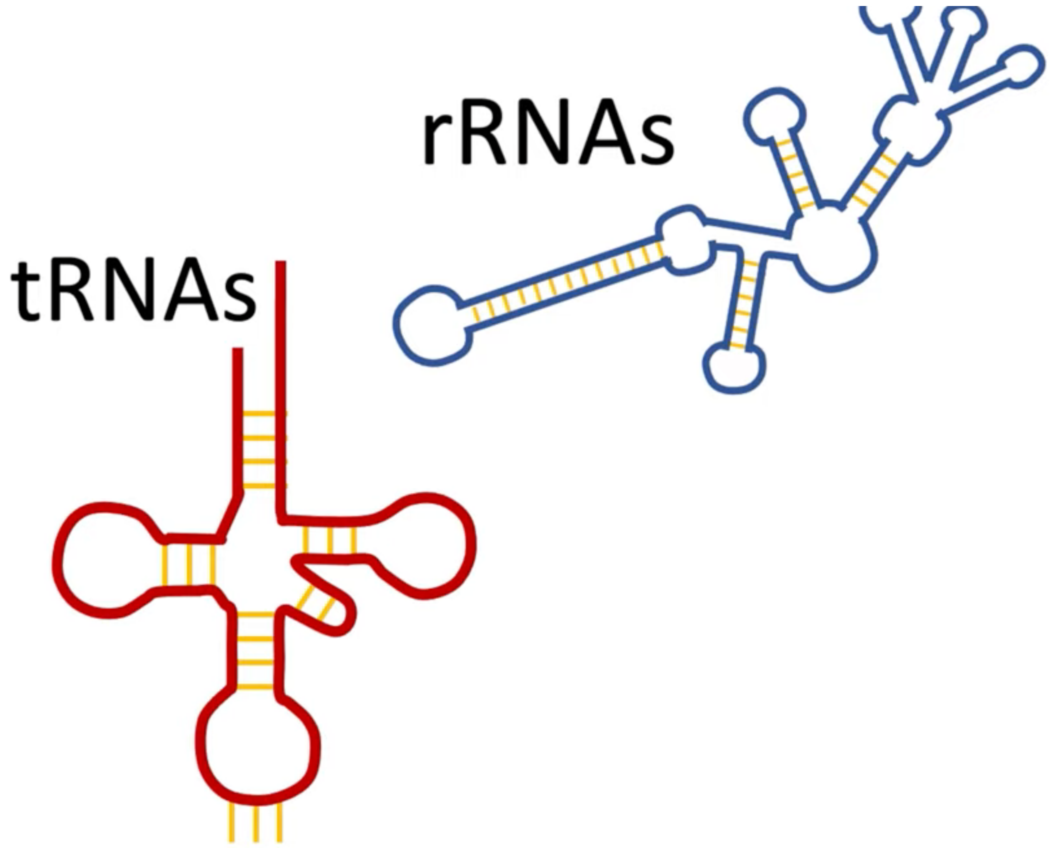
Non-coding DNA: DNA does not code for protein

Gene regulatory sequences

promoters (1% of genome)
enhancers (10% of genome)



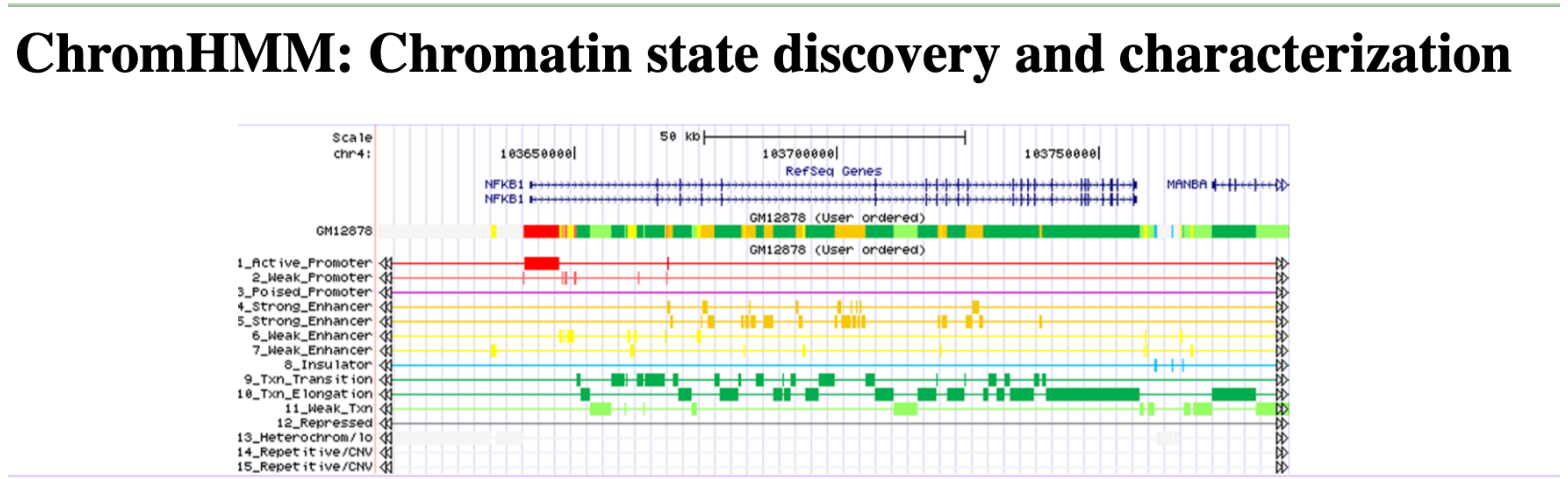
non-coding RNA



Others

introns
telomeres
satellite DNA
…

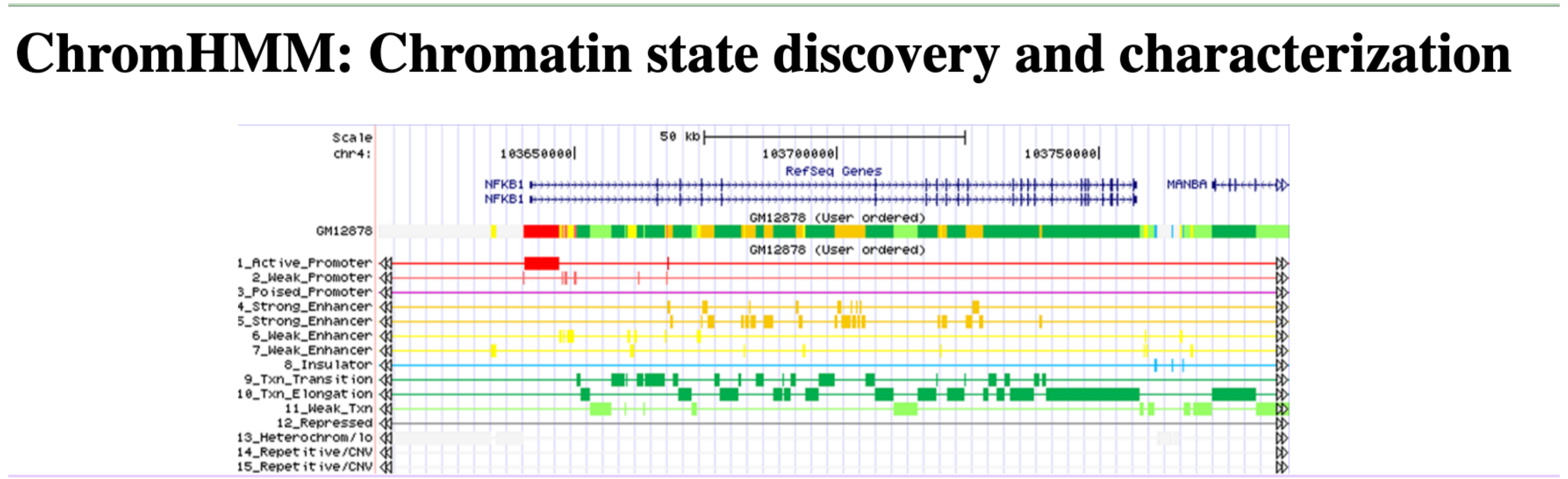
Annotation of non-coding regions


ChromHMM: Chromatin state discovery and characterization

ChromHMM: integrate multiple chromatin datasets such as ChIP-seq data of various histone modifications to annotate chromatin states.

Ernst J and Kellis M, 2012; Vu H and Ernst J, 2022

Annotation of non-coding regions



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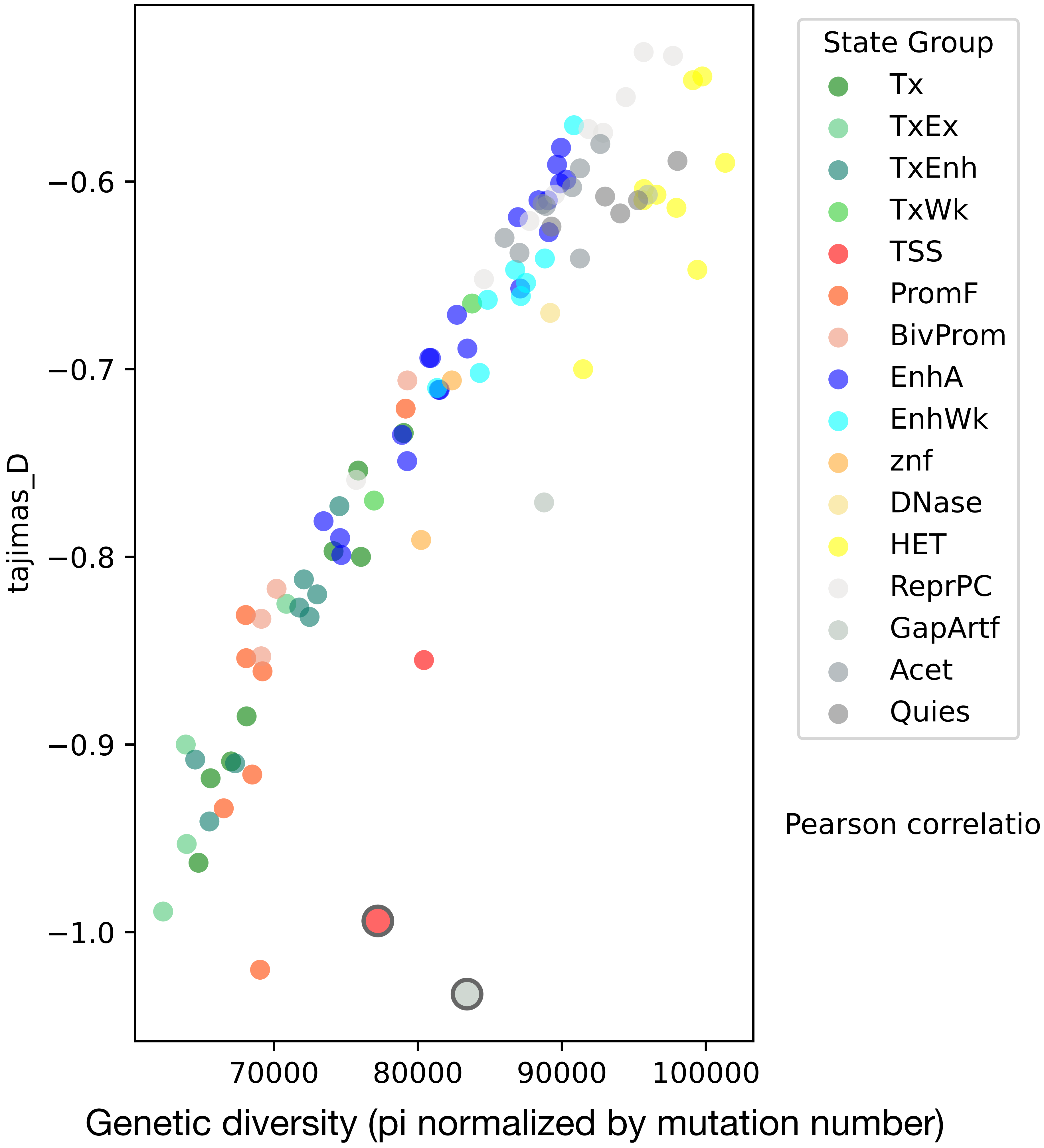
Different chromatin states ~ Selection?

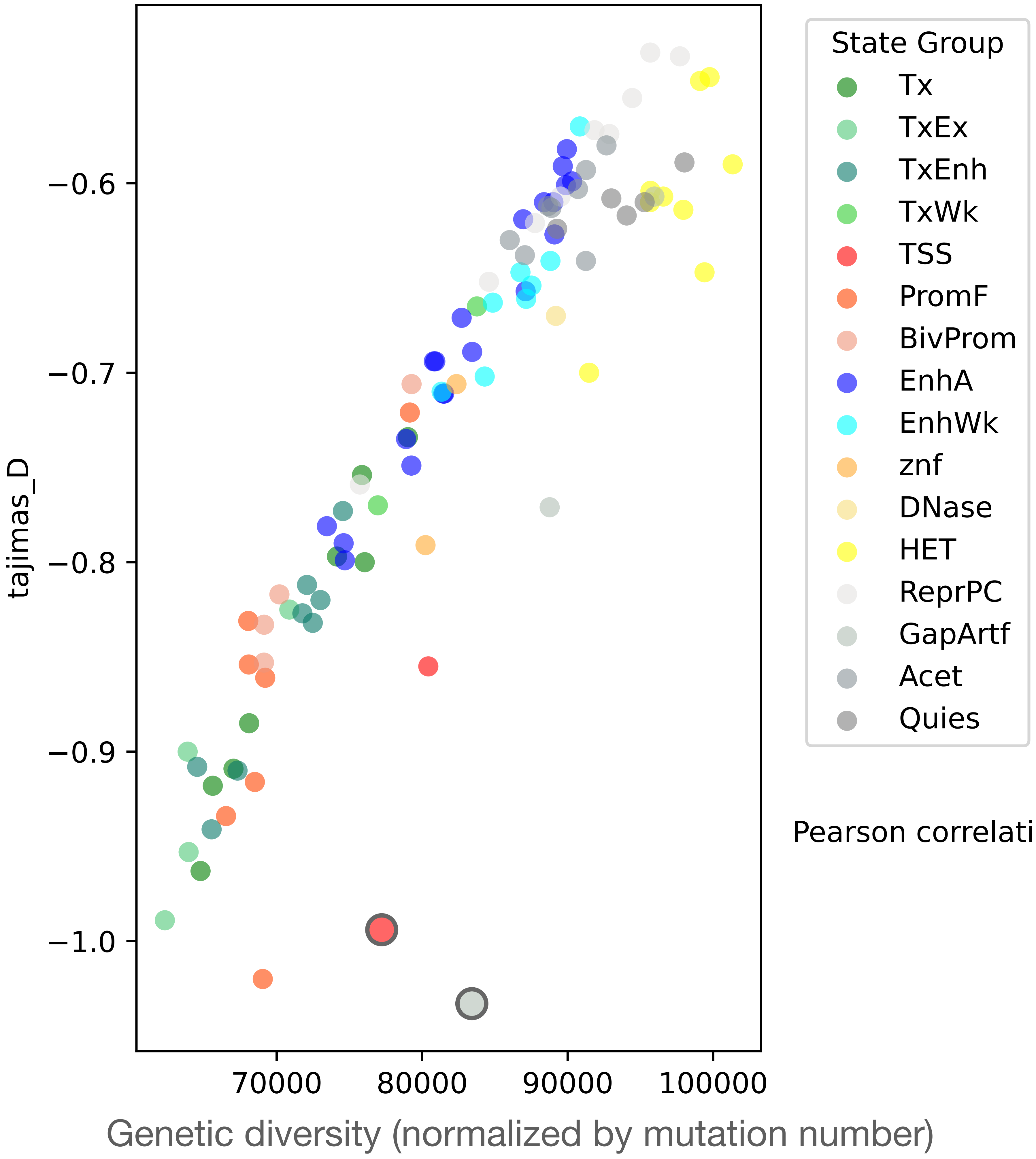
Ernst J and Kellis M, 2012; Vu H and Ernst J, 2022

Patterns of genetic variation vary across noncoding annotations



Pearson correlation: 0.90

Patterns of genetic variation vary across noncoding annotations



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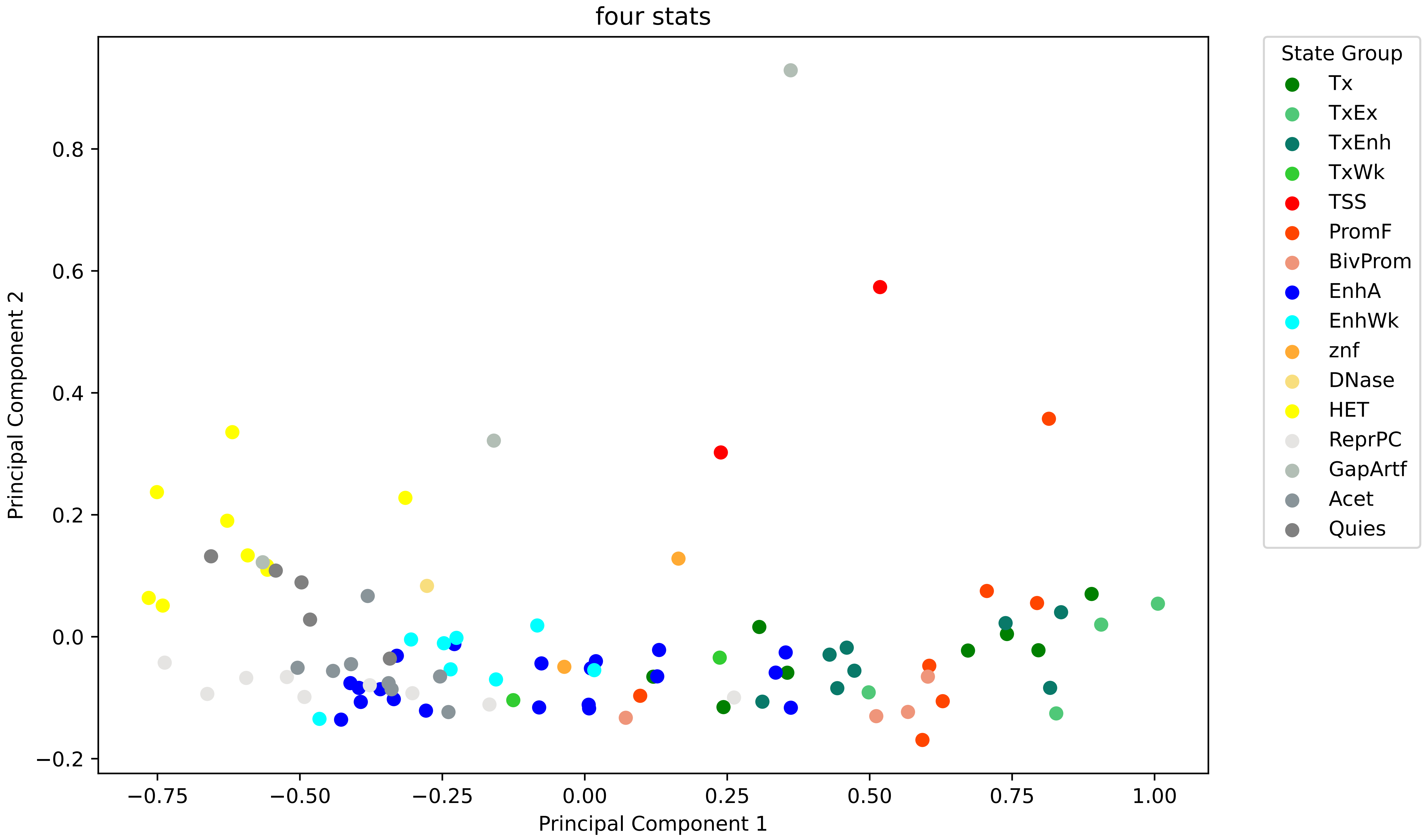

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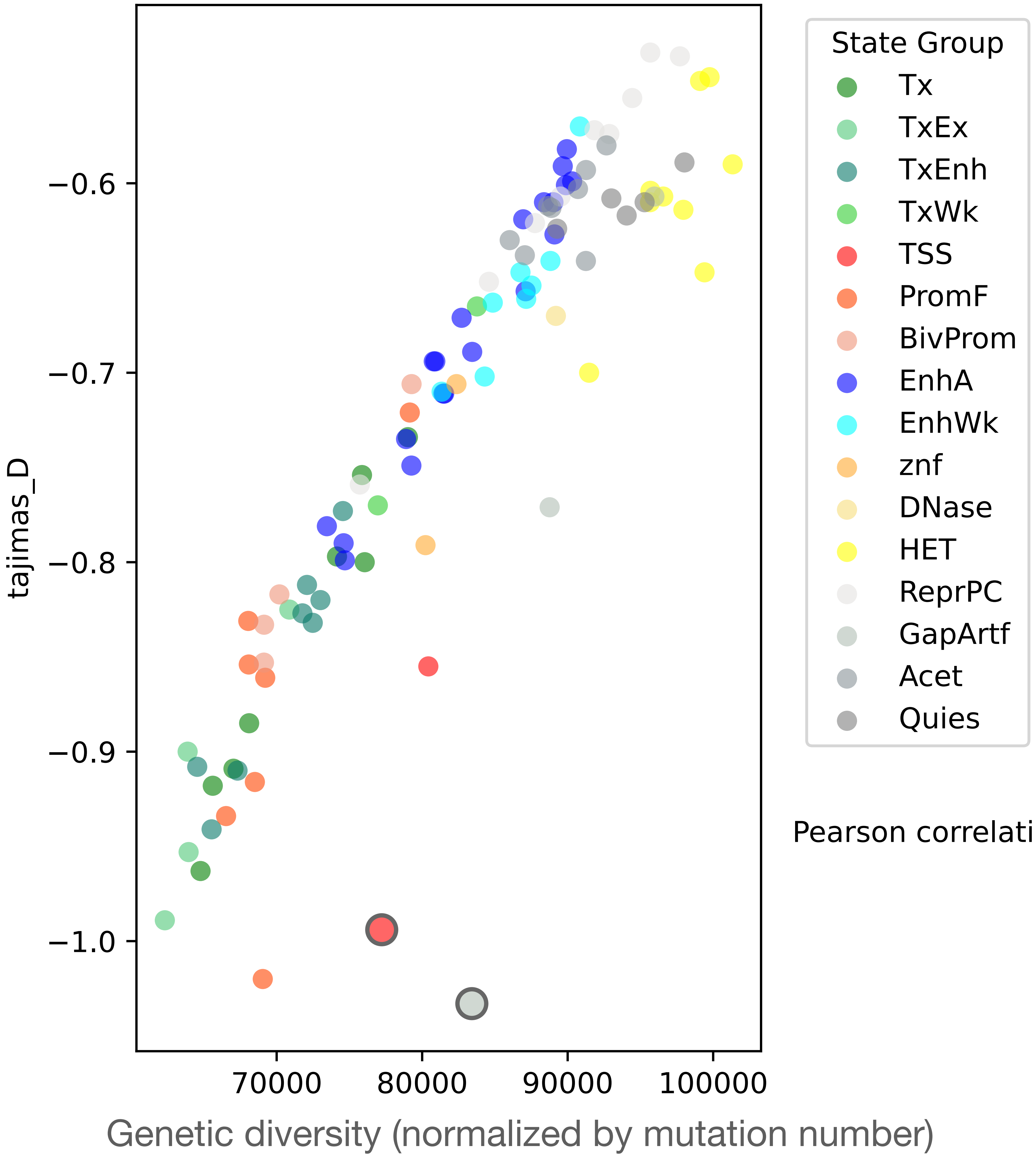

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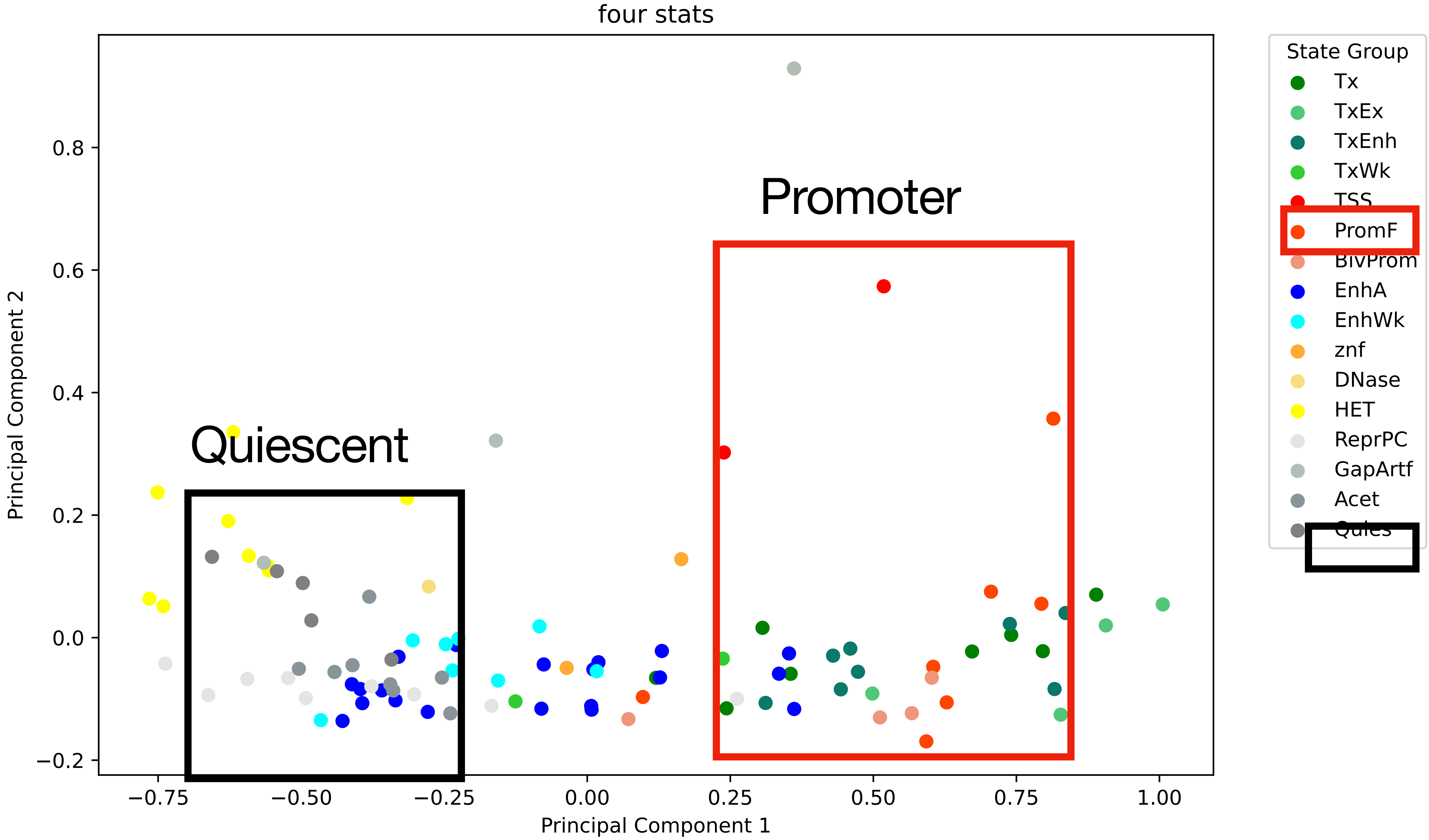

What are the fitness effects of non-coding mutations?

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Fitness effects: selection coefficients

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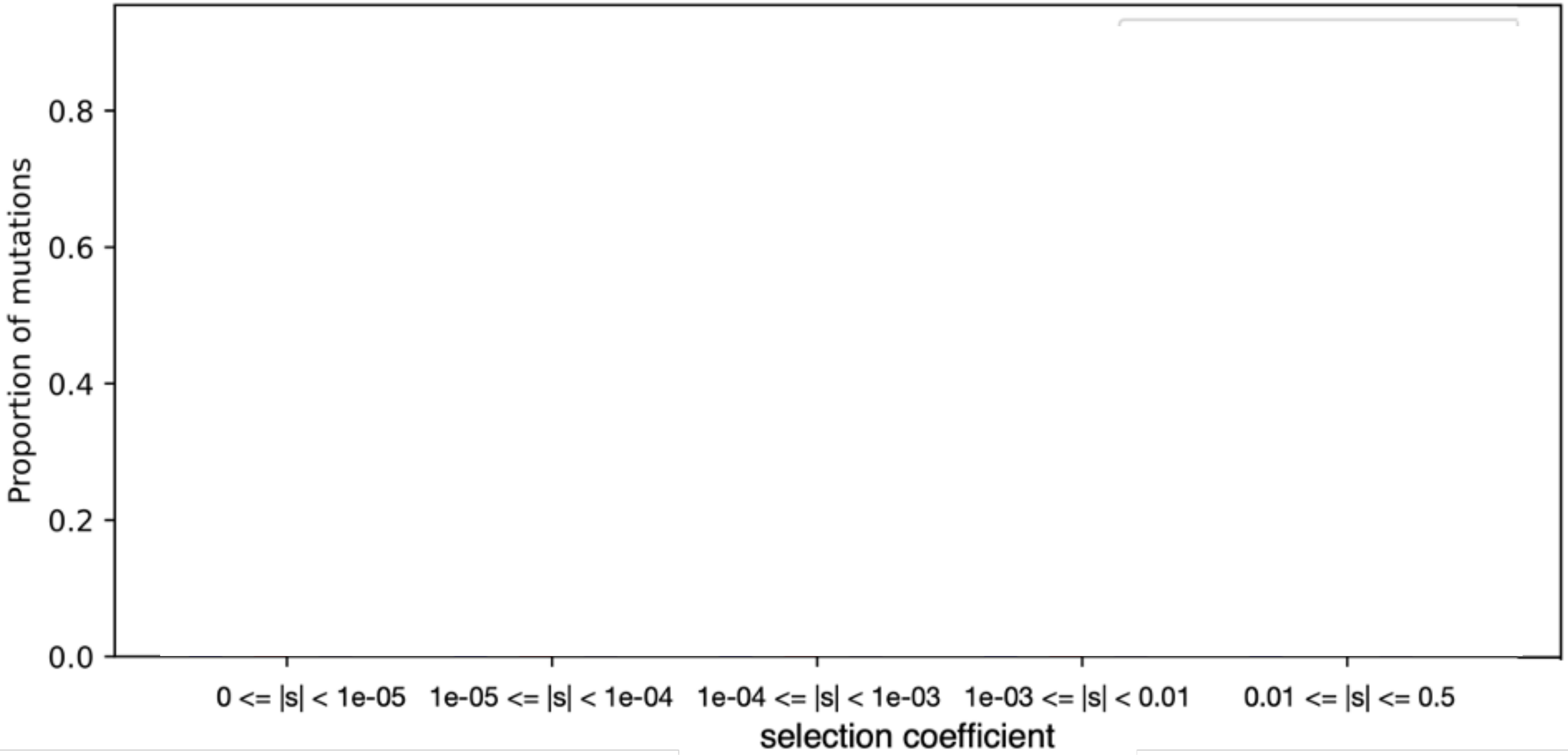
Fitness effects: selection coefficients

Distribution of Fitness Effects (DFE)



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Fitness effects: selection coefficients

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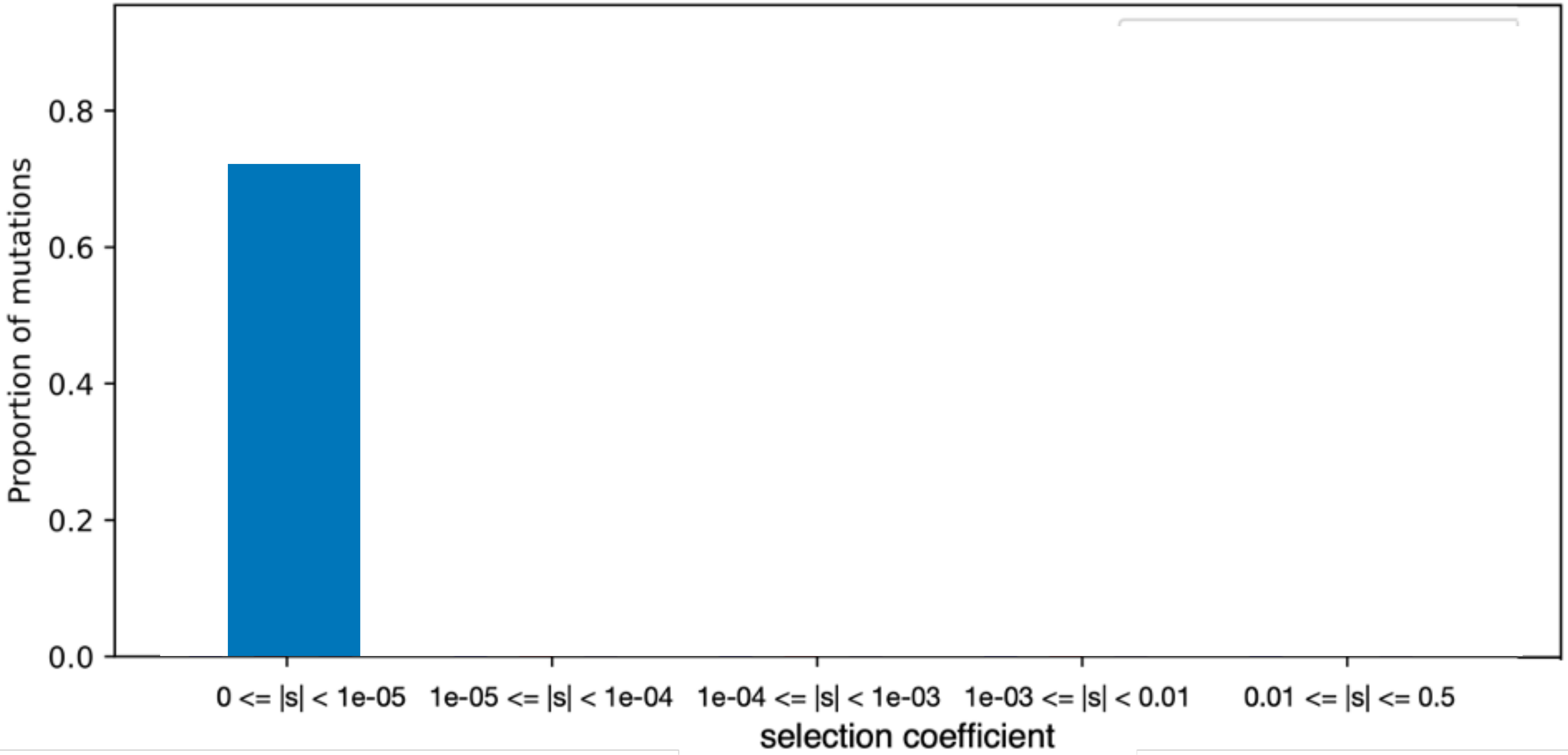
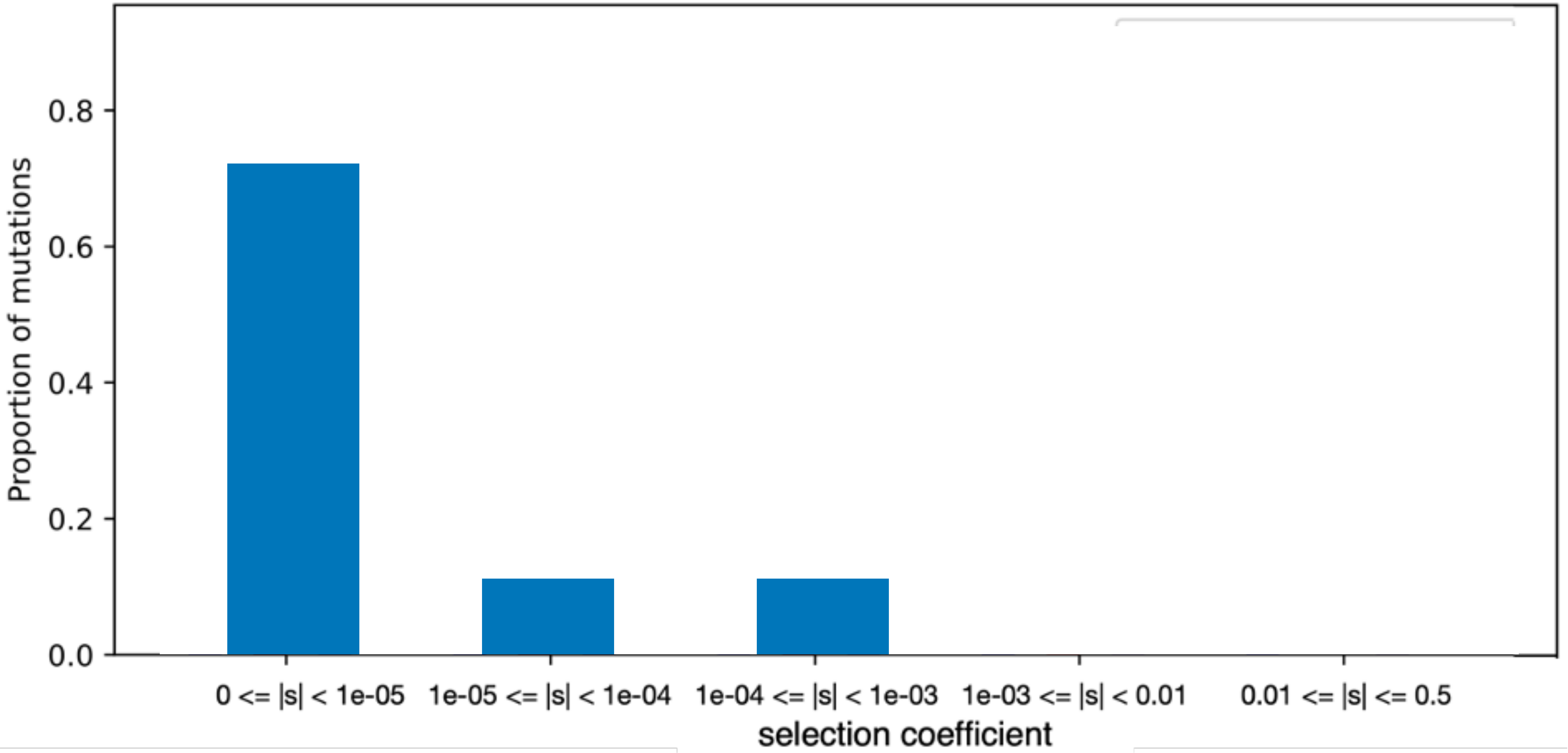


Neutral

What are the fitness effects of non-coding mutations?

Fitness effects: selection coefficients

Distribution of Fitness Effects (DFE)



Neutral Weakly deleterious

What are the fitness effects of non-coding mutations?

Fitness effects: selection coefficients

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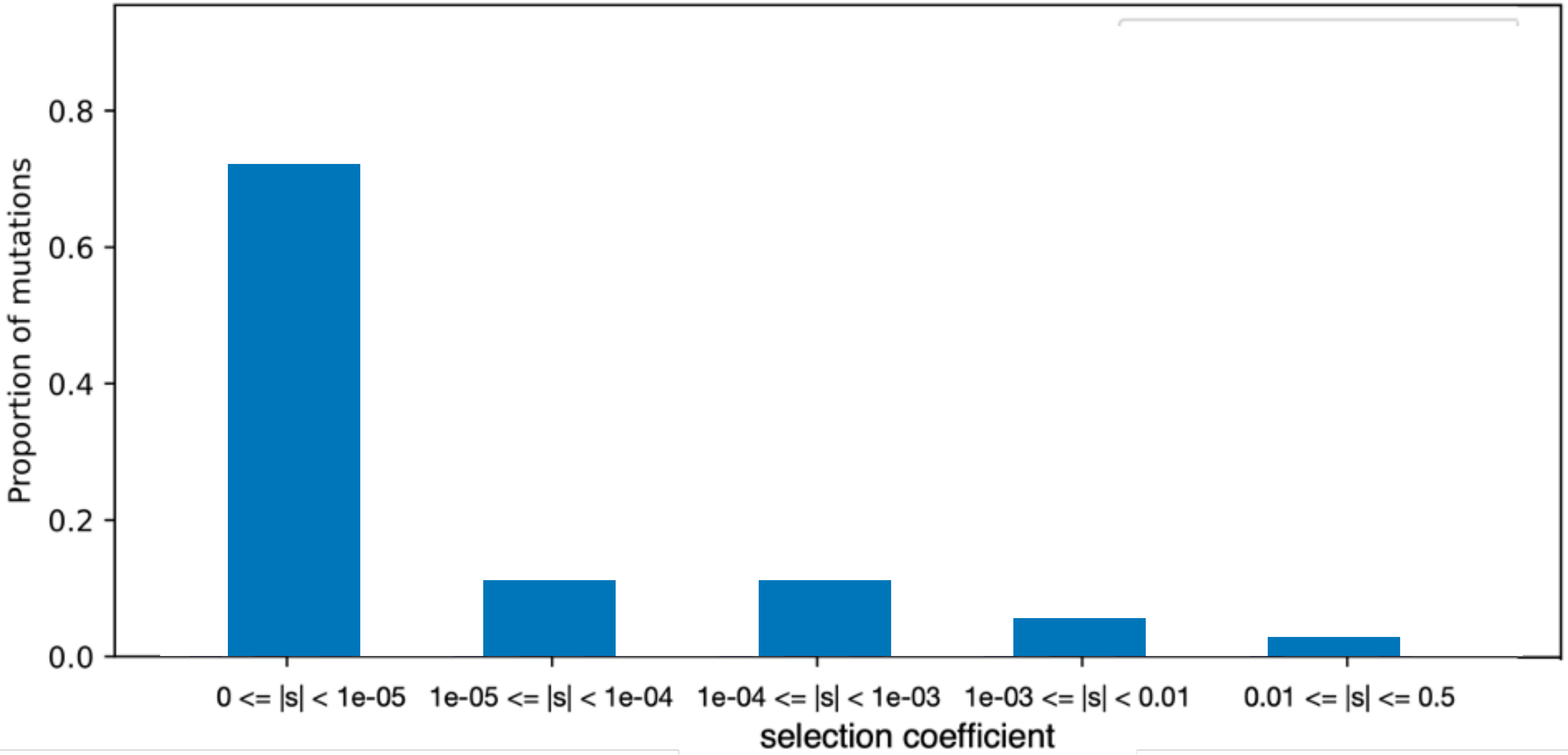
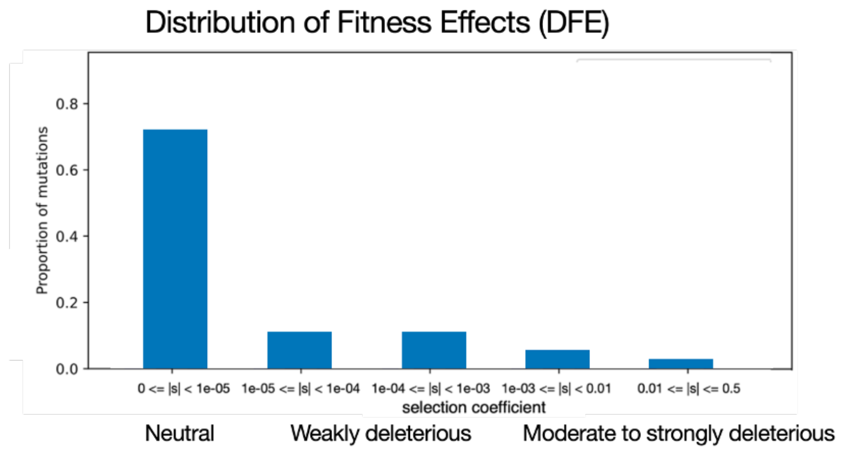
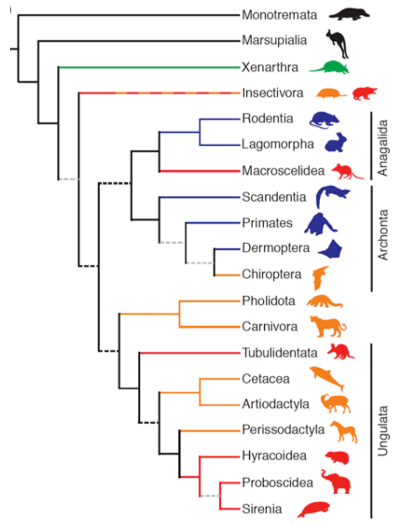


Neutral Weakly deleterious Moderate to strongly deleterious

DFE of non-coding mutations





- Model-based method for inferring Distribution of Fitness effects (DFE)

- DFE of annotated functional non-coding regions in human genome

- Negative selection in conserved and non-conserved human genomic region

picture is from https://www.phonandroid.com/tesla-continue-de-decliner-le-cybertruck-a-toutes-les-sauces-avec-un-marteau-de-gym.html
Phylogeny is from Springer et al., 2004

Infer selection coefficient by site frequency spectrum (SFS)

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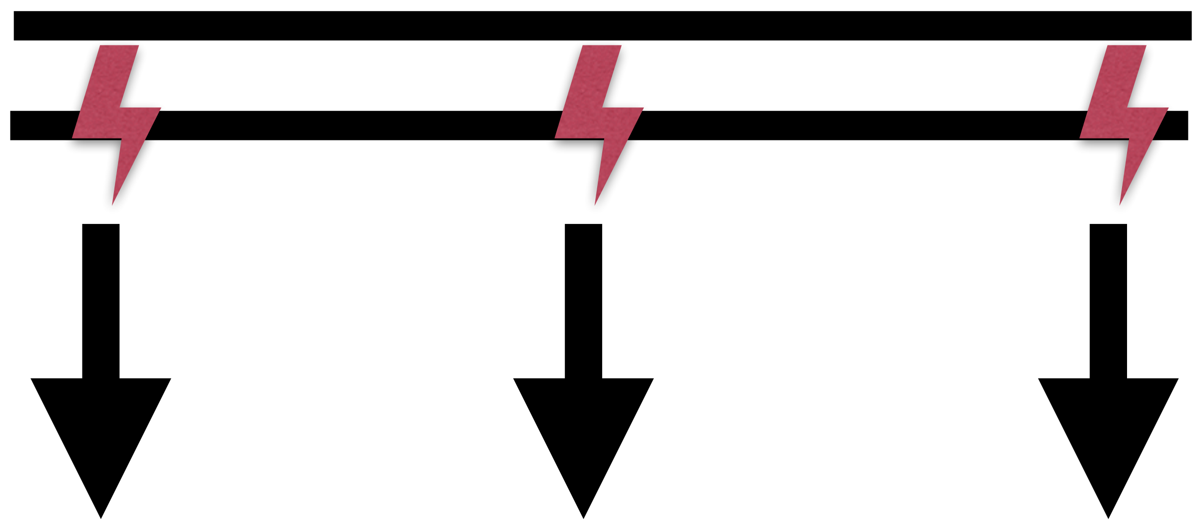
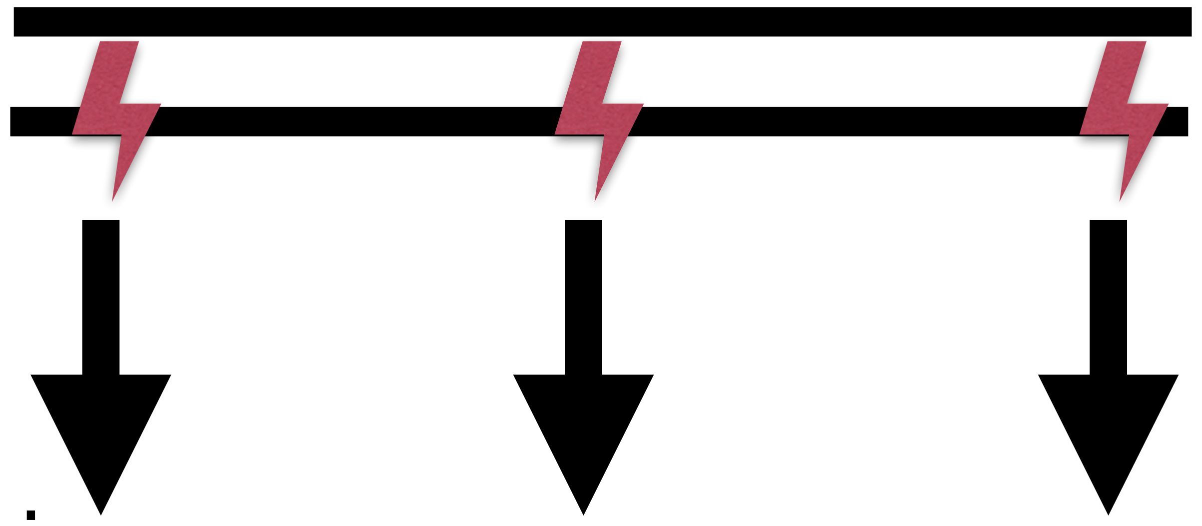
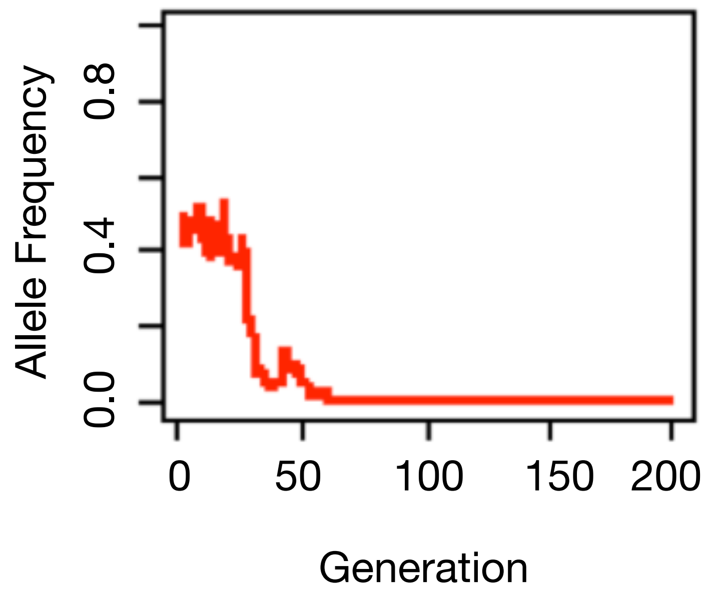


