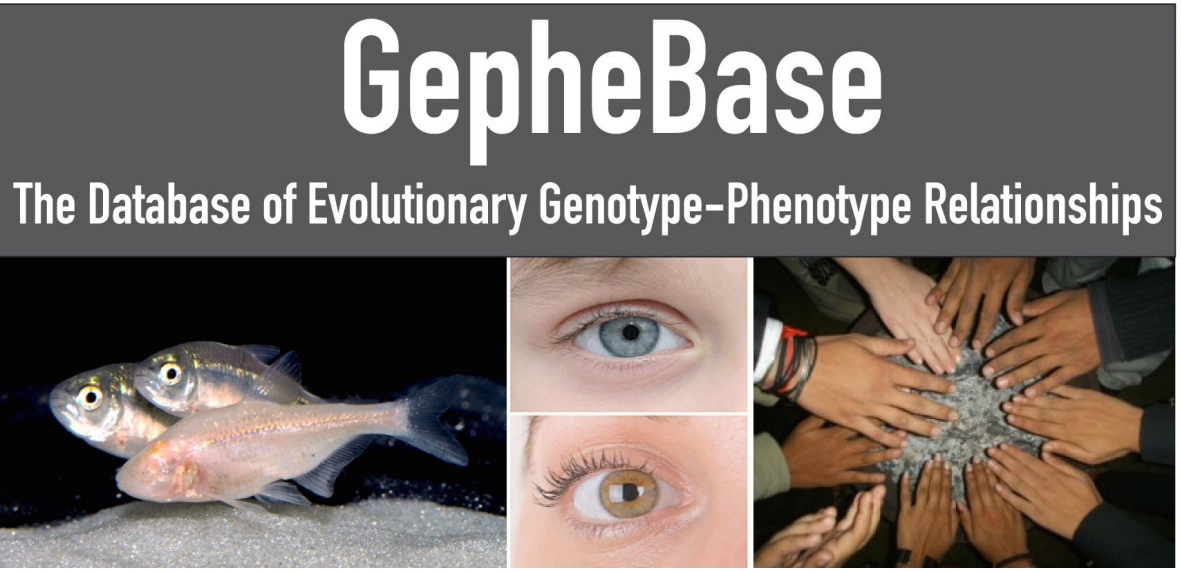
www.gephebase.org



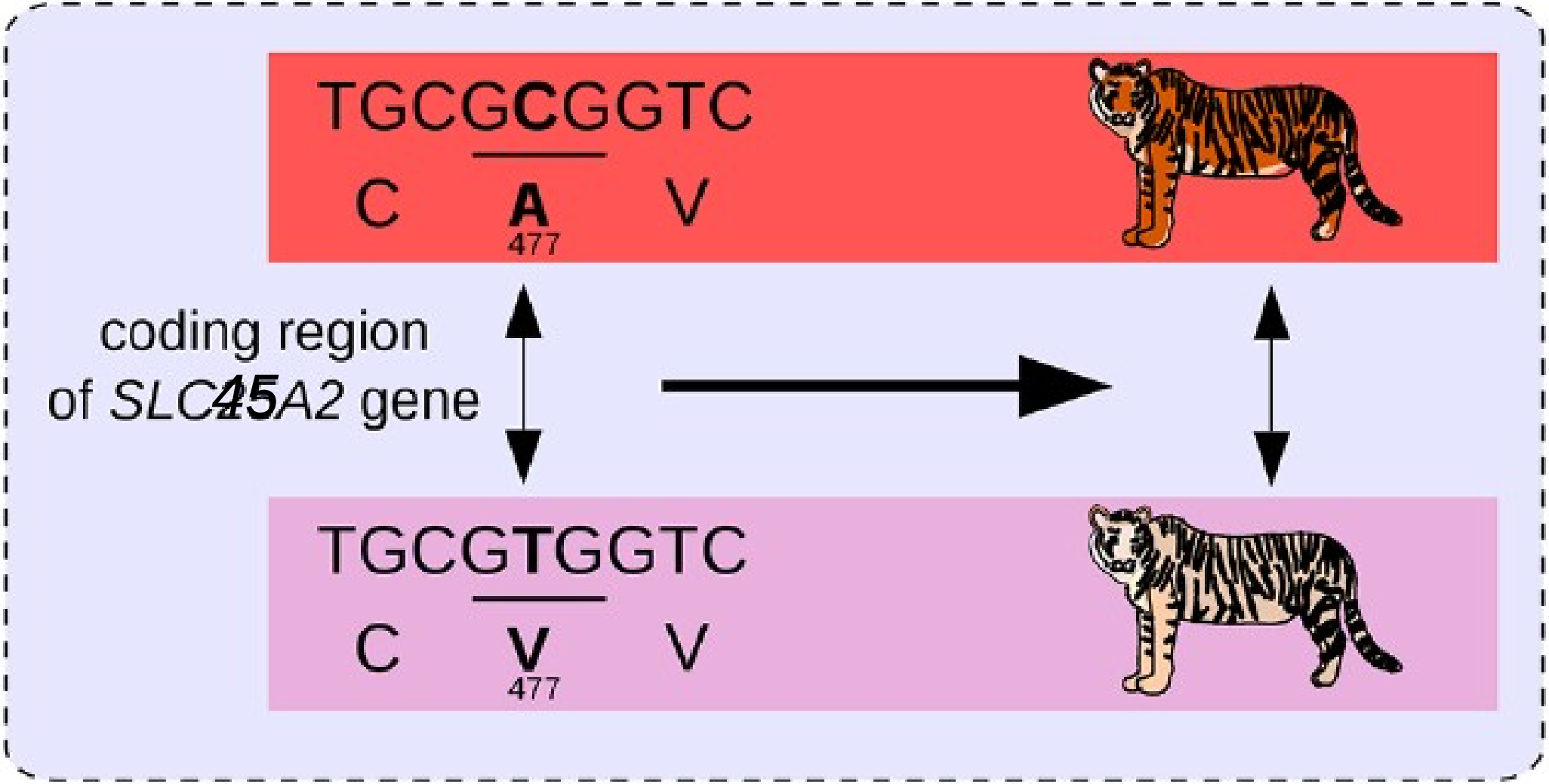
Includes Natural, Domesticated and Experimental Variation
but NO *LAB MUTANTS* and NO *CLINICAL TRAITS*

>2000 genes and mutations
associated with
natural phenotypic changes
in animals and plants

- What is Gephebase?
- Main findings so far using Gephebase
- Your work with Gephebase

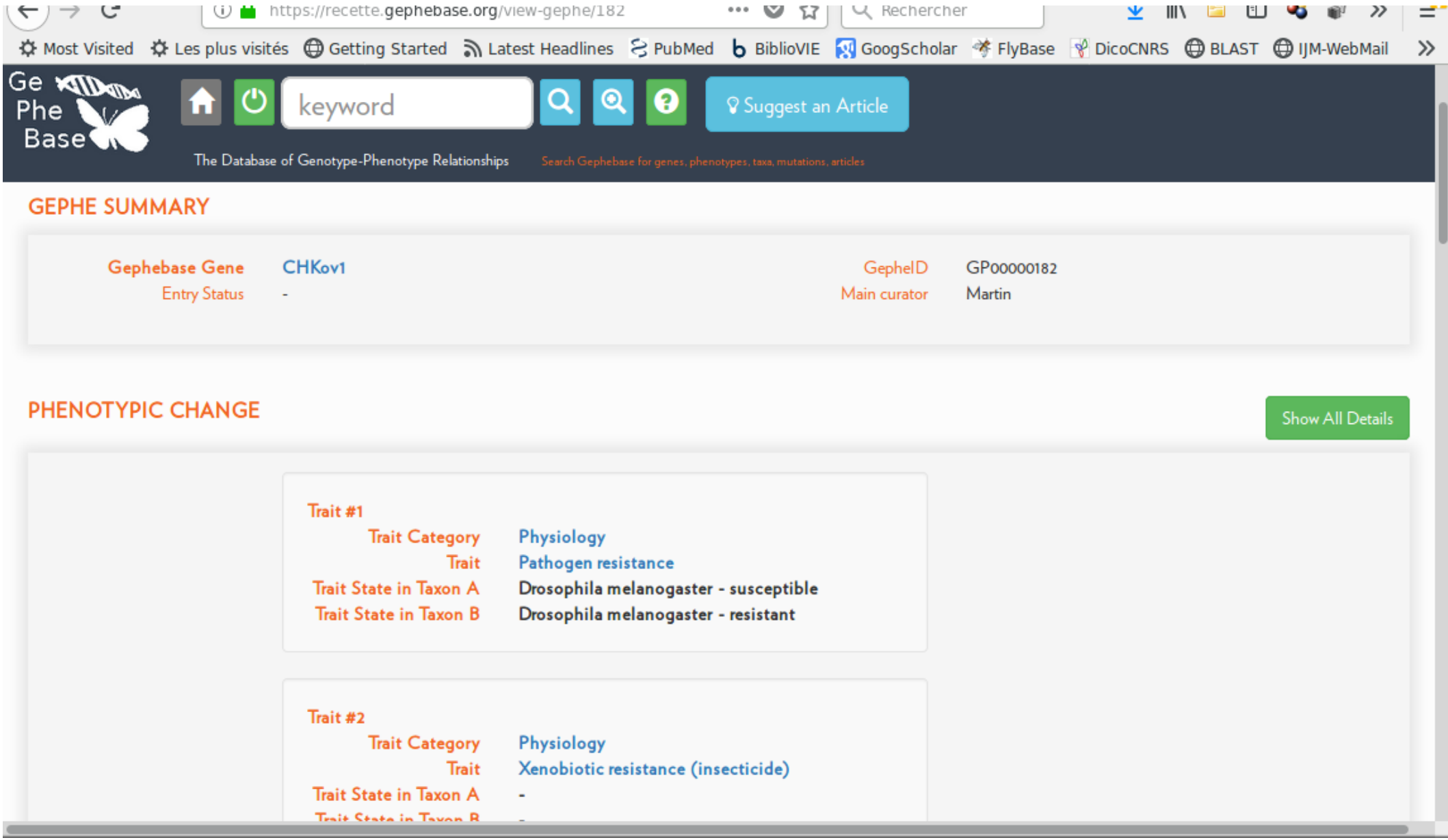
Ge-phe

a Genetic VARIATION *causing* a Phenotypic VARIATION



Orgogozo, Morizot & Martin *Frontiers Genet*. 2015

CHKov1


https://recette.gephebase.org/view-gephe/182
Rechercher
Most Visited
Les plus visités
Getting Started
Latest Headlines
PubMed
BiblioVIE
GoogScholar
FlyBase
DicoCNRS
BLAST
IJM-WebMail
Ge Phe Base
keyword
Suggest an Article
The Database of Genotype-Phenotype Relationships
Search Gephebase for genes, phenotypes, taxa, mutations, articles
GEPHE SUMMARY
Gephebase Gene
CHKov1
Entry Status
-
GepheID
GP00000182
Main curator
Martin
PHENOTYPIC CHANGE
Show All Details
Trait #1
Trait Category
Physiology
Trait
Pathogen resistance
Trait State in Taxon A
Drosophila melanogaster - susceptible
Trait State in Taxon B
Drosophila melanogaster - resistant
Trait #2
Trait Category
Physiology
Trait
Xenobiotic resistance (insecticide)
Trait State in Taxon A
-