Infer selection coefficient by site frequency spectrum (SFS)



deleterious



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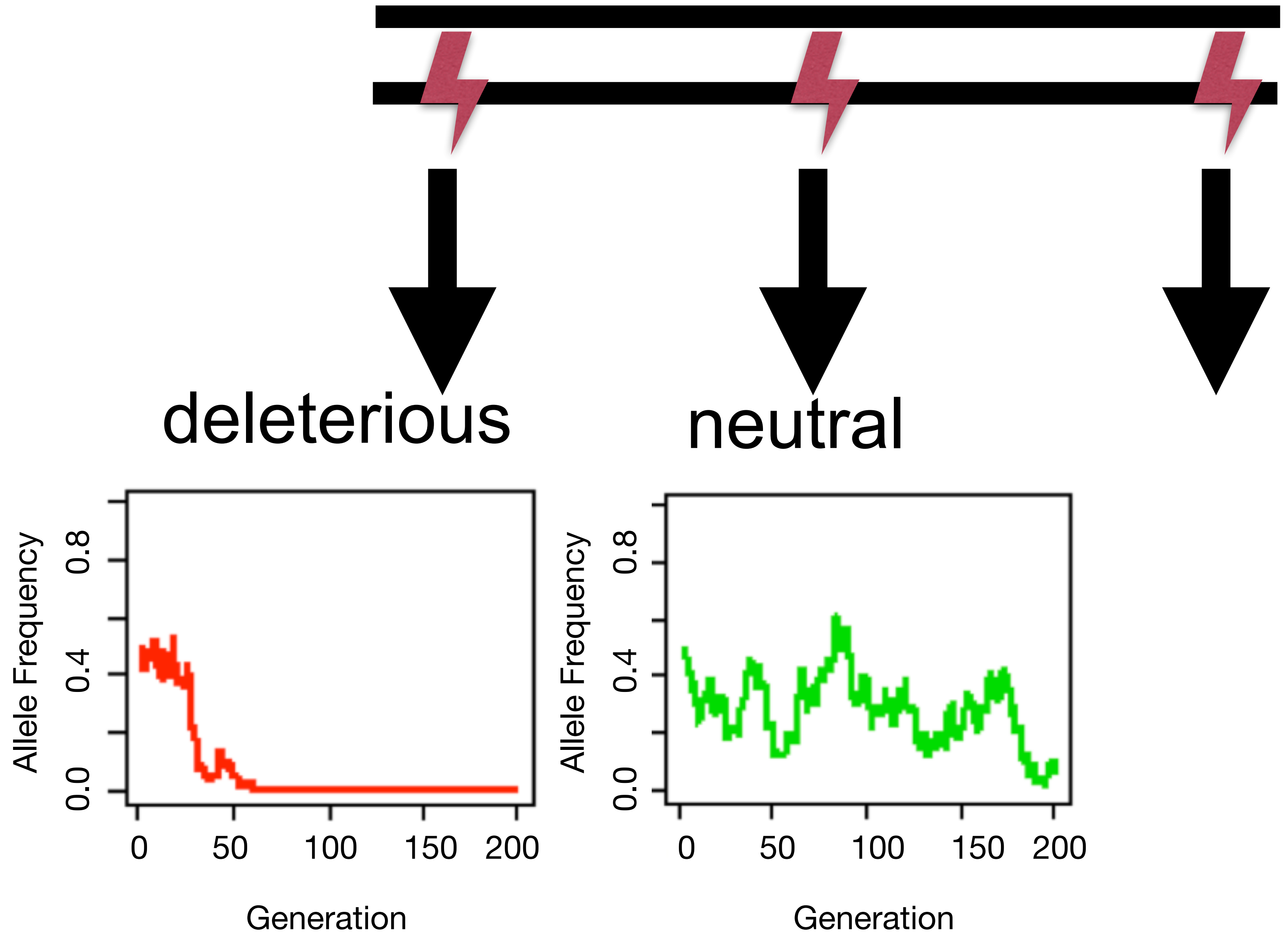

deleterious

neutral

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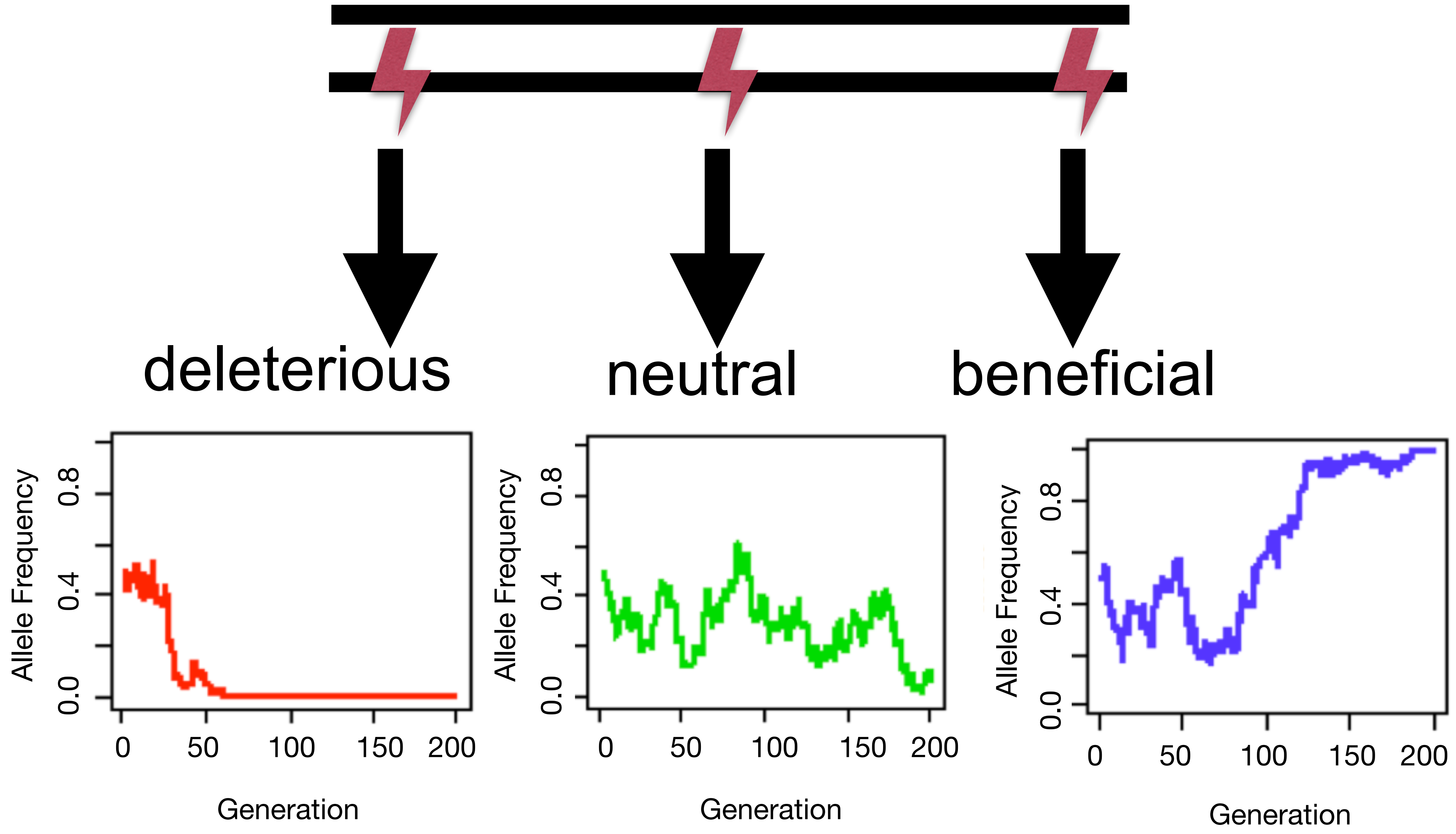

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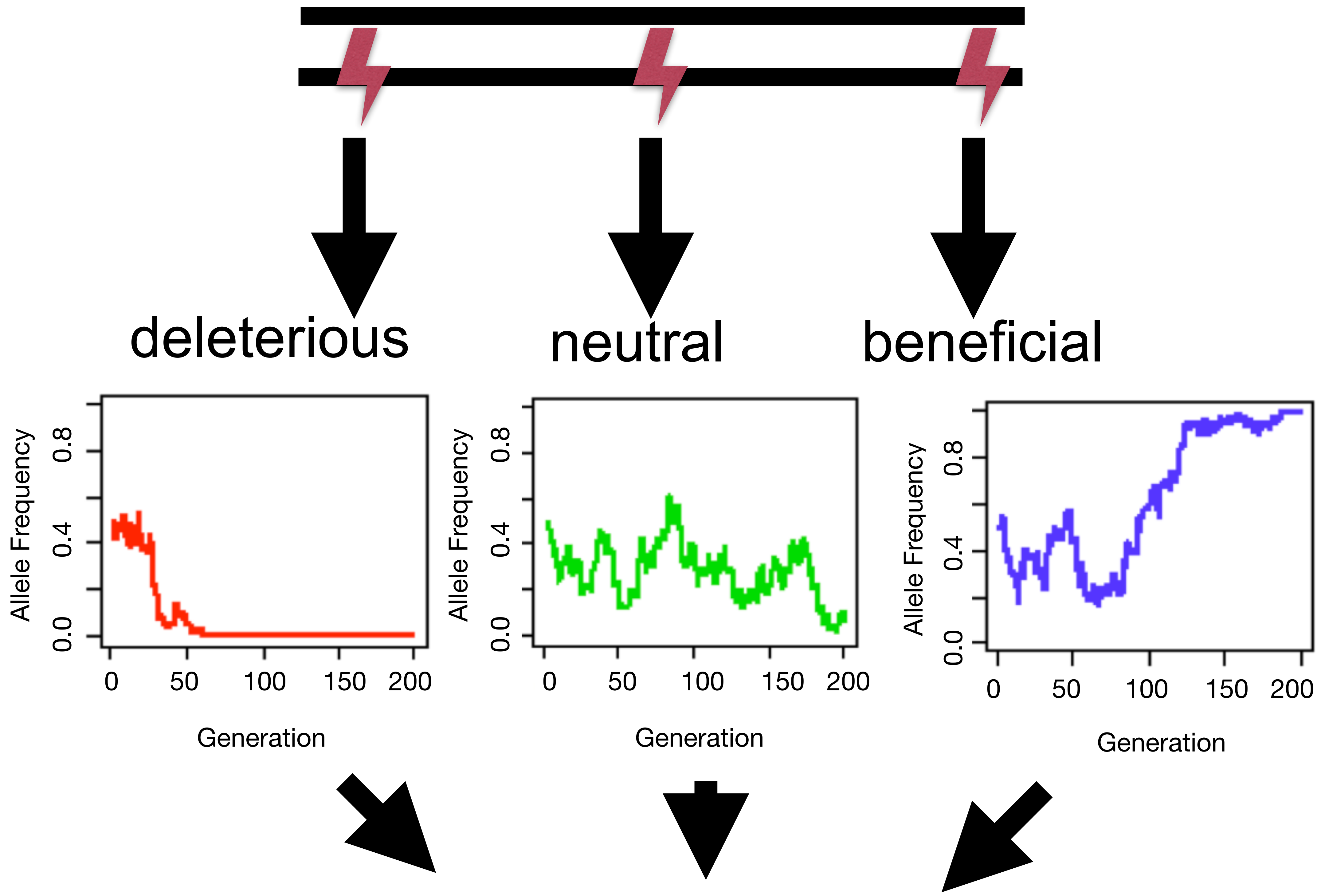

deleterious

neutral

beneficial

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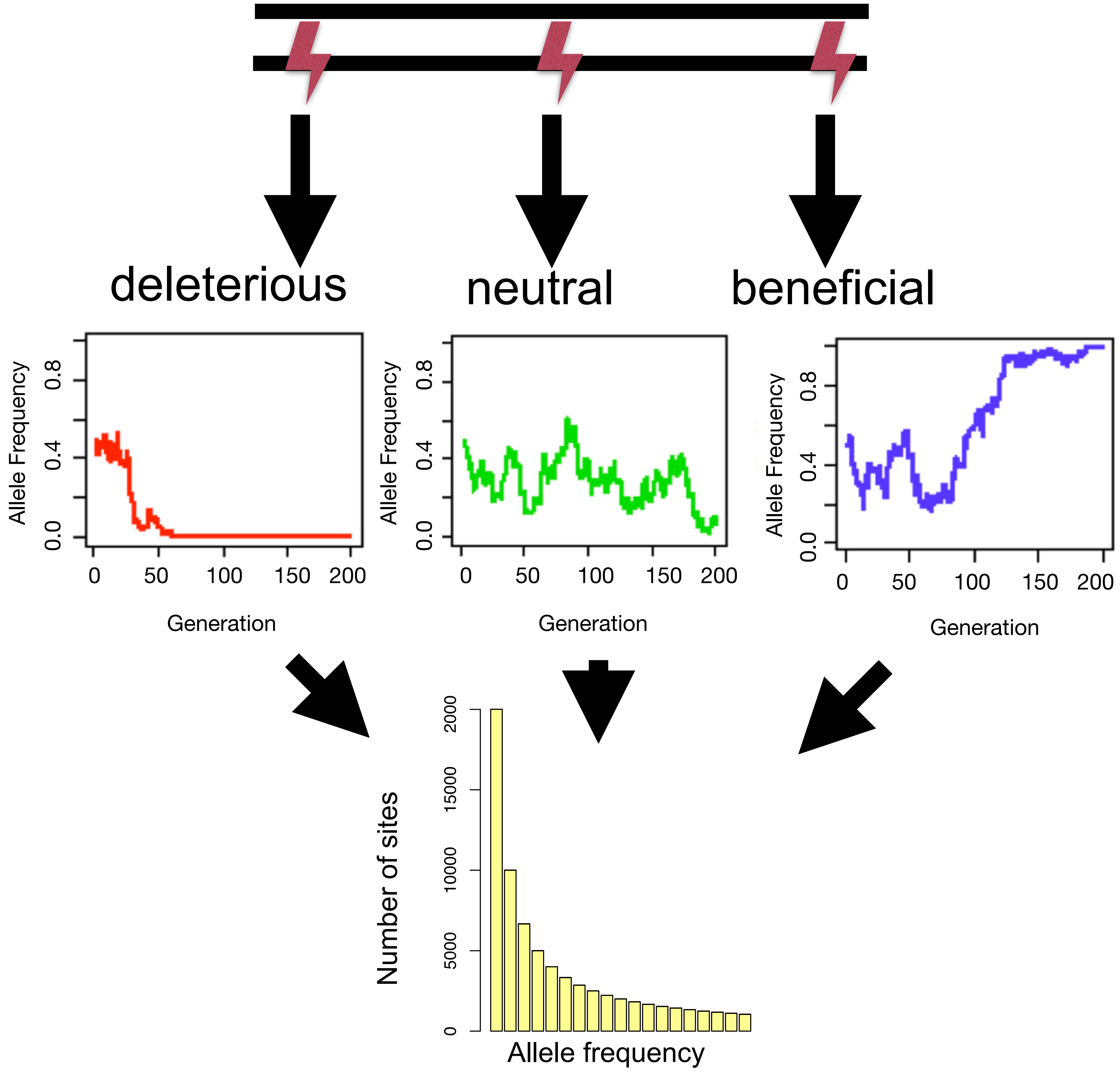

deleterious

neutral

beneficial

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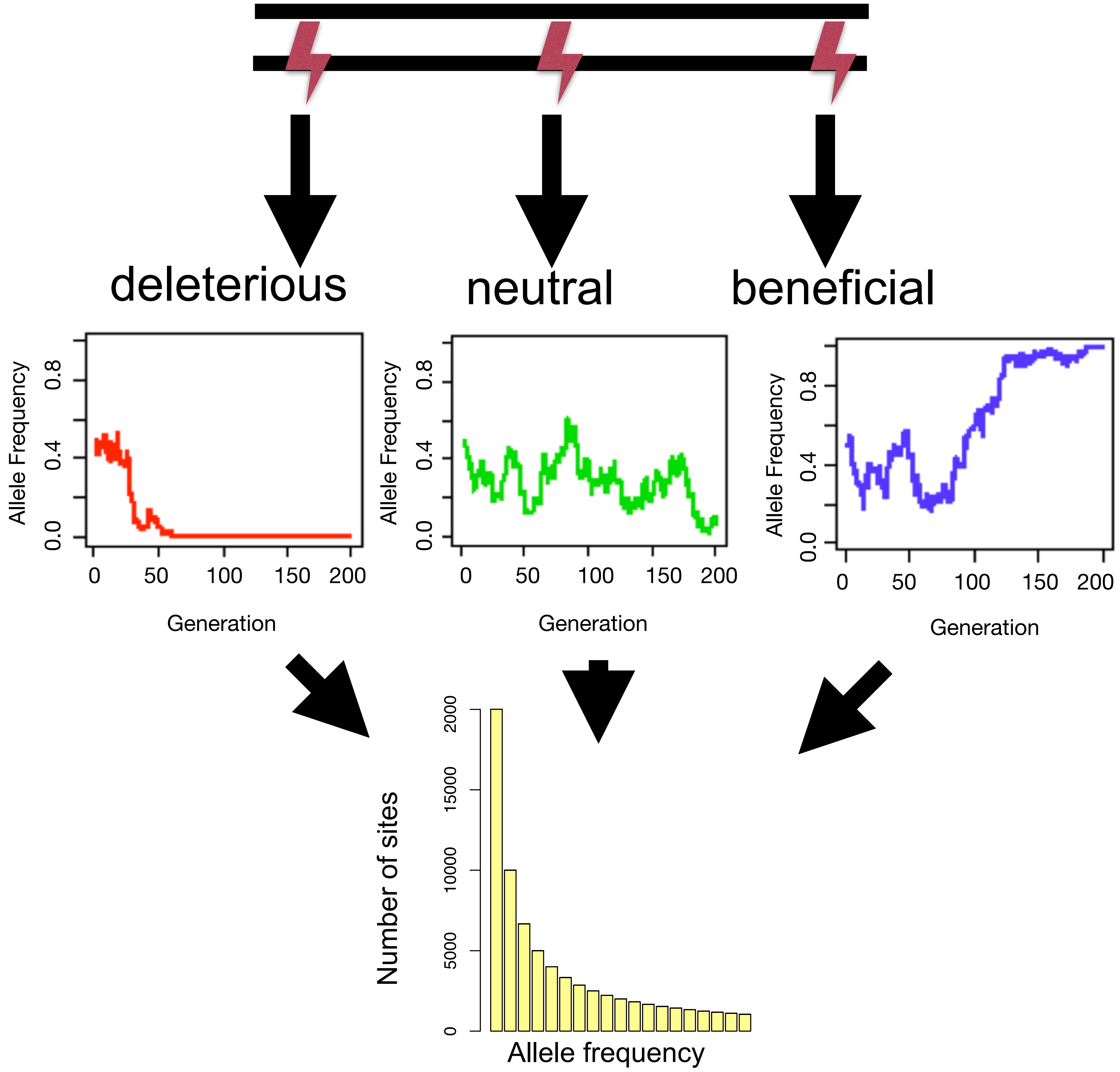


deleterious

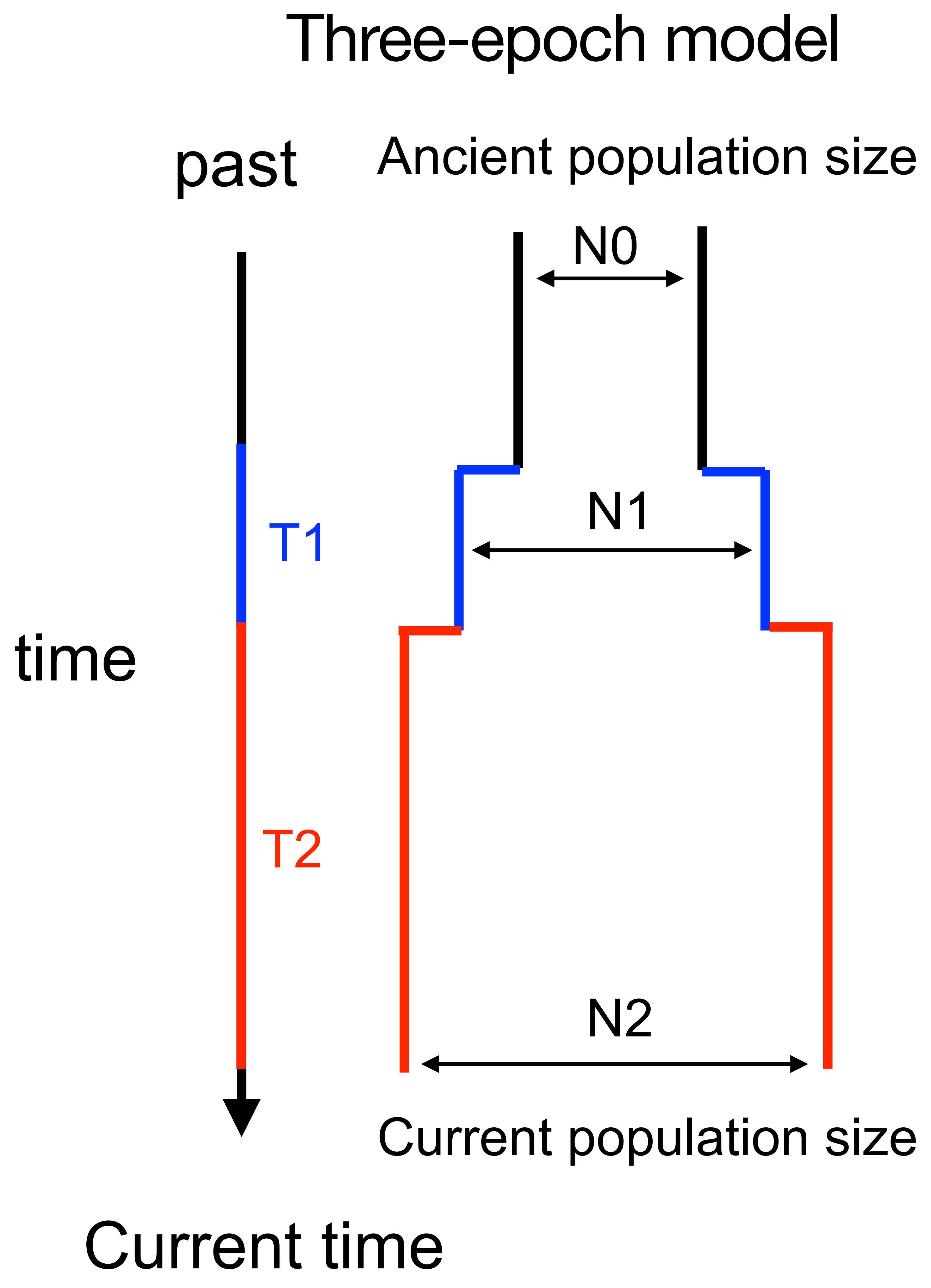
neutral

beneficial

1000 genome project:
Yoruba population (YRI)

Demographic history influences SFS

Demographic history: Changes of population size

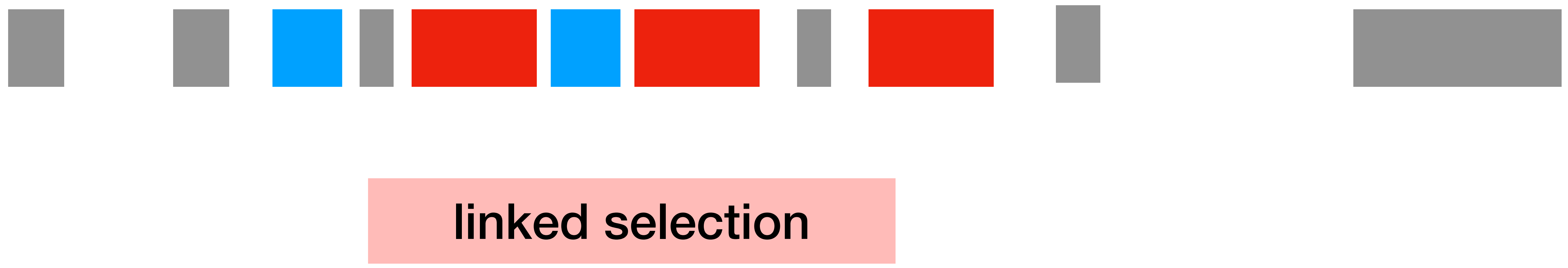


Linked selection influences SFS

◼ quiescent region

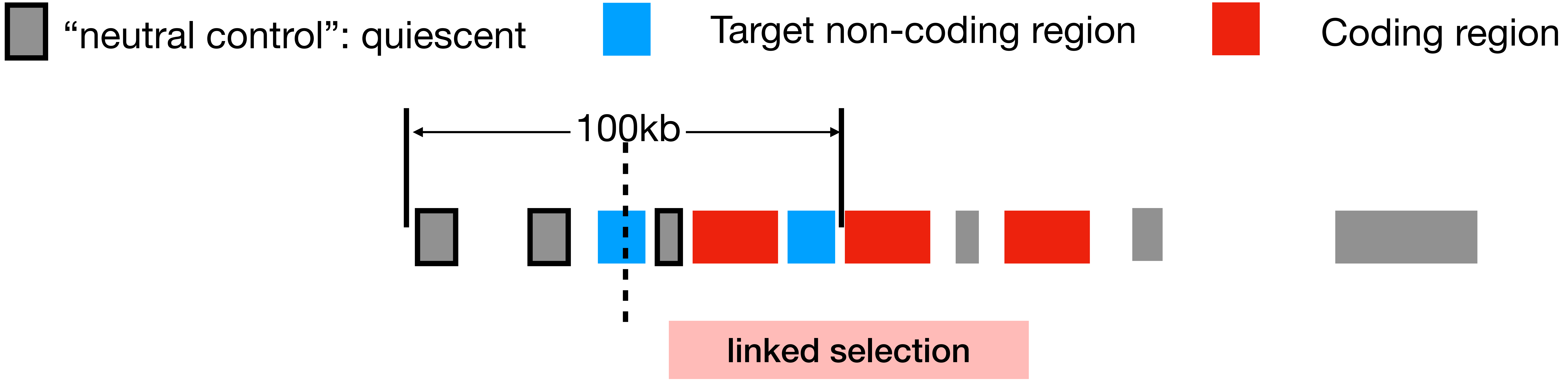
🟦 Target non-coding region

🟥 Coding region



linked selection

Method: Finding “neutral” controls

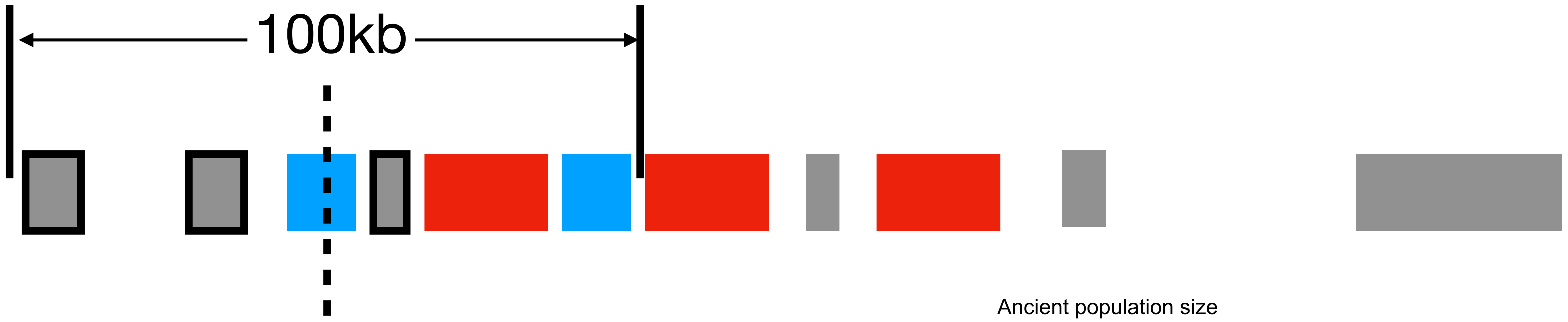


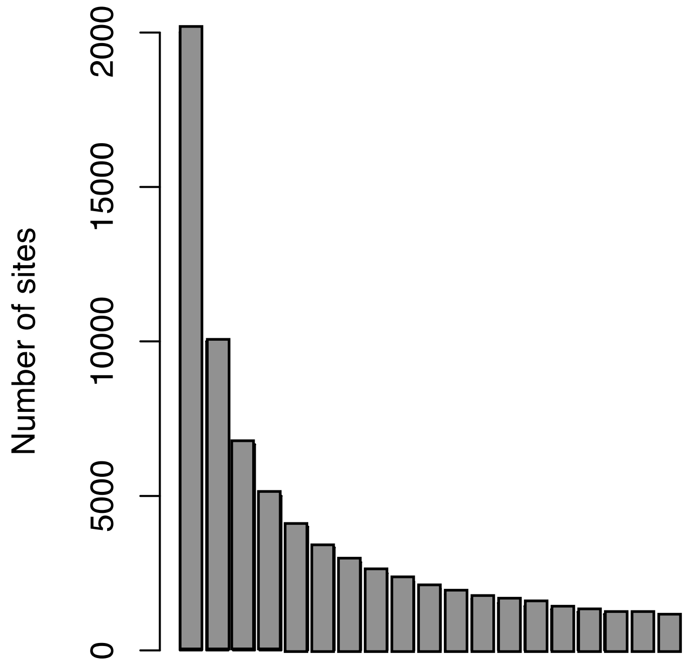
▨ “neutral control”: quiescent 🟦 Target non-coding region 🟥 Coding region

Gutenkunst et al., 2009; Kim et al., 2017

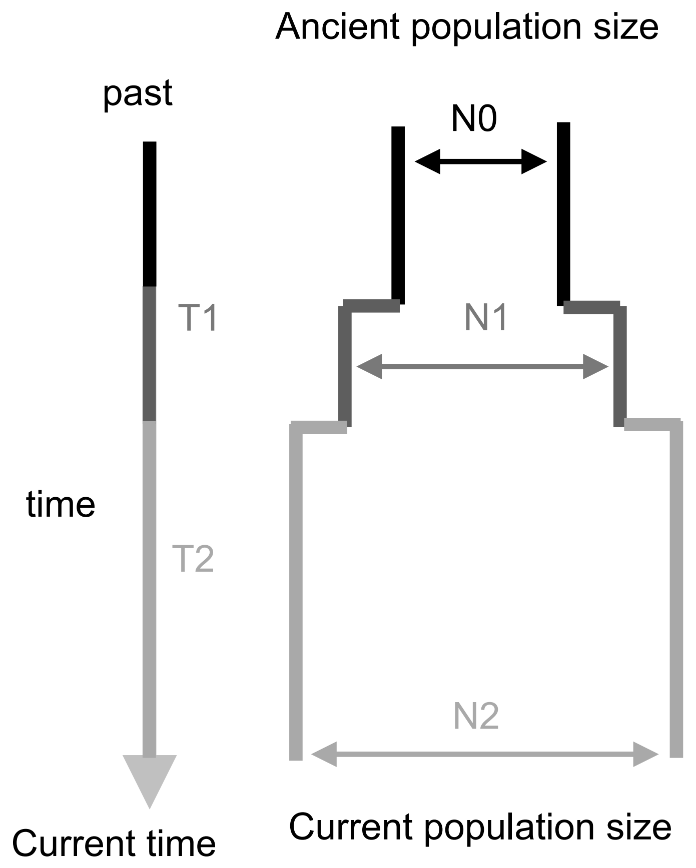
dadi: Infer models of demographic history

▨ “neutral control”: quiescent 🟦 Target non-coding region 🟥 Coding region





Site Frequency Spectrum (SFS)
of control sites



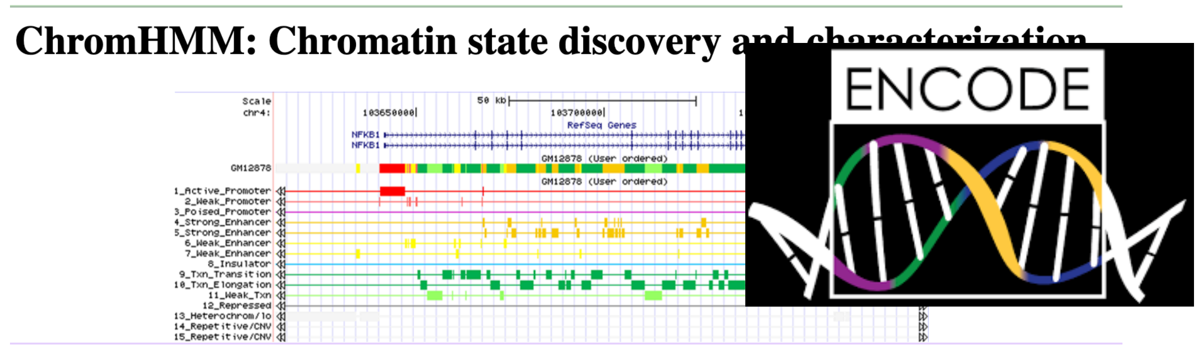
Demographic model

Gutenkunst et al., 2009; Kim et al., 2017

Workflow

Step1: Annotate genomic regions

🟦 Target non-coding region



ChromHMM: Chromatin state discovery and characterization

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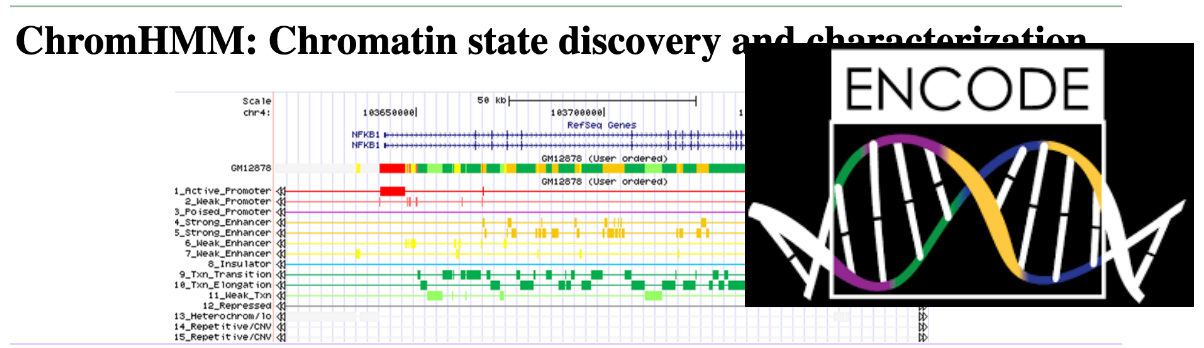
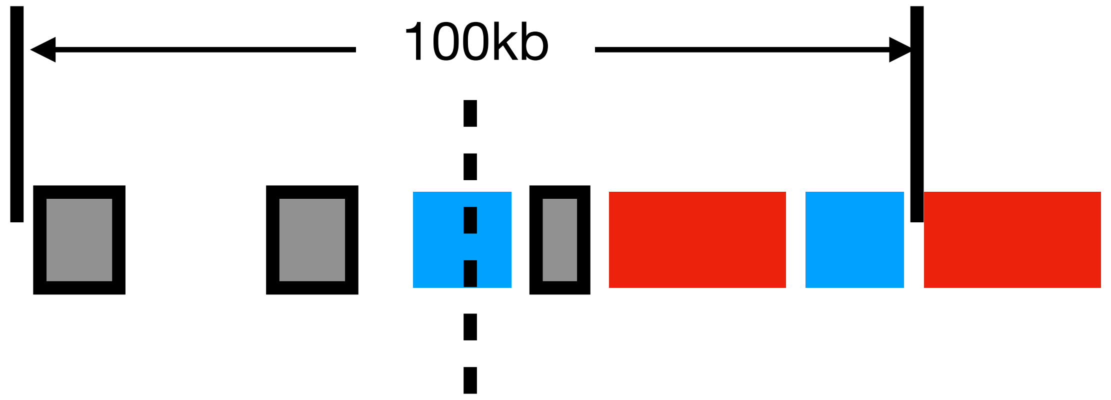


ChromHMM: Chromatin state discovery and characterization

Step2: Find quiescent control

▨ “neutral control”: quiescent



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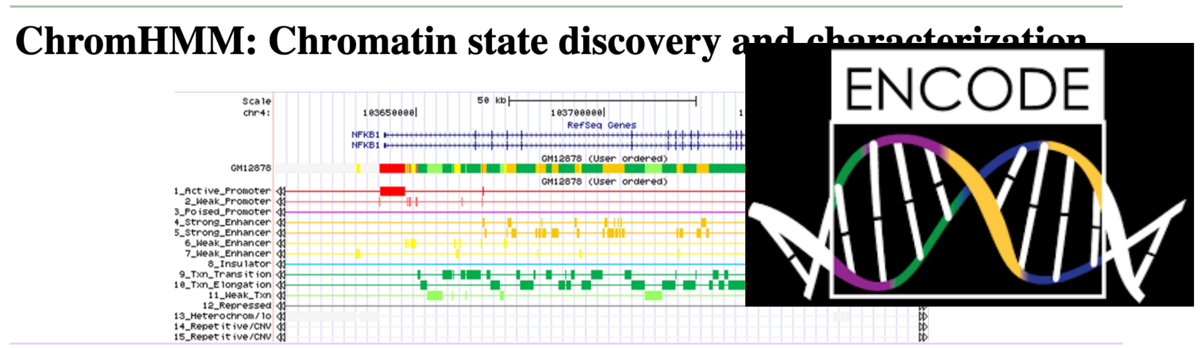
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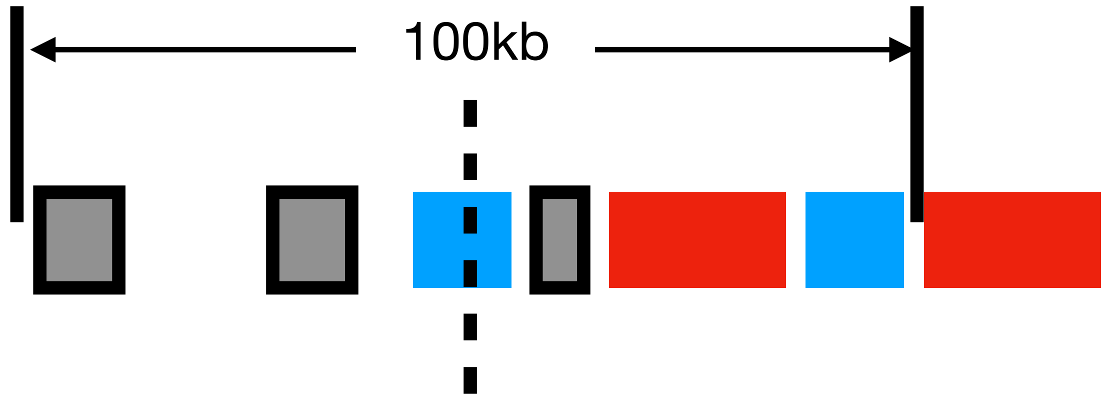
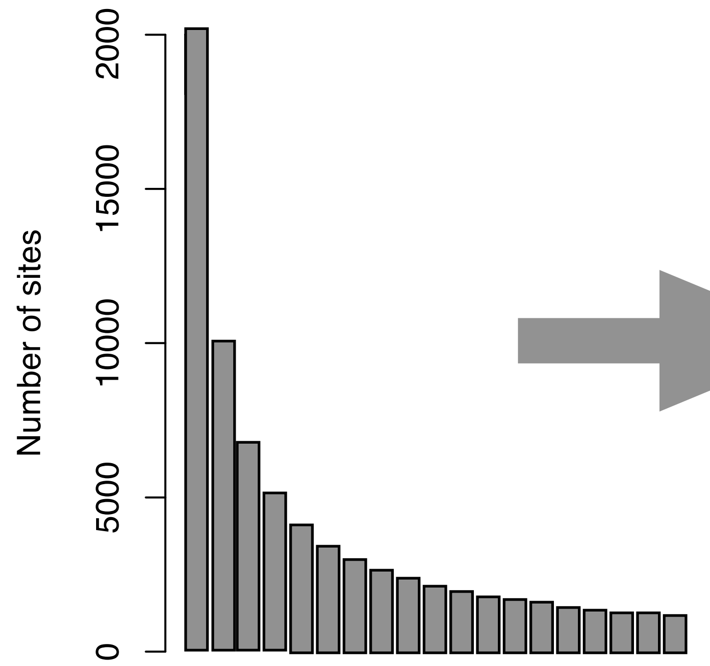
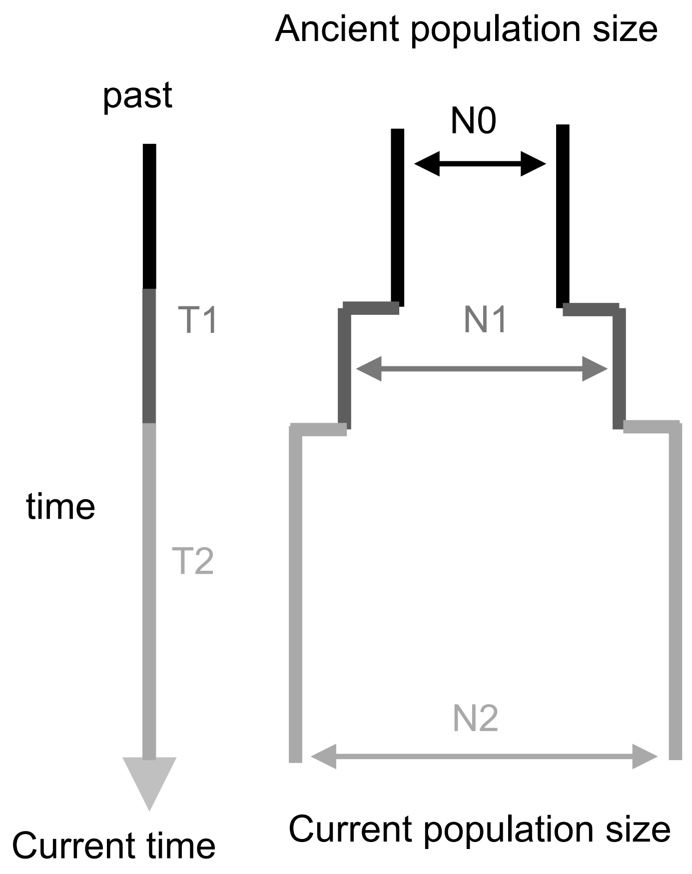


Step3: Infer demographic model





Workflow

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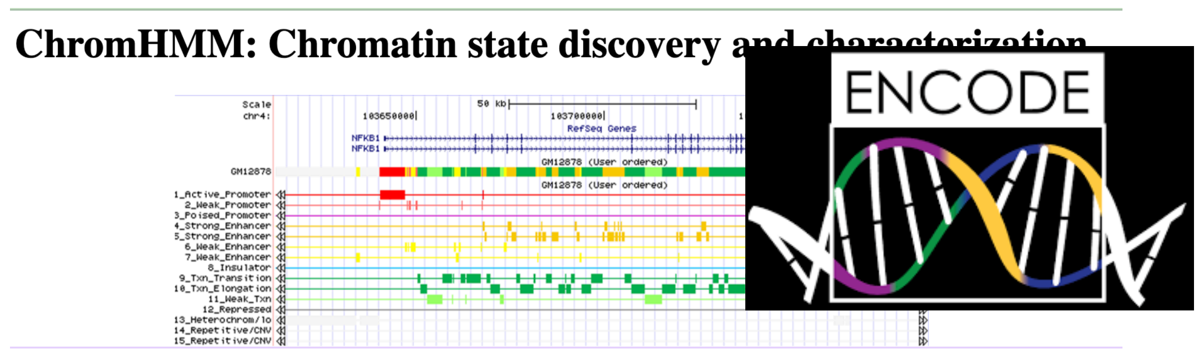
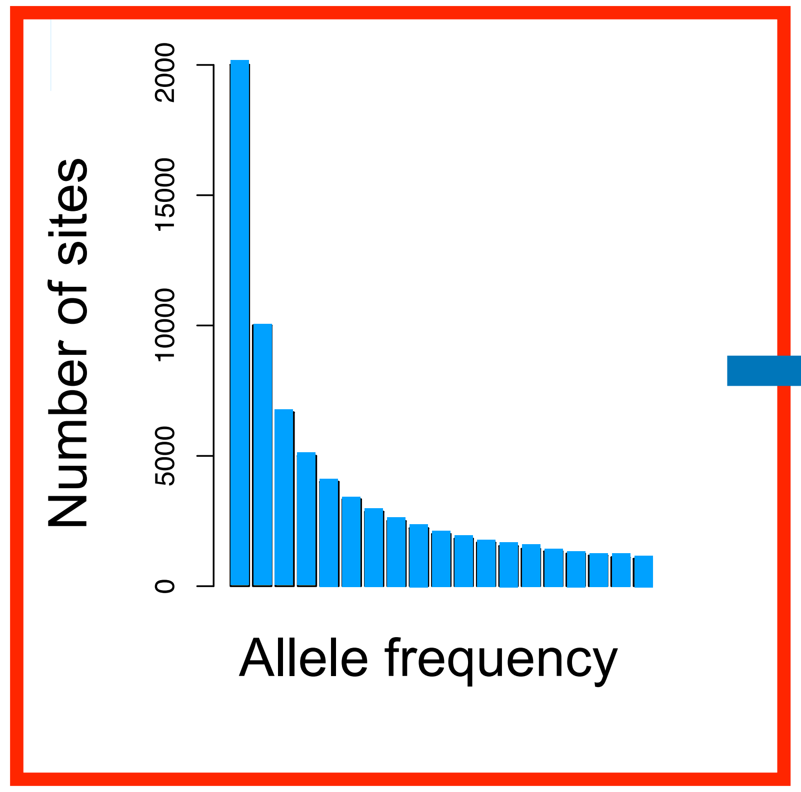