Generic Gene Name	CHKov1
Synonyms	CG10618
String	-
Sequence Similarities	-
GO - Molecular Function	-
GO - Biological Process	-
GO - Cellular Component	-

UniProtKB Drosophila melanogaster	Q961V7
GenebankID or UniProtKB	AY047531

Presumptive Null	No
Molecular Type	Coding
Aberration Type	Insertion
Insertion Size	1-10 kb
Molecular Details of the Mutation	**Insertion of a Doc TE element resulting in novel; seemingly functional short protein**
Experimental Evidence	Linkage Mapping
Main Reference	Successive increases in the resistance of Drosophila to viral infection through a transposon insertion followed by a Duplication. (2011)
Authors	Magwire MM; Bayer F; Webster CL; Cao C; Jiggins FM
Abstract	To understand the molecular basis of how hosts evolve resistance to their parasites, we have investigated the genes that cause variation in the susceptibility of Drosophila melanogaster to viral infection. Using a host-specific pathogen of D. melanogaster called the sigma virus (Rhabdoviridae), we mapped a major-effect polymorphism to a region containing two paralogous genes called CHKov1 and CHKov2. In a panel of inbred fly lines, we found that a transposable element insertion in the protein coding sequence of CHKov1 is associated with increased resistance to infection. Previous research has shown that this insertion results in a

RELATED GEPHE

Related Genes	15 (18-wheeler, Diptericin, GNBP1, GNBP2, Immune deficiency, pastrel, PGRP-LC, SR-CII, Tehao, Acetylcholinesterase (Ace-2), alcohol dehydrogenase (Adh), Cyp12d1, cyp6g1, GSTE1-E10 cluster, resistance to dieldrin)	Related Haplotypes	No matches found.

EXTERNAL LINKS

FLYBASE	A database of drosophila genes and genomes. FBal0190391
DFAM	Open database of collection of DNA Transposable Element sequence alignments, hidden Markov Models (HMMs), consensus sequences, and genome annotations. DF0001587

COMMENTS

@TE

ADVANCED SEARCH

	Field	Term	
AND	Trait Category	Morphology	✖
AND	Molecular Type	Cis-regulatory	✖
AND	Comments	@TE	✖
AND	Aberration Type	Deletion	✖

+ Add search criteria

- [ ] Split Mutations
- [ ] Group Haplotypes
- [ ] Group Genes

Submit

Complete Export | Print

Your research retrieved 3 results.

Summary | Others

Show All Additional References

Show 100 entries

Select All	Gene	Trait	Mutation	Taxon B	Taxonomic Status	Evidence	Main Reference
☐	Kit (type III receptor protein-tyrosine kinase)	Coloration (coat)	Cis-regulatory, Deletion	*Felis catus* domestic cat - (species) D	Domesticated	Association Mapping	David VA; Menotti-Raymond M; Wallace AC ; et al. **(2014)** Endogenous retrovirus insertion in the KIT oncogene determines white and white spotting in domestic [...]
☐	VvMYBA1	Coloration (fruit)	Cis-regulatory, Deletion	*Vitis vinifera* wine grape - (species) D	Domesticated	Candidate Gene	Kobayashi S; Goto-Yamamoto N; Hirochika H **(2004)** Retrotransposon-induced mutations in grape skin color. 1 Additional References
☐	VvMYBA1	Coloration (fruit)	Cis-regulatory, Deletion	*Vitis vinifera* wine grape - (species) D	Domesticated	Candidate Gene	Ferreira V; Matus JT; Pinto-Carnide O ; et al. **(2019)** Genetic analysis of a white-to-red berry skin color reversion and its transcriptomic and metabolic c[...]

Previous 1 Next

Presumptive Null	No
Molecular Type	Cis-regulatory
Aberration Type	Deletion
Deletion Size	1-10 kb
Molecular Details of the Mutation	Excision of the full-length FERV1 elevement leaving the two LTR residues
Experimental Evidence	Association Mapping
Main Reference	Endogenous retrovirus insertion in the KIT oncogene determines white and white spotting in domestic cats. (2014)
Authors	David VA; Menotti-Raymond M; Wallace AC; Roelke M; Kehler J; Leighty R; Eizirik E; Hannah SS; et al. ... show more
Abstract	The Dominant White locus (W) in the domestic cat demonstrates pleiotropic effects exhibiting complete penetrance for absence of coat pigmentation and incomplete penetrance for deafness and iris hypopigmentation. We performed linkage analysis using a pedigree segregating White to identify KIT (Chr. B1) as the feline W locus. Segregation and sequence analysis of the KIT gene in two pedigrees (P1 and P2) revealed the remarkable retrotransposition and evolution of a feline endogenous retrovirus (FERV1) as responsible for two distinct phenotypes of the W locus, Dominant White, and white spotting. A full-length (7125 bp) FERV1 element is associated with white spotting, whereas a FERV1 long terminal repeat (LTR) is associated with all Dominant White individuals. For purposes of statistical analysis, the alternatives of wild-type sequence, FERV1 element, and LTR-only define a triallelic marker. Taking into account pedigree relationships, deafness is genetically linked and associated with this marker; estimated P values for association are in the range of 0.007 to 0.10. The retrotransposition interrupts a DNAase I hypersensitive site in KIT intron 1 that is highly conserved across mammals and was previously demonstrated to regulate temporal and tissue-specific expression of KIT in murine hematopoietic and melanocytic cells. A large-population genetic survey of cats (n = 270), representing 30 cat breeds, supports our findings and demonstrates statistical significance of the FERV1 LTR and full-length element with Dominant White/blue iris ($P < 0.0001$) and white spotting ($P < 0.0001$), respectively.

RELATED GEPHE

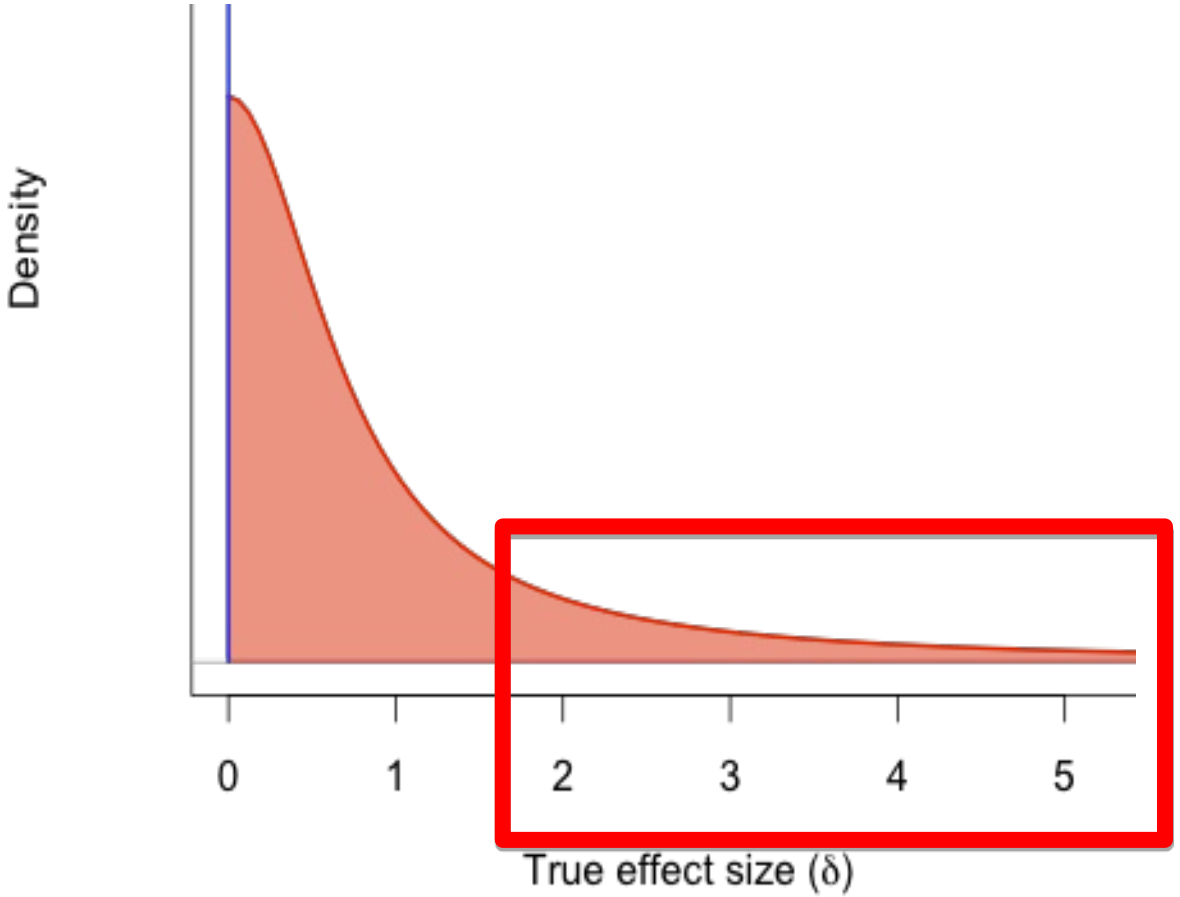
Related Genes	6 (Agouti, MC1R, Melanophilin (MLPH), Taqpep, tyrosinase (TYR), tyrosinase-related protein 1 (TYRP1))	Related Haplotypes	2