ChromHMM: Chromatin state discovery and characterization

Step4: Infer Distribution of Fitness Effecs (DFE)



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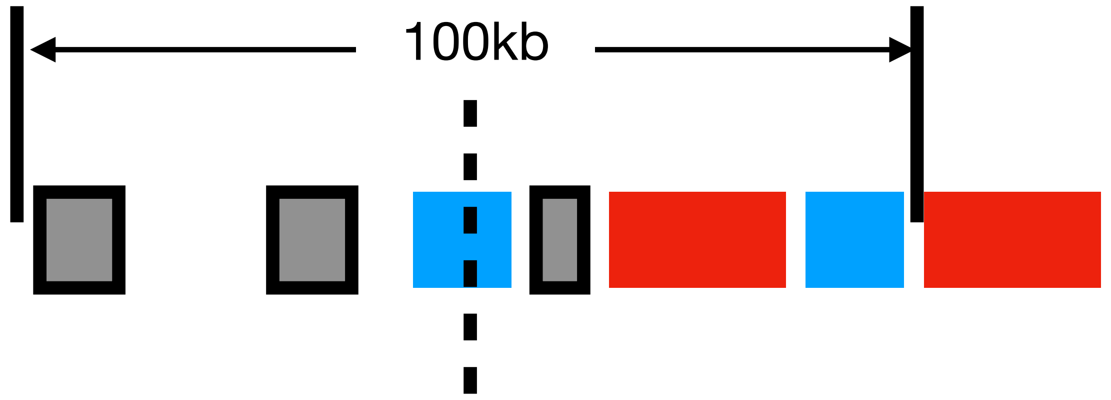

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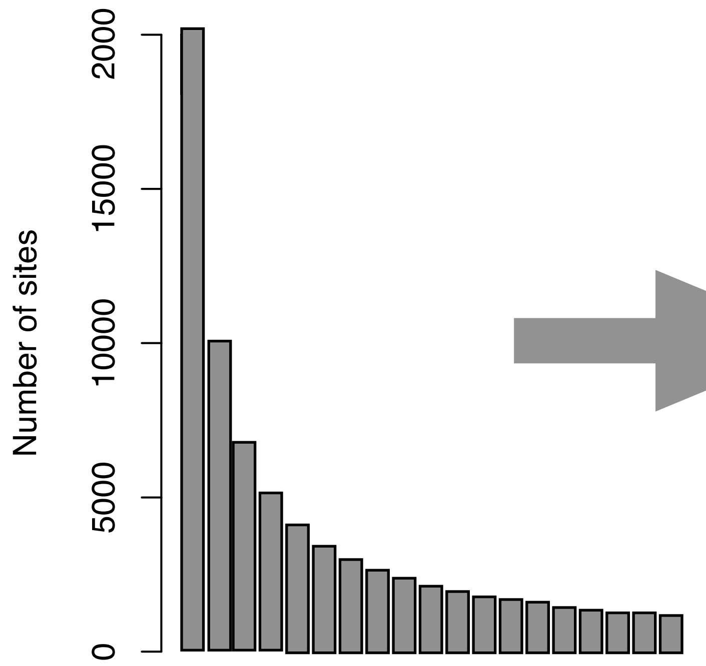
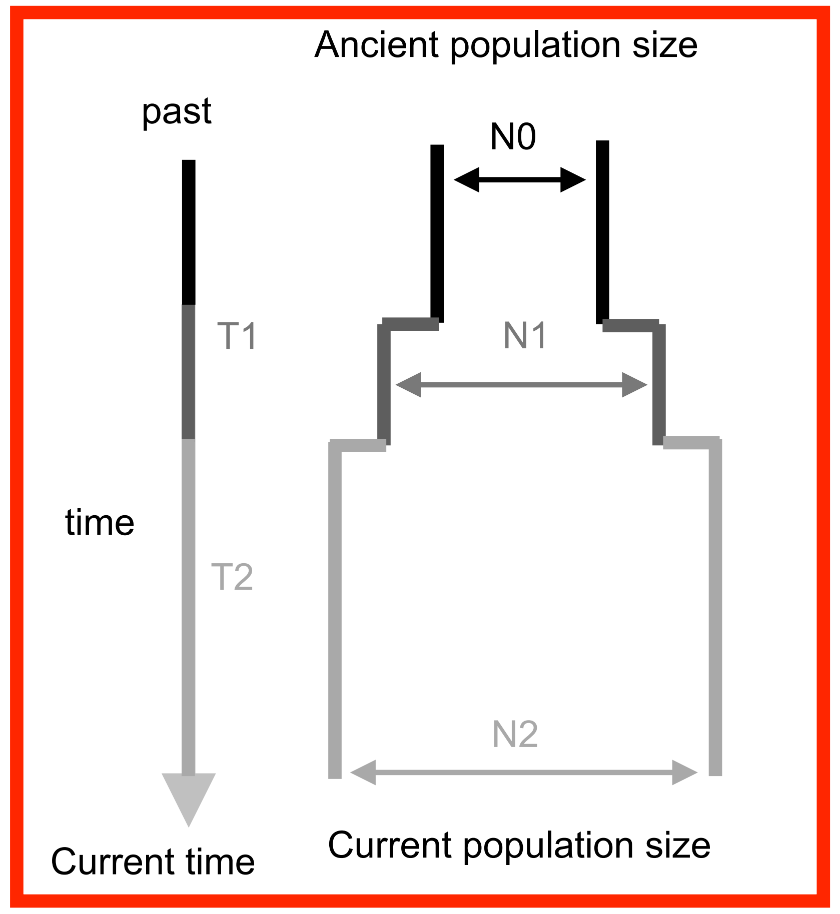
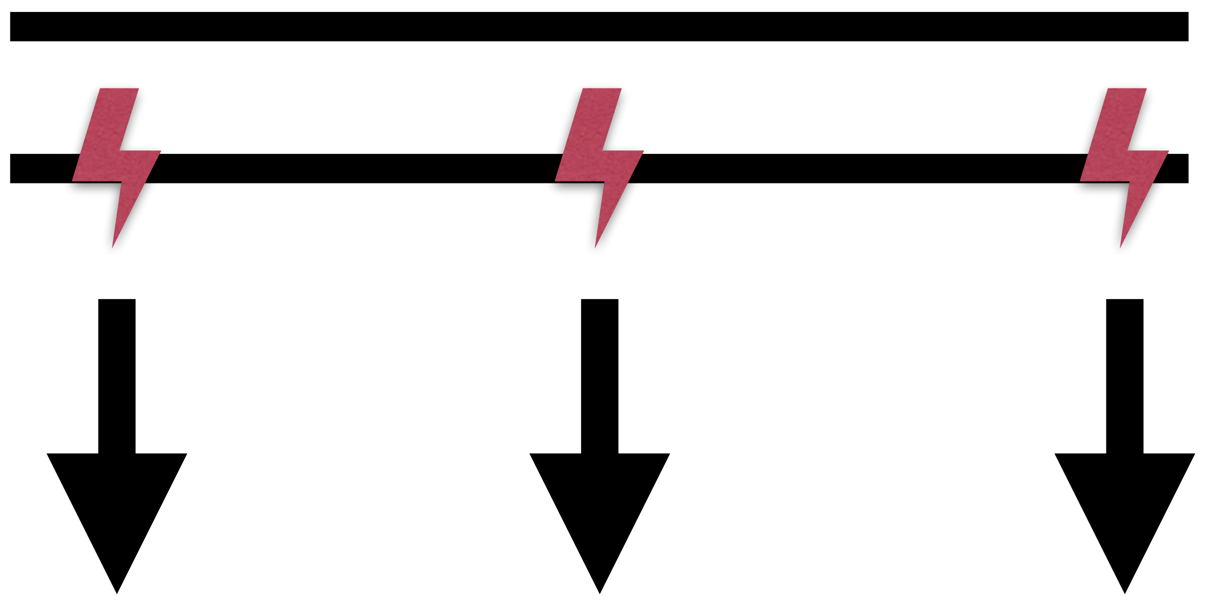




Fit-dadi: models of demographic history and natural selection

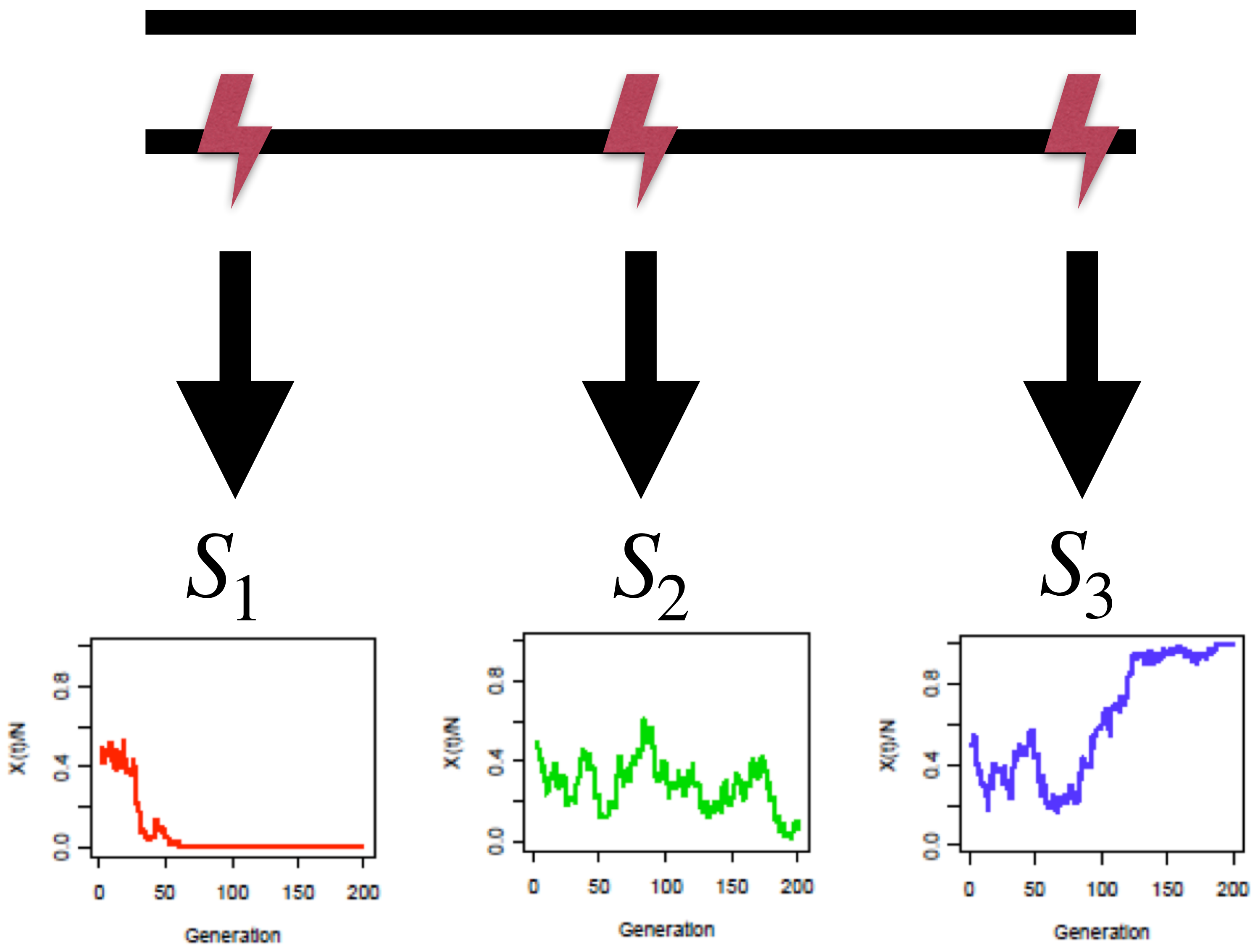


Sequence with L bases

mutations~Poisson(λ=2$N\mu L$)

Gutenkunst et al., 2009; Kim et al., 2017

Fit-dadi: models of demographic history and natural selection



Sequence with L bases

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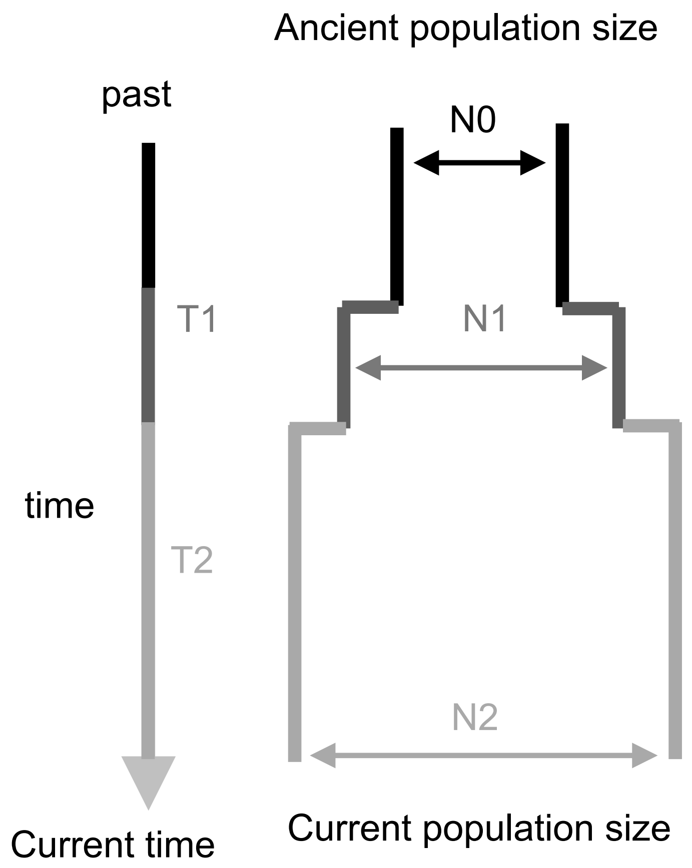
Frequency of each mutation follows the: Wright-Fisher and inferred demographic model



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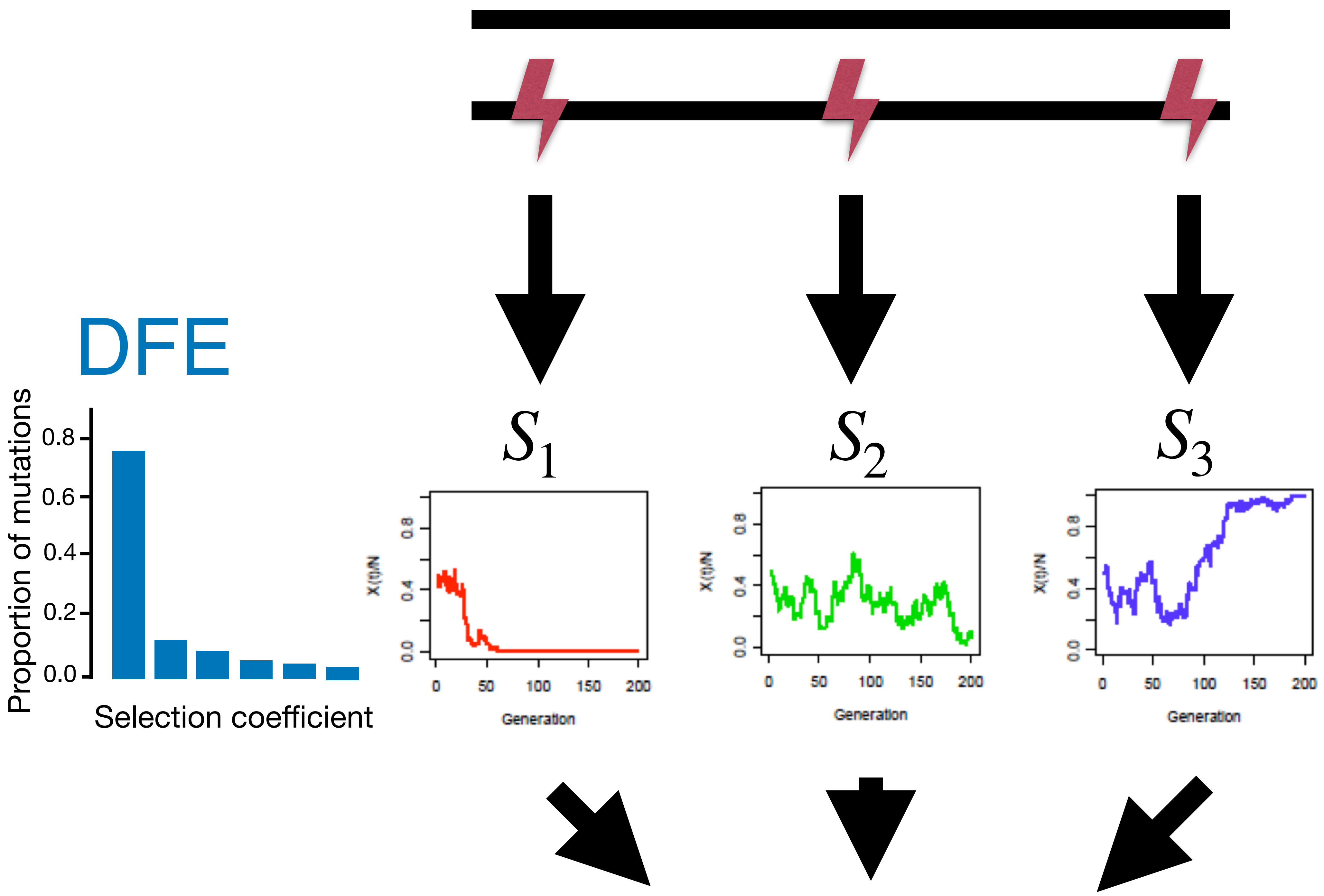

Sequence with *L* bases

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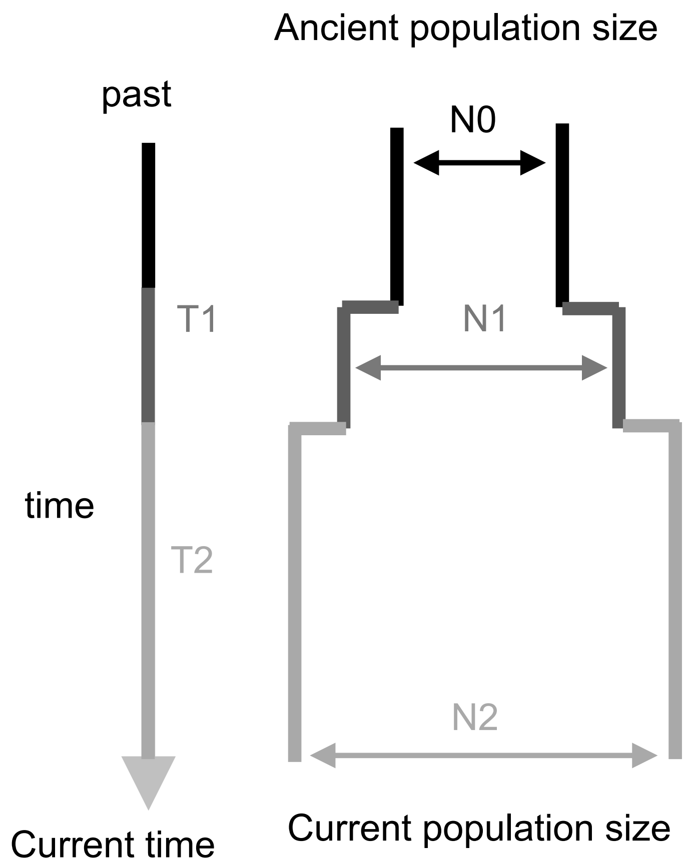
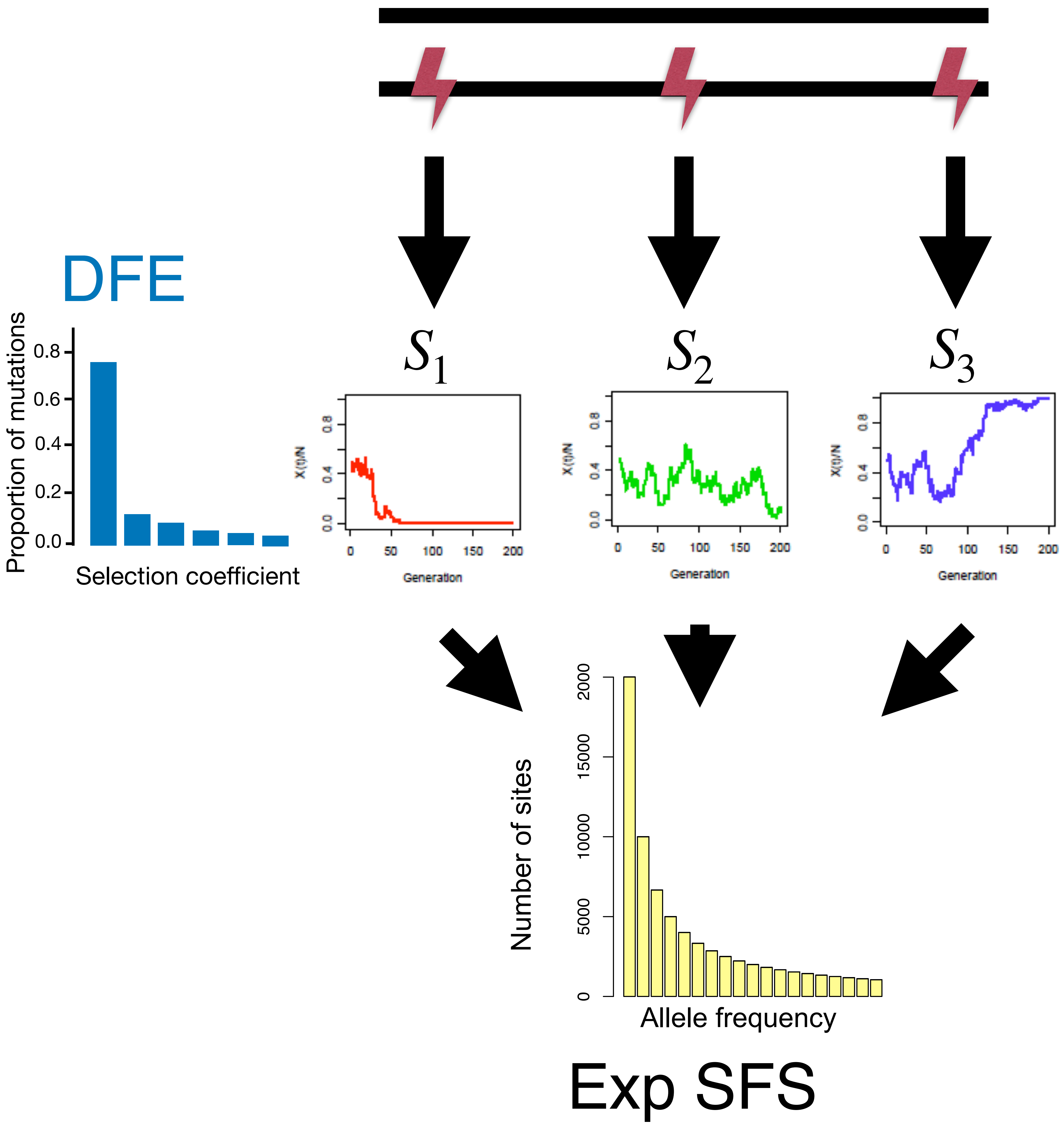


Parameter: Distribution of Fitness effects

Gutenkunst et al., 2009; Kim et al., 2017

Fit-dadi: models of demographic history and natural selection



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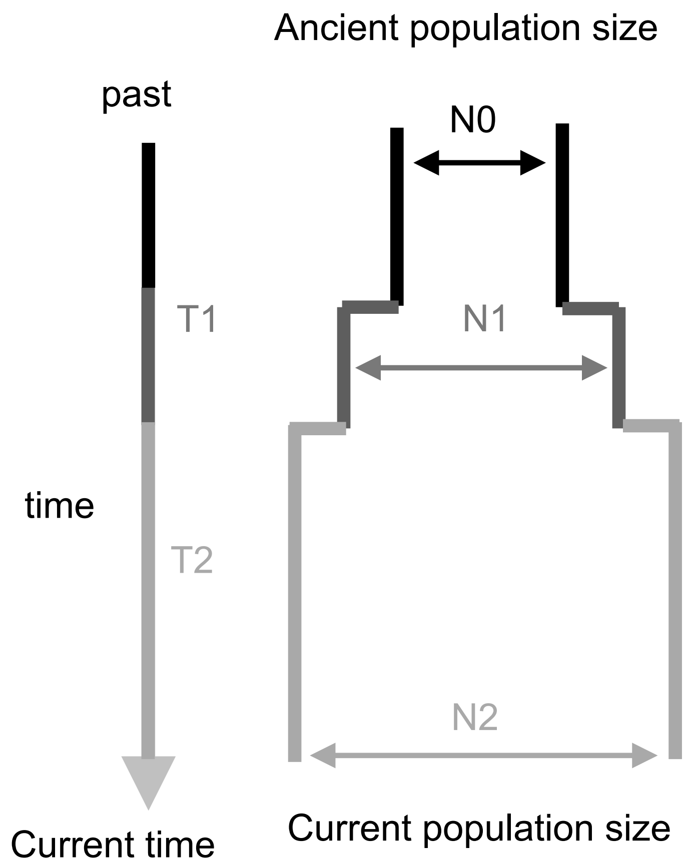
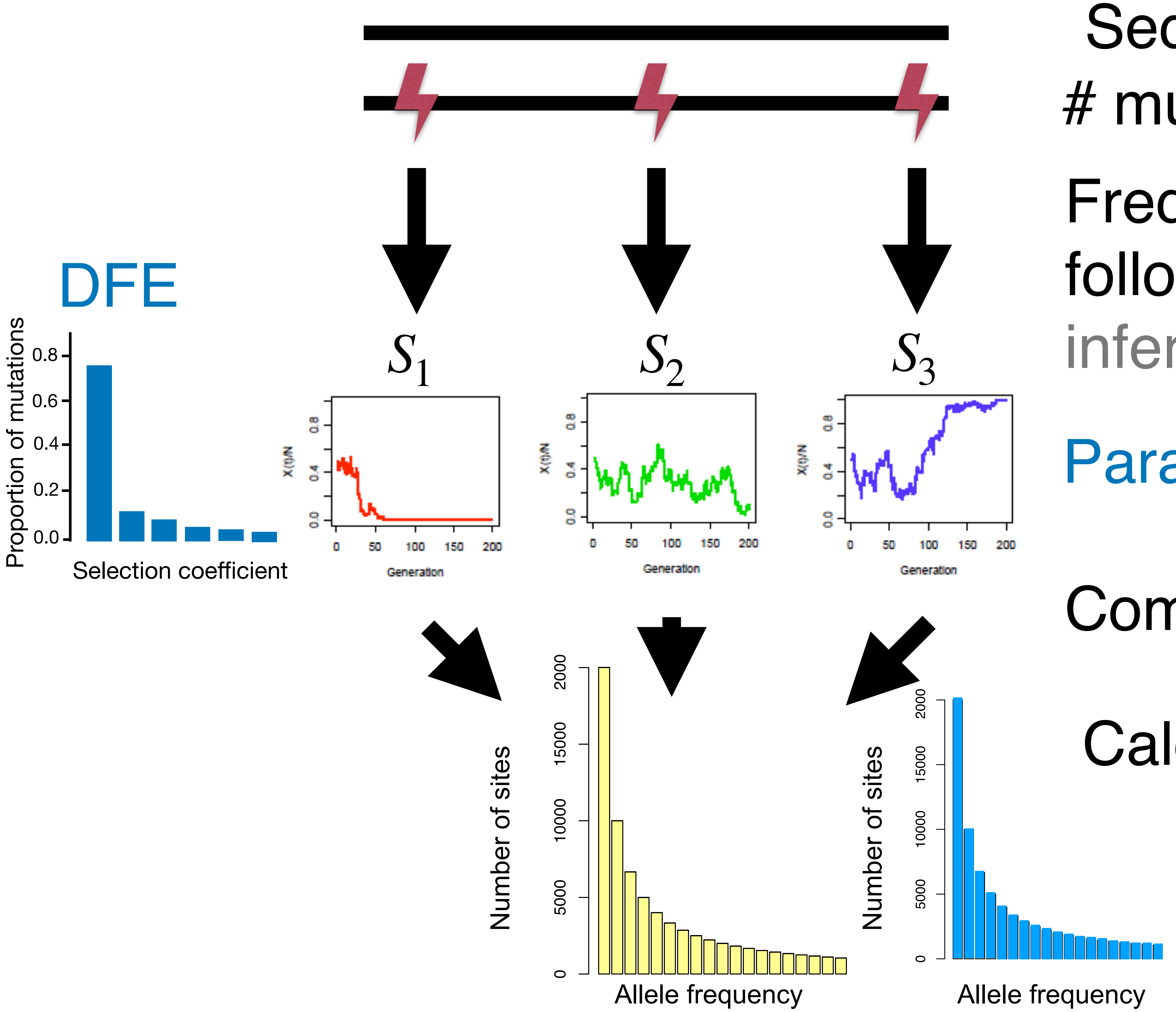


Parameter: Distribution of Fitness effects

Combine mutations to make SFS

Gutenkunst et al., 2009; Kim et al., 2017

dadi: models of demographic history and natural selection



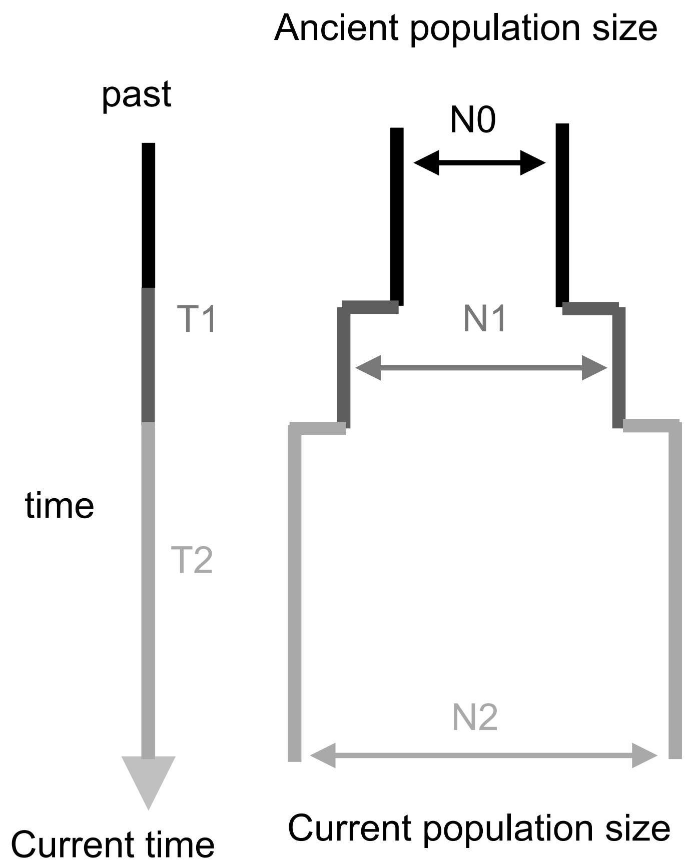
Exp SFS

Obs SFS from non-coding region

Sequence with *L* bases

\# mutations~Poisson($\lambda=2N\mu L$)

Frequency of each mutation follows the: Wright-Fisher and inferred demographic model



Parameter: Distribution of Fitness effects

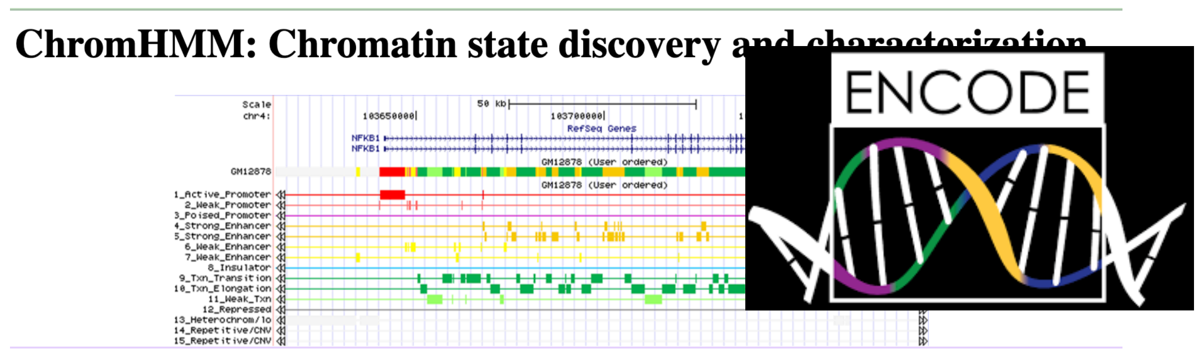
Combine mutations to make SFS

Calculate likelihood of models

Workflow

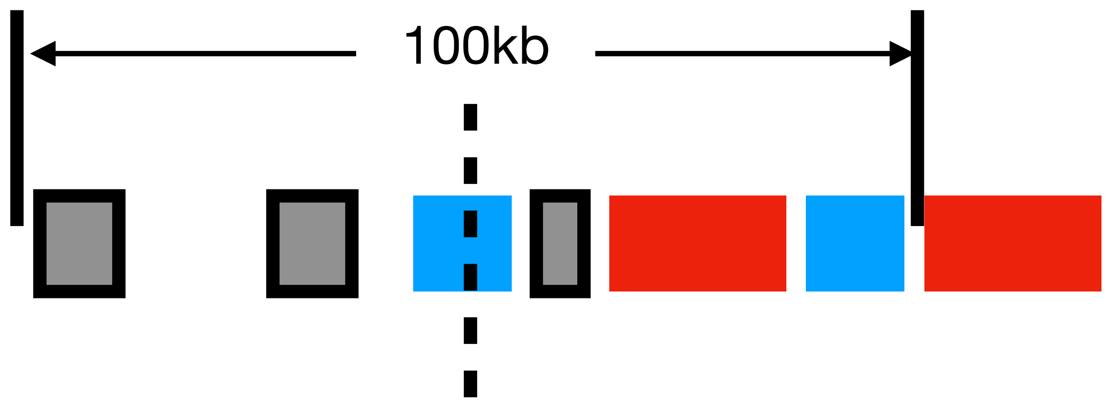
Step1: Annotate genomic regions

🟦 Target non-coding region

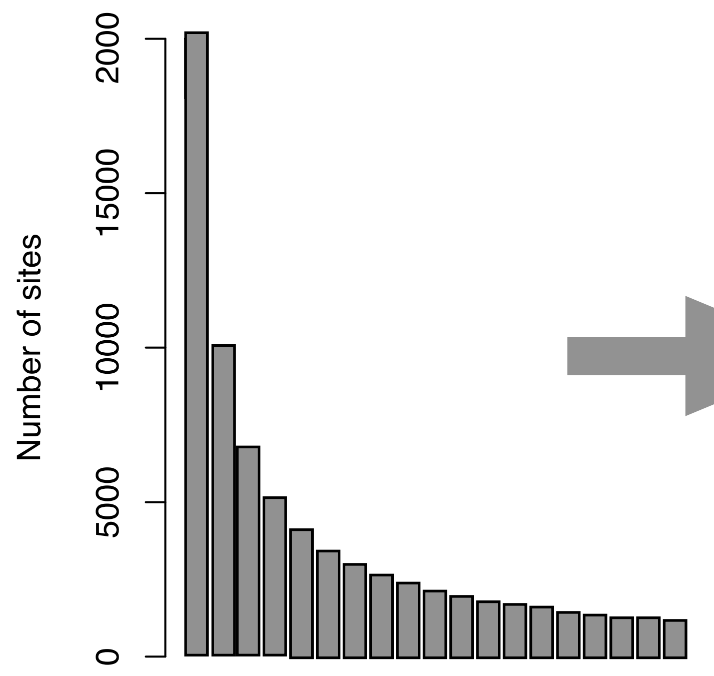


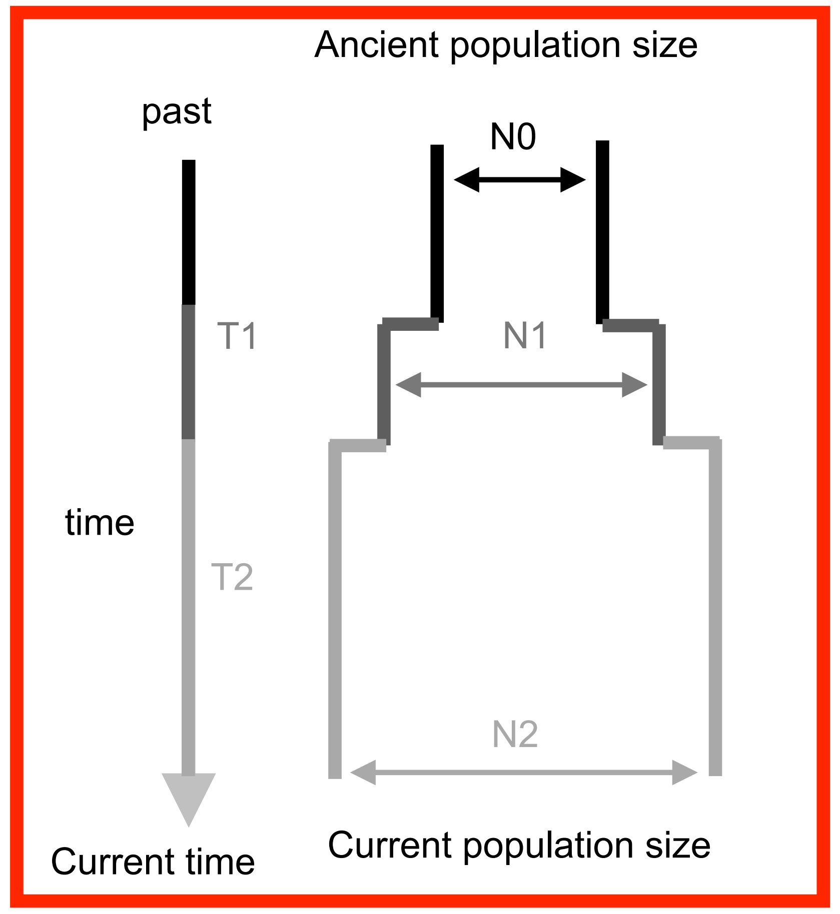
Step2: Find quiescent control

▨ "neutral control": quiescent

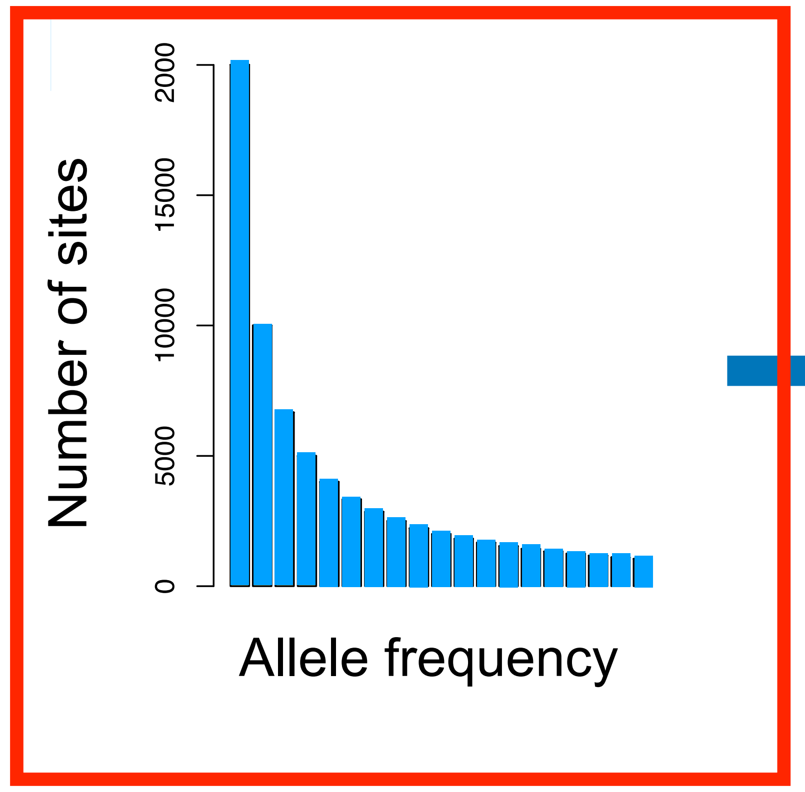


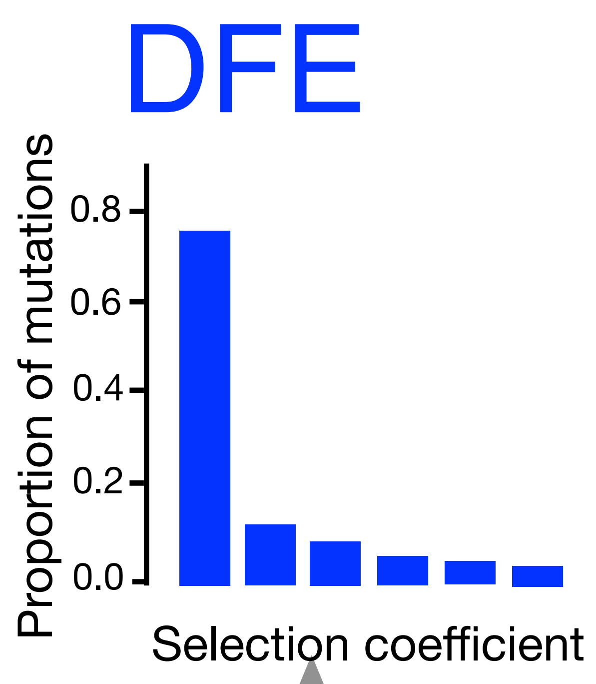
Step3: Infer demographic model



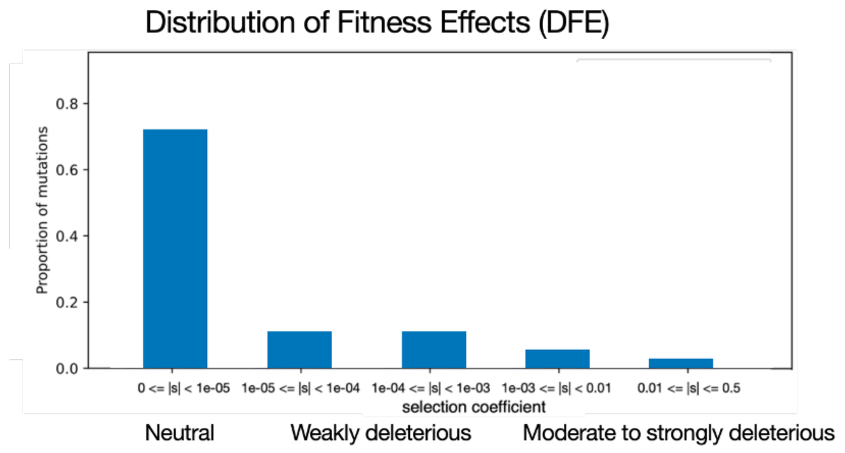


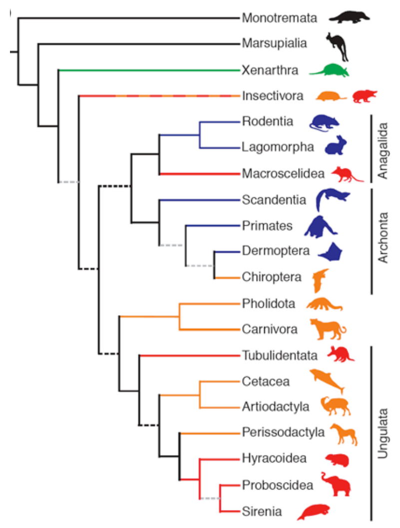
Step4: Infer Distribution of Fitness Effecs (DFE)





DFE of non-coding mutations

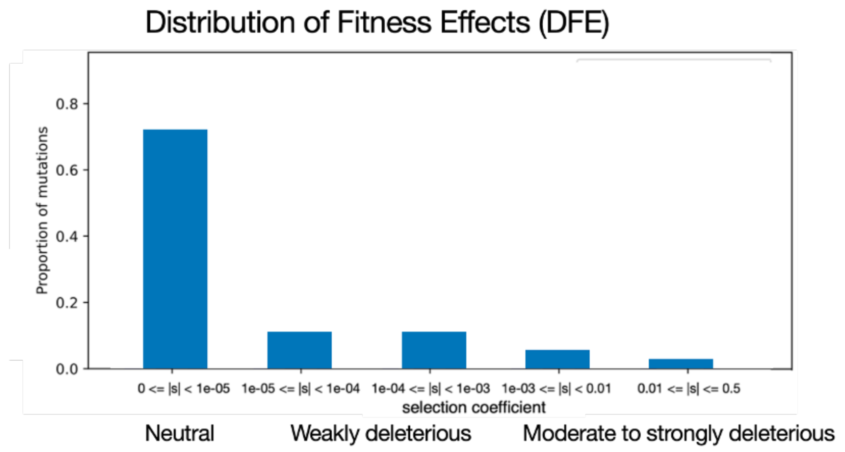


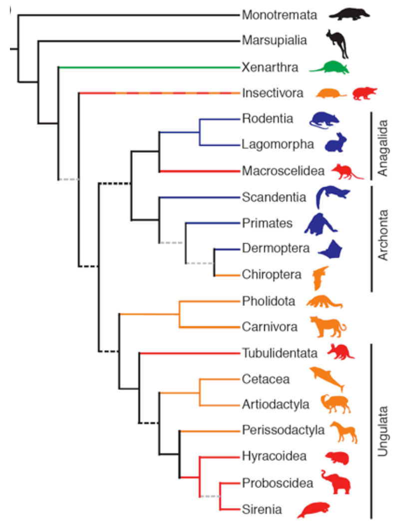


- Model-based method for inferring Distribution of Fitness effects (DFE)
- DFE of annotated functional non-coding regions in human genome
- Negative selection in conserved and non-conserved human genomic region

picture is from https://www.phonandroid.com/tesla-continue-de-decliner-le-cybertruck-a-toutes-les-sauces-avec-un-marteau-de-gym.html
Phylogeny is from Springer et al., 2004