COMMENTS

@Pleiotropy @TE; Affects a conserved melanocyte enhancer

THE QTN PROGRAM AND THE ALLELES THAT MATTER FOR EVOLUTION: ALL THAT'S GOLD DOES NOT GLITTER

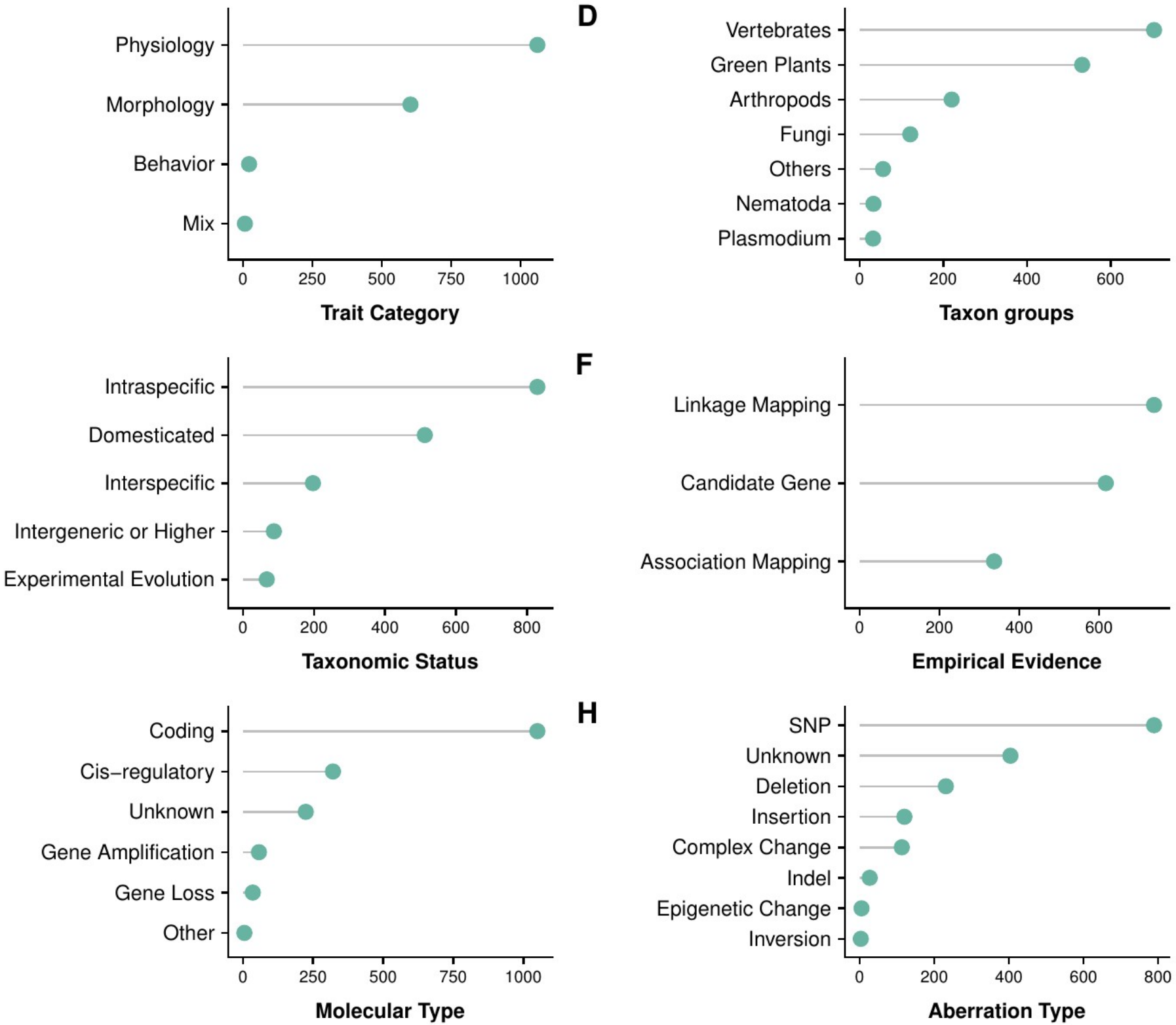
Matthew V. Rockman[1,2]



The shiny
"**large effect**" loci we can document experimentally

The Wrinkled-Seed Character of Pea Described by Mendel Is Caused by a Transposon-like Insertion in a Gene Encoding Starch-Branching Enzyme

Since 2015:
hard to keep up with all the publications…


D
Physiology
Morphology
Behavior
Mix
0
250
500
750
1000
Trait Category
Vertebrates
Green Plants
Arthropods
Fungi
Others
Nematoda
Plasmodium
0
200
400
600
Taxon groups
F
Intraspecific
Domesticated
Interspecific
Intergeneric or Higher
Experimental Evolution
0
200
400
600
800
Taxonomic Status
Linkage Mapping
Candidate Gene
Association Mapping
0
200
400
600
Empirical Evidence
H
Coding
Cis−regulatory
Unknown
Gene Amplification
Gene Loss
Other
0
250
500
750
1000
Molecular Type
SNP
Unknown
Deletion
Insertion
Complex Change
Indel
Epigenetic Change
Inversion
0
200
400
600
800
Aberration Type

Experimental Evidence

3 categories, each with biases

	Candidate Gene	Linkage Mapping	Association Mapping
Experimental Principle	**Reverse Genetics**: looking for sequence differences and trait effects based on previous studies of a given gene	**Forward Genetics**: trait mapping in hybrids obtained from laboratory crosses, using recombination over a few generations	**Forward Genetics**: statistical SNP/character state association in large cohorts, using recombination over many generations
Example	66 cases of color variation associated to *MC1R* coding mutations in vertebrates	F2 crosses between melanic and amelanic phenotypes in cavefish : identification of *MC1R* and *Oca2* alleles in distinct cave populations	GWAS of human pigmentation (skin, hair, eyes): identification and confirmation of causal variants at >15 genes including *Oca2* p.His615Arg in Eastern Asia
Ascertainment Bias on Locus Identification	**High**	**Low to Intermediate** (depending on resolution / cross size)	**Low**
Molecular Type Bias	Favors identification of **coding mutations**	Little molecular bias	Can miss structural variants (short read genotyping)
Trait Type Bias	Favors traits with small molecular targets, large-effect size	Amenable to dissection of complex traits with small-effect size (large crosses, multiparental families)	Most common approach for complex traits with small-effect size
Taxonomic Breadth	**Large**	**Narrow**, limited to interfertile lineages (populations or sister species)	**Very narrow**, limited to polymorphic or intermixing populations

Gephebase can be used in various ways

- as a powerful bibliographic tool

- as a place to formulate hypotheses

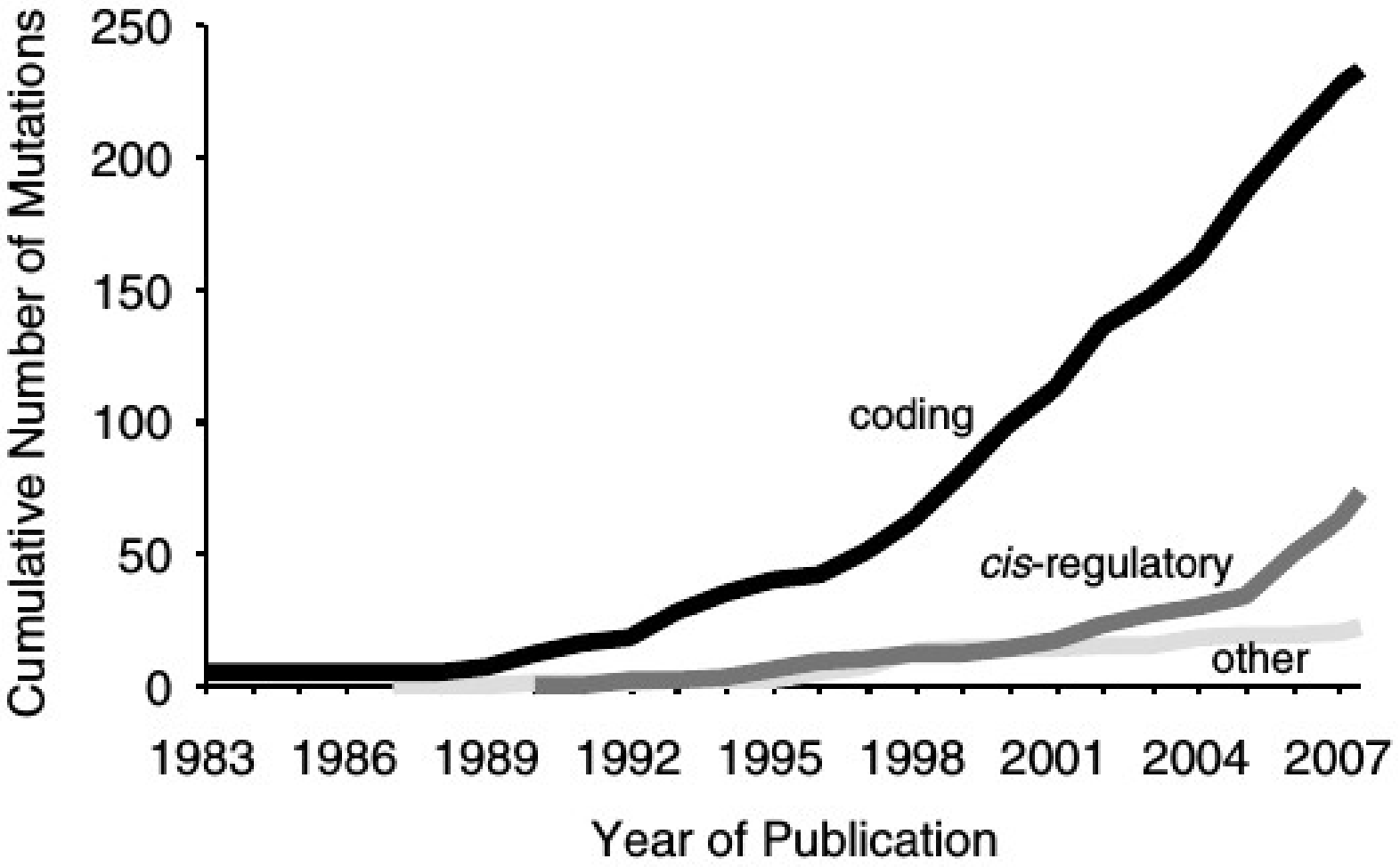
- as a list of potential targets for breeders interested in transferring traits of interest to new species

- as an extensive compilation for broad meta-analyses on the genetic loci of evolution

- as a resource for epistemologists interested in biases and sociological aspects in the field of genetic evolution

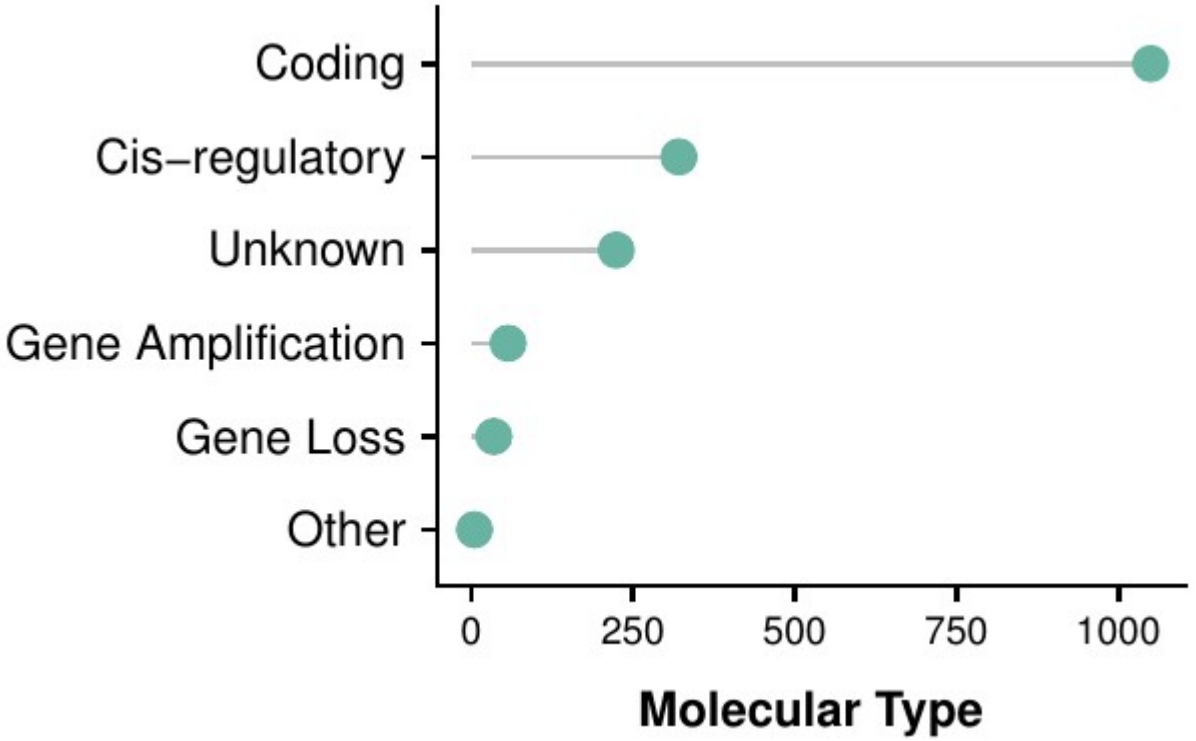
- What is Gephebase?
- Main findings so far using Gephebase
- Your work with Gephebase