DFE of non-coding mutations





- Model-based method for inferring Distribution of Fitness effects (DFE)
- DFE of annotated functional non-coding regions in human genome
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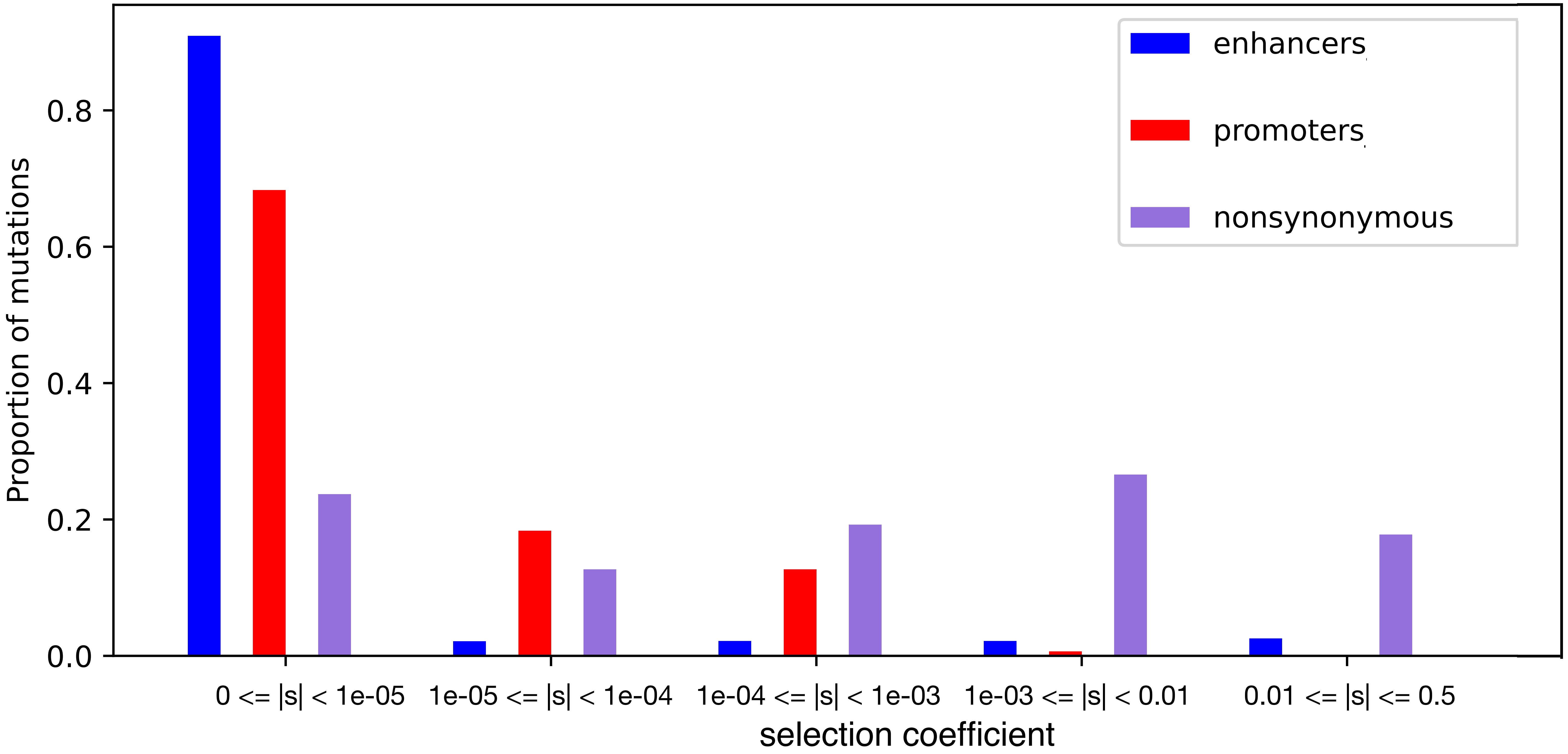
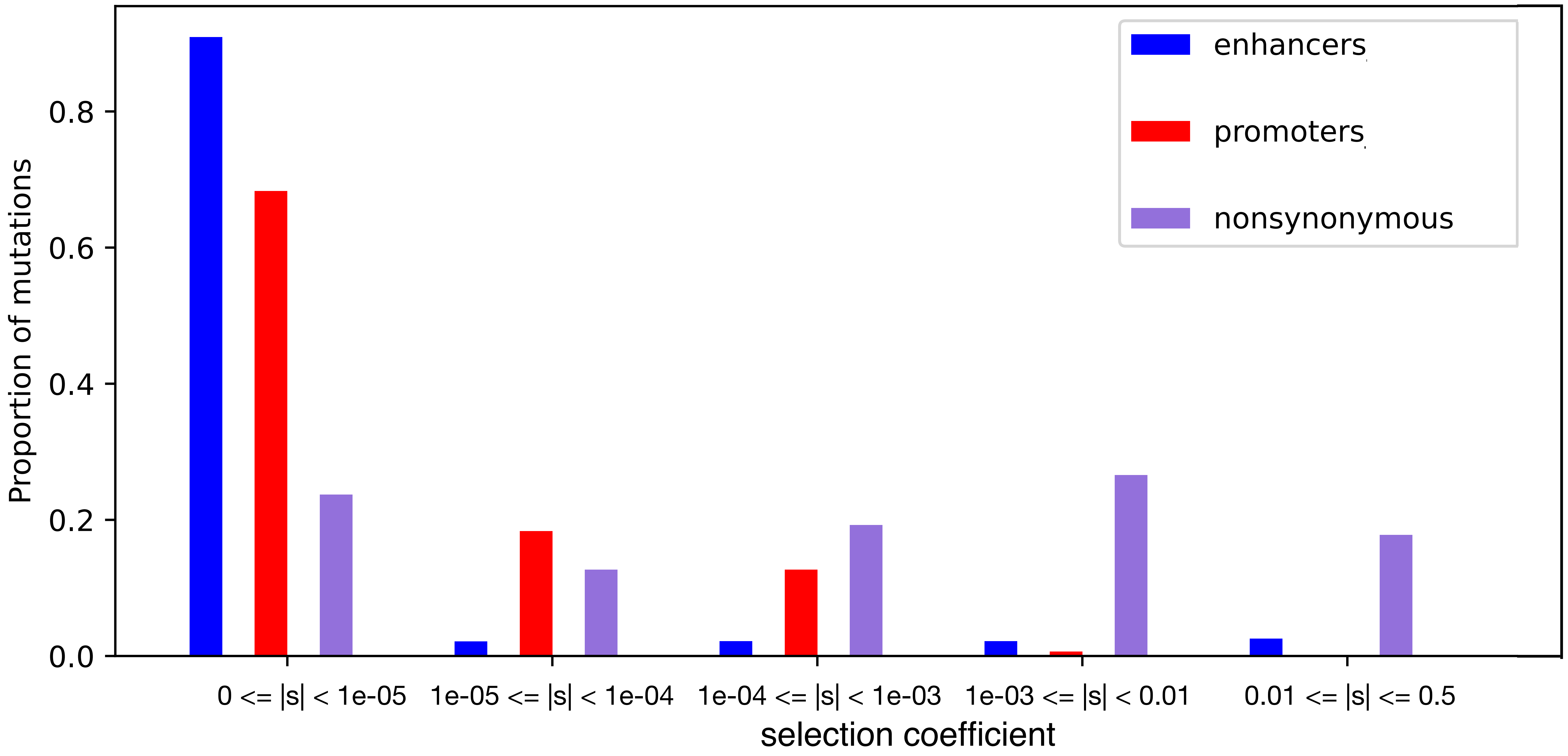
Phylogeny is from Springer et al., 2004

DFE of enhancers and promoters



DFE of non-synonymous sites from Kim et al., 2017, 1KG, EUR

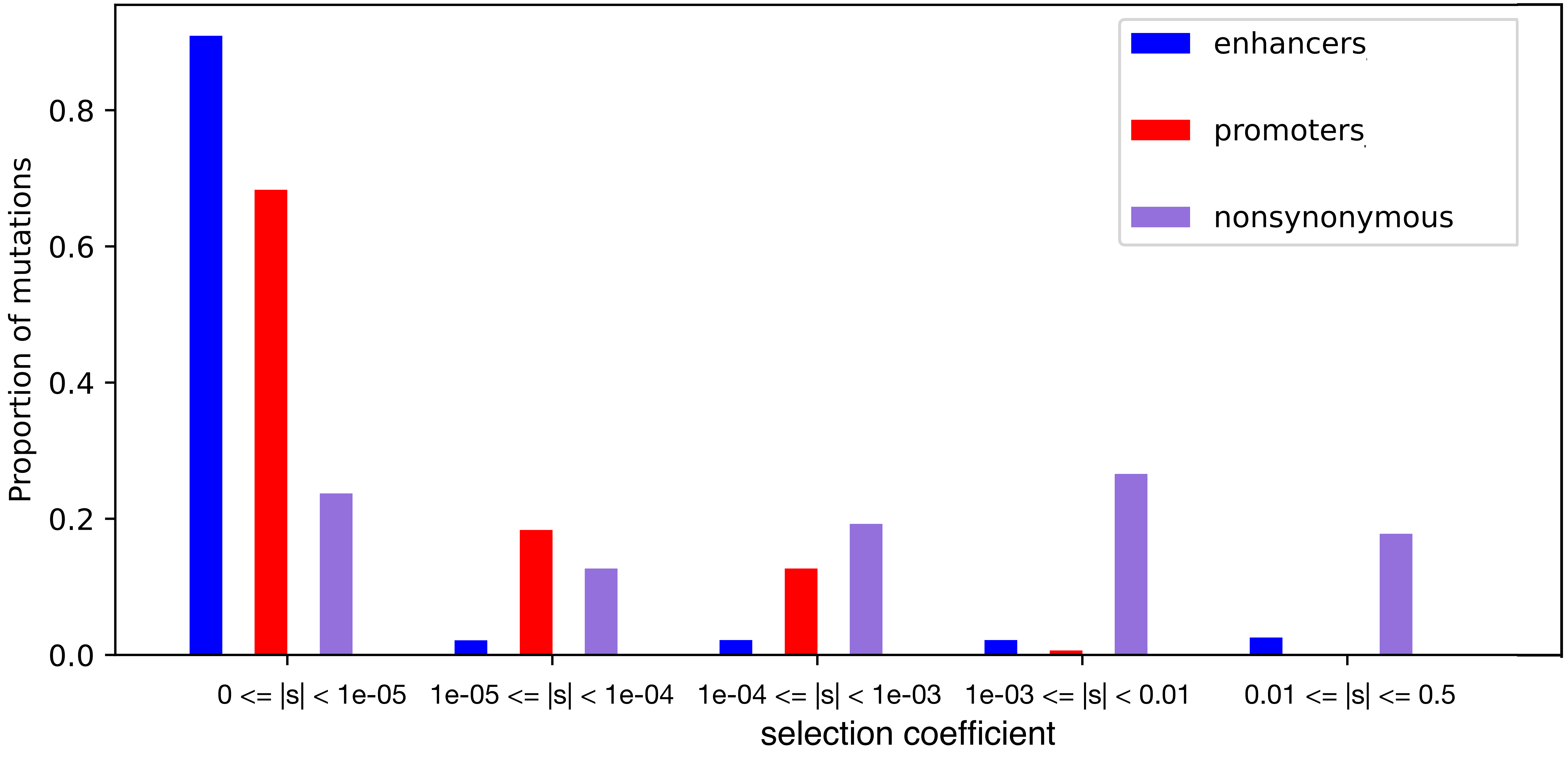
DFE of enhancers and promoters



Neutral

DFE of non-synonymous sites from Kim et al., 2017, 1KG, EUR

DFE of enhancers and promoters

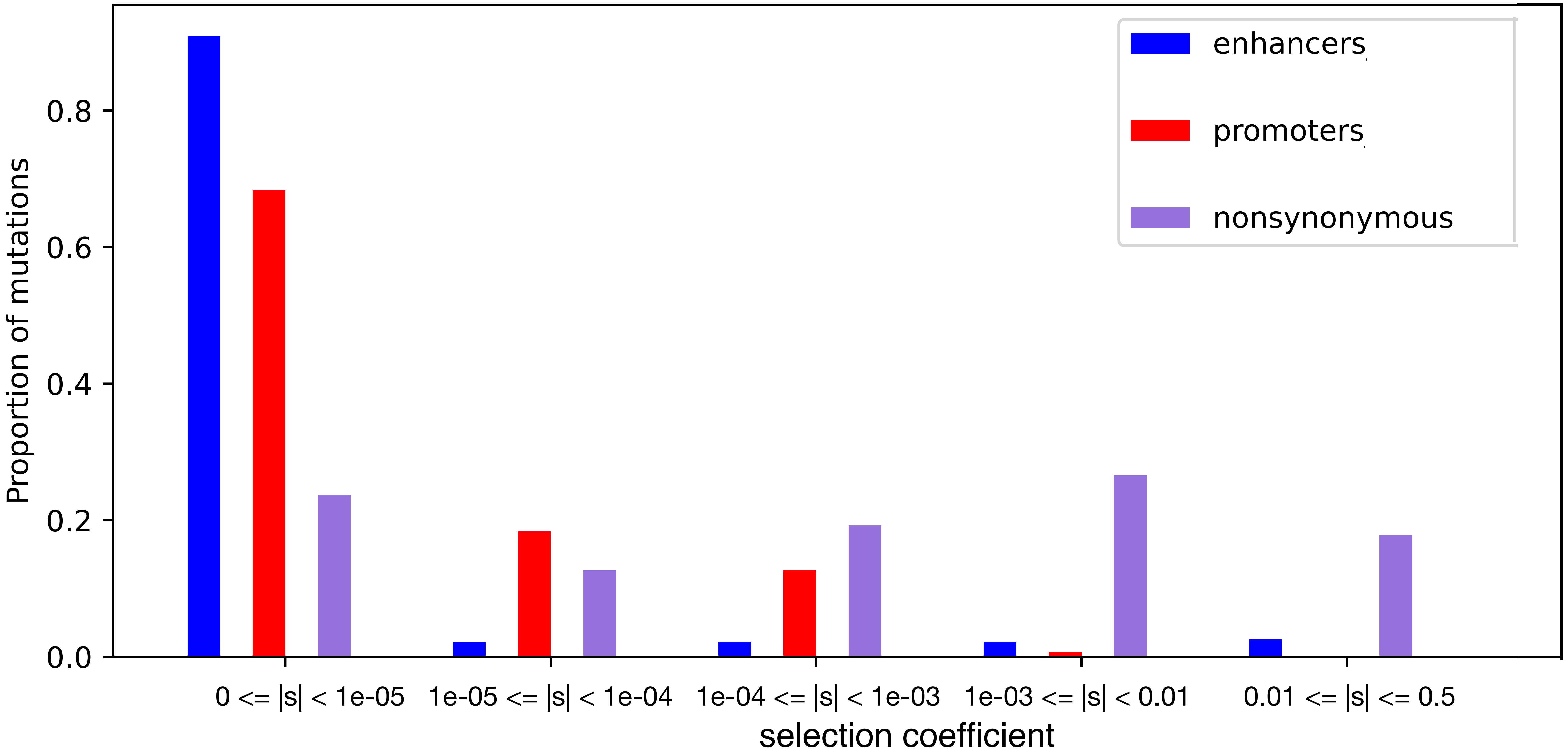


Neutral

enhancers > promoters

DFE of non-synonymous sites from Kim et al., 2017, 1KG, EUR

DFE of enhancers and promoters



Neutral

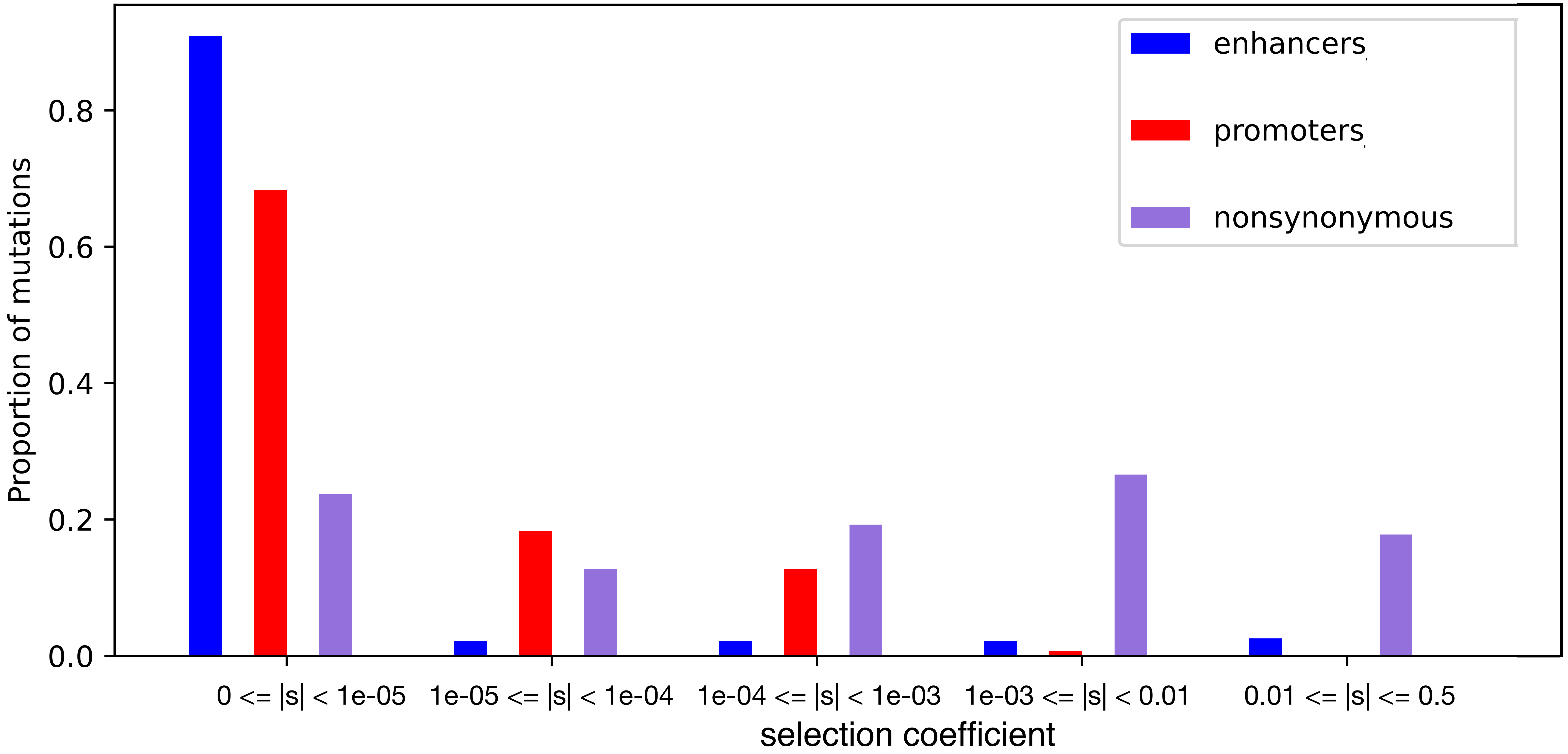
enhancers > promoters

Weakly deleterious

promoters > enhancers

DFE of non-synonymous sites from Kim et al., 2017, 1KG, EUR

DFE of enhancers and promoters



Neutral

enhancers > promoters

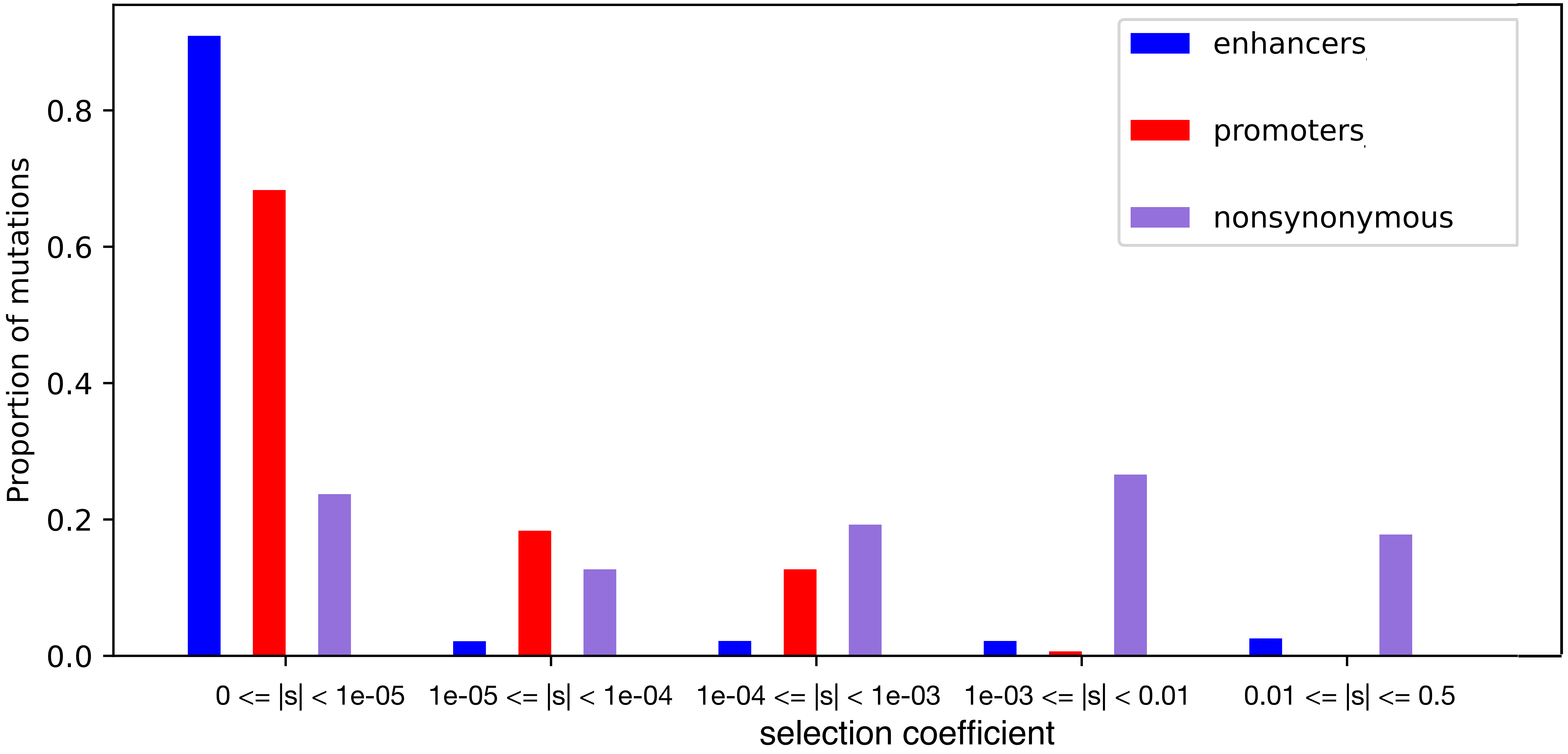
Weakly deleterious

promoters > enhancers

Moderate to strongly deleterious

DFE of non-synonymous sites from Kim et al., 2017, 1KG, EUR

DFE of enhancers and promoters



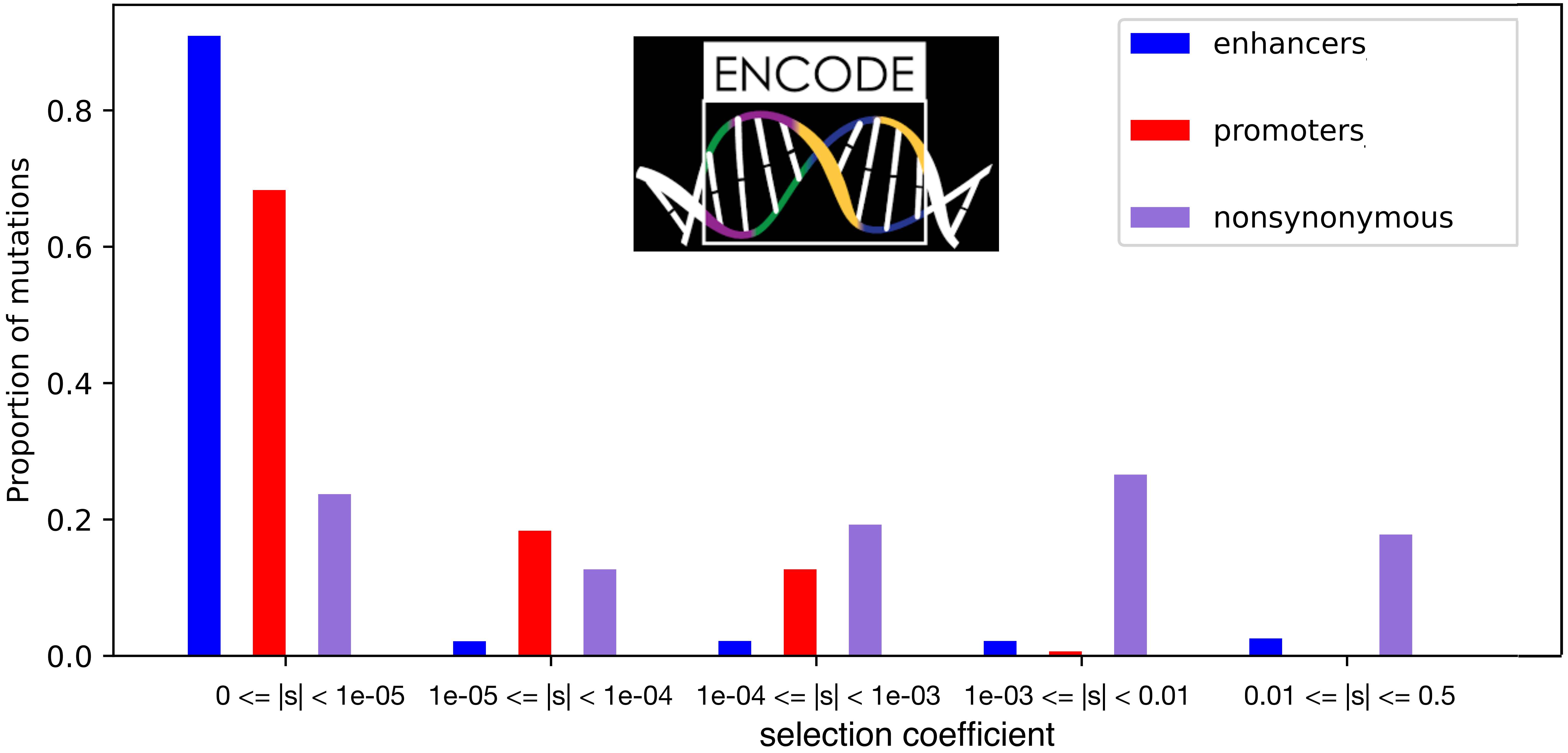
Neutral
enhancers > promoters

Weakly deleterious
promoters > enhancers

Moderate to strongly deleterious
small proportion

DFE of non-synonymous sites from Kim et al., 2017, 1KG, EUR

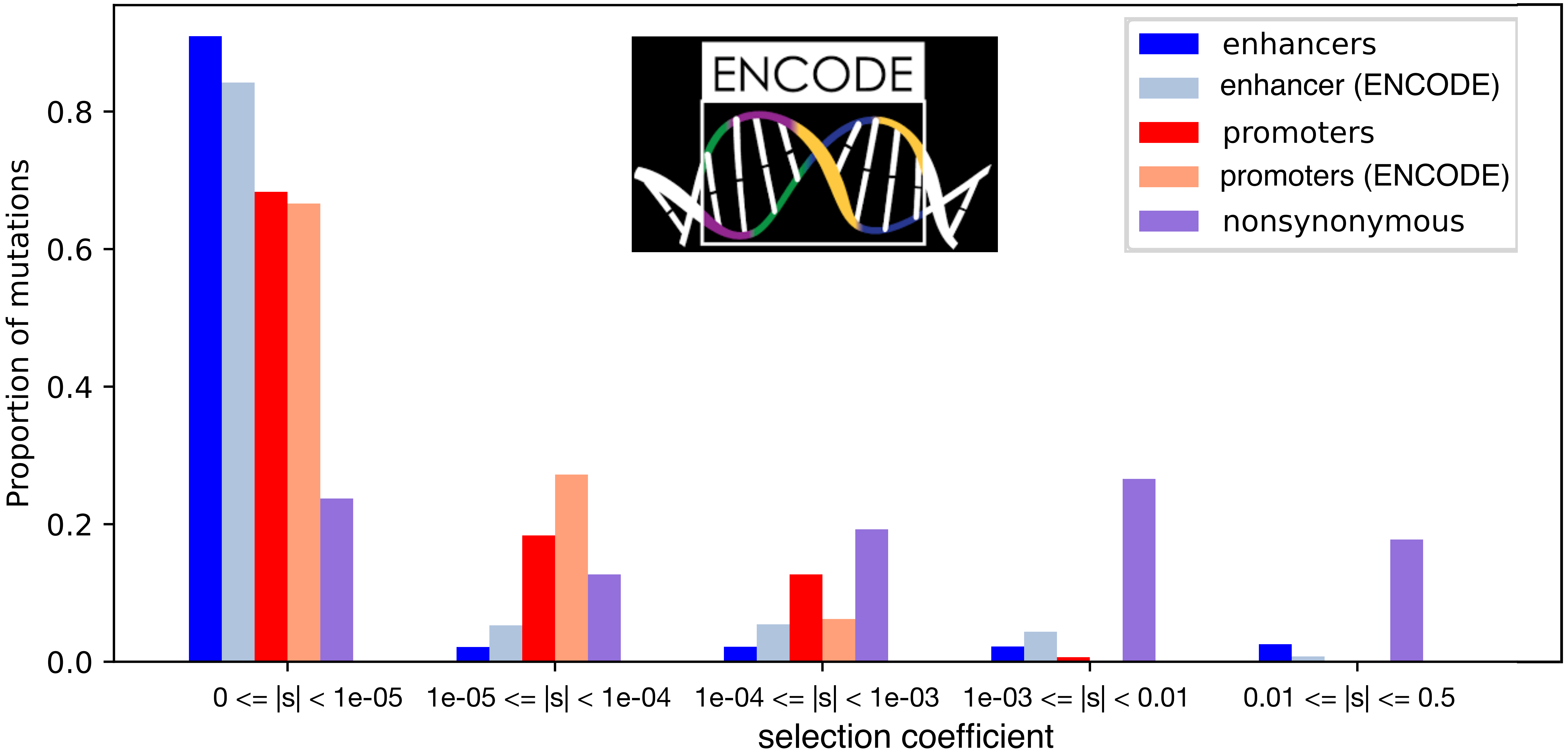
DFE of enhancers and promoters



Neutral	Weakly deleterious	Moderate to strongly deleterious
enhancers > promoters	promoters > enhancers	small proportion

DFE of non-synonymous sites from Kim et al., 2017, 1KG, EUR

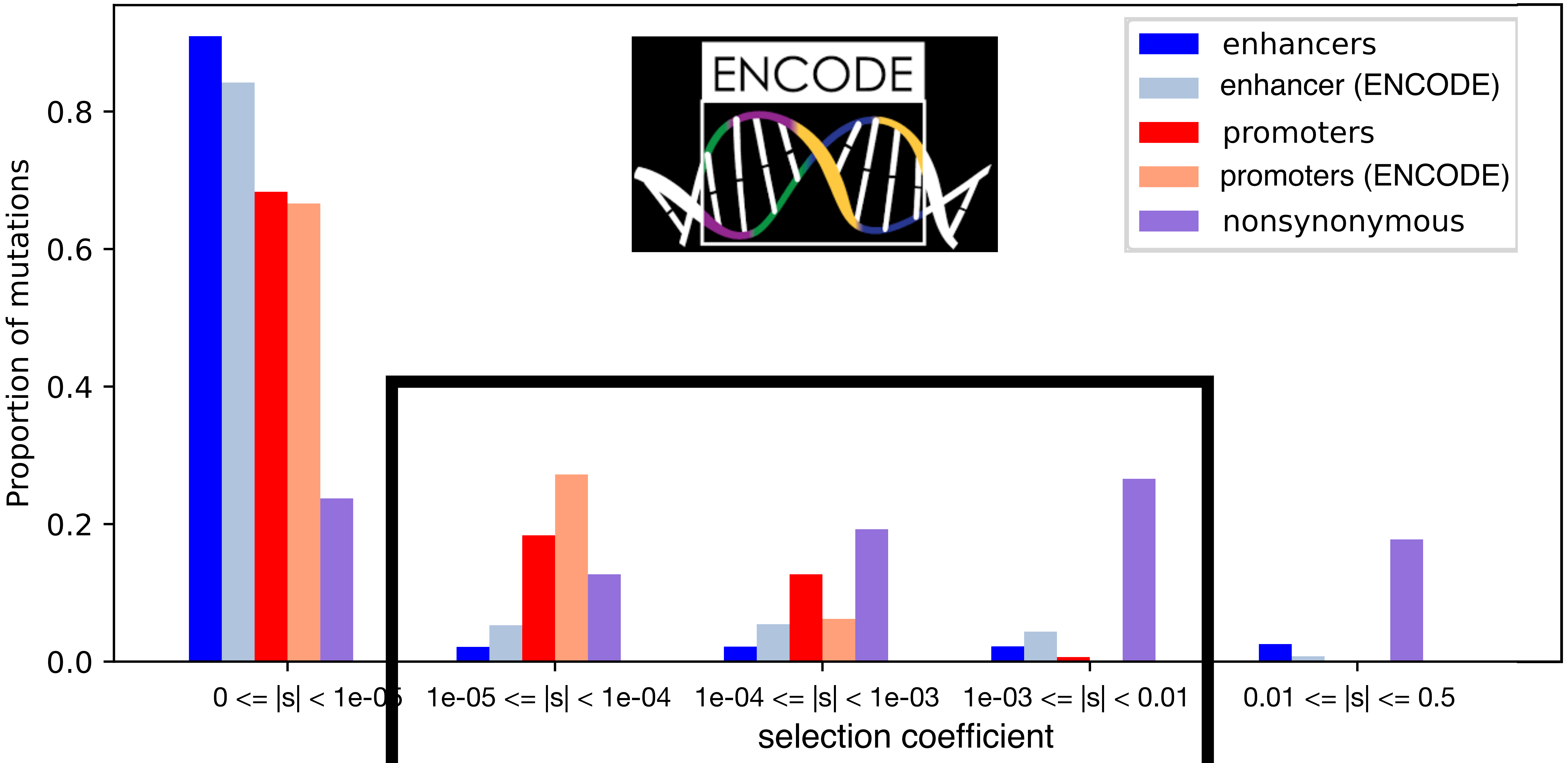
DFE of enhancers and promoters



Neutral	Weakly deleterious	Moderate to strongly deleterious
enhancers > promoters	promoters > enhancers	small proportion

DFE of non-synonymous sites from Kim et al., 2017, 1KG, EUR

DFE of enhancers and promoters



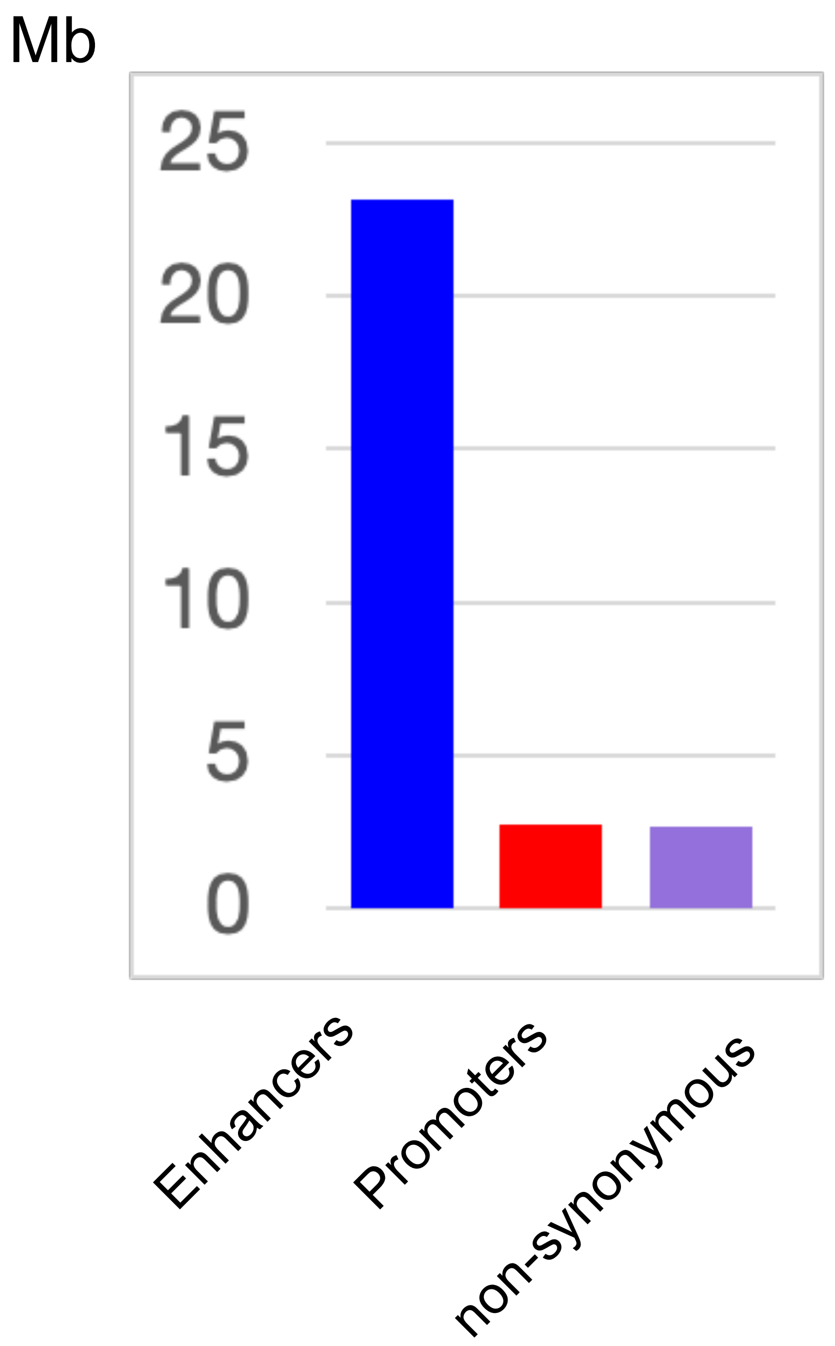
Neutral Weakly deleterious Moderate to strongly deleterious

enhancers > promoters promoters > enhancers small proportion

DFE of non-synonymous sites from Kim et al., 2017, 1KG, EUR

Large number of deleterious mutations

number of sites



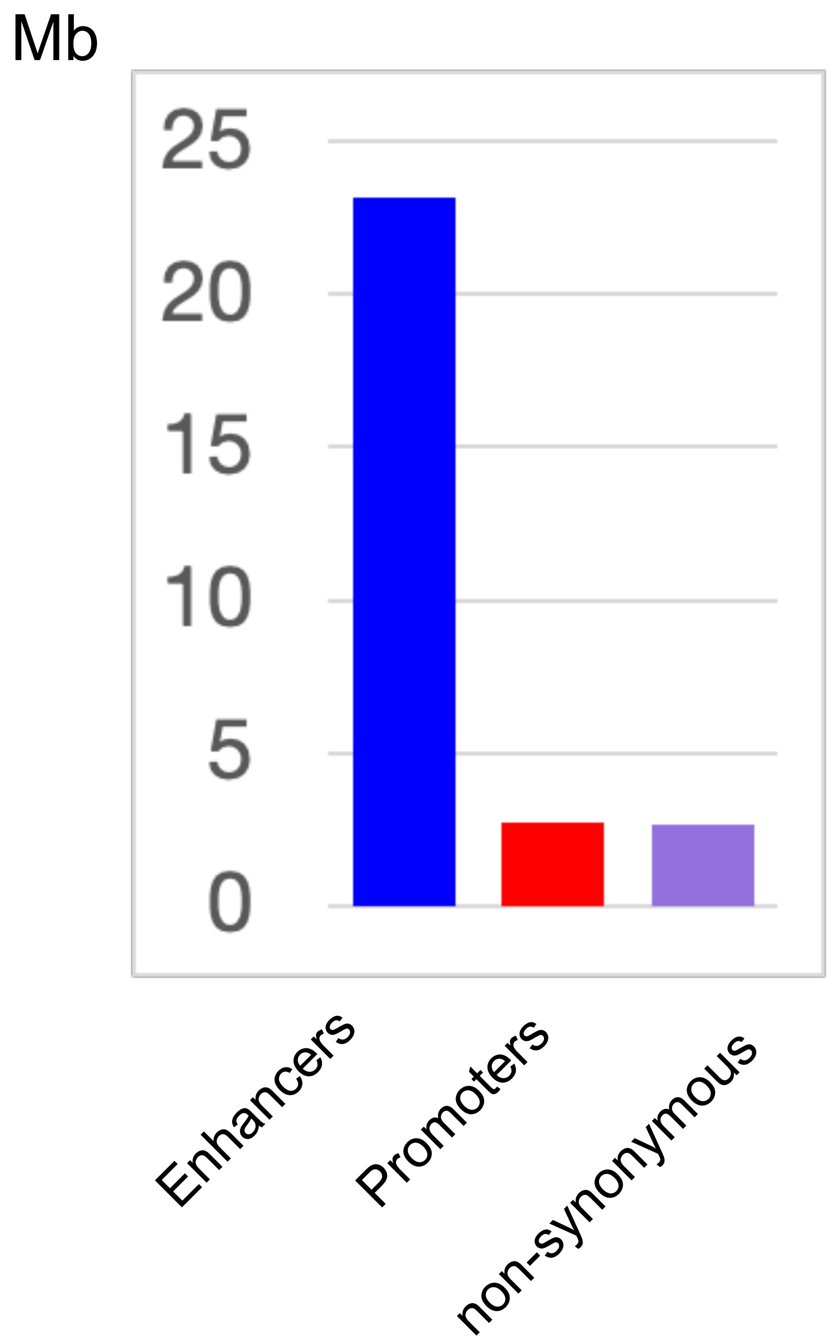
Large number of deleterious mutations

of mutations

$= L \times \mu$

L ↓ number of sites

μ ↓ mutation rate



Large number of deleterious mutations

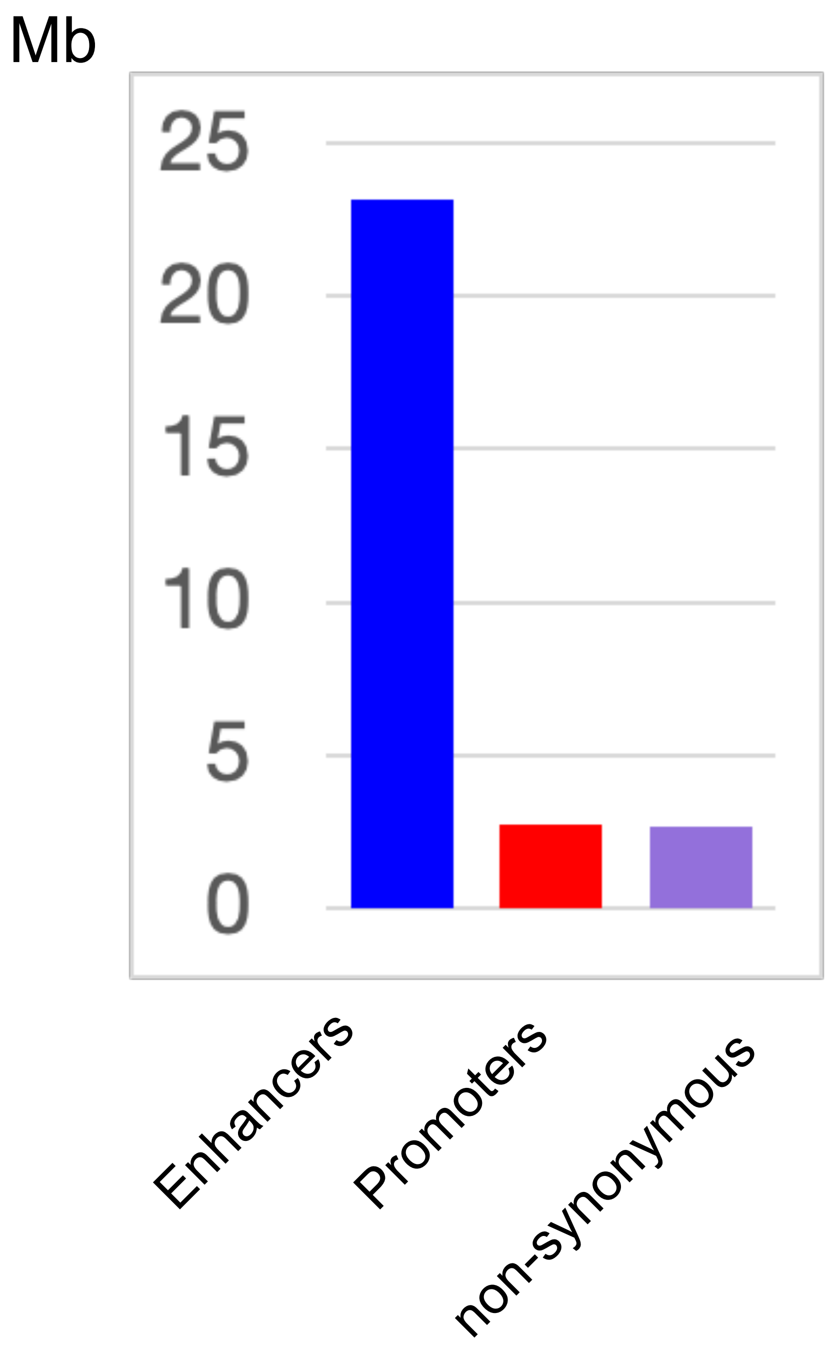
of mutations with given S

$$= L \times \mu \times P(s)$$

L ↓ number of sites

μ ↓ mutation rate

$P(s)$ ↓ probability of mutations with selection coefficient *s*



Large number of deleterious mutations

of mutations with given S

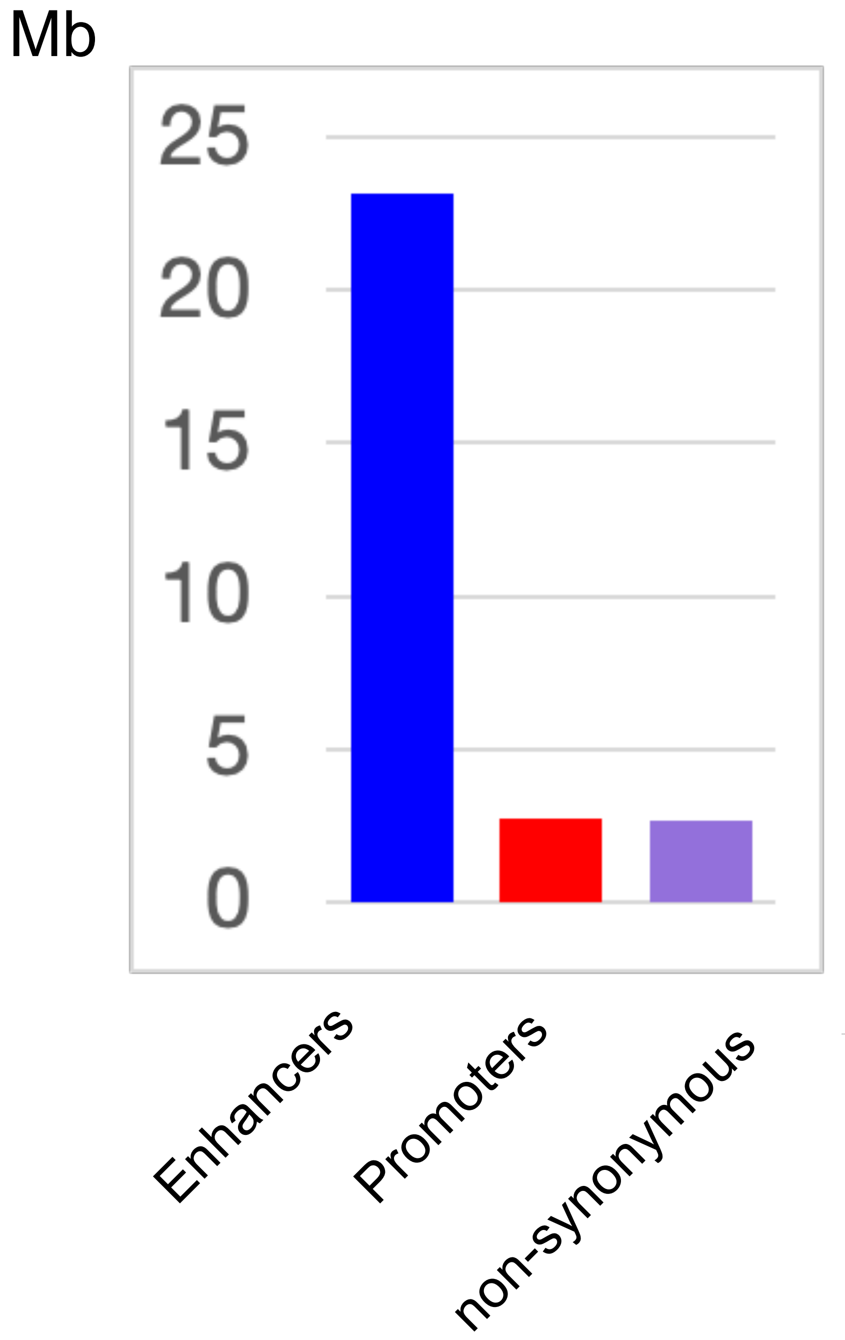
= L × μ × $P(s)$

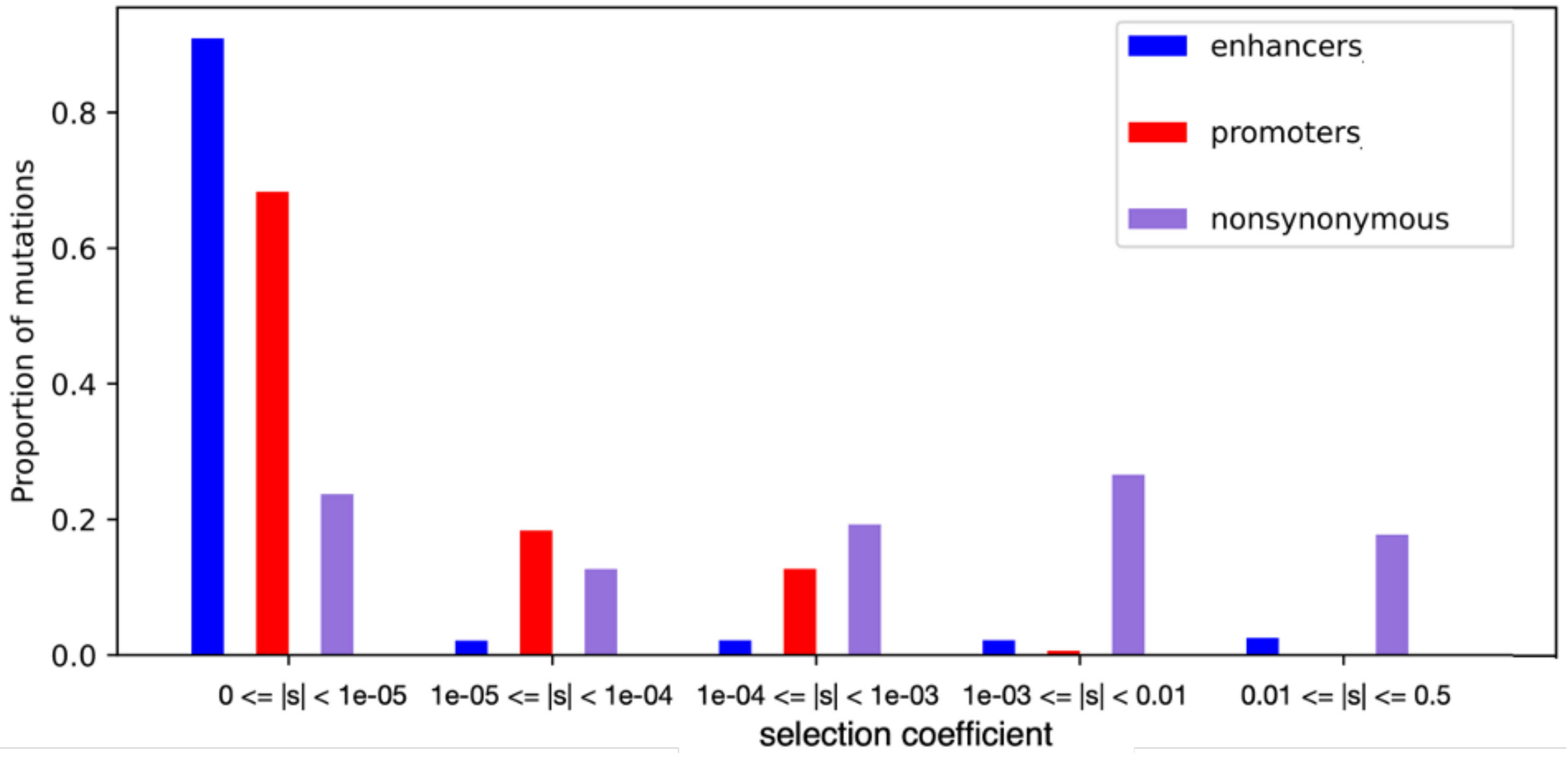
L ↓ number of sites

μ ↓ mutation rate

$P(s)$ ↓ probability of mutations with selection coefficient s

Distribution of Fitness Effects (DFE)





Large number of deleterious mutations

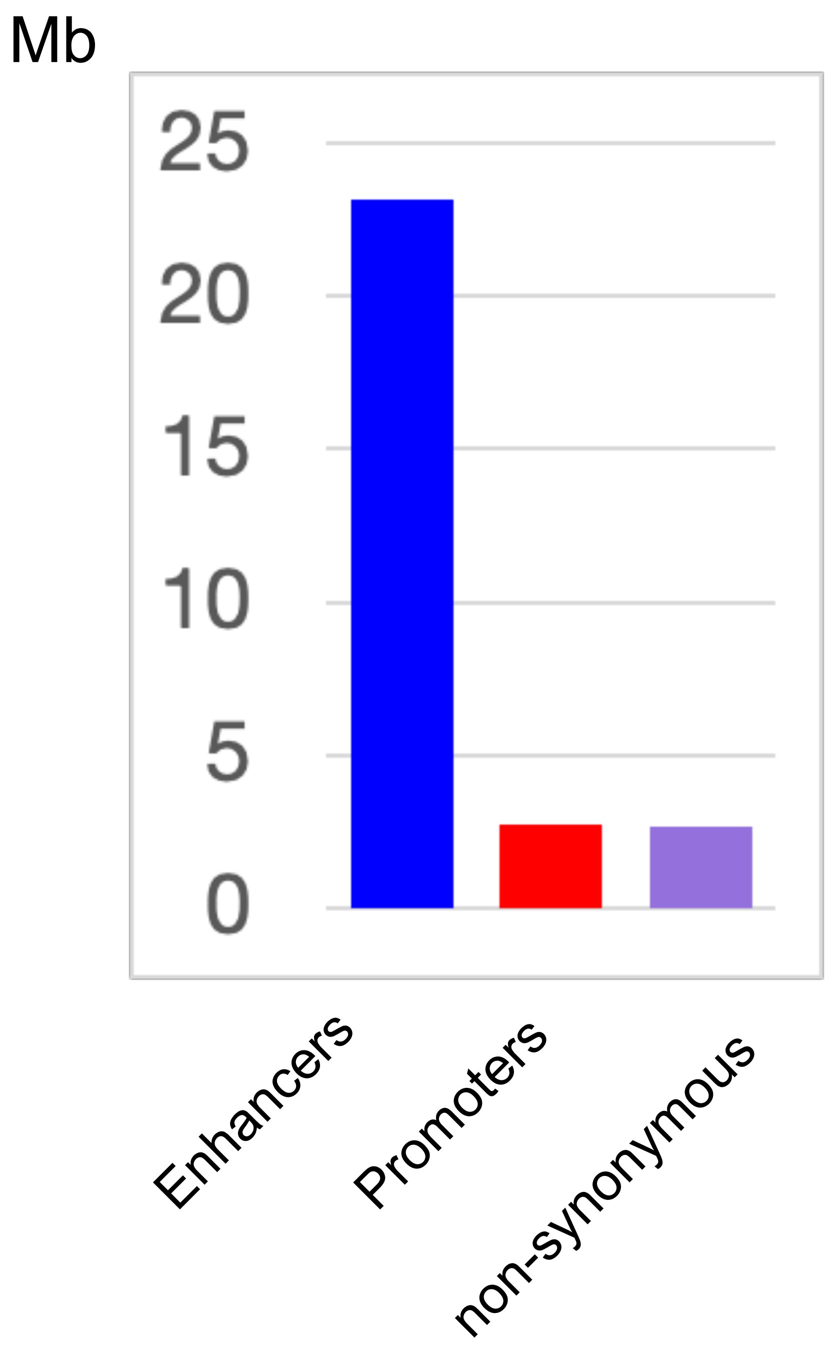
of mutations with given S

= L × μ × $P(s)$

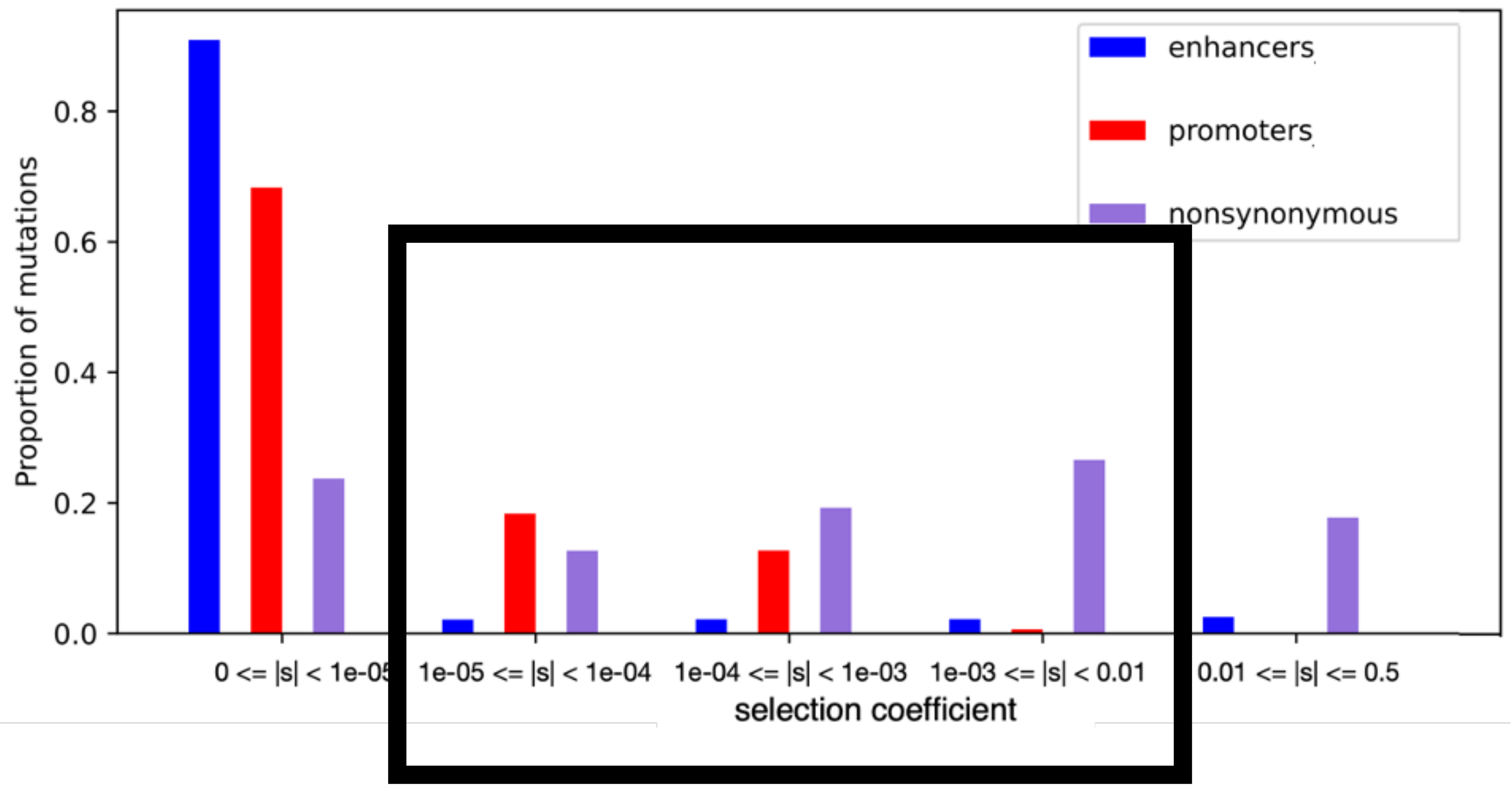
L ↓ number of sites

μ ↓ mutation rate

$P(s)$ ↓ probability of mutations with selection coefficient *s*



Distribution of Fitness Effects (DFE)



Weakly to moderately deleterious

Large number of deleterious mutations

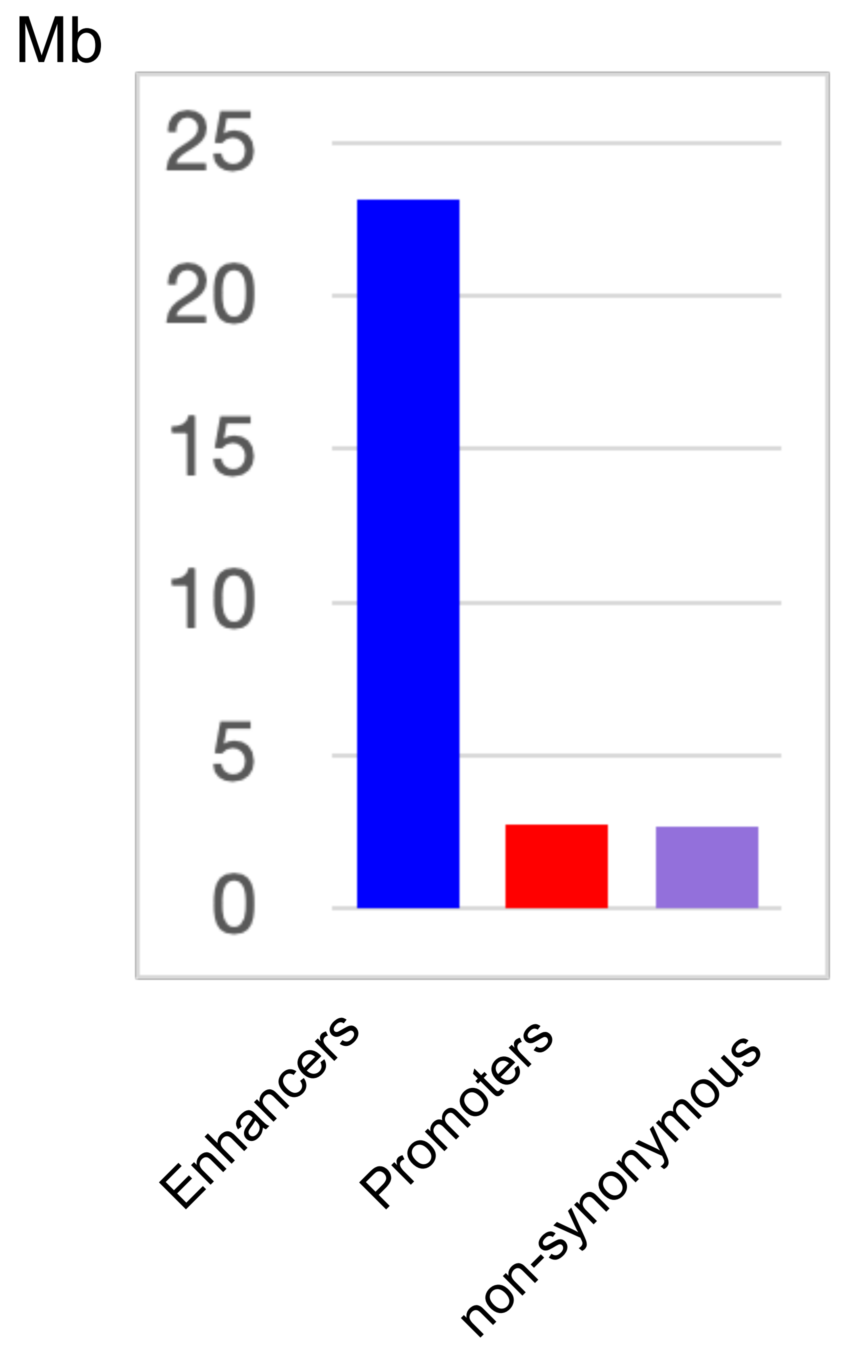
of mutations with given S

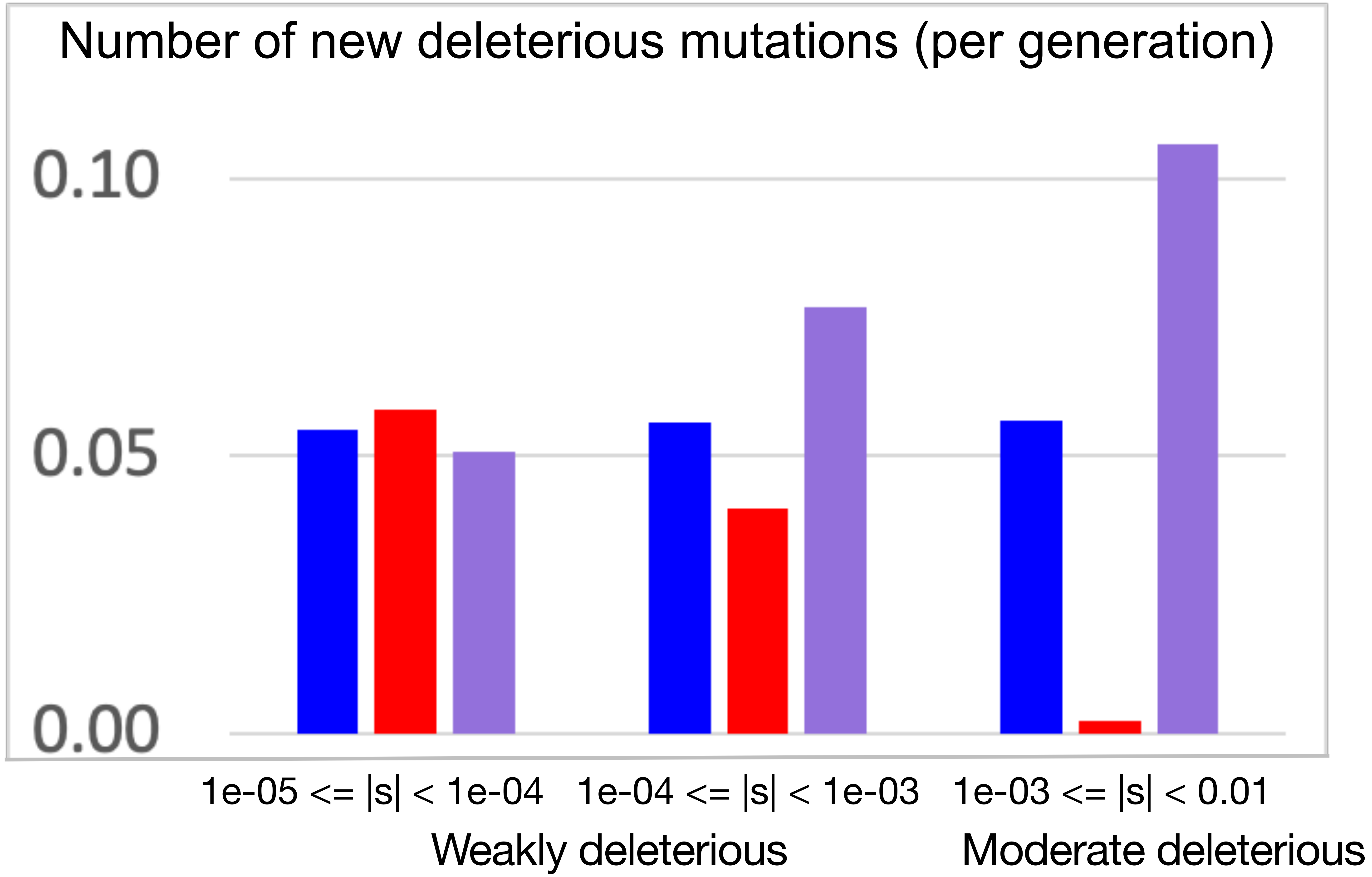
$= L \times \mu \times P(s)$

mutation rate

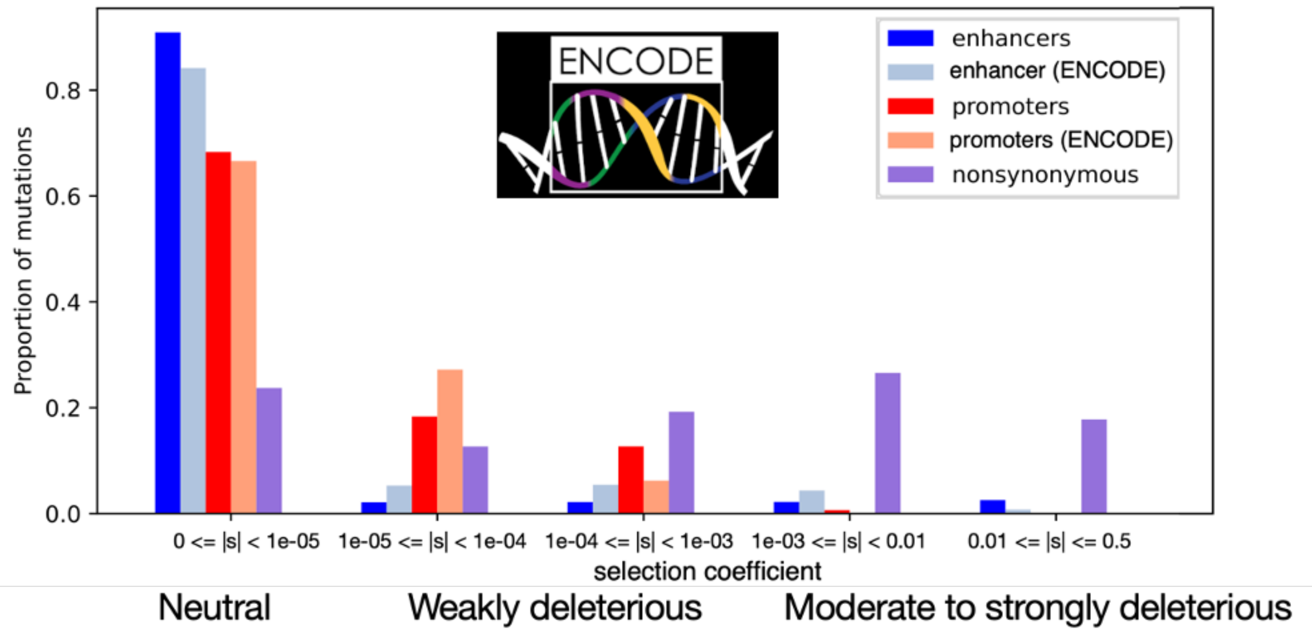
number of sites

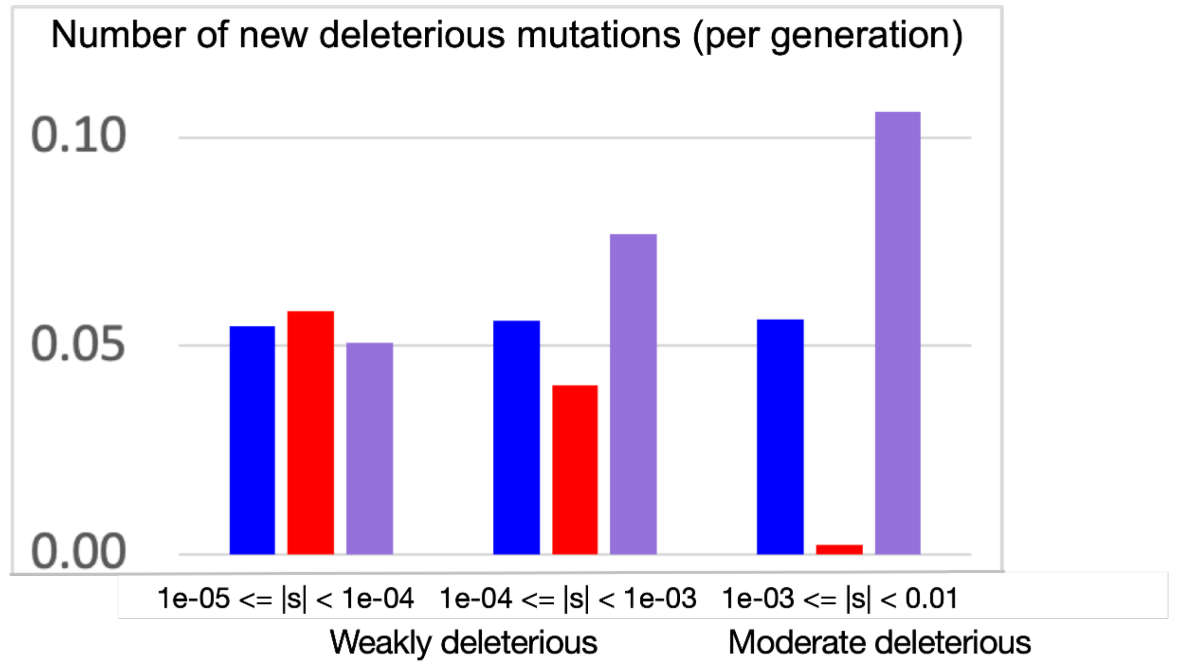
proba





Conclusion

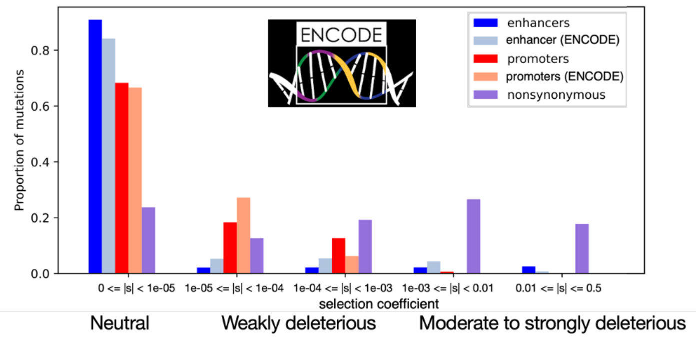




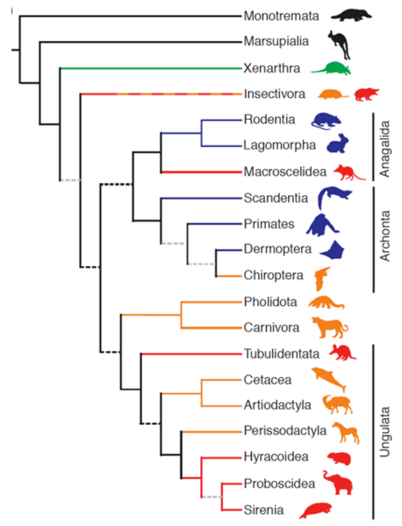
- Negative selection in annotated functional non-coding regions: fitness effects If mutations at enhancers, promoters and other annotated states
- Large number of weak to moderately deleterious mutations in enhancers and promoters that is comparable to non-synonymous sites

DFE of non-coding mutations

- Model-based method for inferring Distribution of Fitness effects (DFE)



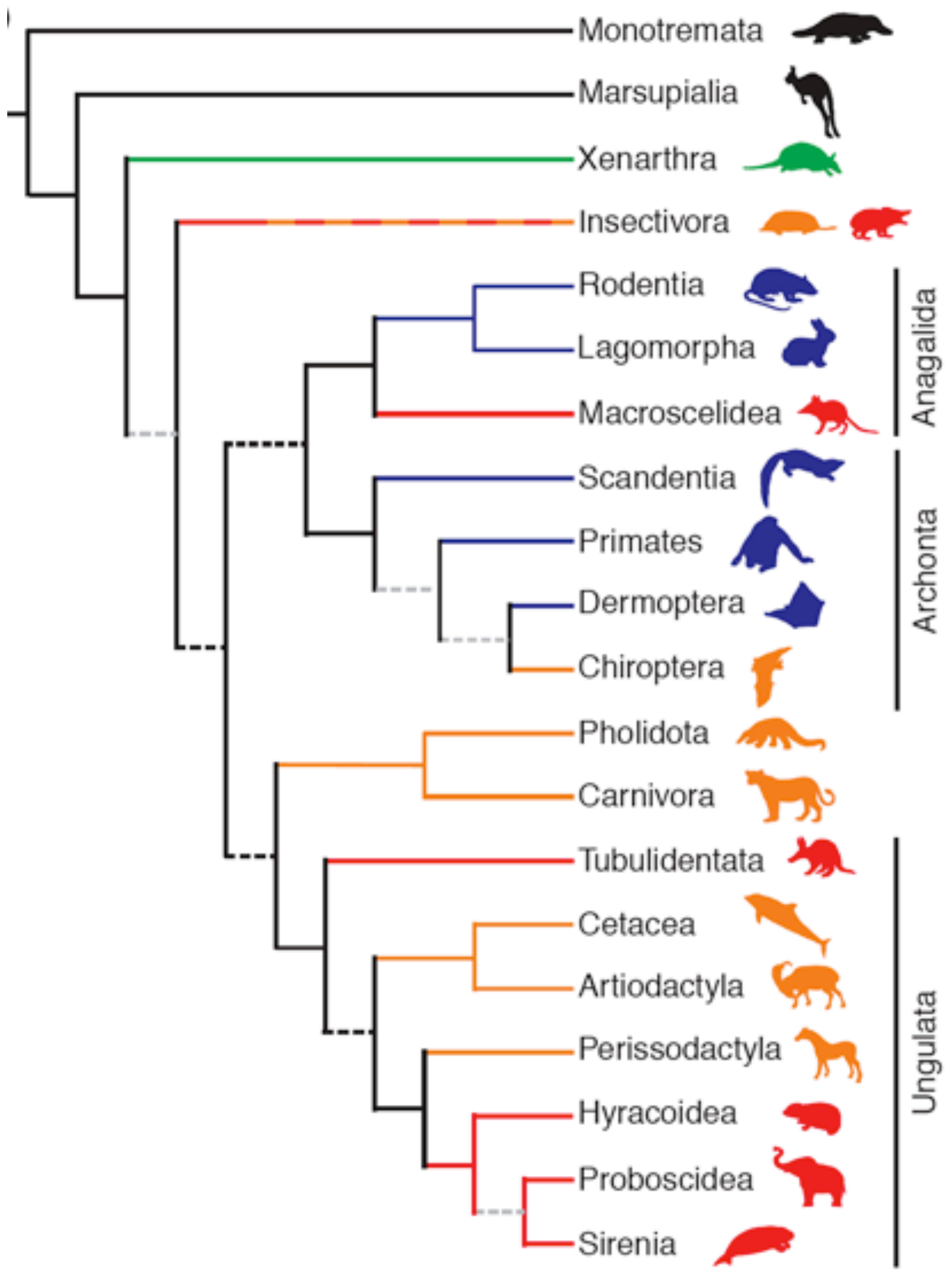
- DFE of annotated functional non-coding regions in human genome



- Negative selection in conserved and non-conserved human genomic region

picture is from https://www.phonandroid.com/tesla-continue-de-decliner-le-cybertruck-a-toutes-les-sauces-avec-un-marteau-de-gym.html
Phylogeny is from Springer et al., 2004

Mutations at conserved sites are more deleterious

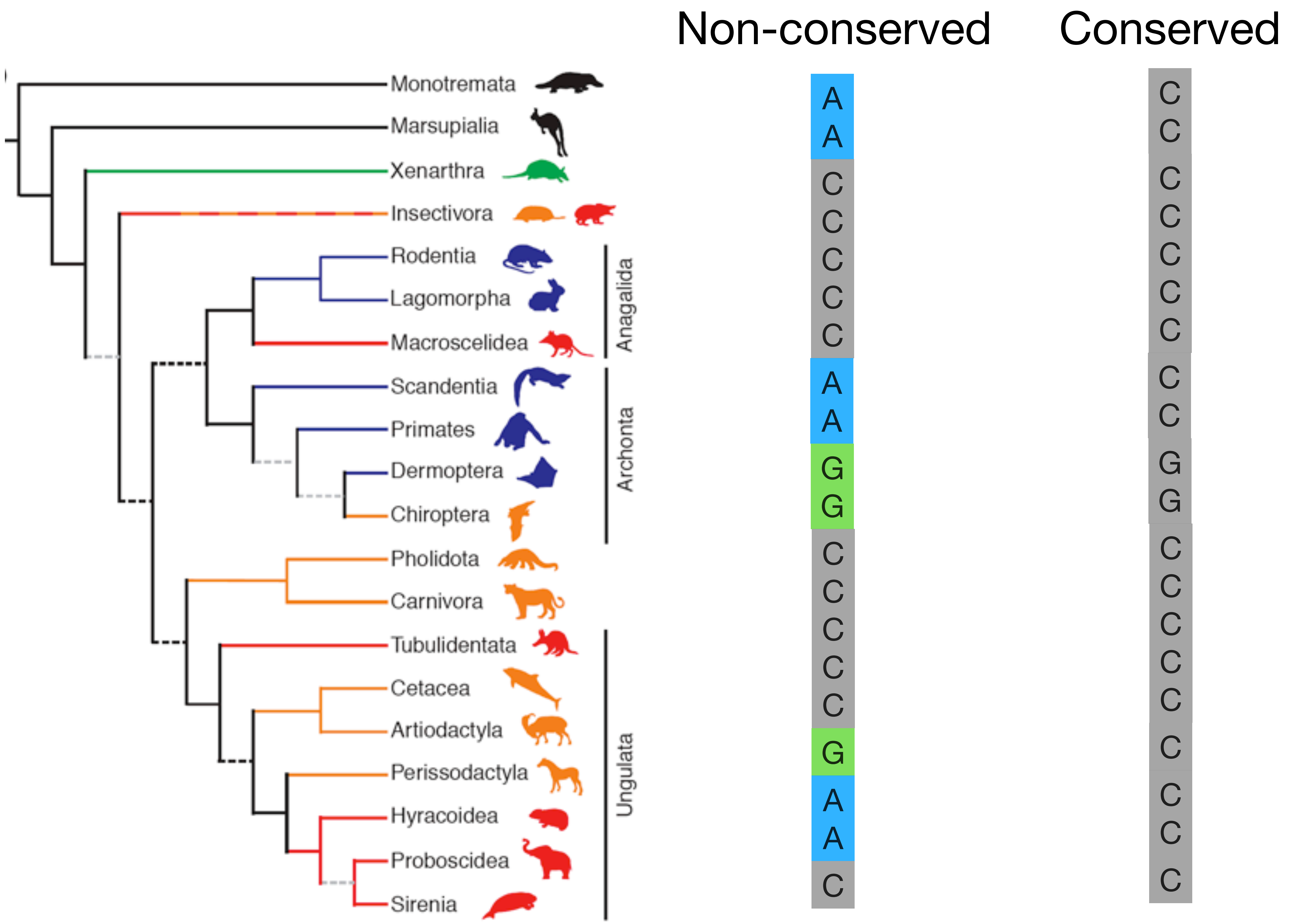


Non-conserved	Conserved
A	C
A	C
C	C
C	C
C	C
C	C
C	C
A	C
A	C
G	C
G	C
C	C
C	C
C	C
C	C
C	C
G	C
A	C
A	C
C	C

Phylogeny is from Springer et al., 2004

Mutations at conserved sites are more deleterious

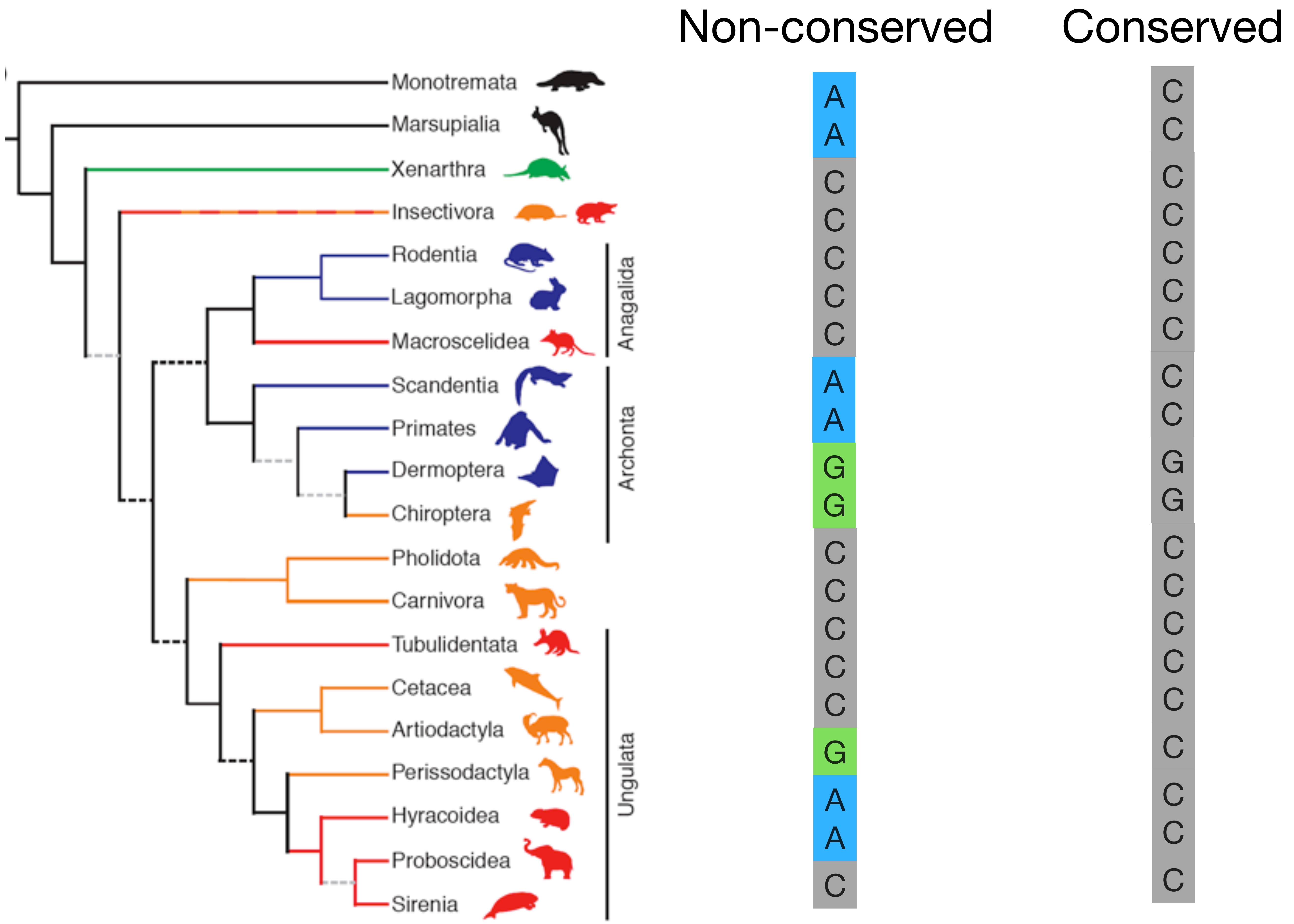
PhastCons scores: PHAST (PHylogenetic Analysis with Space/Time models)



Phylogeny is from Springer et al., 2004

Mutations at conserved sites are more deleterious

PhastCons scores: PHAST (PHylogenetic Analysis with Space/Time models)
Prob(being conserved) ∈ [0,1]. 1 is for the most conserved sites



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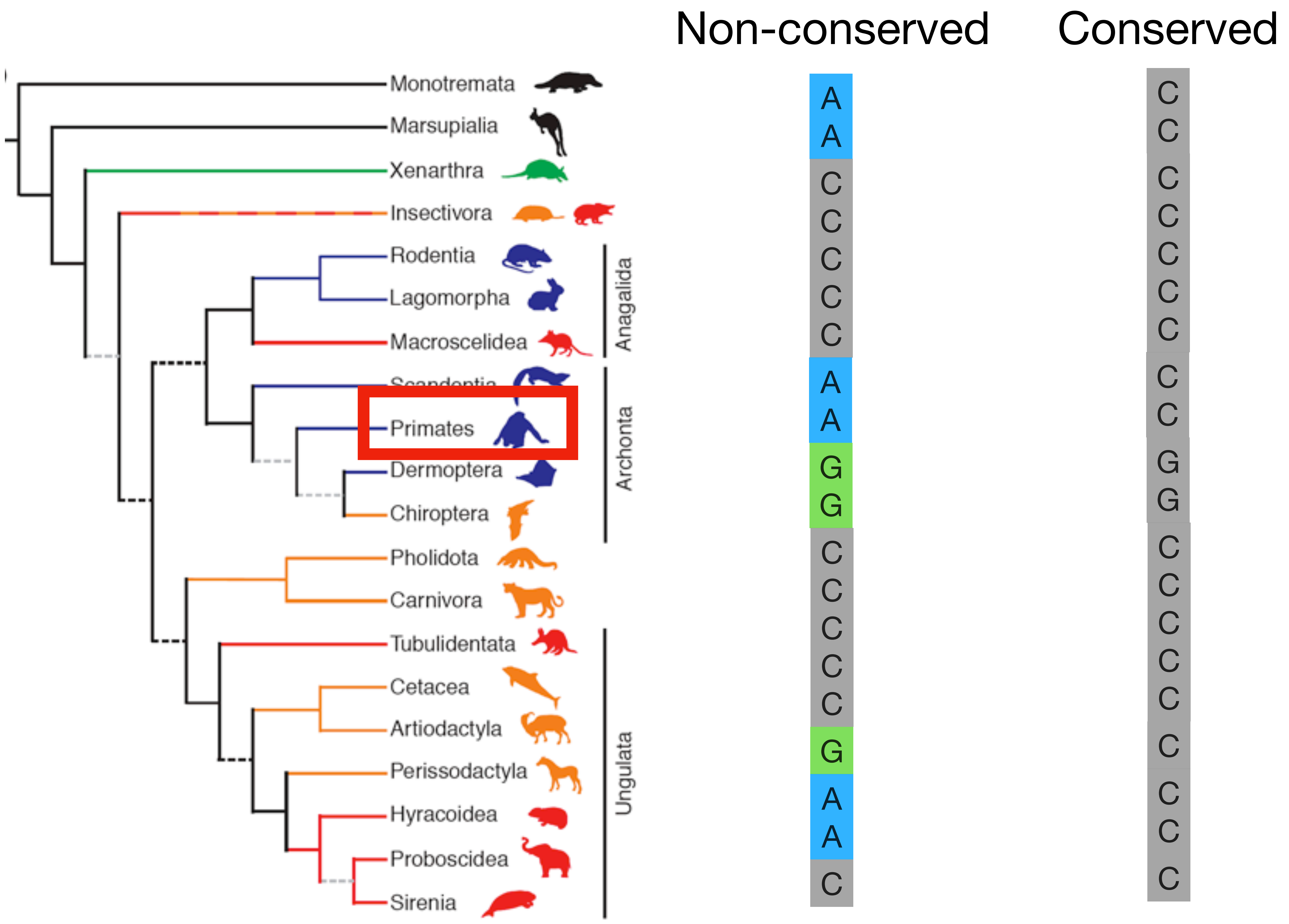
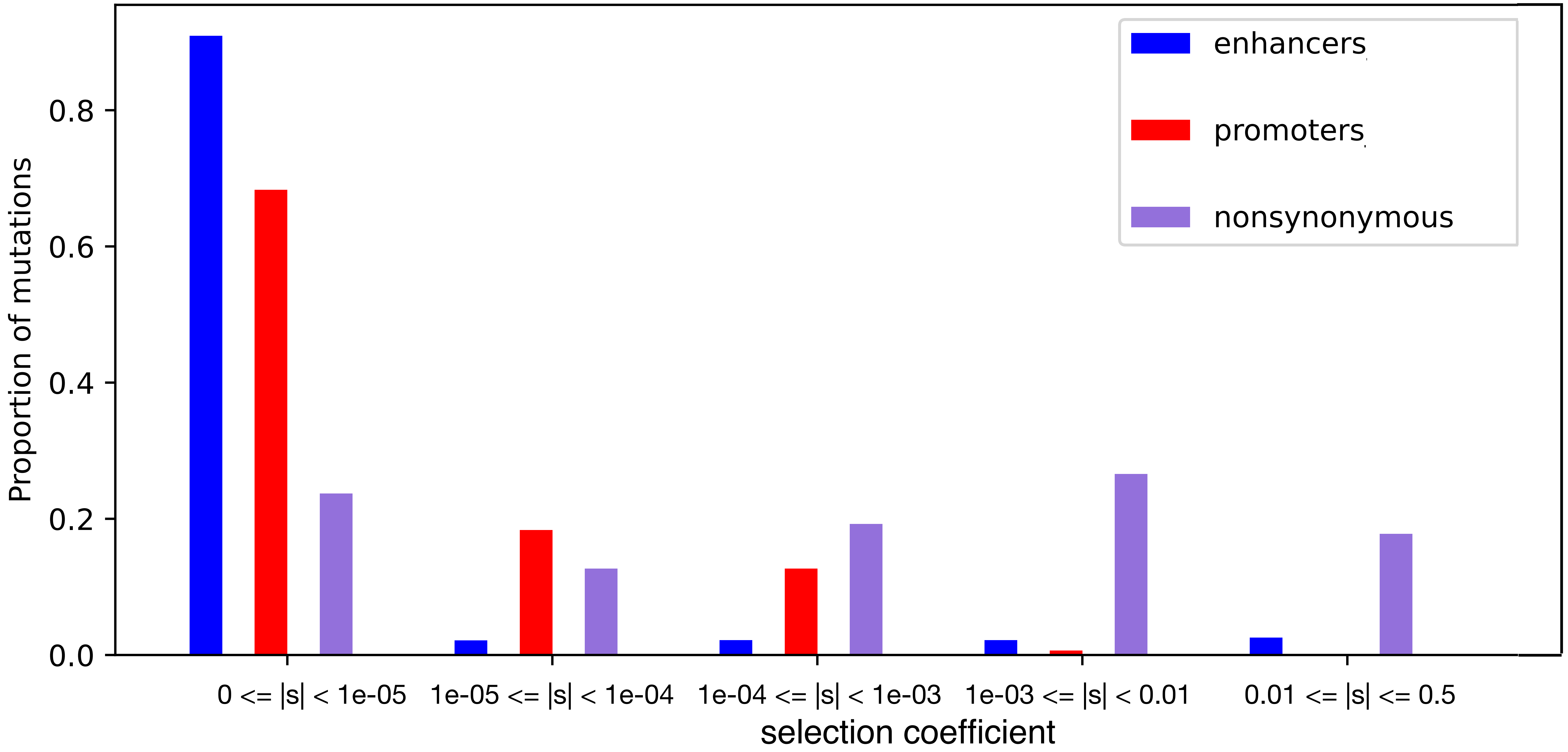


Phylogeny is from Springer et al., 2004

DFE of enhancers and promoters



Neutral

enhancers > promoters

Weakly deleterious

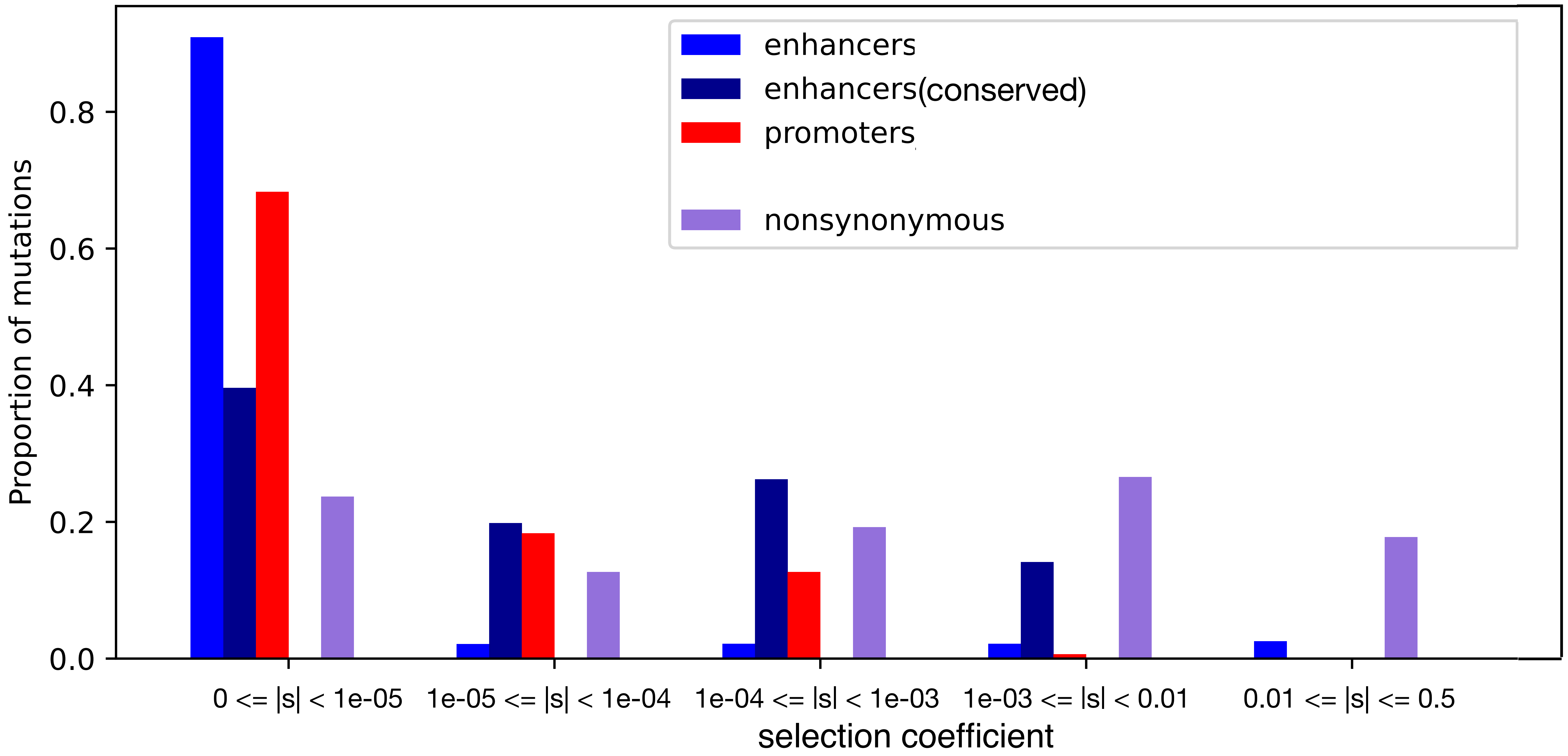
promoters > enhancers

Moderate to strongly deleterious

small proportion, enhancers > promoters

DFE of non-synonymous sites from Kim et al., 2017, 1KG, EUR

Mutations at conserved sites are more delerious

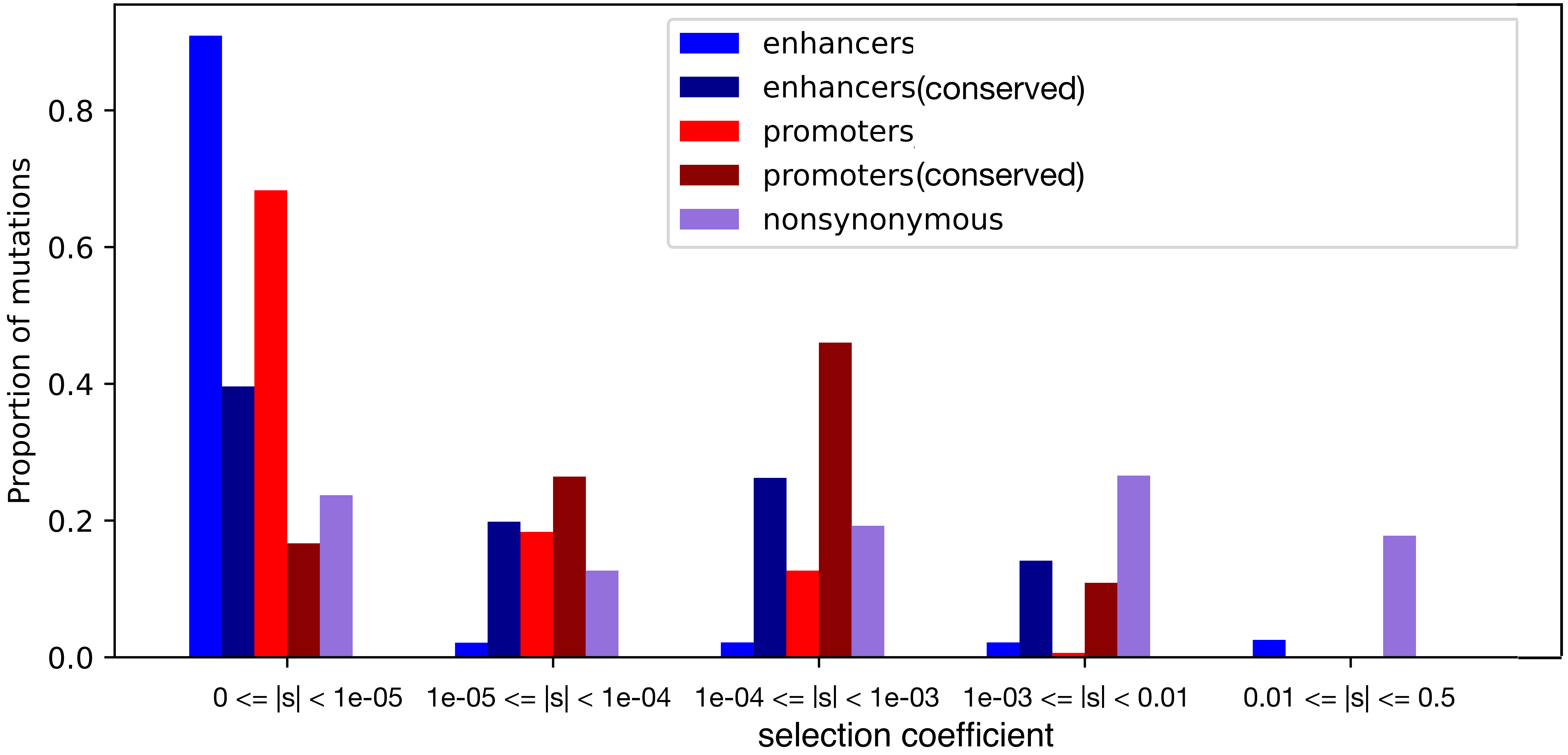


Neutral Weakly deleterious Moderate to strongly deleterious

Negative selection: conserved > non-conserved.