More known cases of coding than cis-regulatory mutations



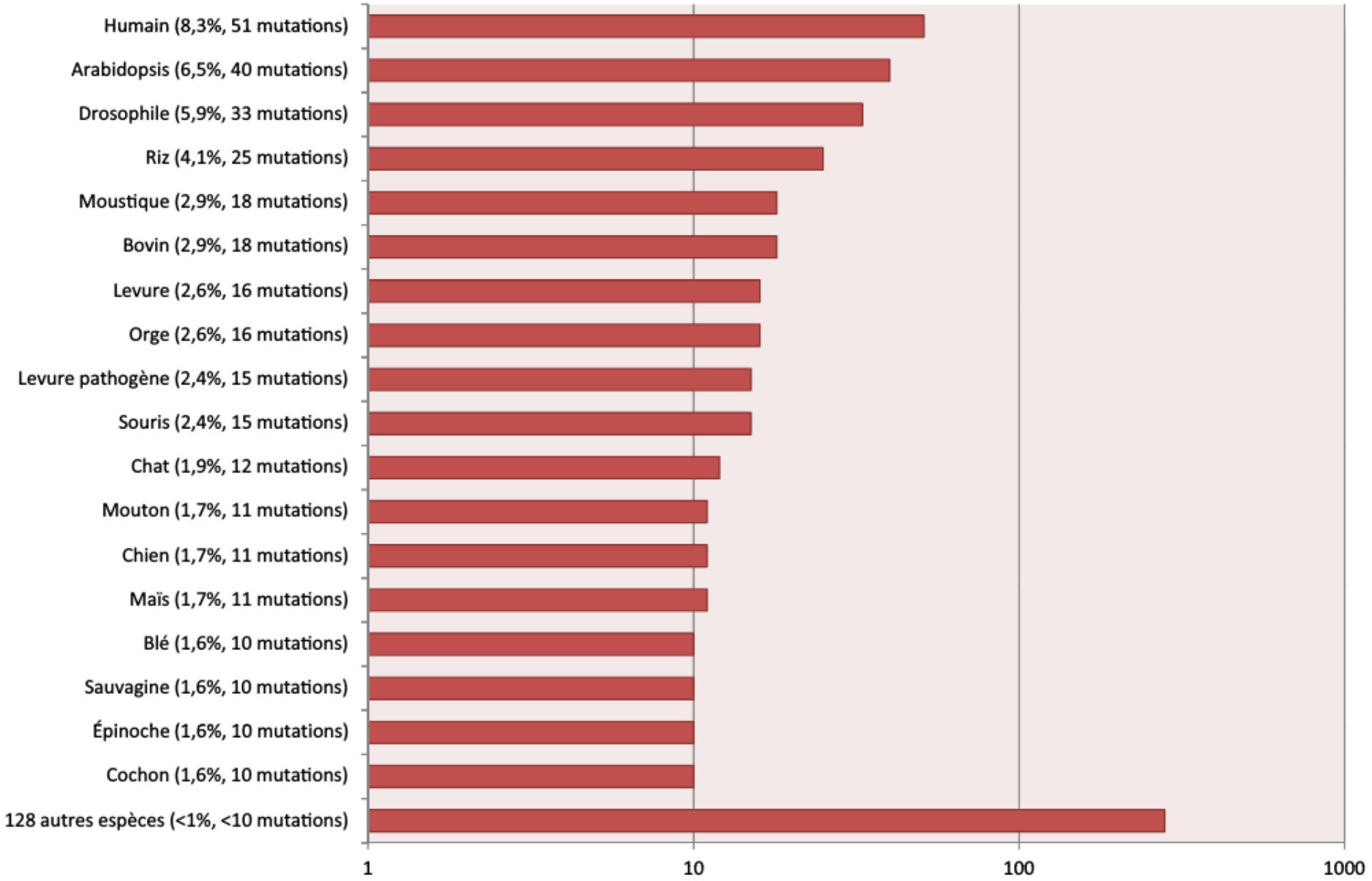
2008: survey of ~300 articles

Stern and Orgogozo 2008 Evolution



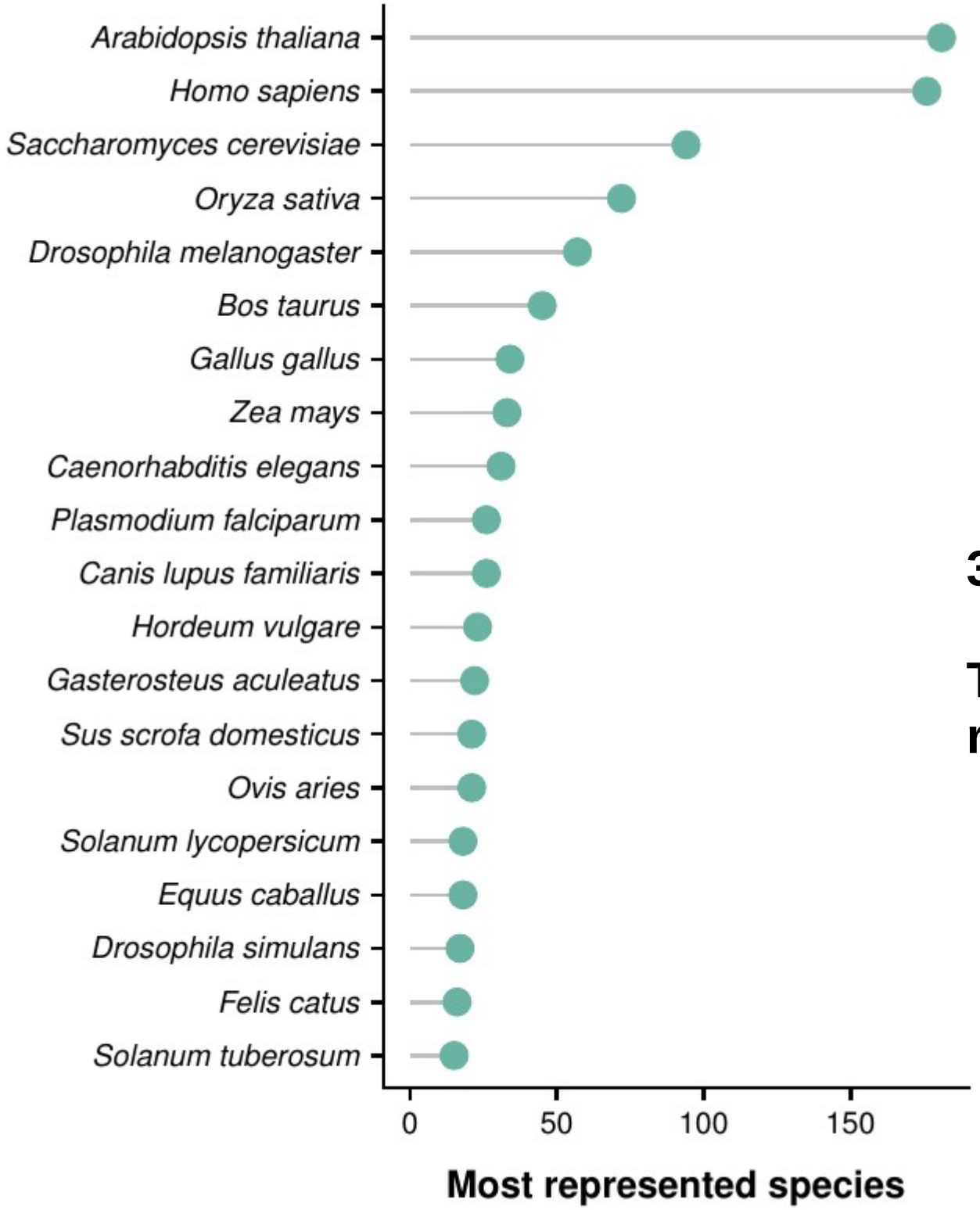
Courtier-Orgogozo et al NAR 2019

Bias towards certain species



survey of 1000 articles

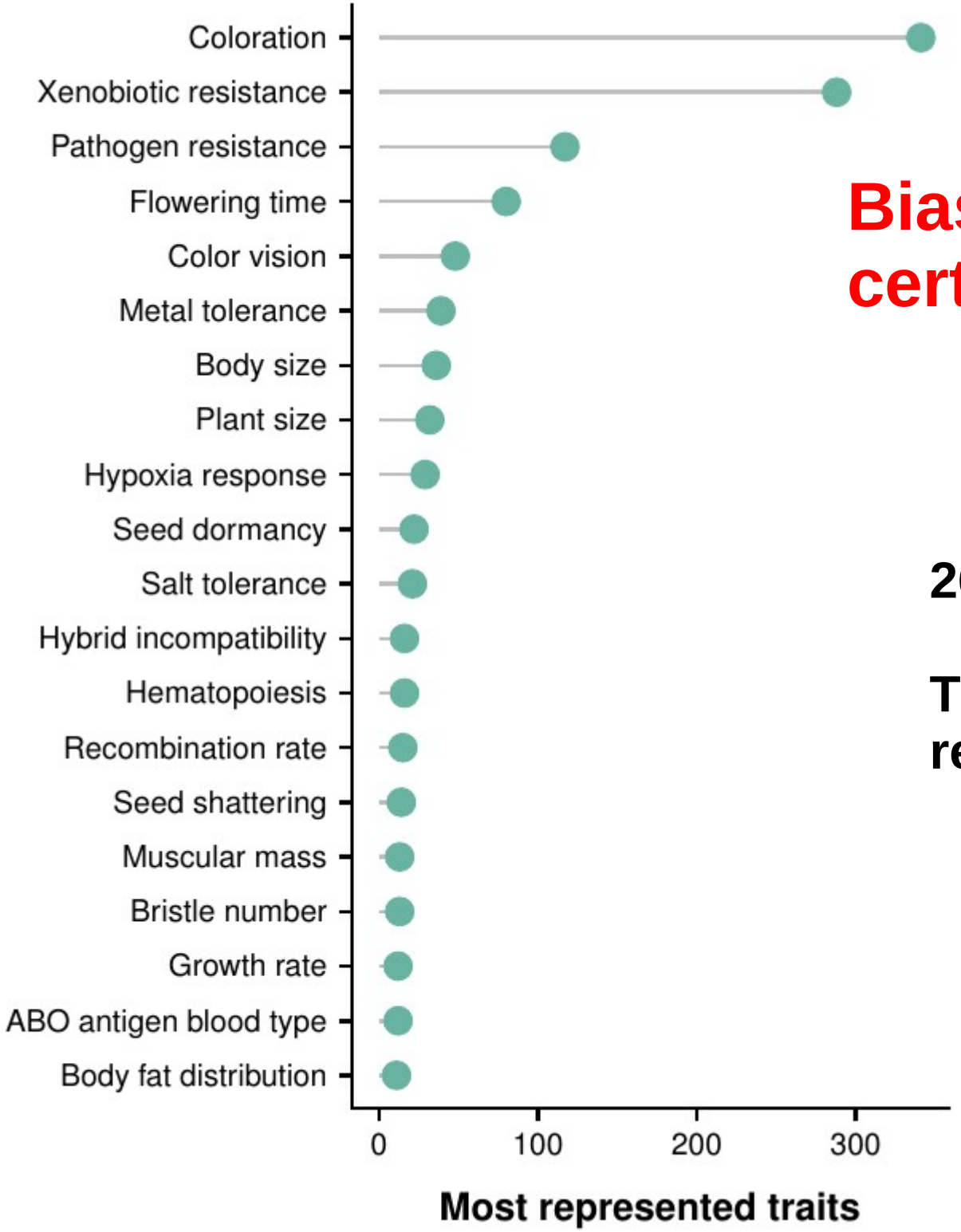
Arnoult 2014
Biologie aujourd'hui