DFE of non-synonymous sites from Kim et al., 2017, 1KG, EUR

Mutations at conserved sites are more delerious



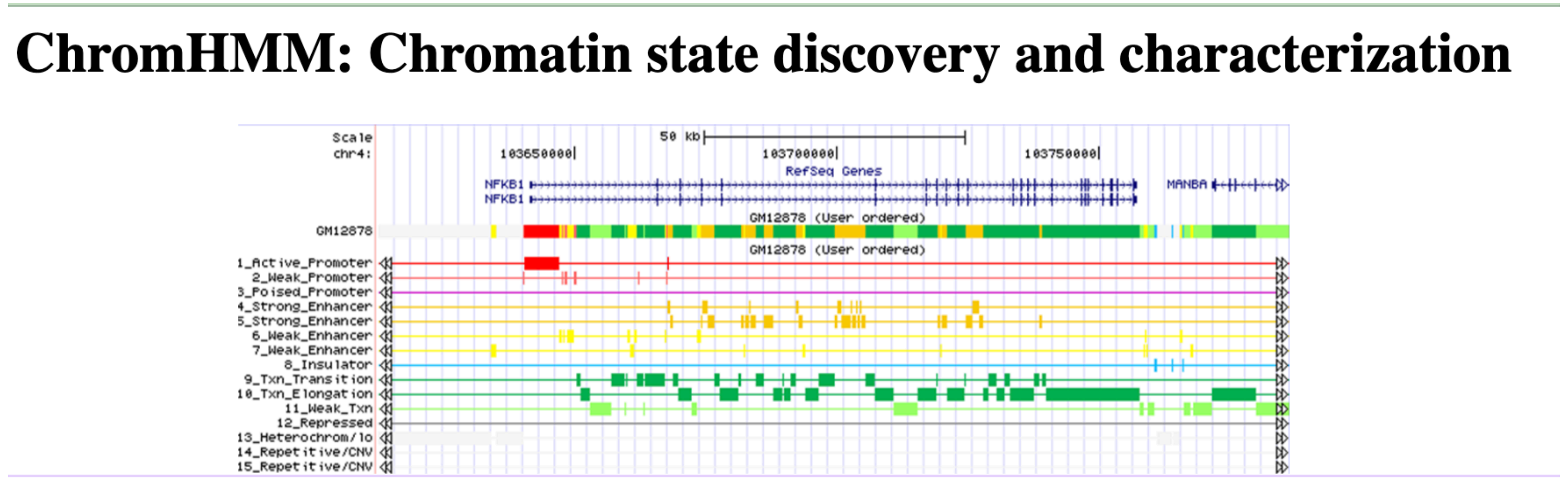
Neutral Weakly deleterious Moderate to strongly deleterious

Negative selection: conserved > non-conserved.

DFE of non-synonymous sites from Kim et al., 2017, 1KG, EUR

DFE of mutations in regions of differing phylogenetic constraint

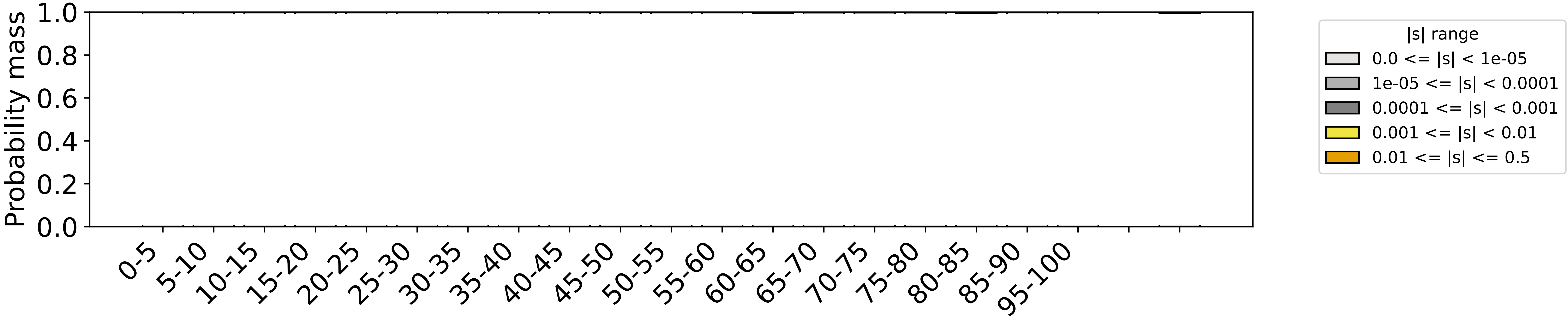
DFE of putative functional non-coding regions
(~50% of the genome)



ChromHMM: Chromatin state discovery and characterization

DFE of mutations in regions of differing phylogenetic constraint

DFE of putative functional non-coding regions



Neutral

Weakly D

Moderately D

Strongly D

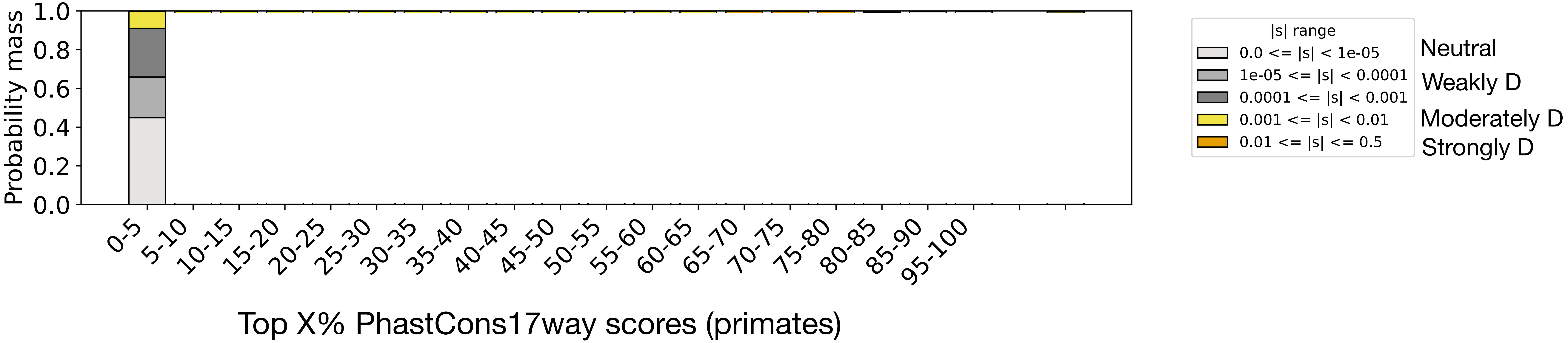
Top X% PhastCons17way scores (primates)

Most conserved

less conserved

DFE of mutations in regions of differing phylogenetic constraint

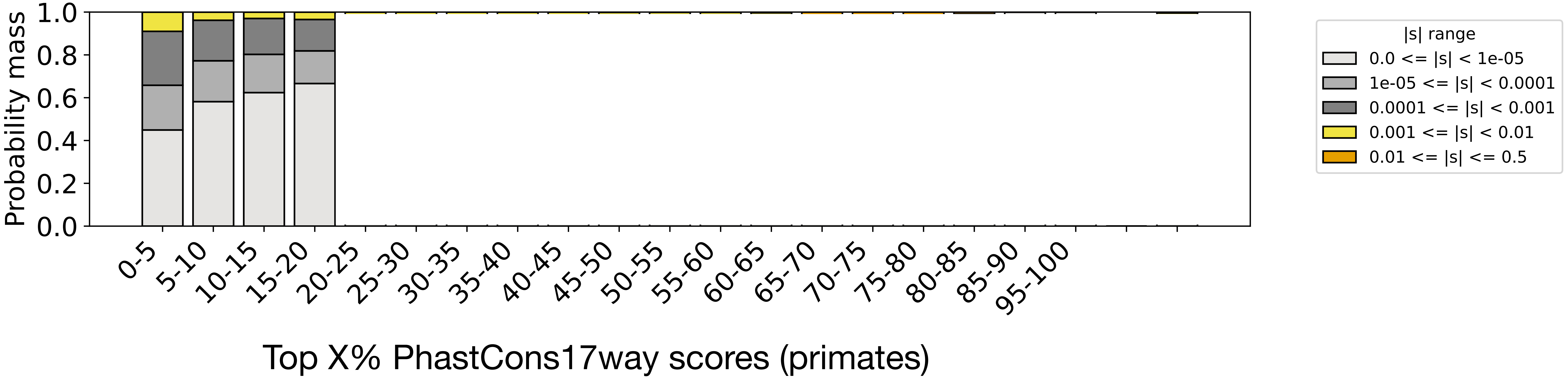
DFE of putative functional non-coding regions



Most conserved less conserved

DFE of mutations in regions of differing phylogenetic constraint

DFE of putative functional non-coding regions



Neutral

Weakly D

Moderately D

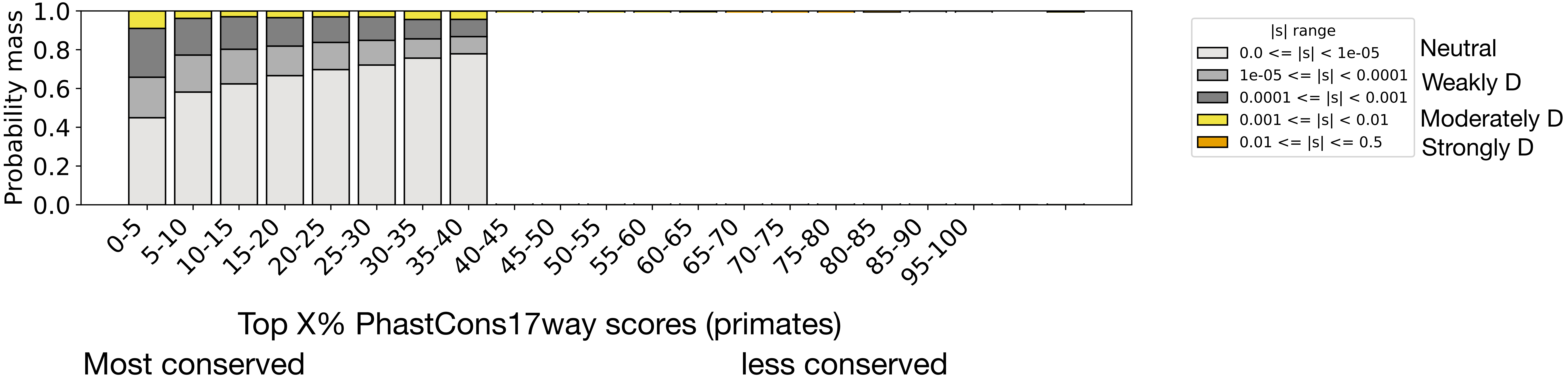
Strongly D

Most conserved

less conserved

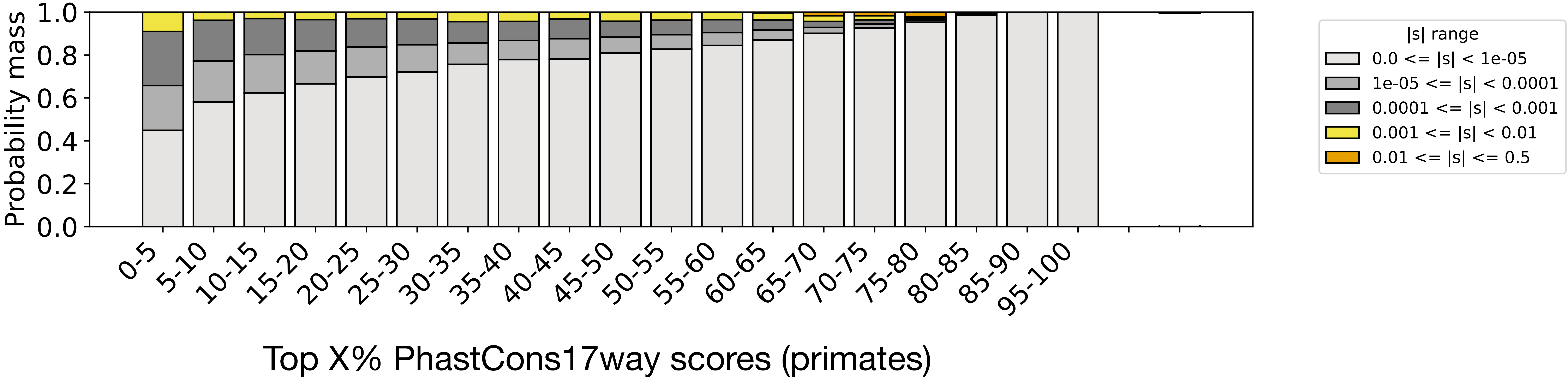
DFE of mutations in regions of differing phylogenetic constraint

DFE of putative functional non-coding regions



DFE of mutations in regions of differing phylogenetic constraint

DFE of putative functional non-coding regions



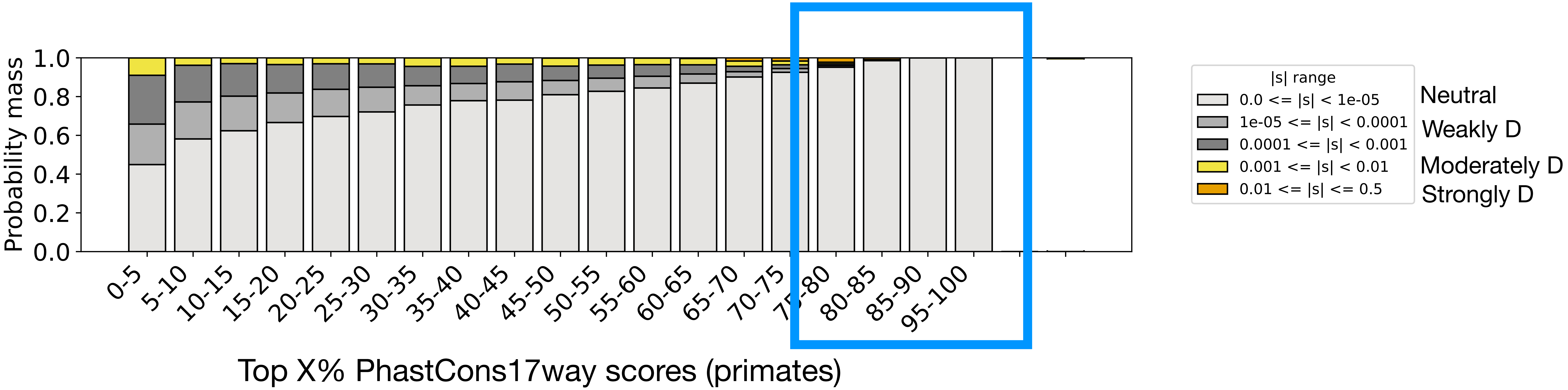
Neutral
Weakly D
Moderately D
Strongly D

Most conserved

less conserved

DFE of mutations in regions of differing phylogenetic constraint

DFE of putative functional non-coding regions



Neutral
Weakly D
Moderately D
Strongly D

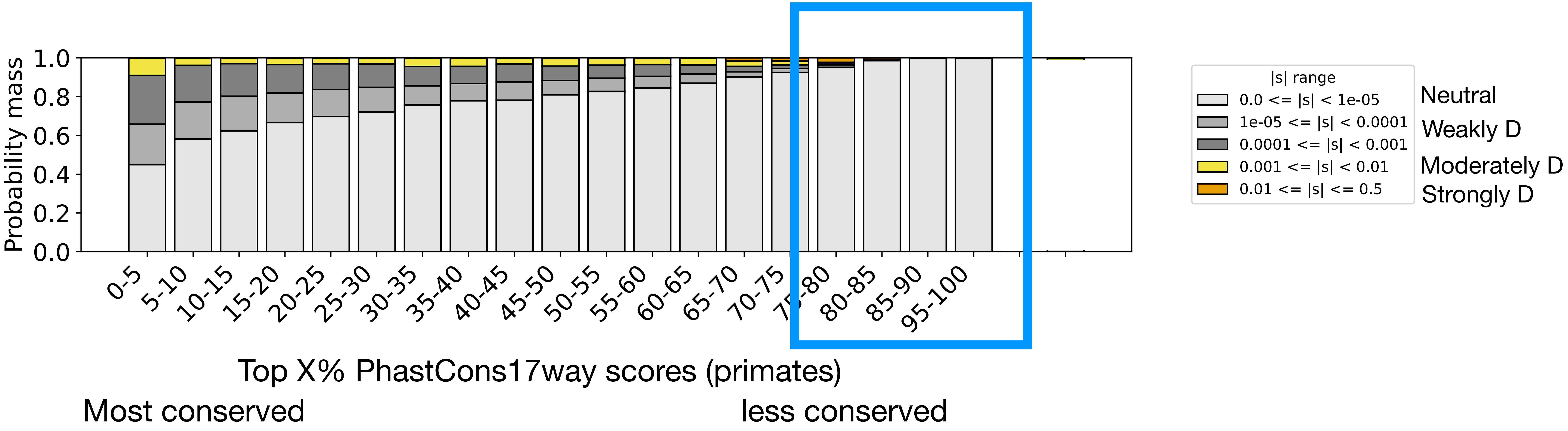
Most conserved

less conserved

DFE of mutations in regions of differing phylogenetic constraint

DFE of putative functional non-coding regions

Models for DFE

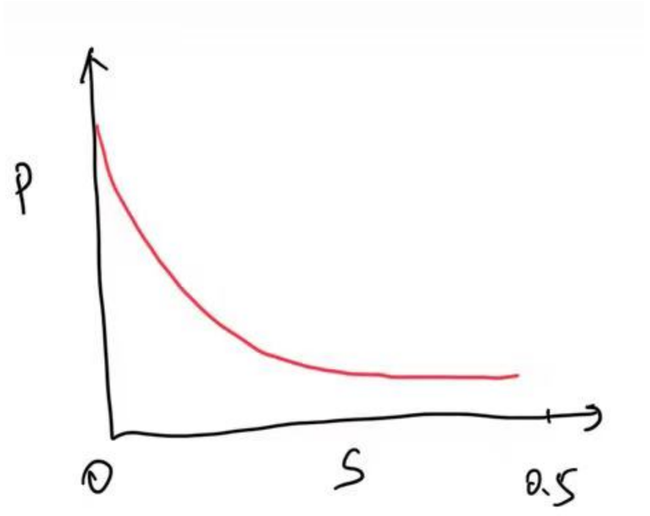


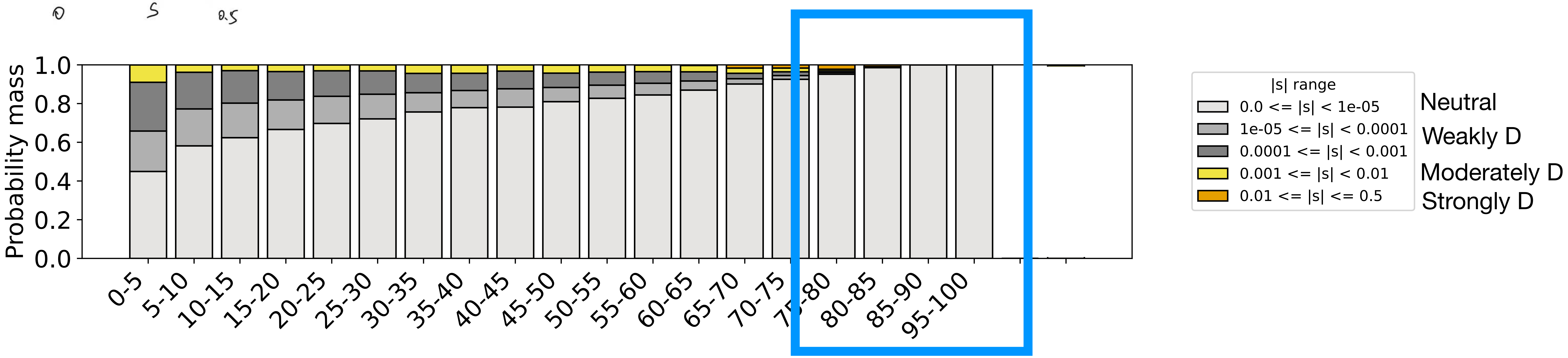
DFE of mutations in regions of differing phylogenetic constraint

DFE of putative functional non-coding regions

Models for DFE

Gamma distribution





Top X% PhastCons17way scores (primates)

Most conserved

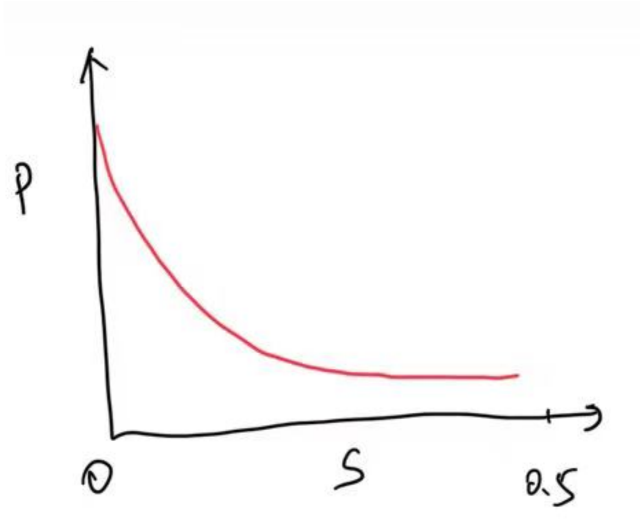
less conserved

DFE of mutations in regions of differing phylogenetic constraint

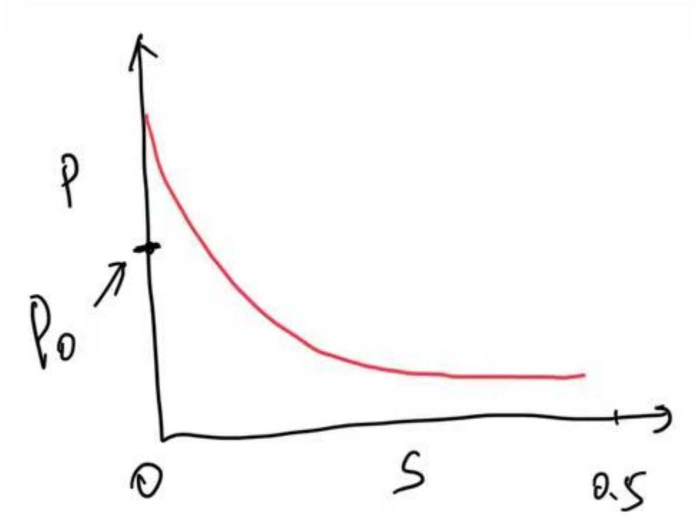
DFE of putative functional non-coding regions

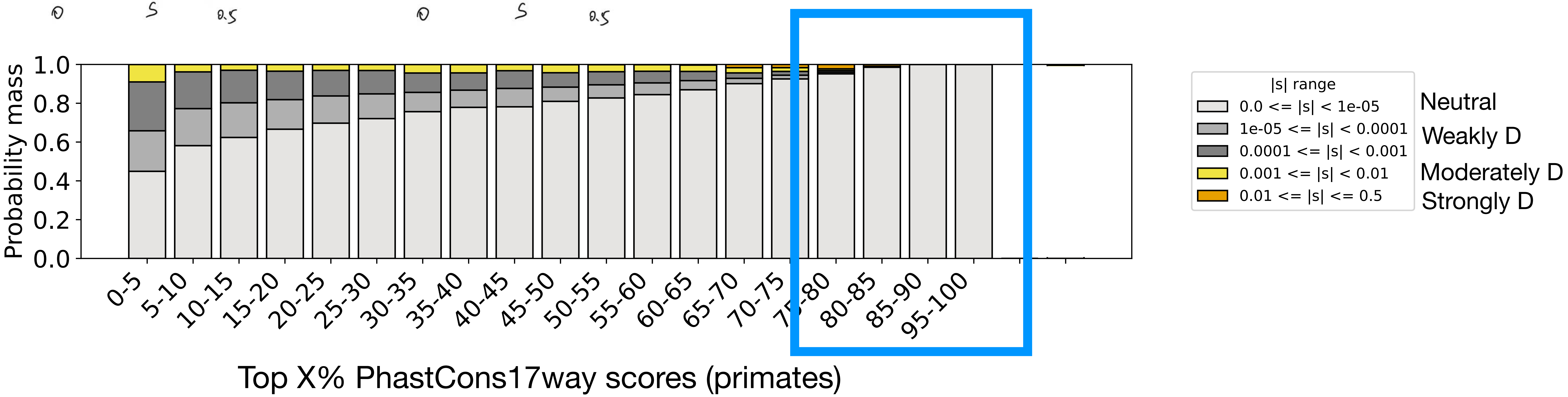
Models for DFE

Gamma distribution



Neu+Gamma distribution





Most conserved

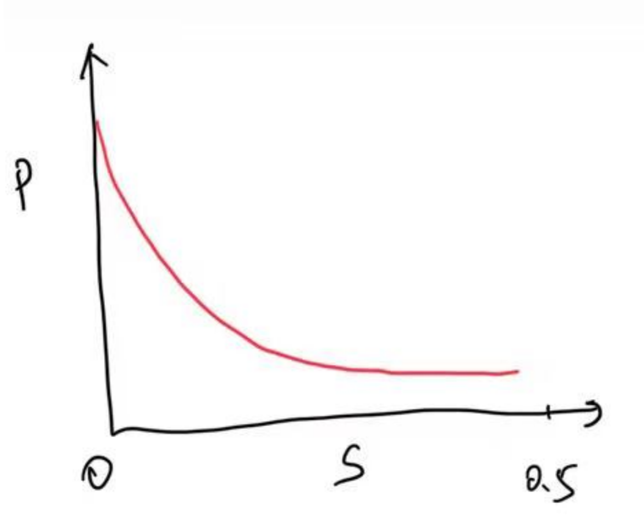
less conserved

DFE of mutations in regions of differing phylogenetic constraint

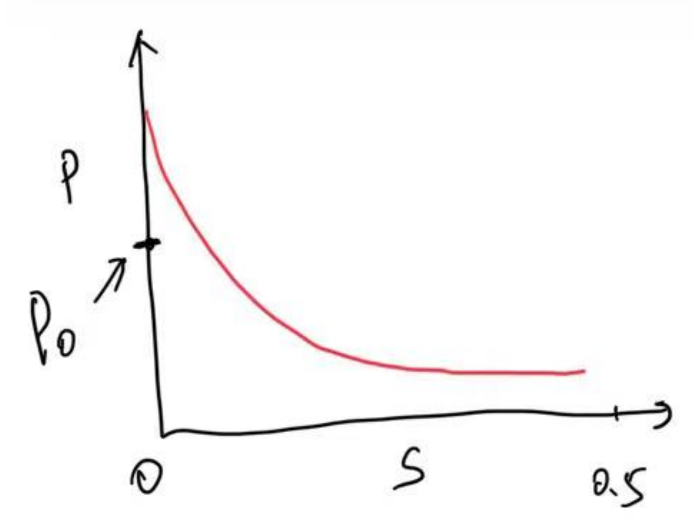
DFE of putative functional non-coding regions

Models for DFE

Gamma distribution

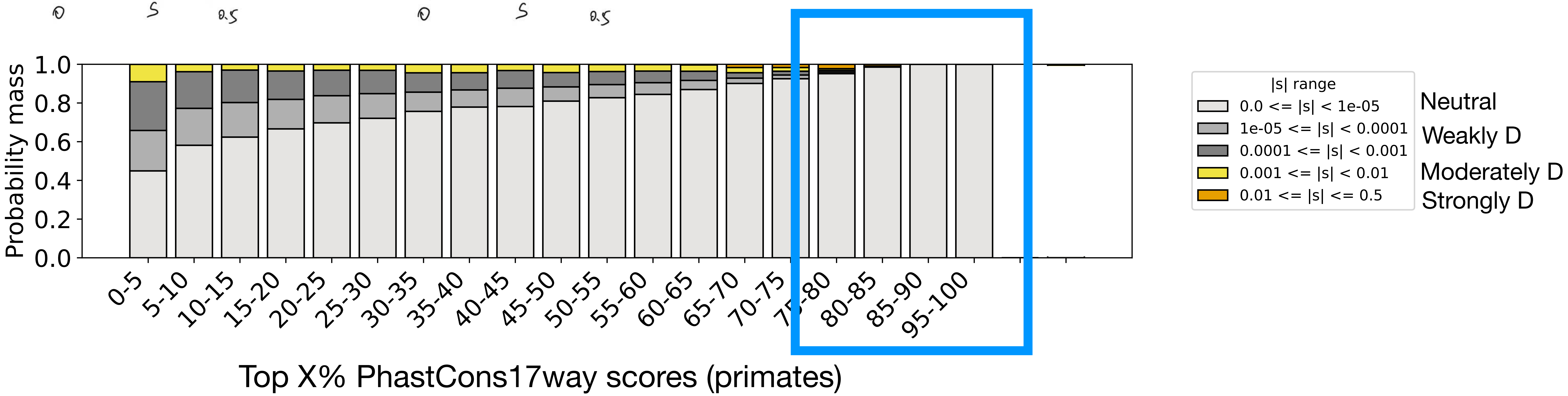


Neu+Gamma distribution



Neutral model

P(s=0)=1

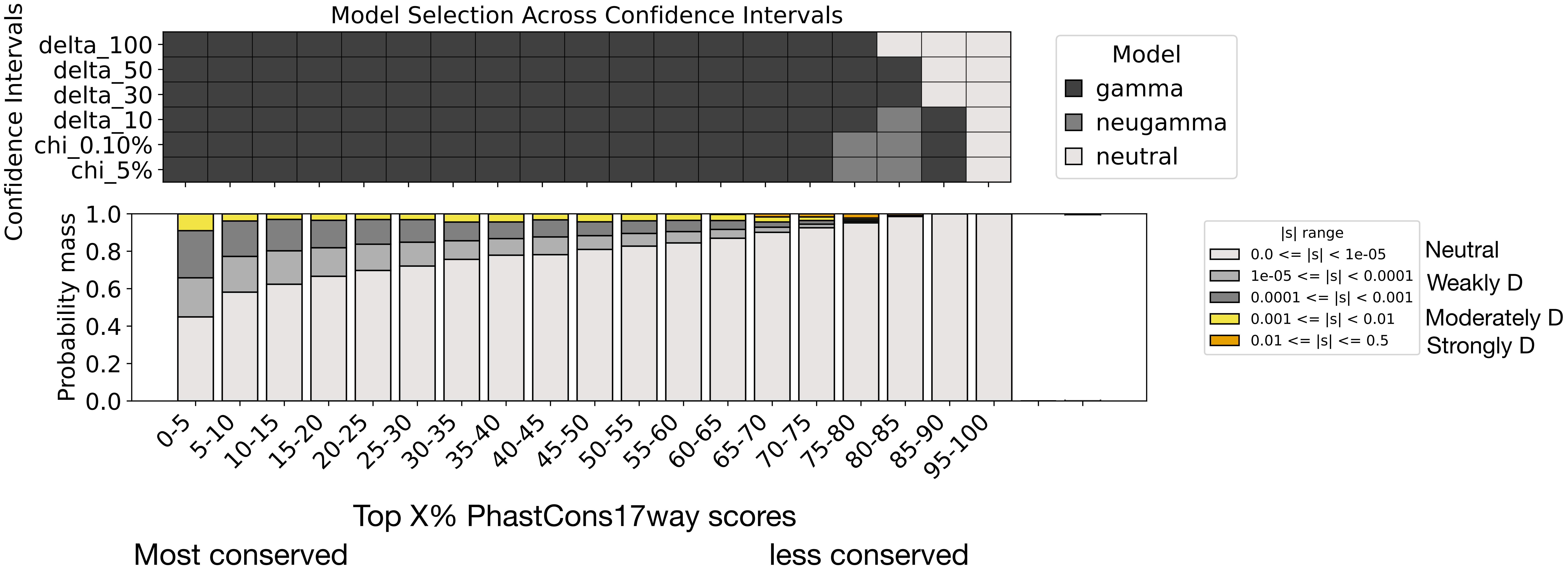


Most conserved

less conserved

DFE of mutations in regions of differing phylogenetic constraint

DFE of putative functional non-coding regions



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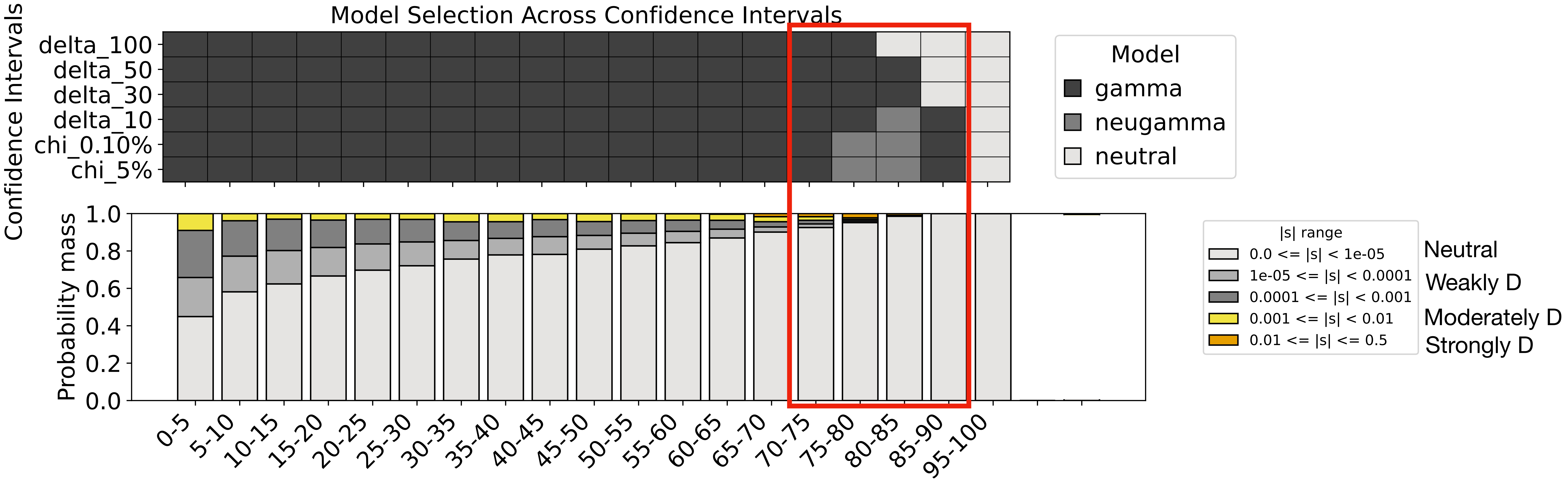

Top X% PhastCons17way scores

Most conserved

less conserved

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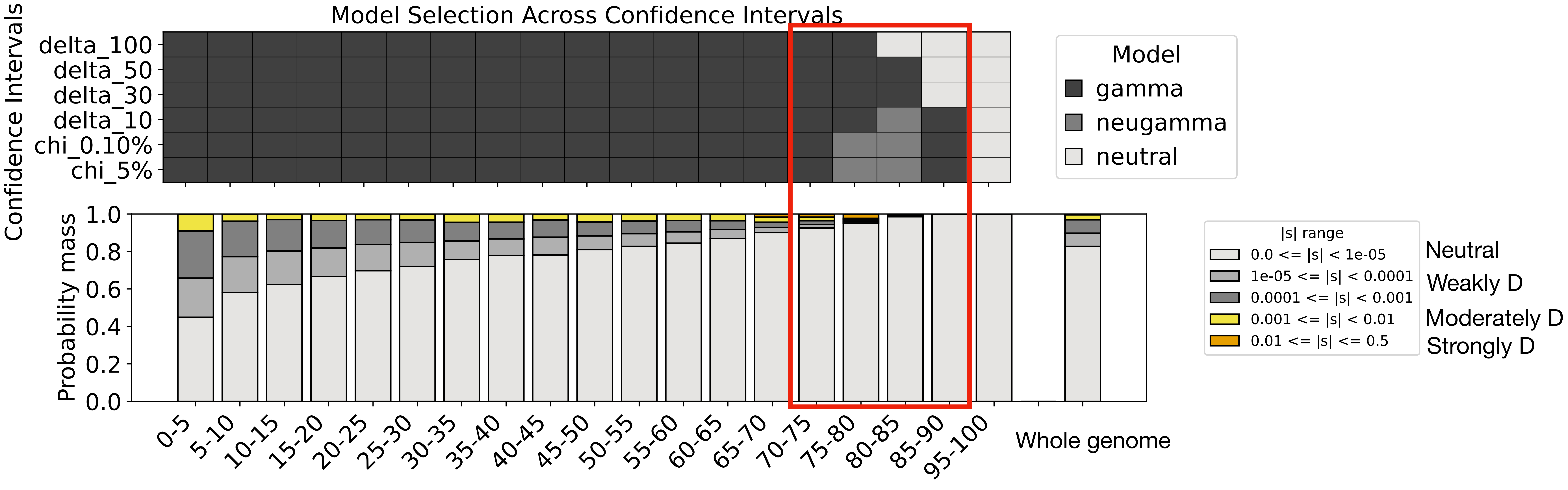

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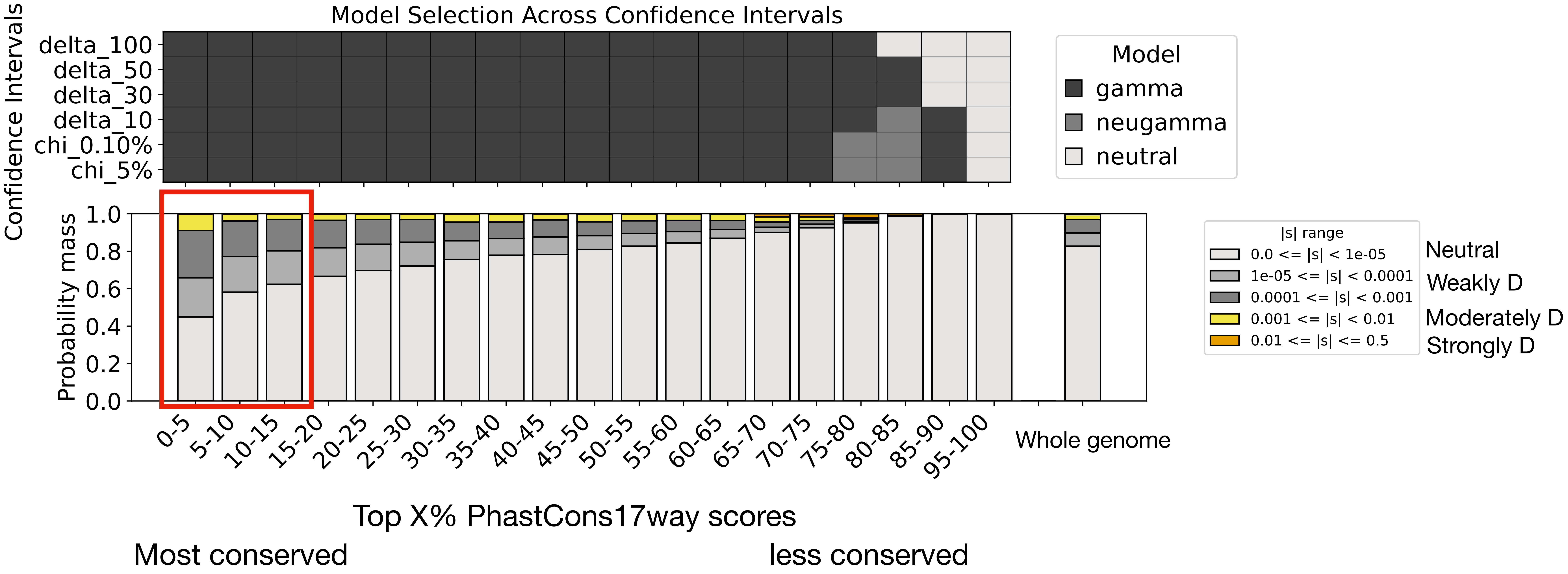

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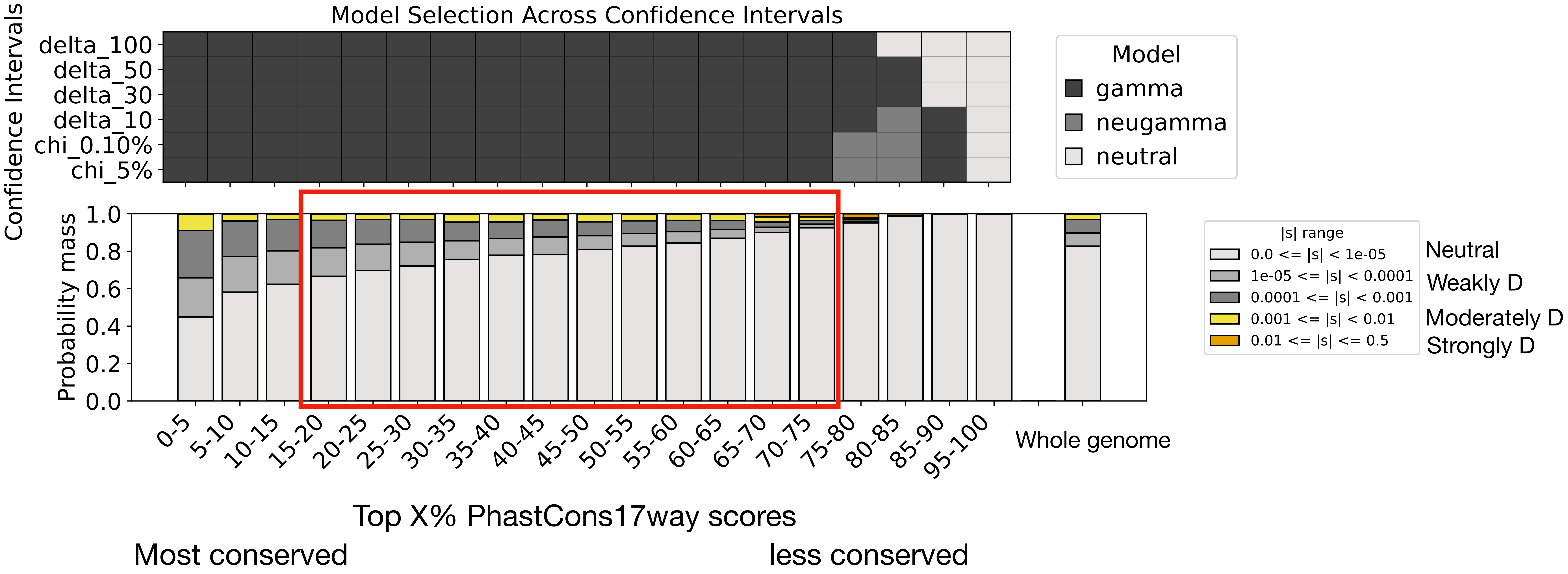