327 species in total

The other species represent 752 entries

Courtier-Orgogozo et al NAR 2019



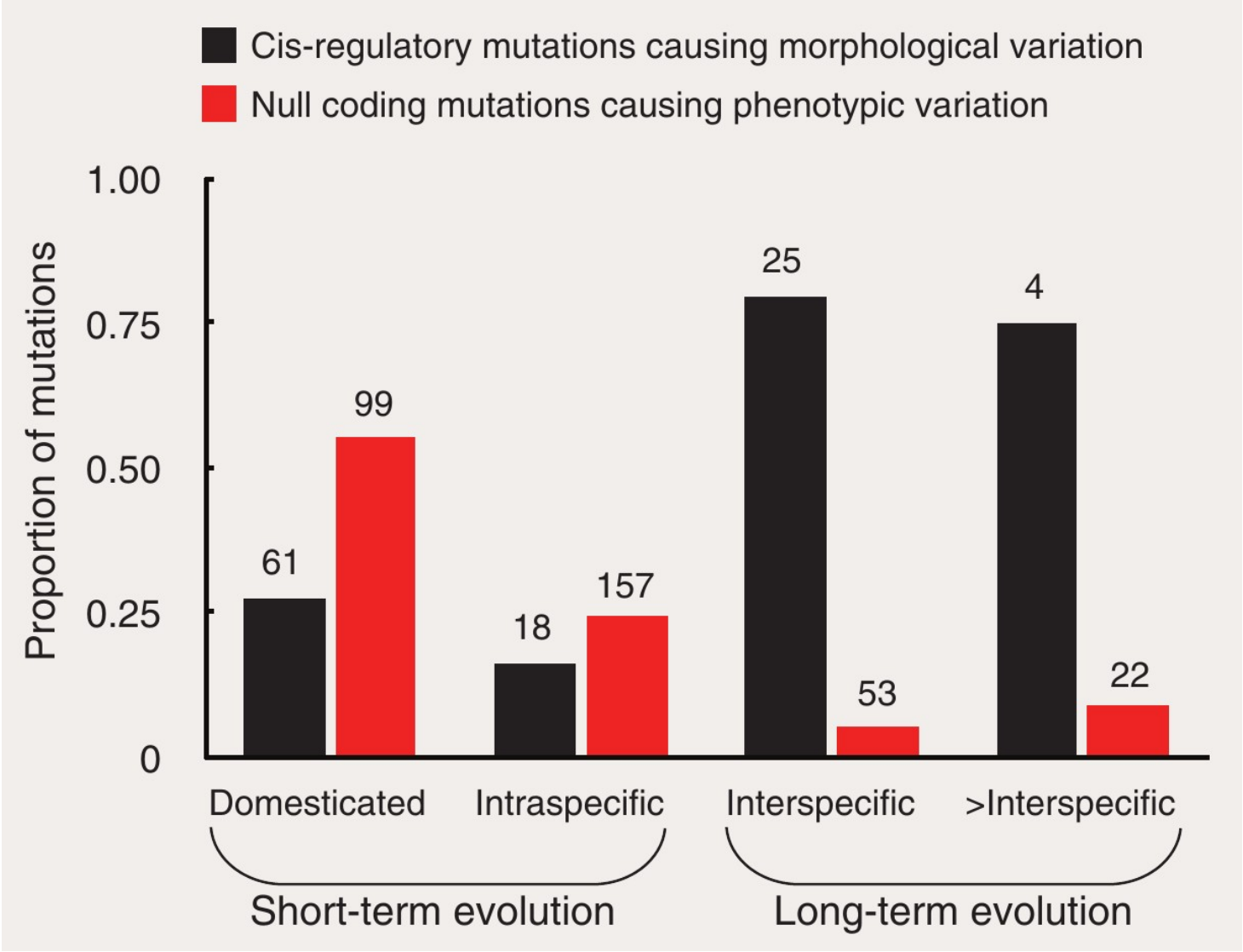
Bias towards certain traits

261 traits in total

The other traits represent 517 entries

Courtier-Orgogozo et al NAR 2019

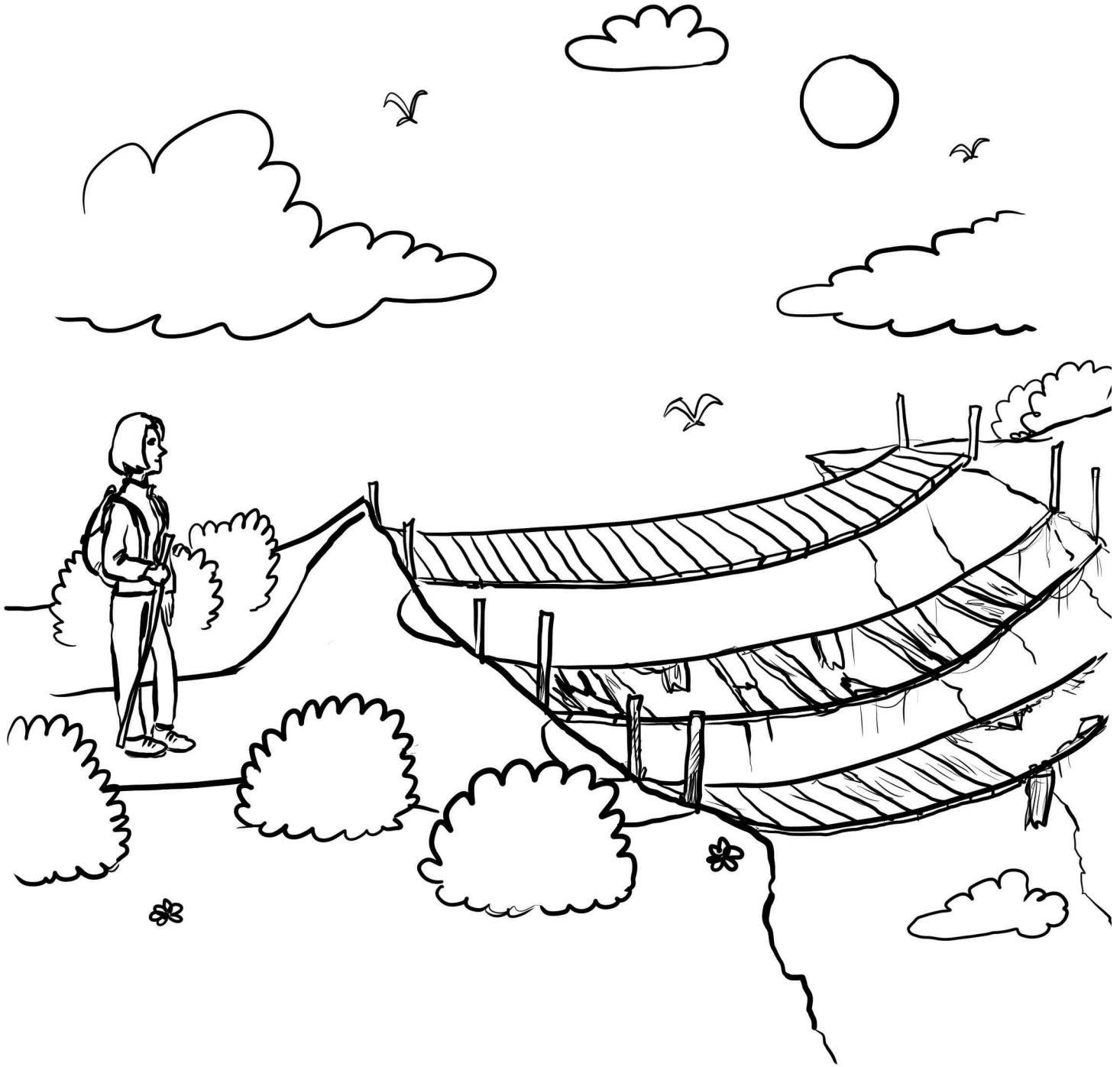
Short-term and long-term evolution involve different types of mutations

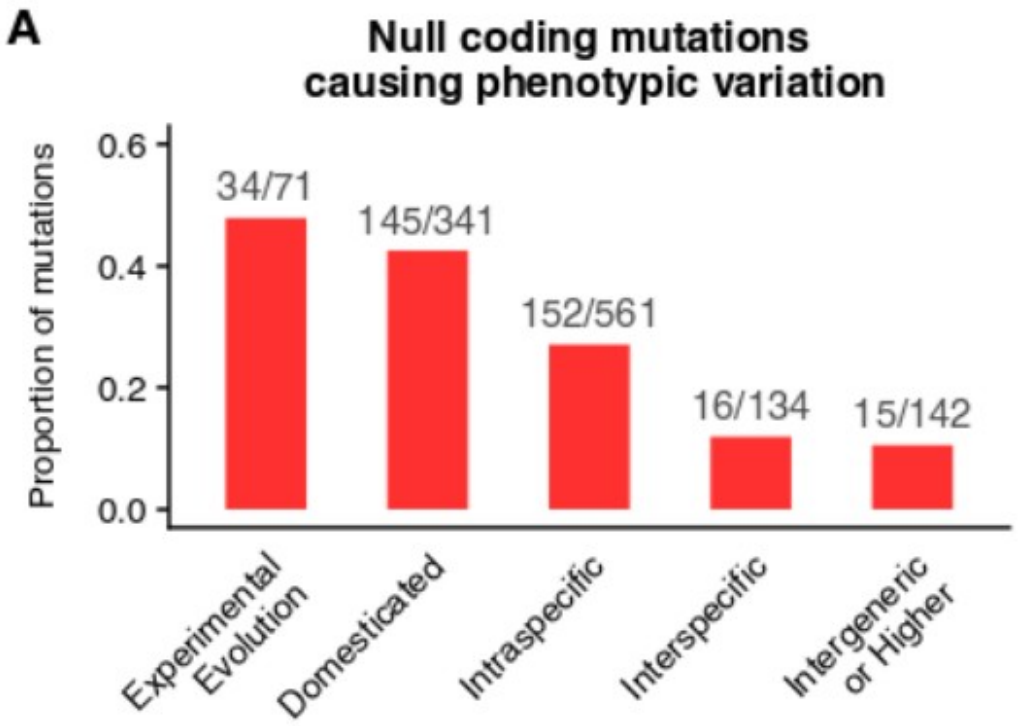


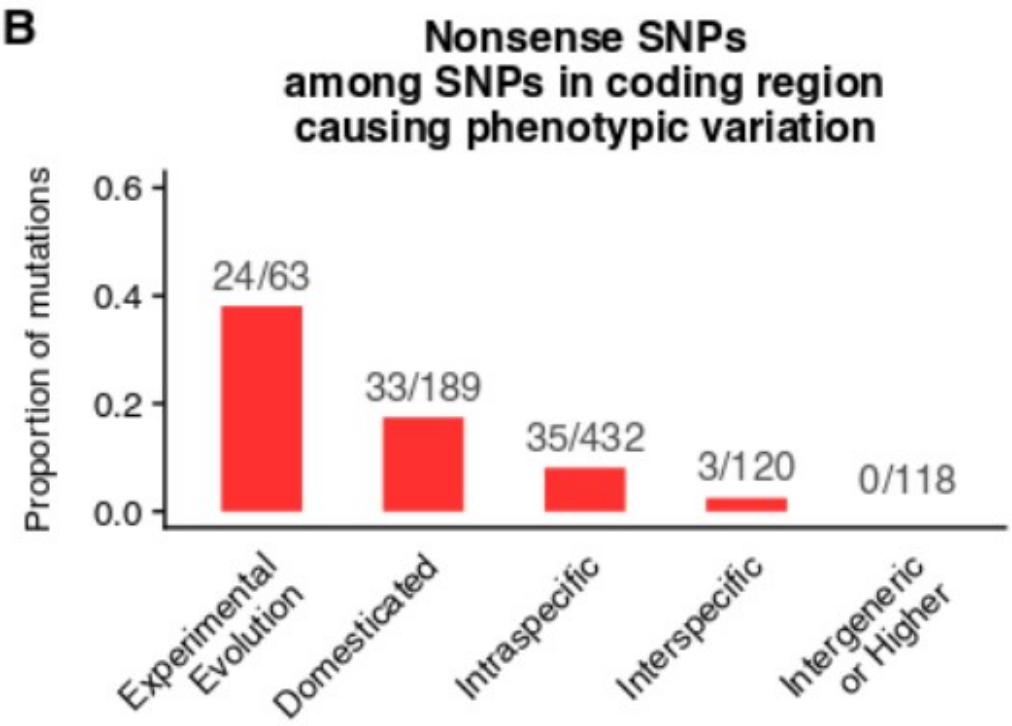
2008: survey of ~300 articles

Stern and Orgogozo 2008 Evolution

Stern and Orgogozo 2009 Science



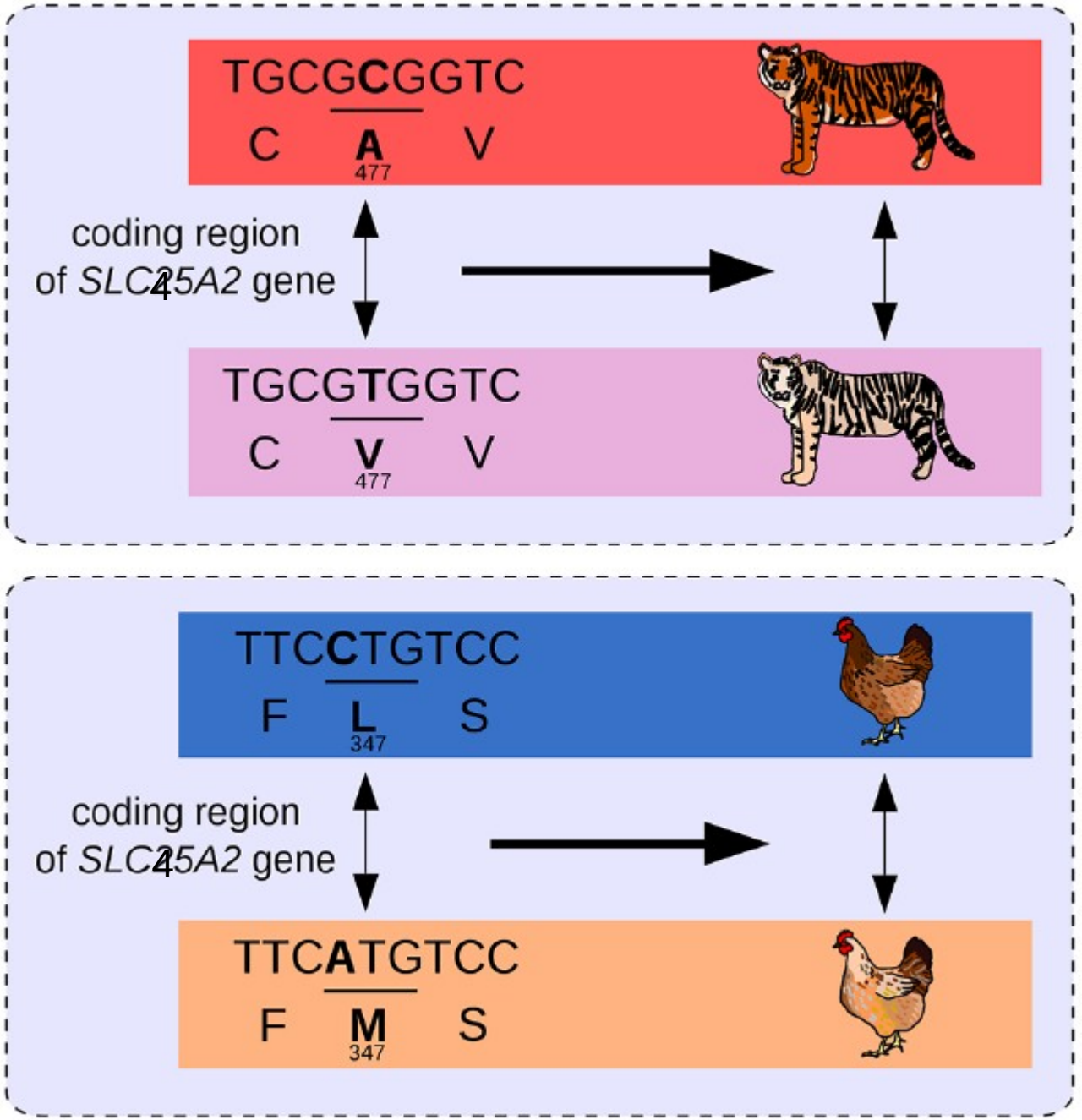




All 1281 coding mutations

Courtier-Orgogozo et al NAR 2019

Hotspot genes: evolution repeats itself



Also in:
Humans
Horses
Quails
Chickens
Mice
Pigeons

Orgogozo et al 2015 Frontiers Genetics

Repeated evolution via the same amino acid change

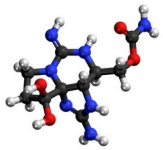
clam

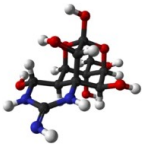
garter snake

Nav1.4 X E945D

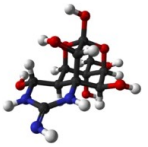
Nav1.4 sodium channel X E945D

Saxitoxin

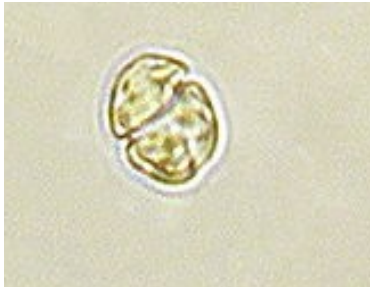




Tetrodotoxin



Nav1.4 E945D X



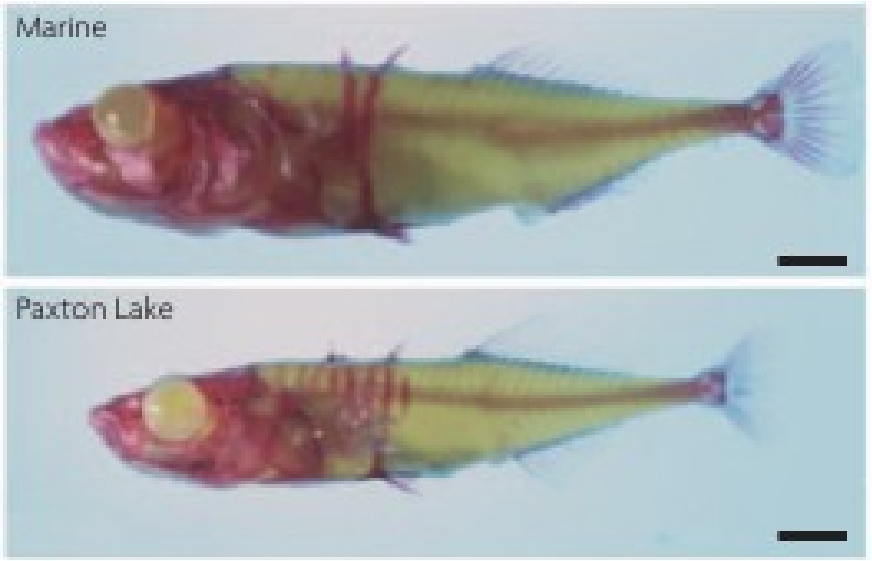
toxic plancton

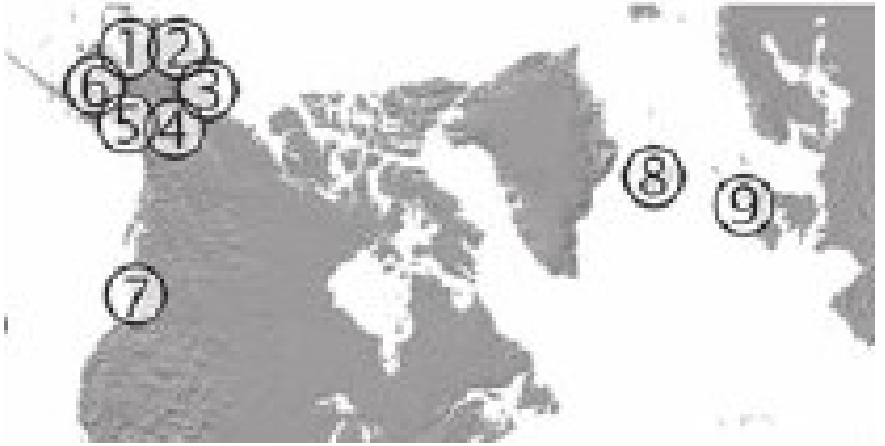
toxic newt

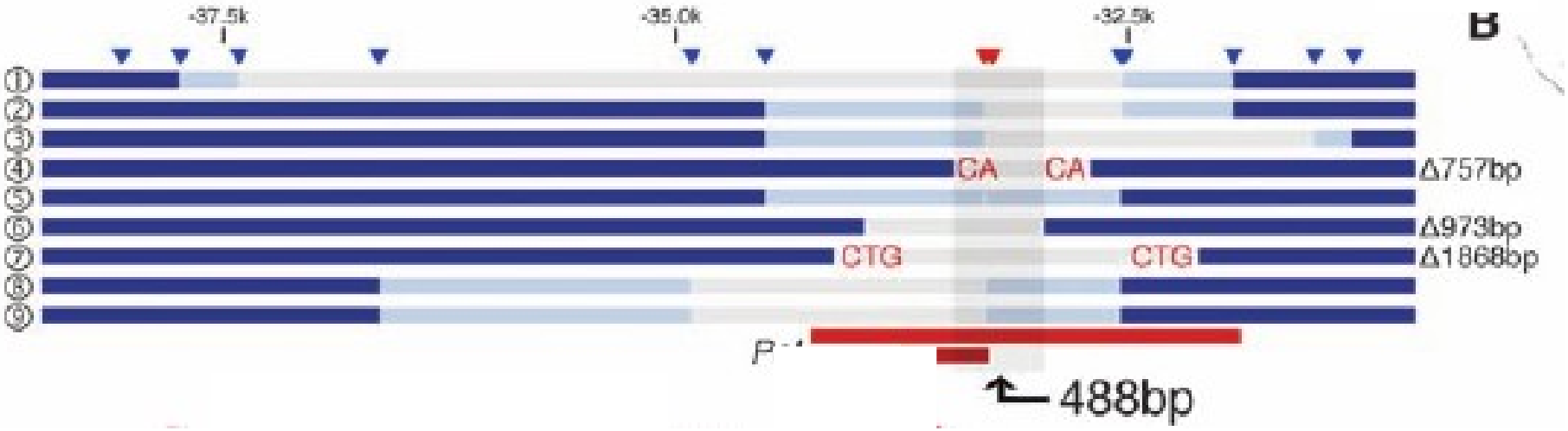
pufferfish (fugu)

Bricelj 2005
Geffeney 2005
Venkatesh 2005

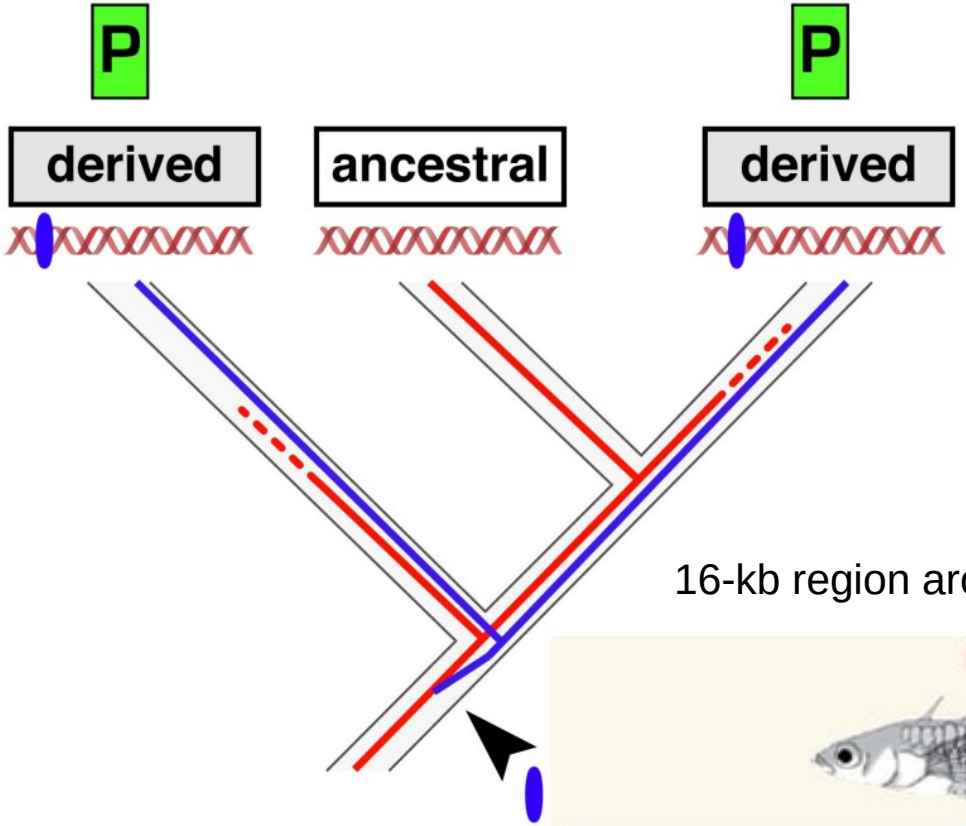
9 independent deletions in the cis-regulatory region of *Pitx1*