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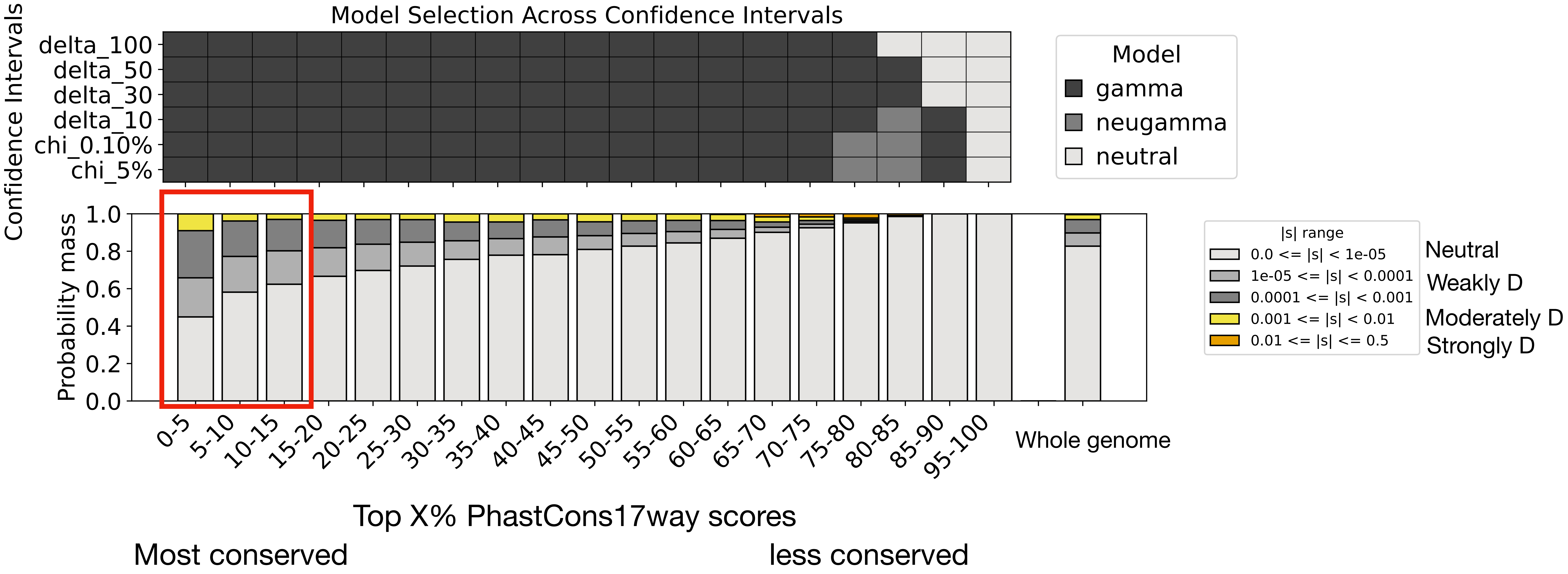
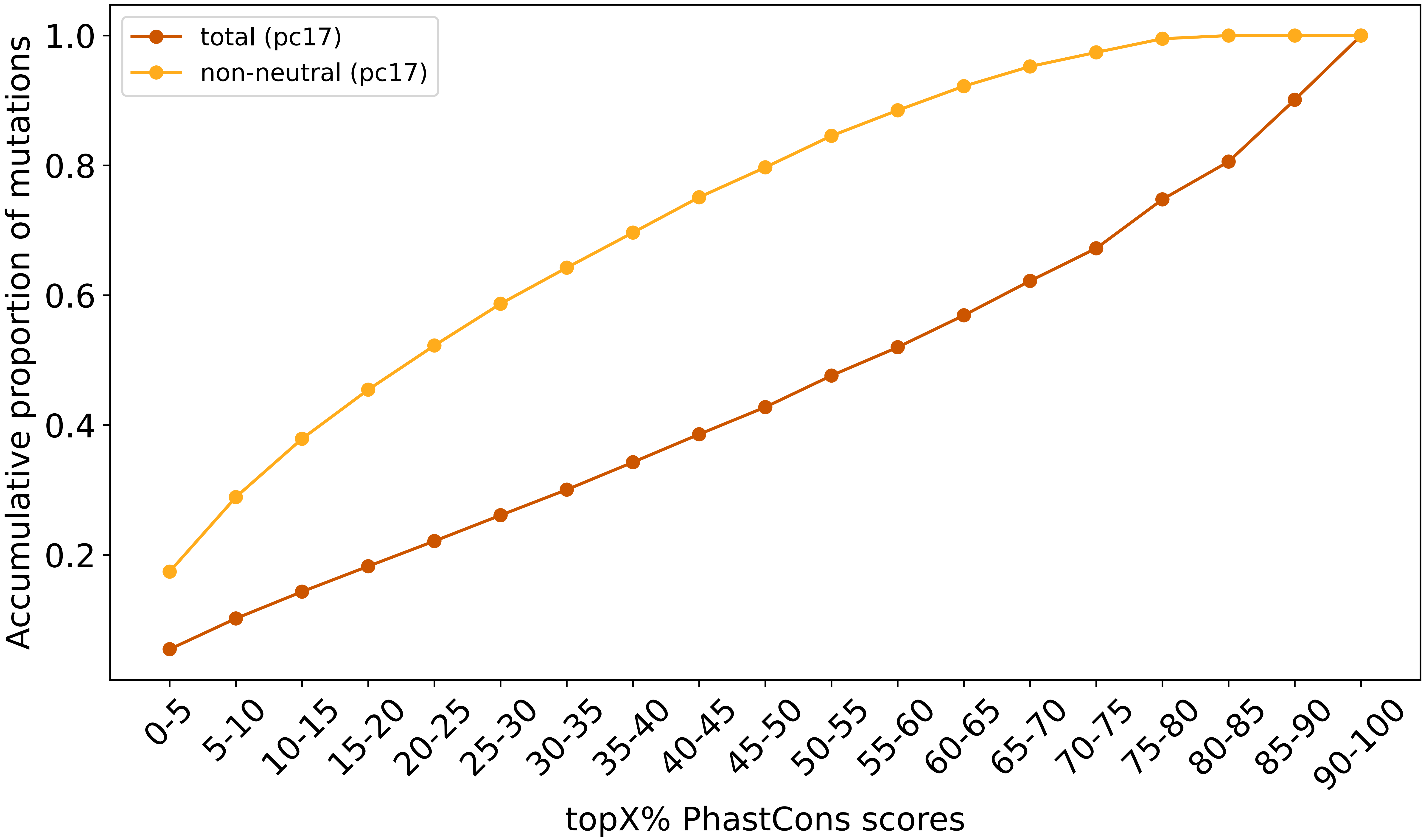


Phylogenetic constraint has limited power to identify deleterious mutations



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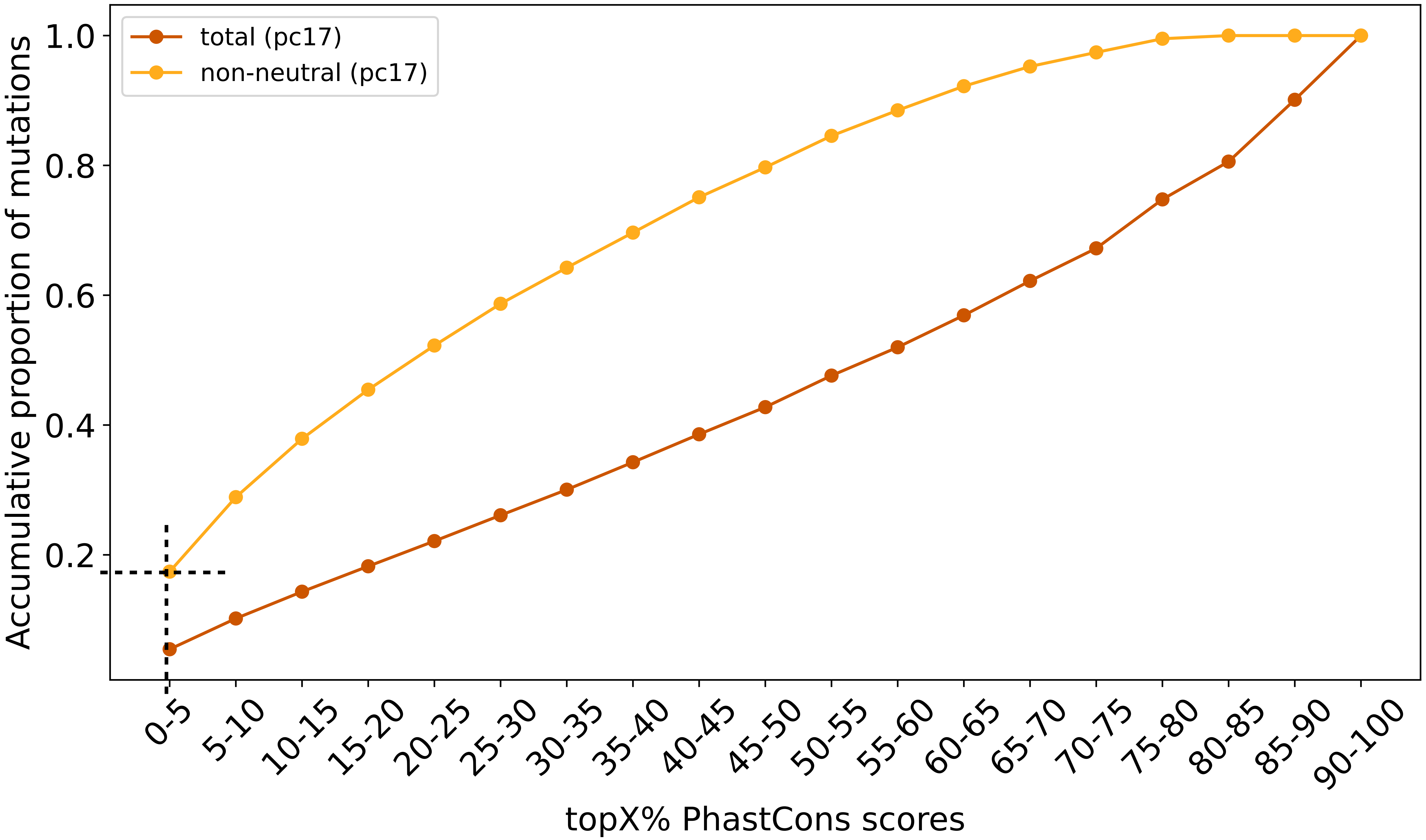

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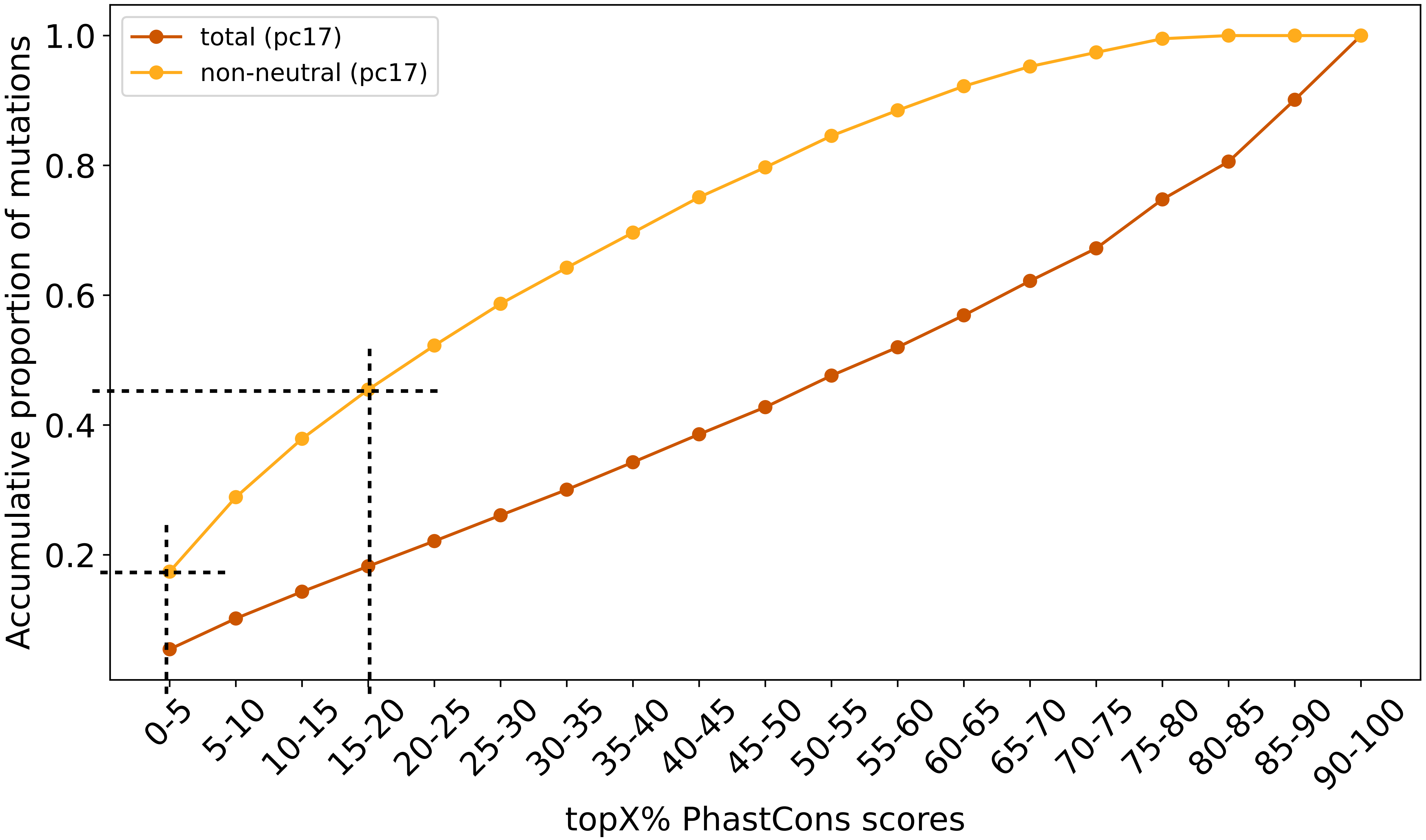

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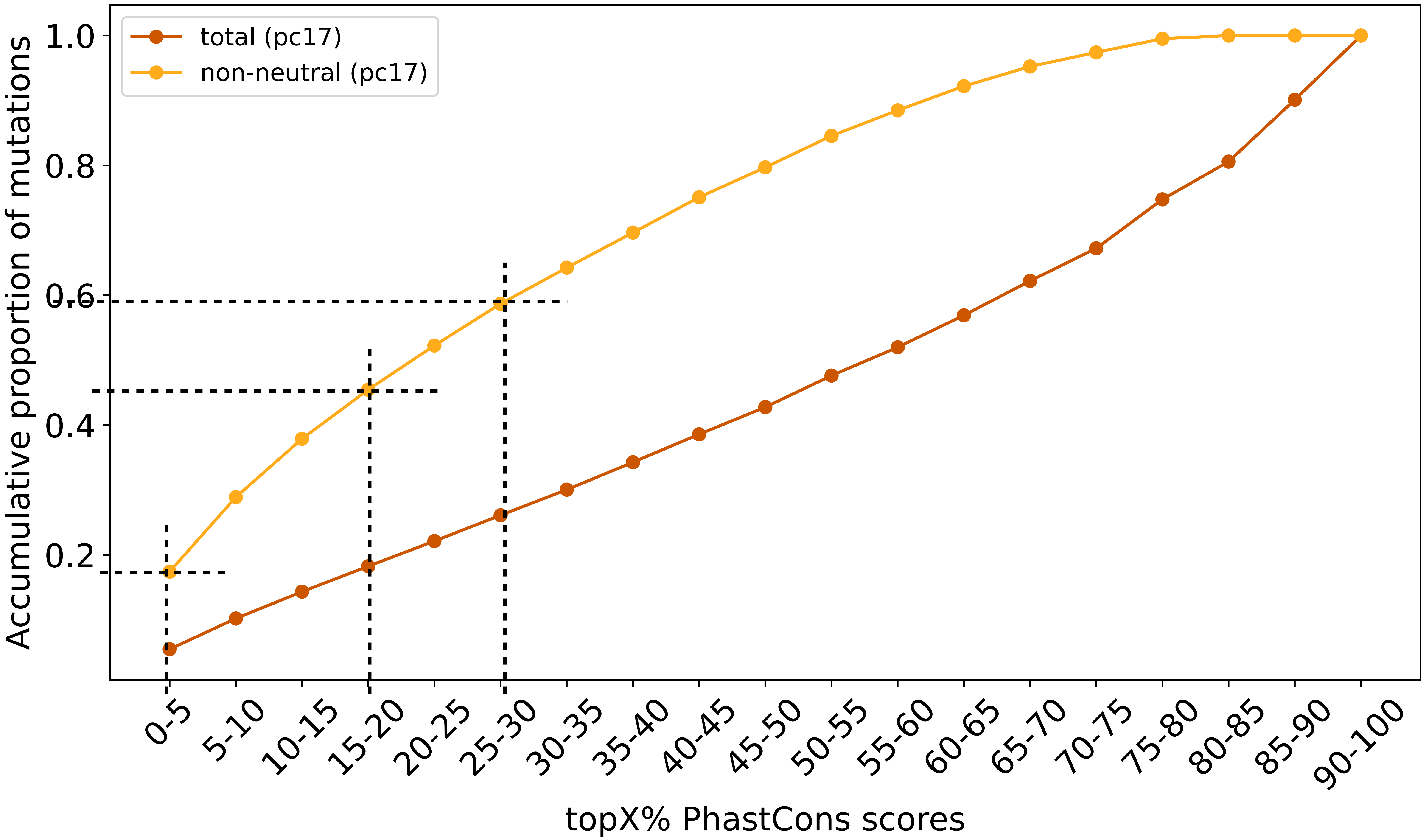

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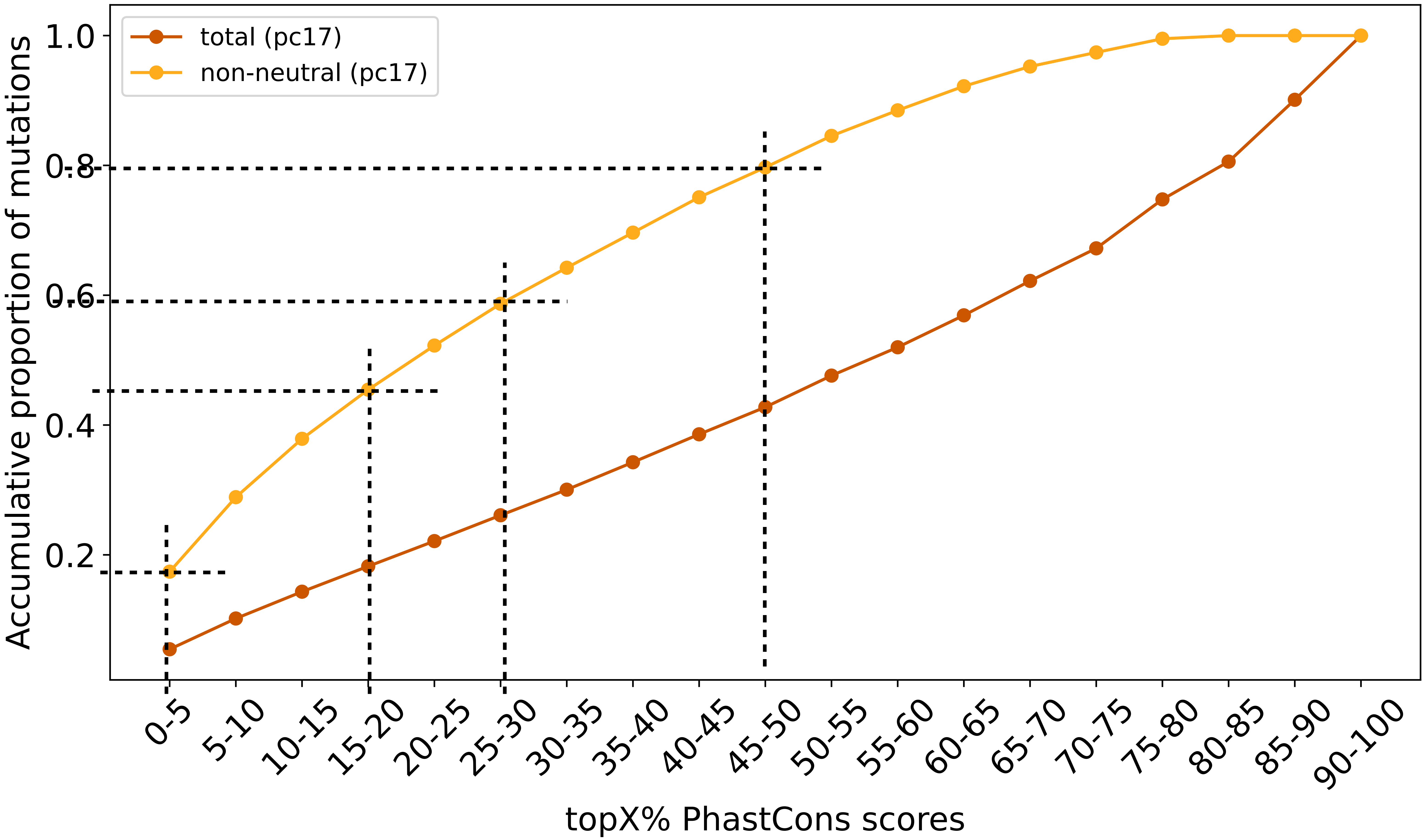
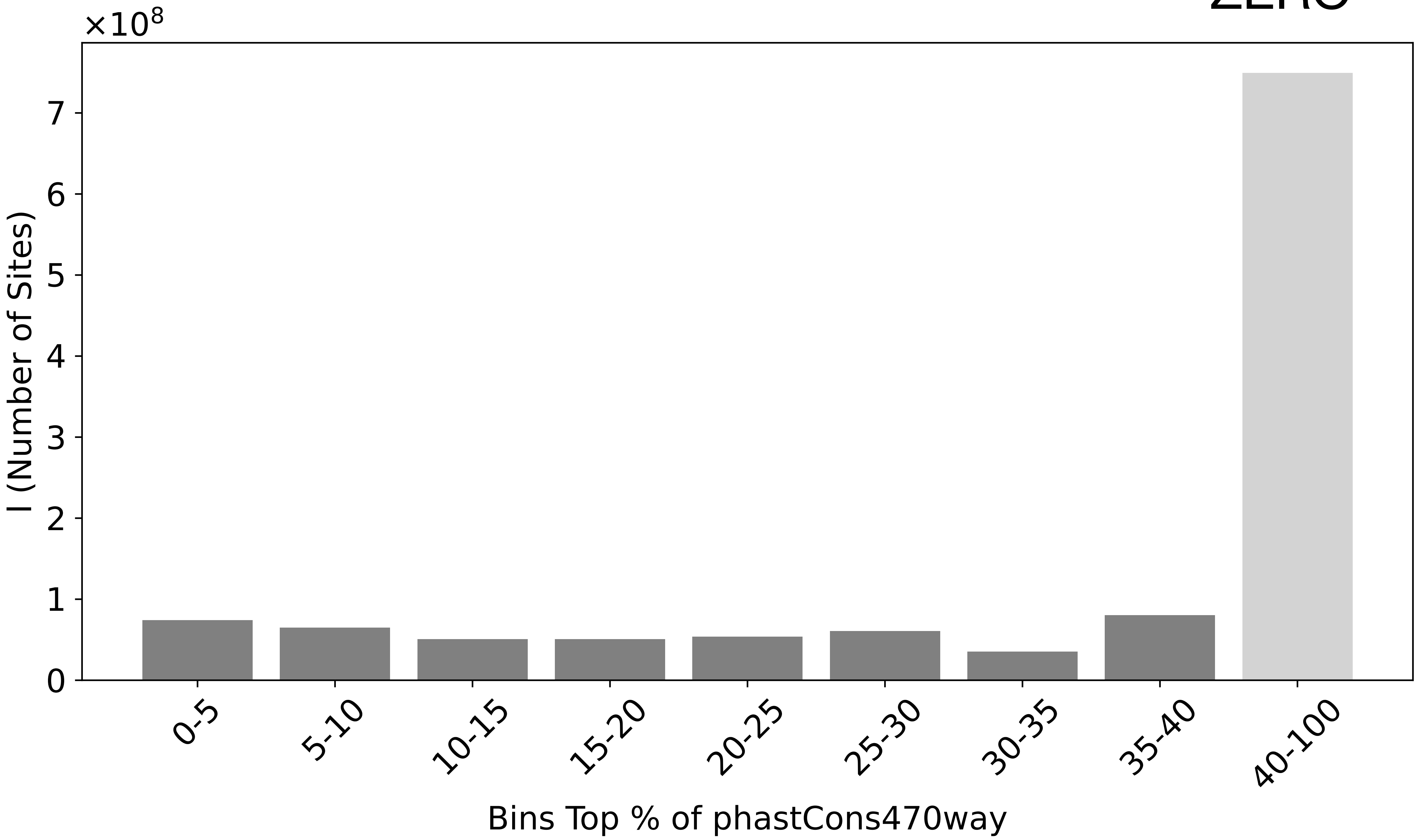


Most conserved

less conserved

Constraint in mammals

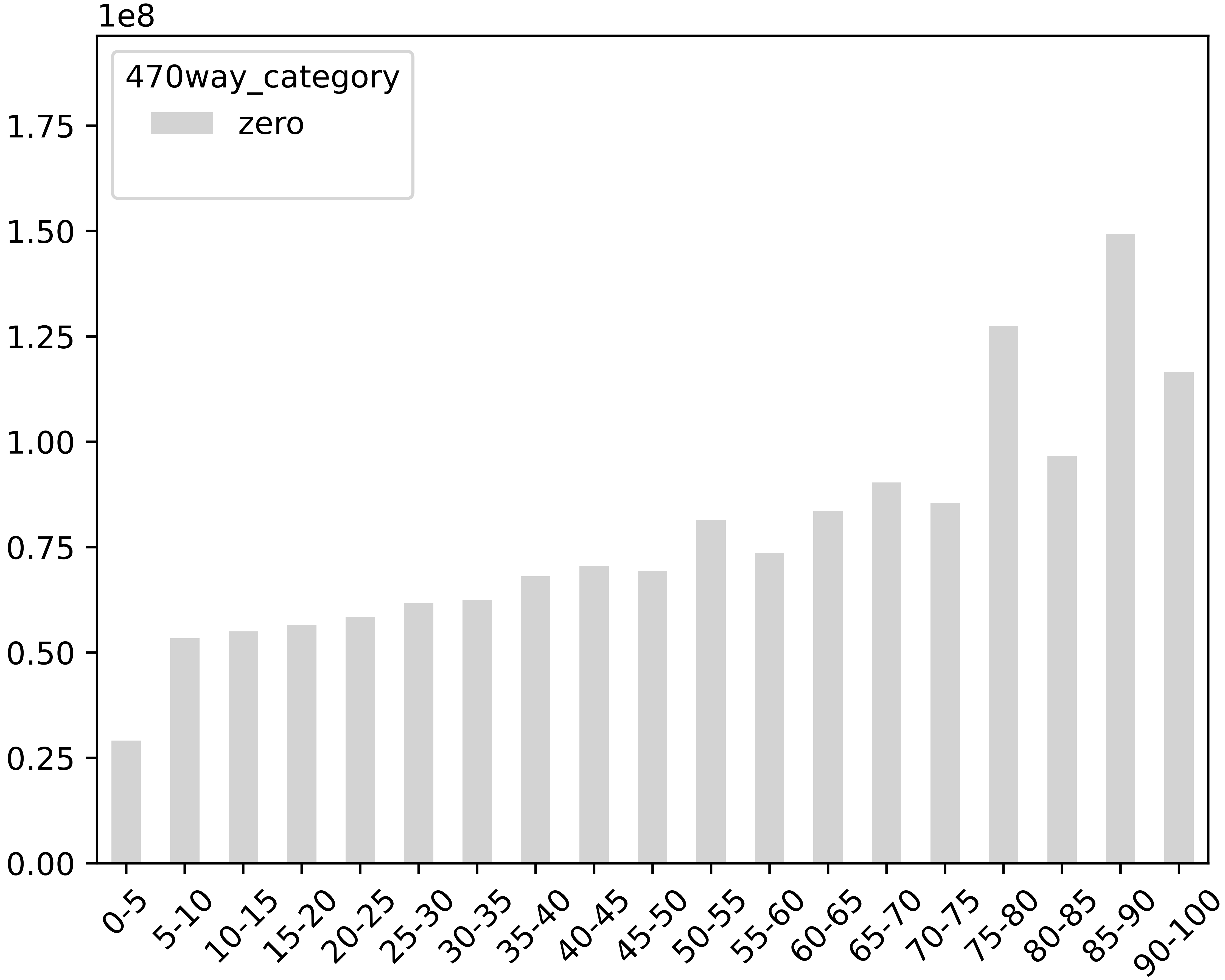


ZERO

Most conserved

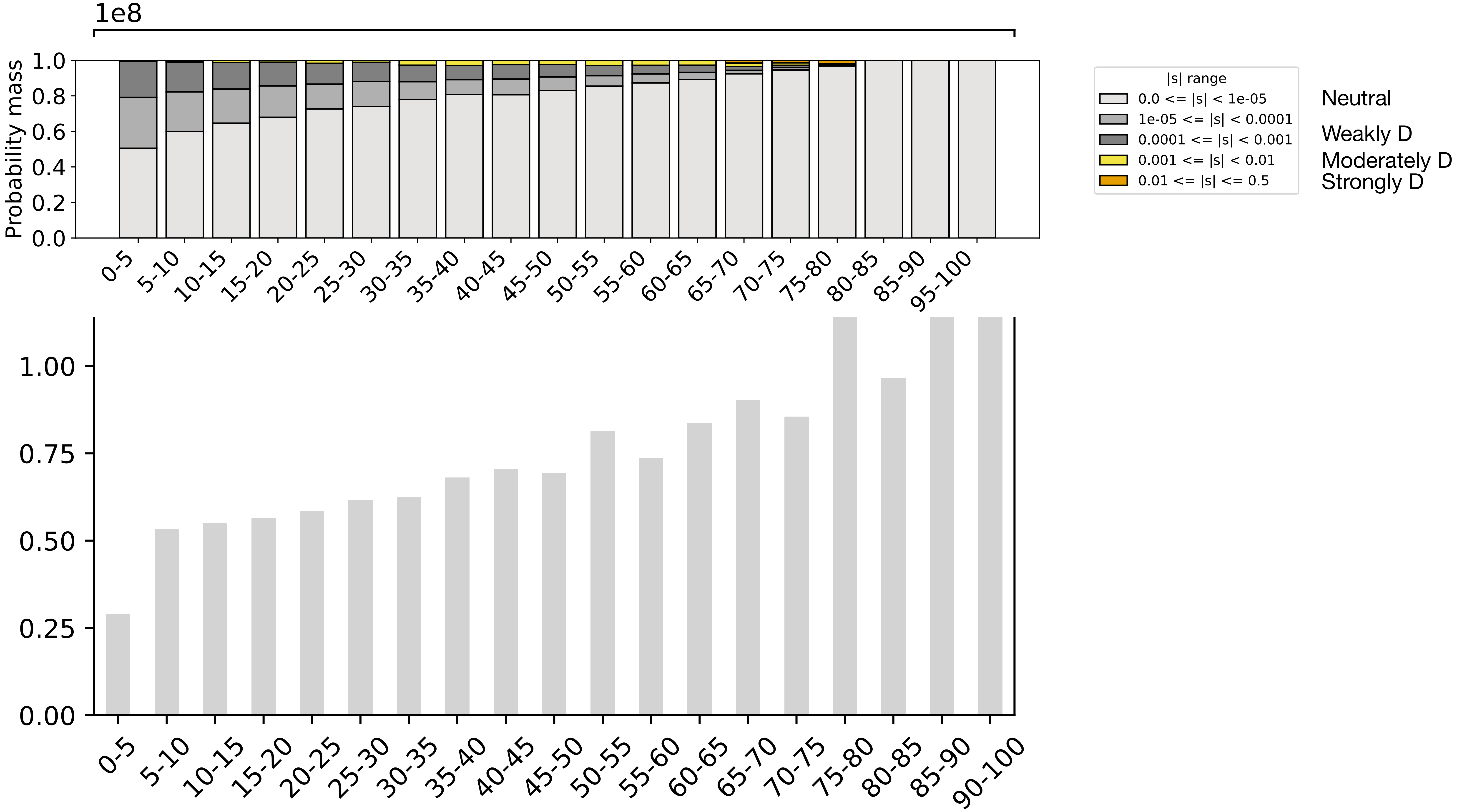
less conserved

Some non-conserved sites in mammals are conserved in primates



PastCons 470way score=0, Top X% PhastCons17way scores

Some non-conserved sites in mammals are conserved in primates



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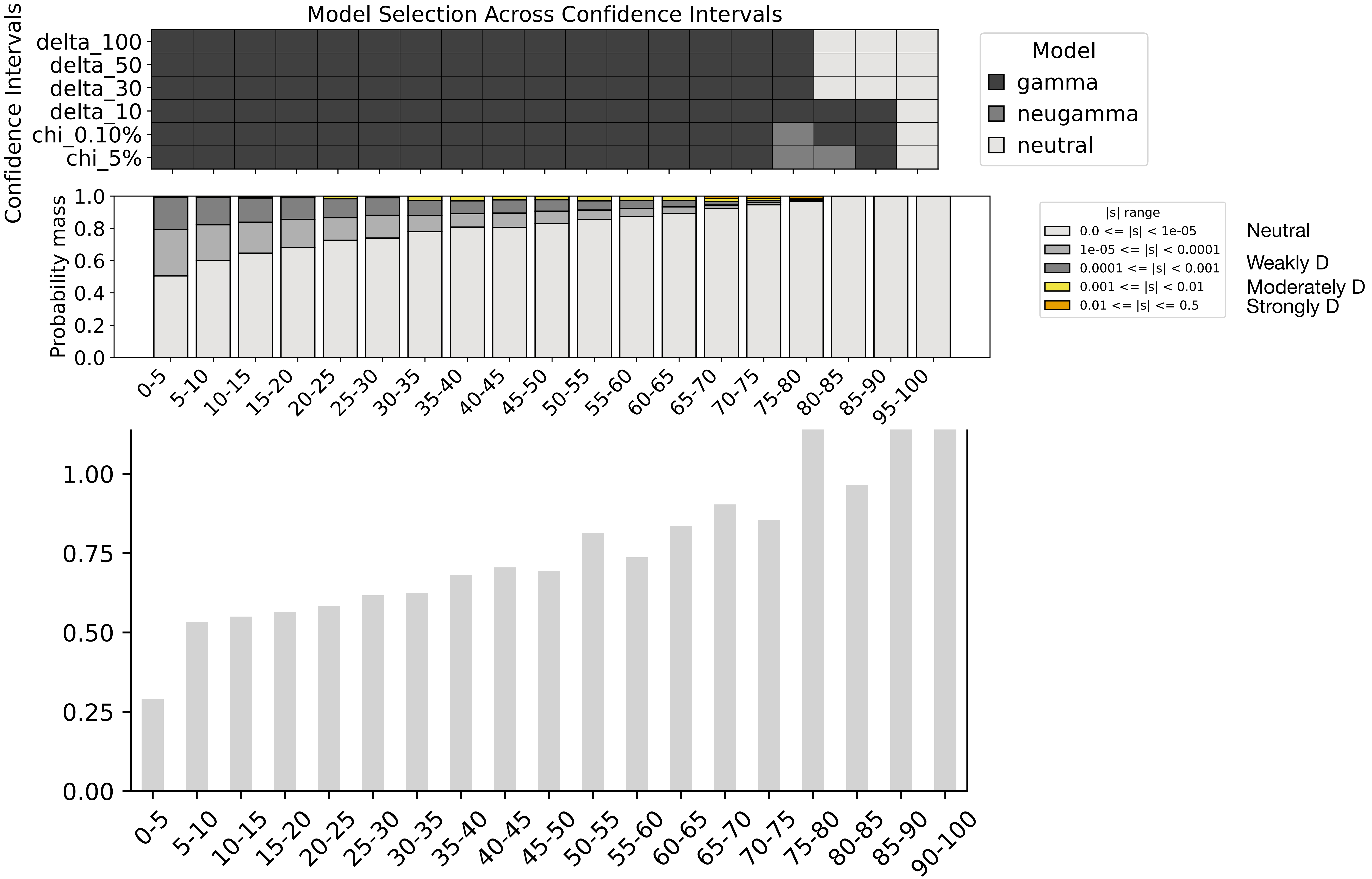
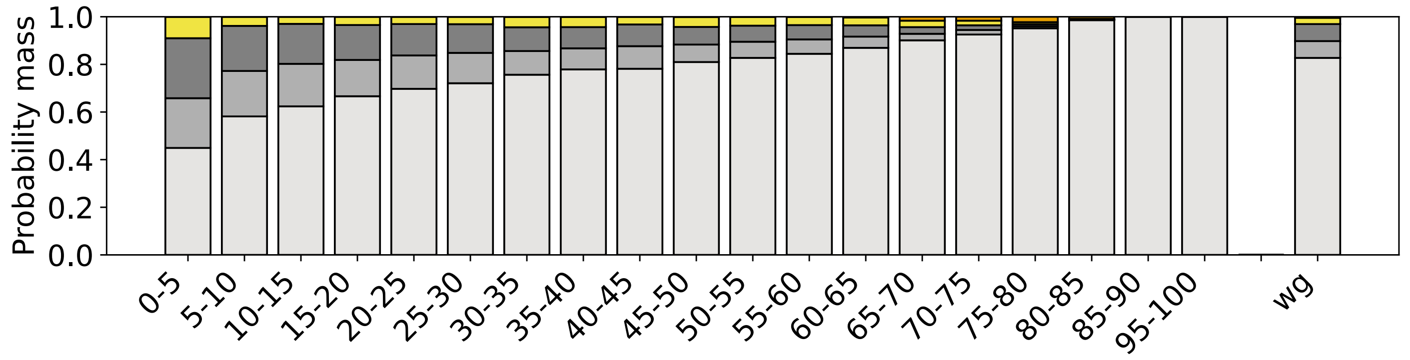
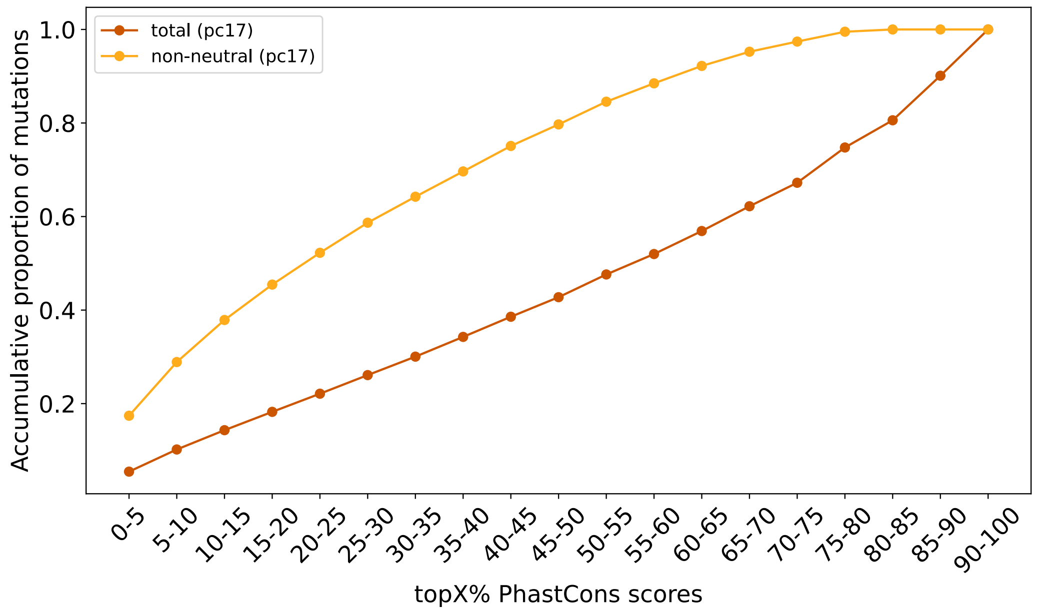


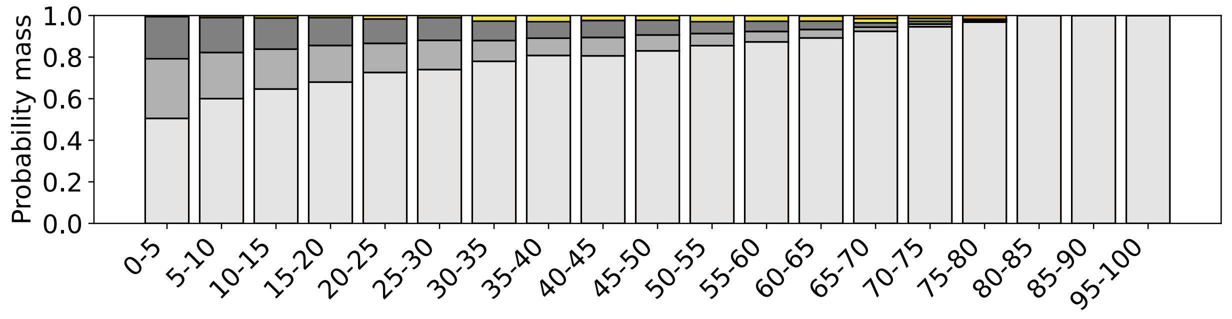
PastCons 470way score=0, Top X% PhastCons17way scores

Conclusion





non-conserved among mammals



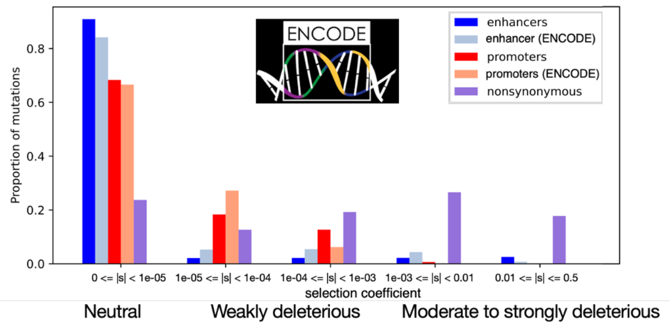
- Conserved sites —— Stronger negative selection

- Highly conserved sites only include limited deleterious mutations

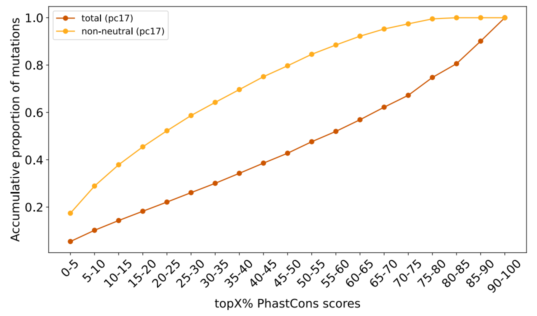
- Non-conserved in mammal but conserved in primates & negative selection in humans: A turnover of selection across evolutionary time.

Take home

- Model-based method for inferring Distribution of Fitness effects (DFE)



- DFE of functional non-coding regions



- Limited negative selection can be captured by constraint.

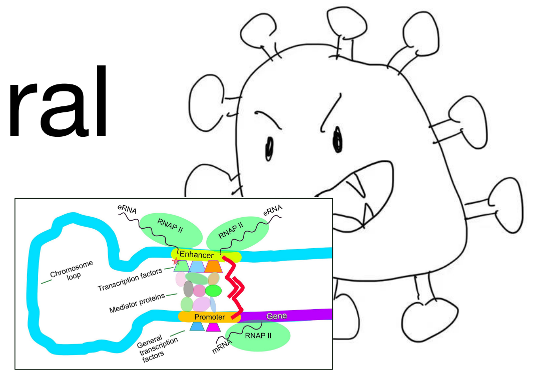
picture is from https://www.phonandroid.com/tesla-continue-de-decliner-le-cybertruck-a-toutes-les-sauces-avec-un-marteau-de-gym.html
Phylogeny is from Springer et al., 2004

Current and future work:

Kirk Lohmueller

Sriram Sankararaman

- How do regulatory elements contribute to defending against viral infections?



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Ucla

Kirk Lohmueller

Sriram Sankararaman

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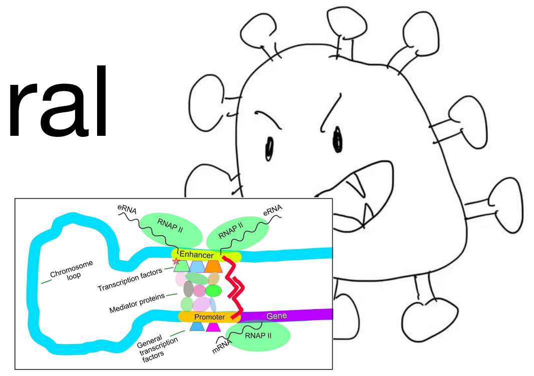

- How do proteins and REs evolve together?

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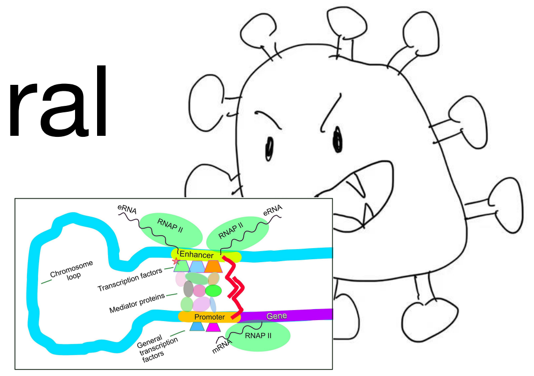
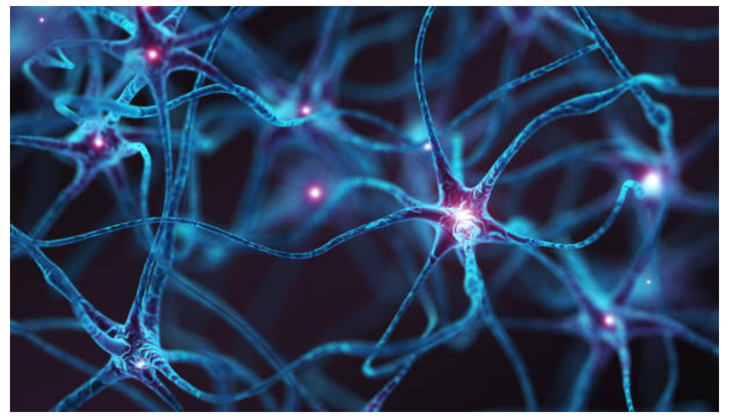


- How do proteins and REs evolve together?

Cal State

Northridge

Eduardo Guerra Amorim



Daniela Soto Jonathan Flint

- Natural selection in regulatory elements involved in different neural pathways

Gustavo Barosso Aaron Ragsdale

- Inference of background selection

Acknowledgement

Lohmueller Lab!

Kirk Lohmueller
Diana Aguilar
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Chris Kyriazis
Aina Martinez Zurita
Joh Mah
Swetha Ramesh

Thank yoU!

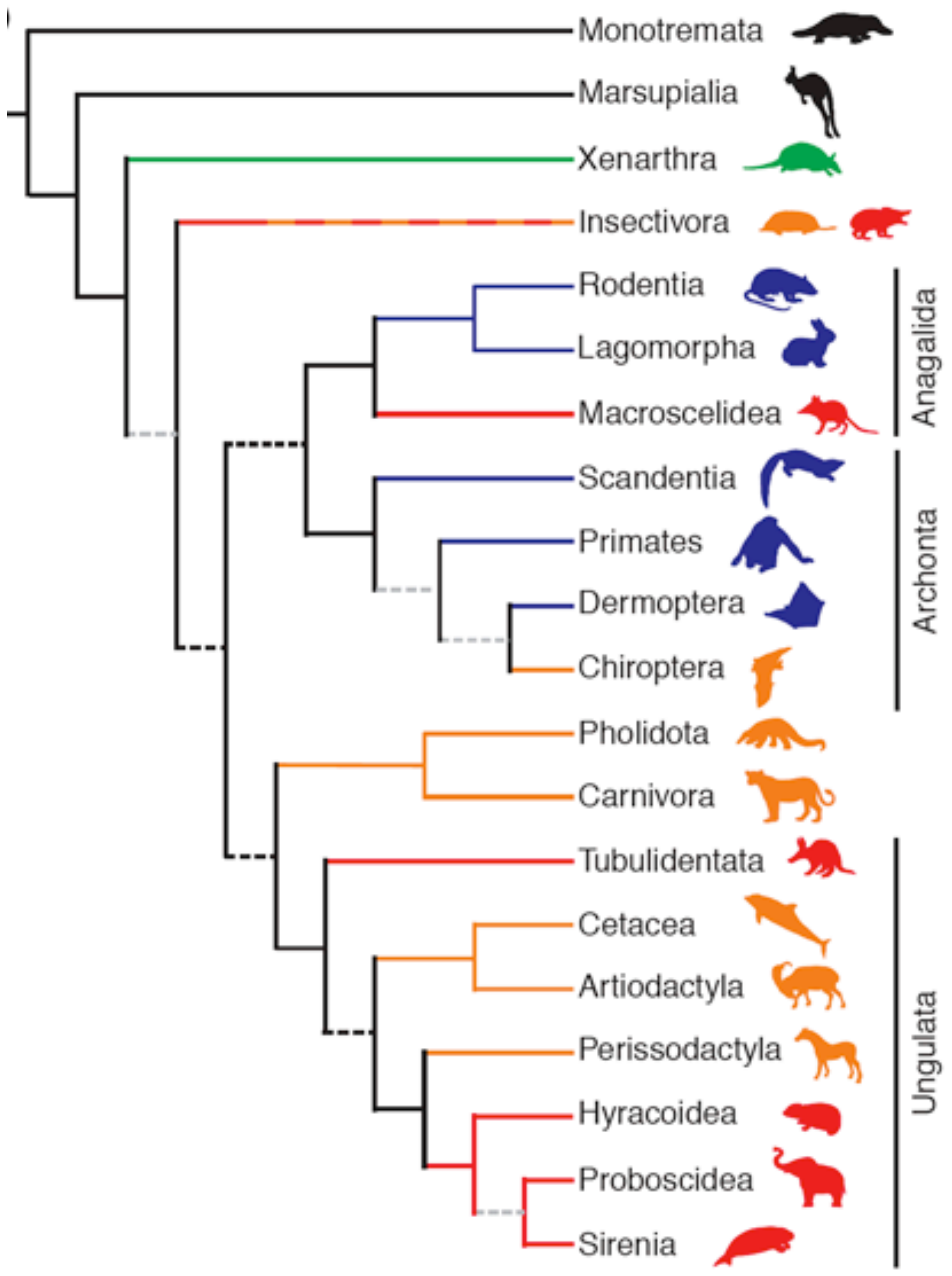
Q & A

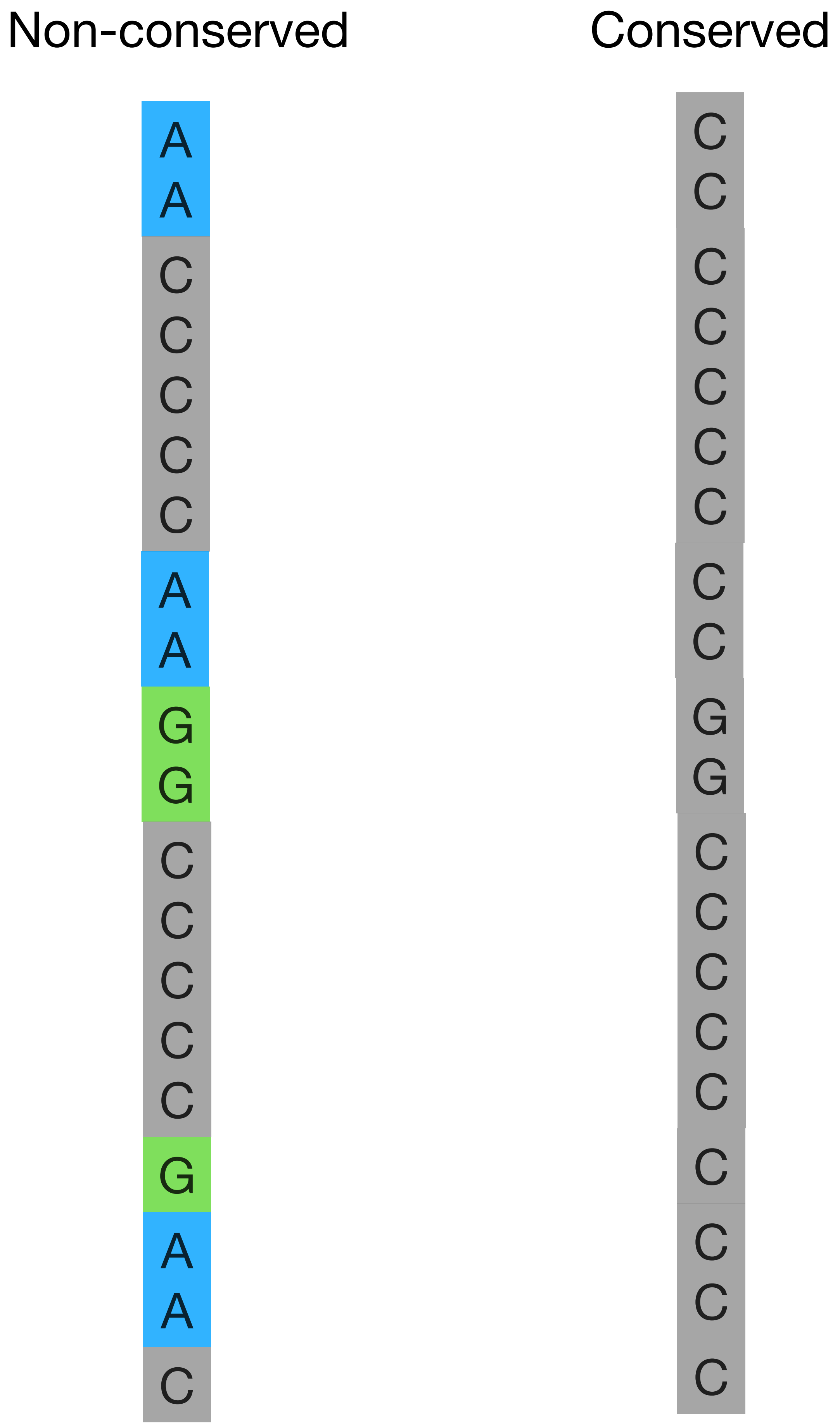
cdi@ucla.edu

X: DiChenlu

Mutations at conserved sites are more deleterious

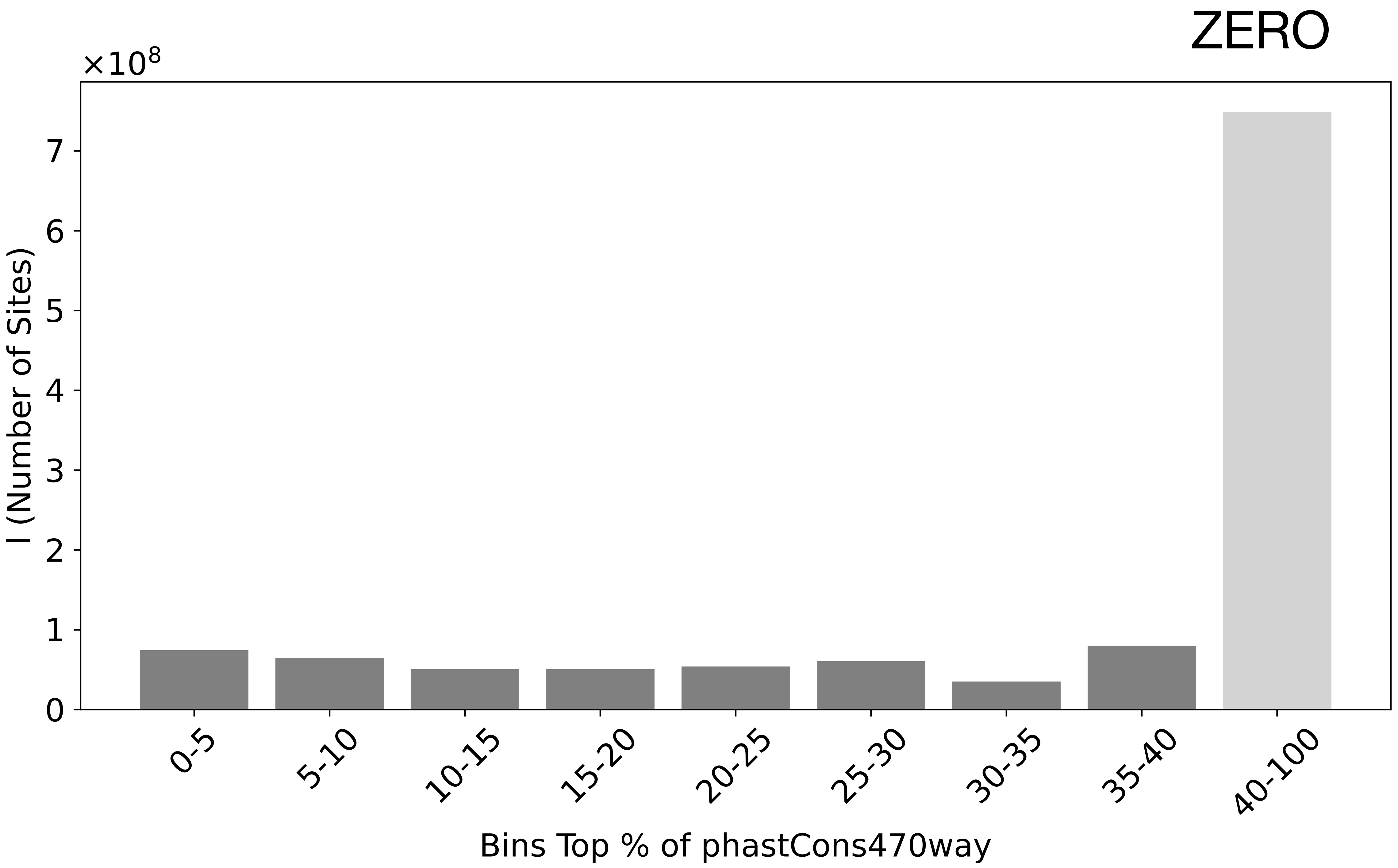
Go deeper: Mammal phylogeny

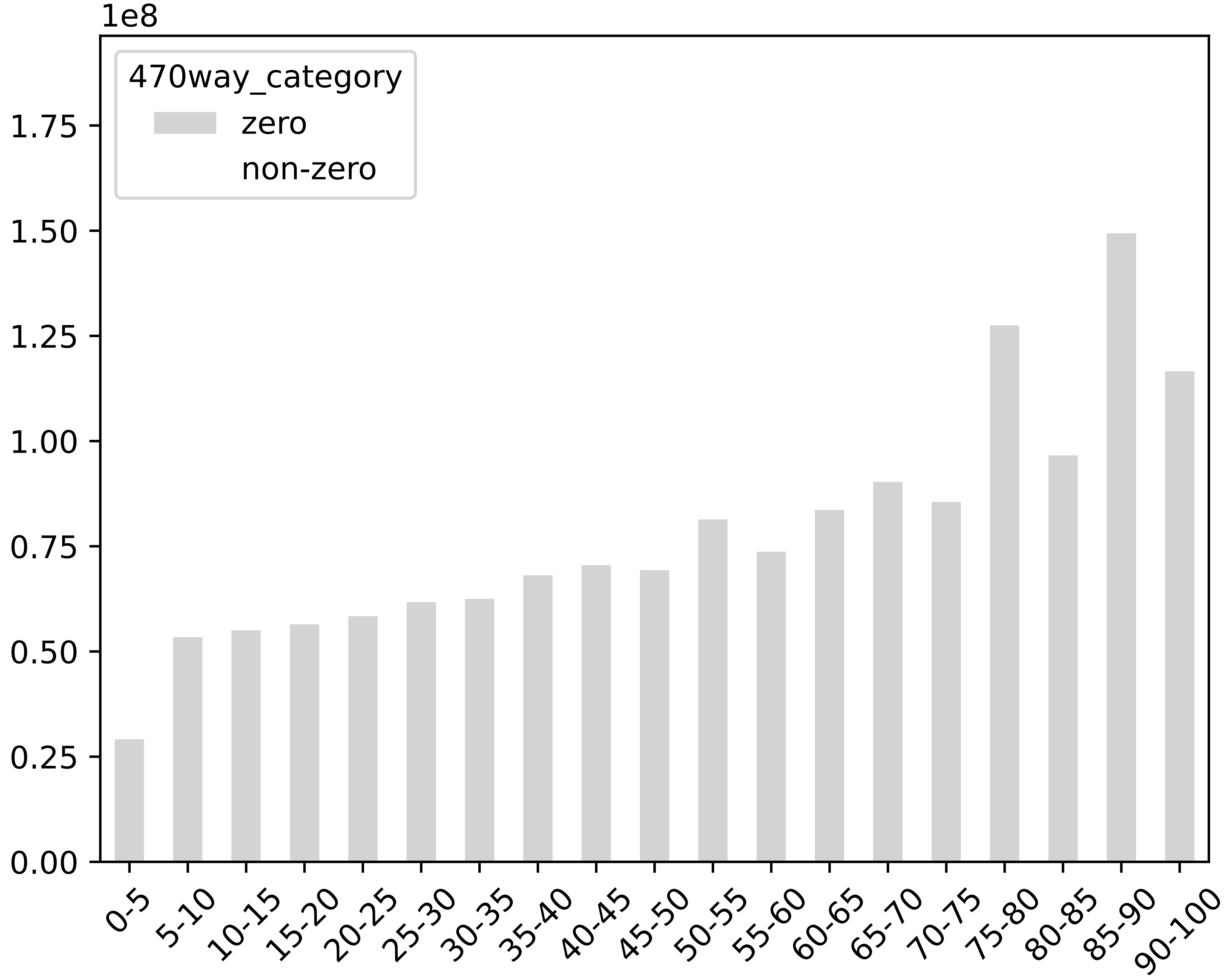




Non-conserved	Conserved
A	C
A	C
C	C
C	C
C	C
C	C
C	C
A	C
A	C
G	G
G	G
C	C
C	C
C	C
C	C
C	C
G	C
A	C
A	C
C	C

Constraint in mammals

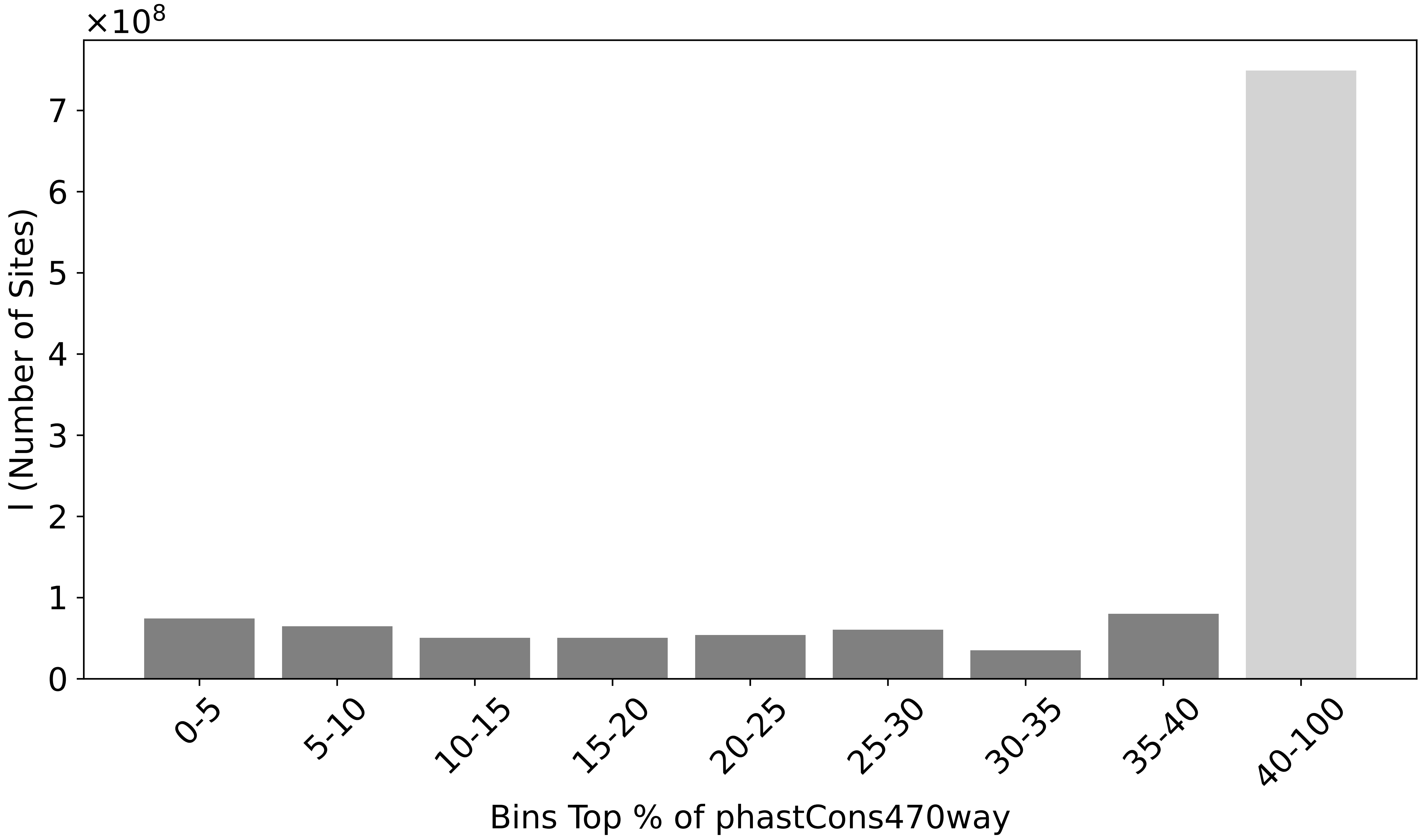


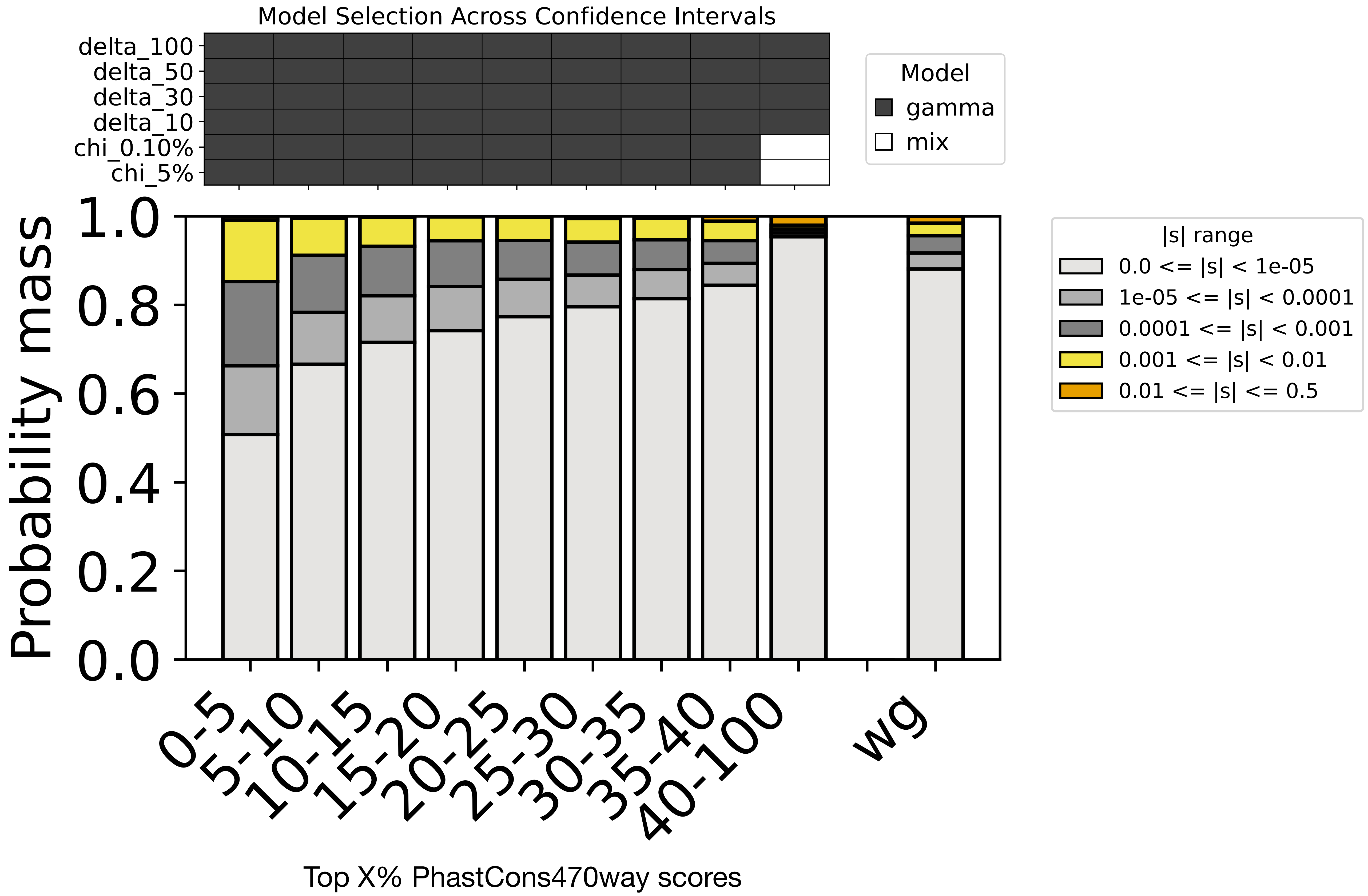


PastCons 470way score=0, Top X% PhastCons17way scores

Constraint in mammals

ZERO





Top X% PhastCons470way scores

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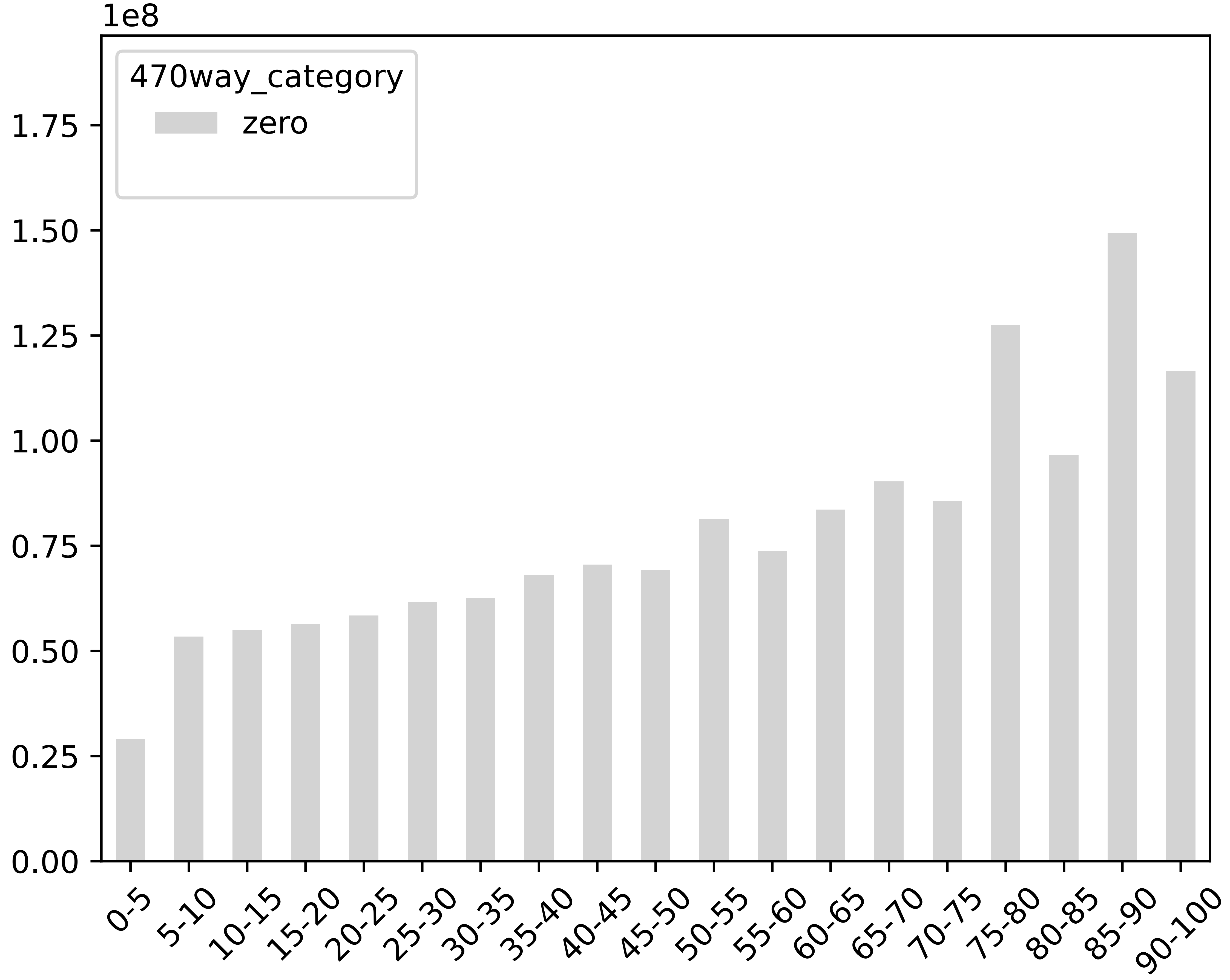

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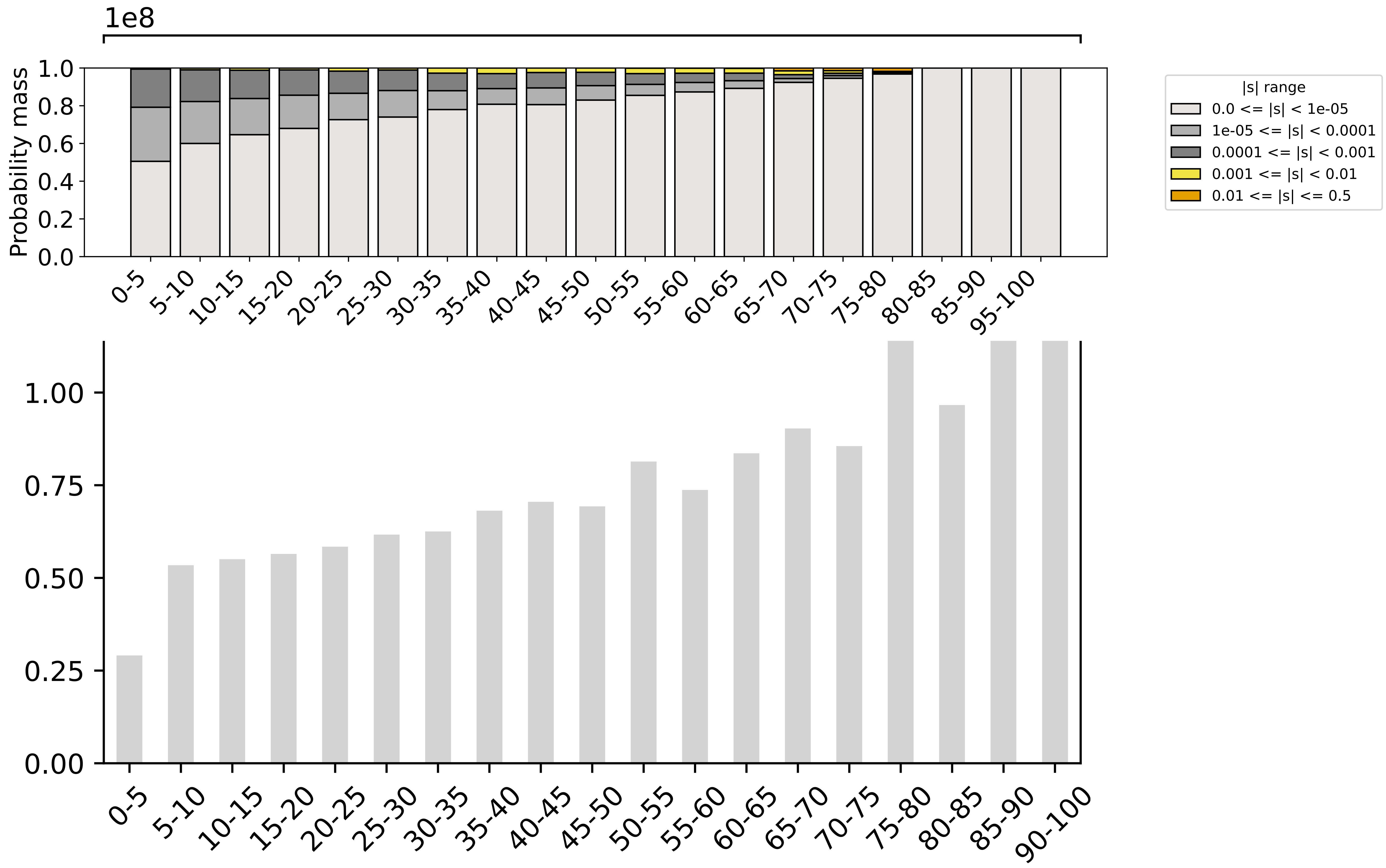

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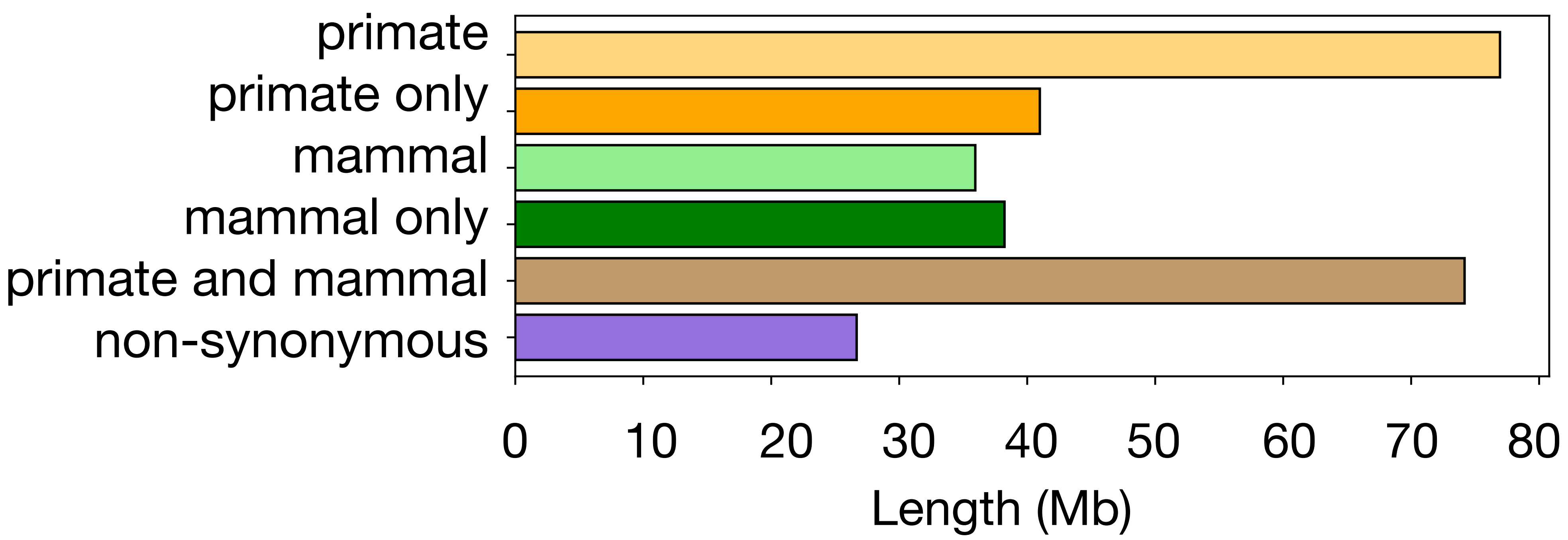
Evidence for changing selection pressures over recent time



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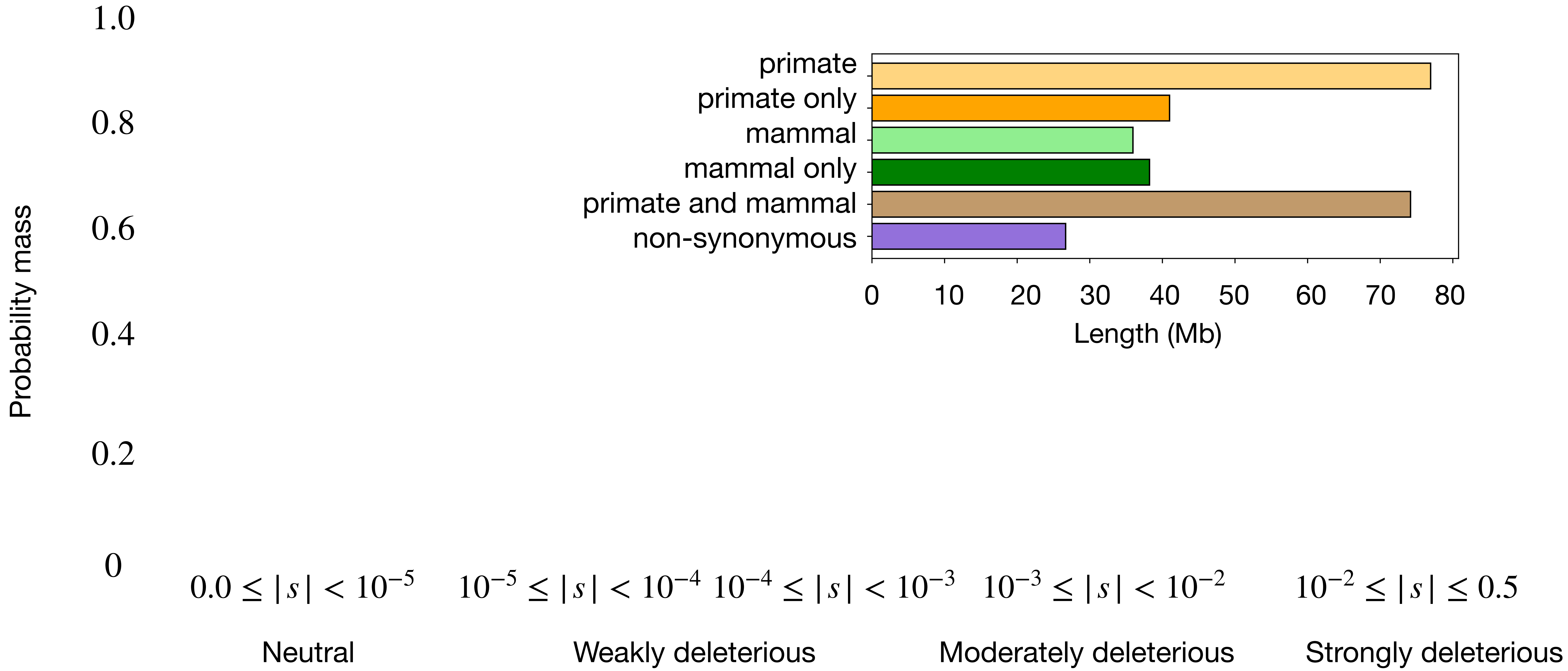
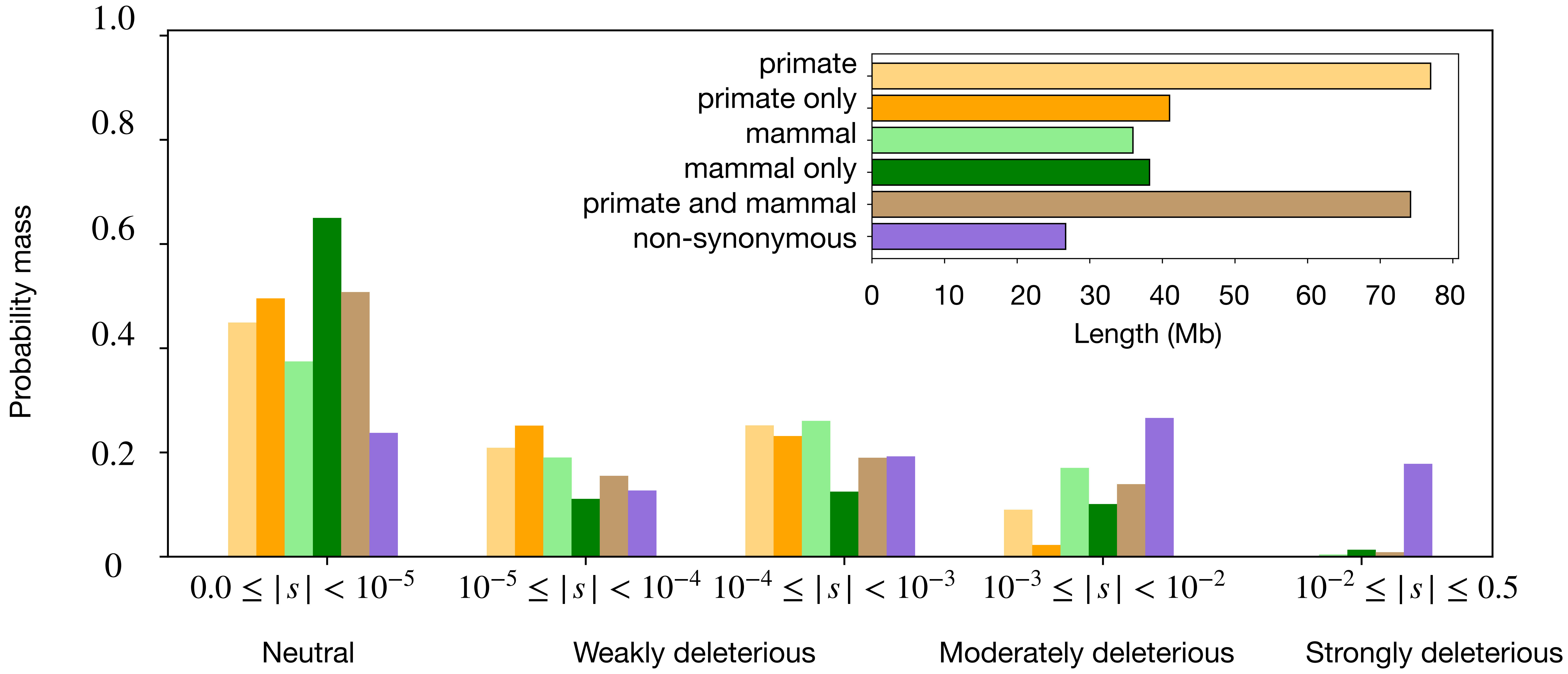


DFEs of the top 5% conserved sites

Evidence for changing selection pressures over recent time

DFEs of the top 5% conserved sites



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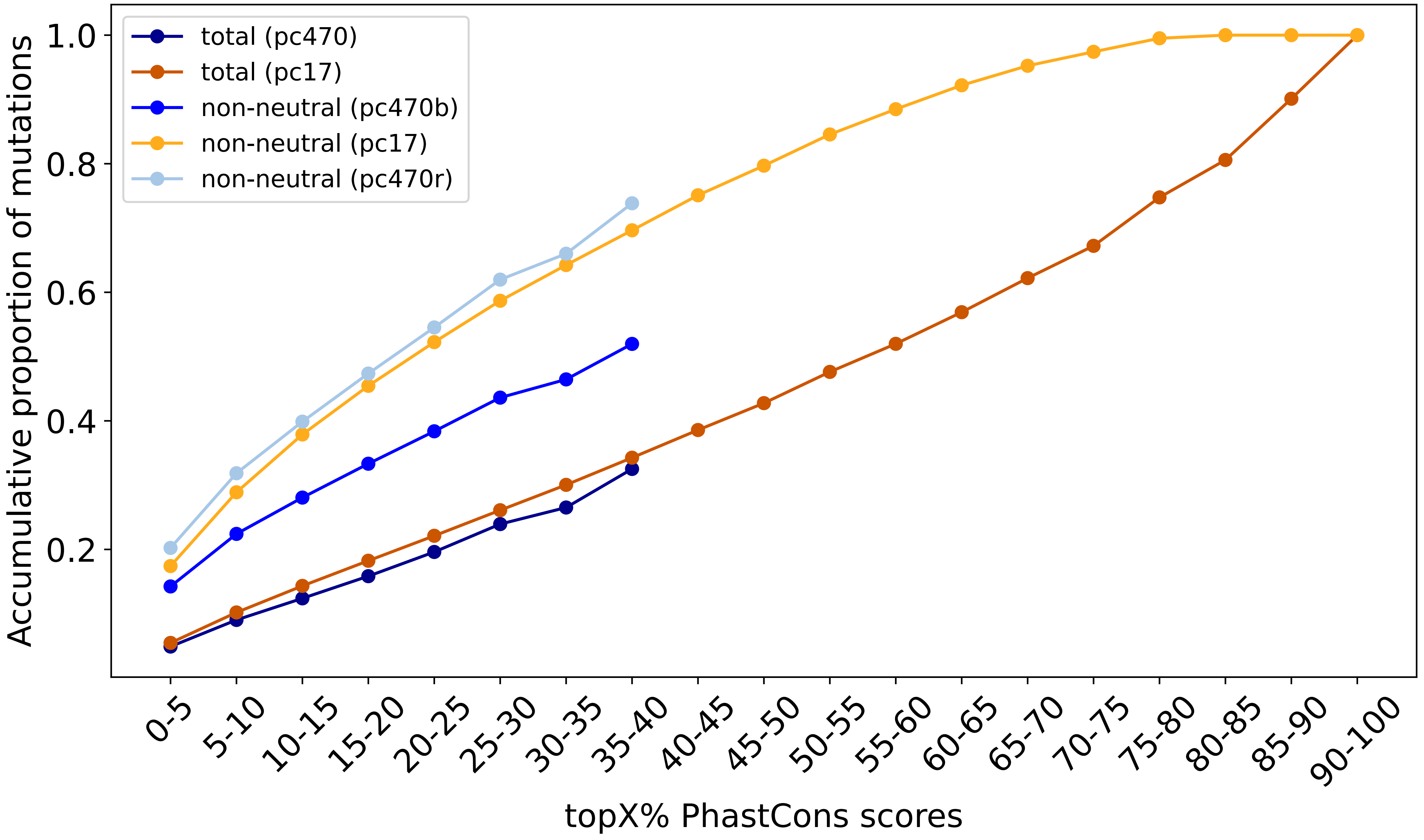
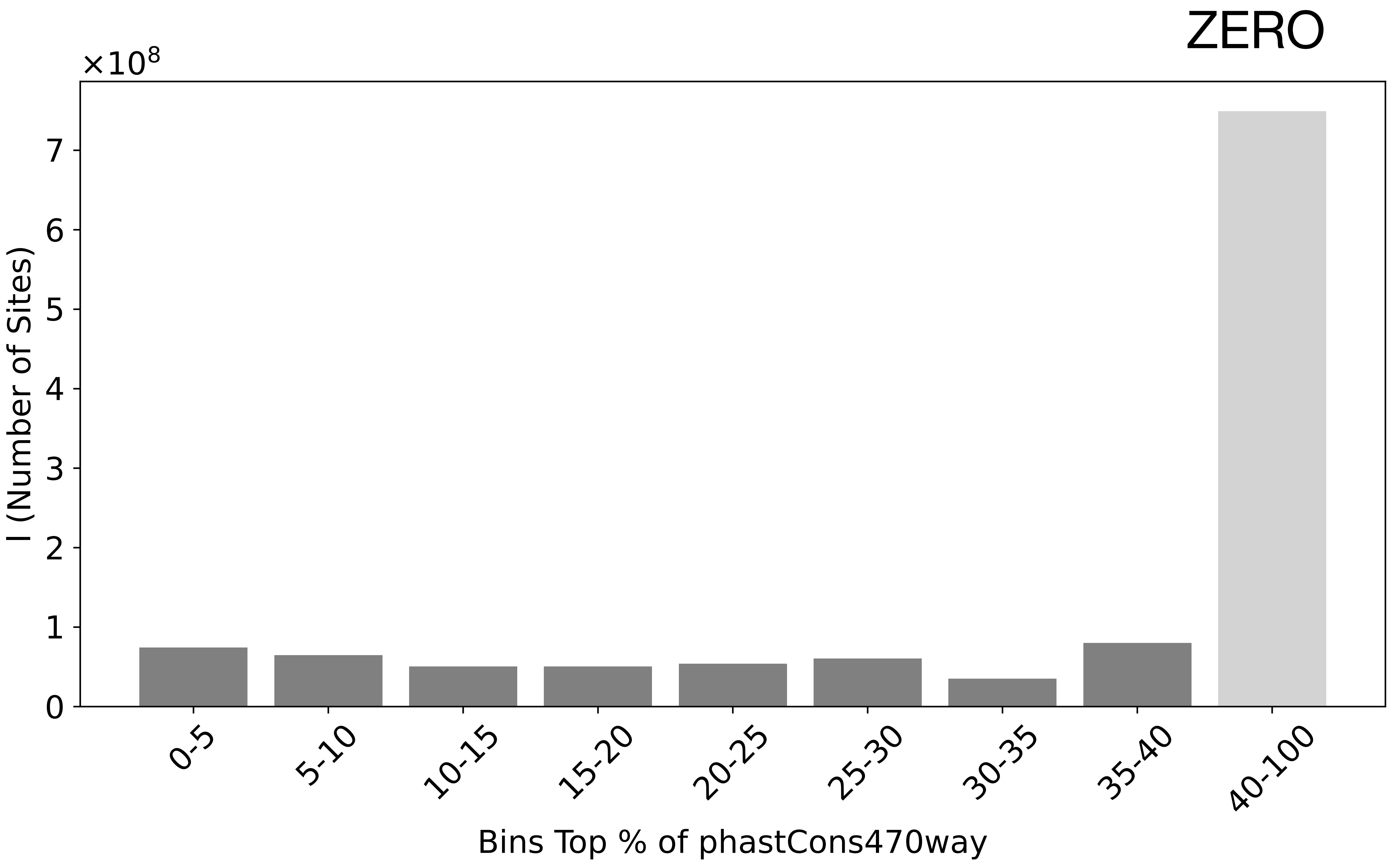


Constraint in mammals



PastCons 470way scores