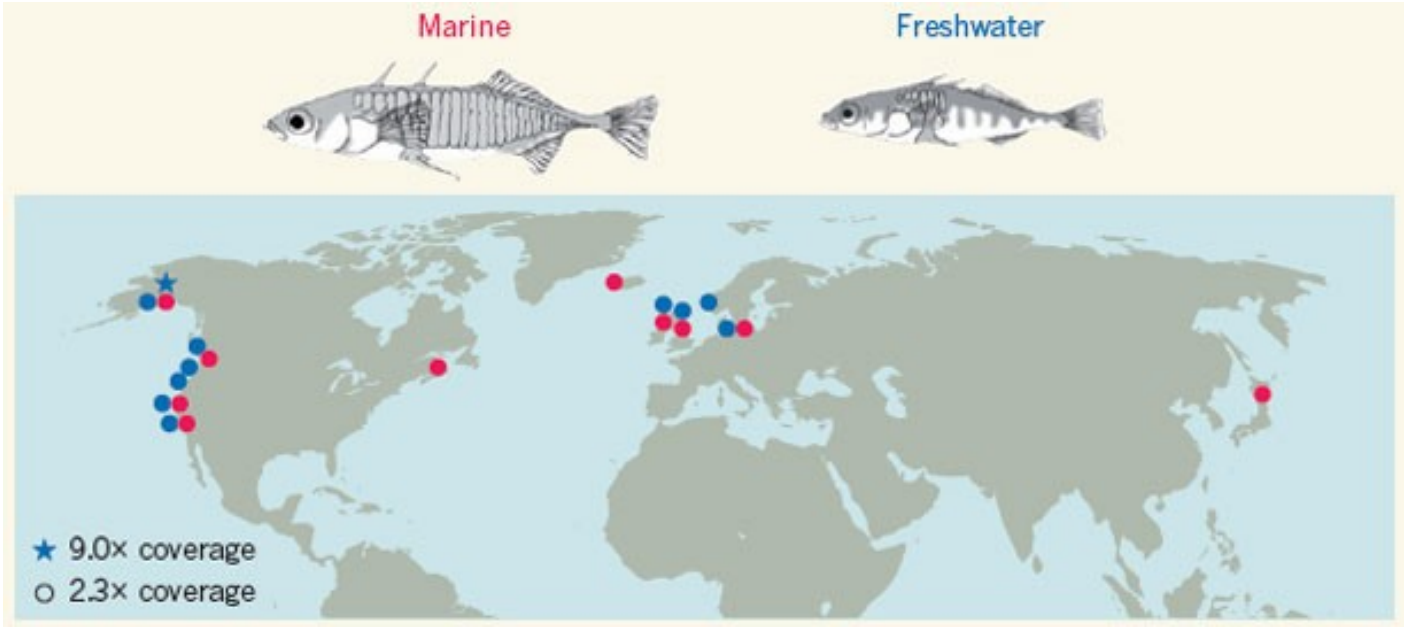


Repeated evolution via ancestral polymorphisms

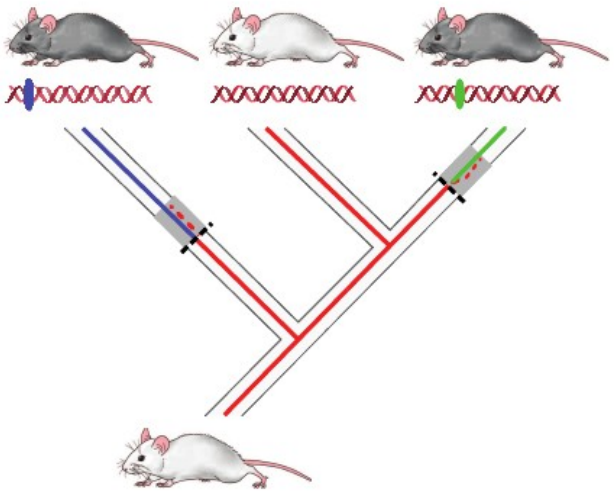


Incomplete lineage sorting
Standing genetic variation

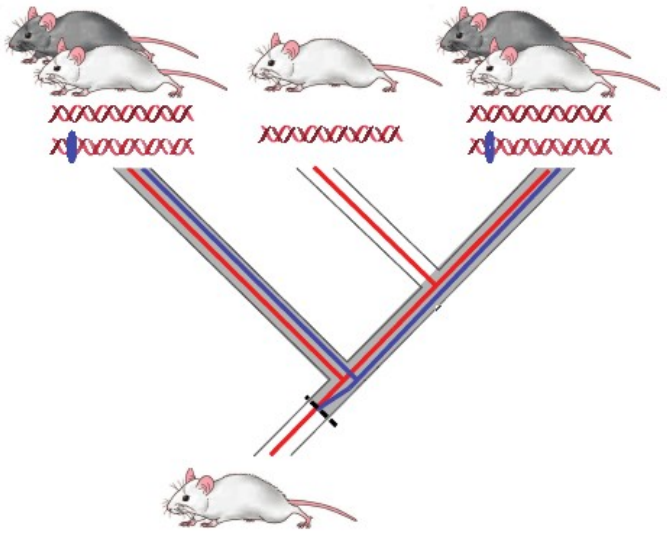
16-kb region around *Eda* shared by all freshwater fishes



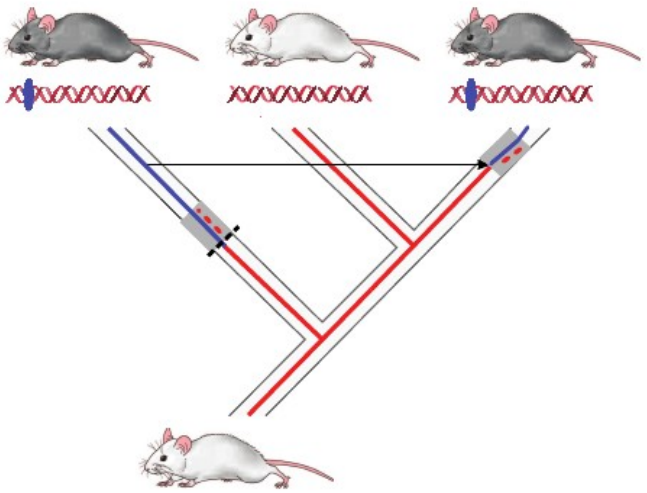
Armor plate
(Colosimo 2005
Jones 2012)



Genetic convergence



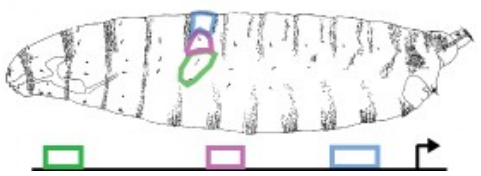
Ancestral polymorphism



Lateral transfer

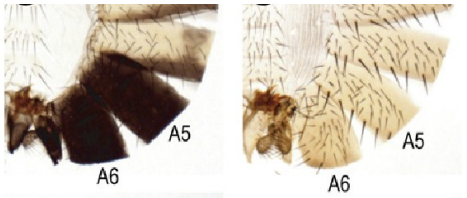
Accumulation of evolutionary-relevant mutations at the same locus

6 mutations in *svb*



(McGregor, Orgogozo et al. 2007 Nature)

3 mutations in *tan*



(Jeong et al., 2008 Cell)

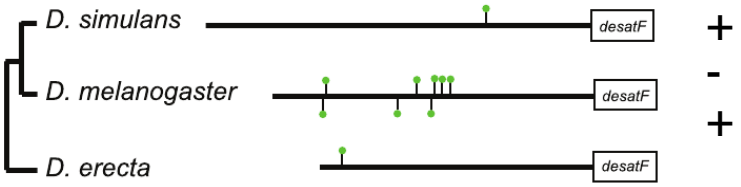
2-4 mutations in *nvd*

(Lang et al. 2012 Science)

5 mutations in *ebony*

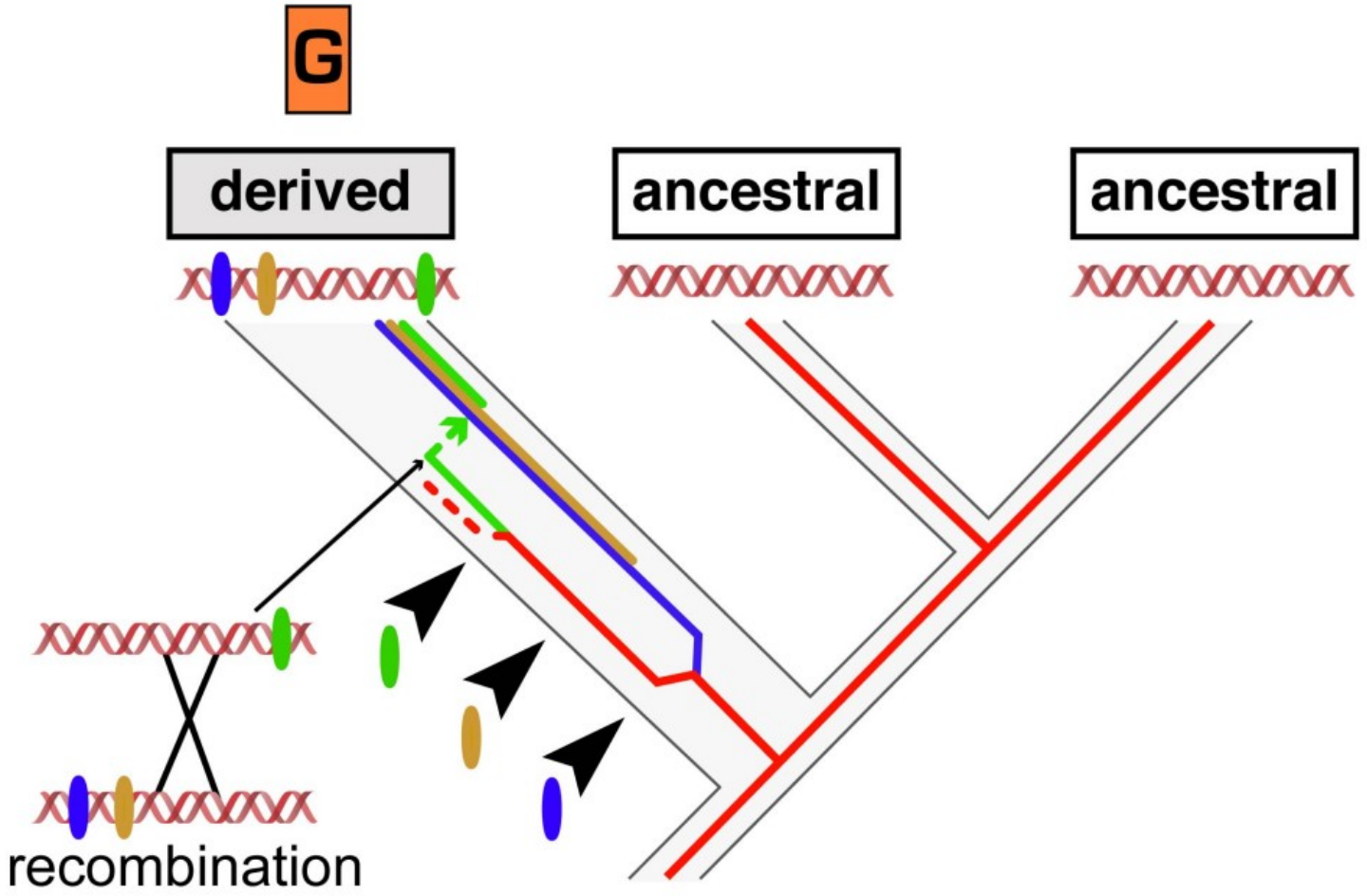
(Rebeiz et al., 2009 Cell)

3 deletions in *desatF*

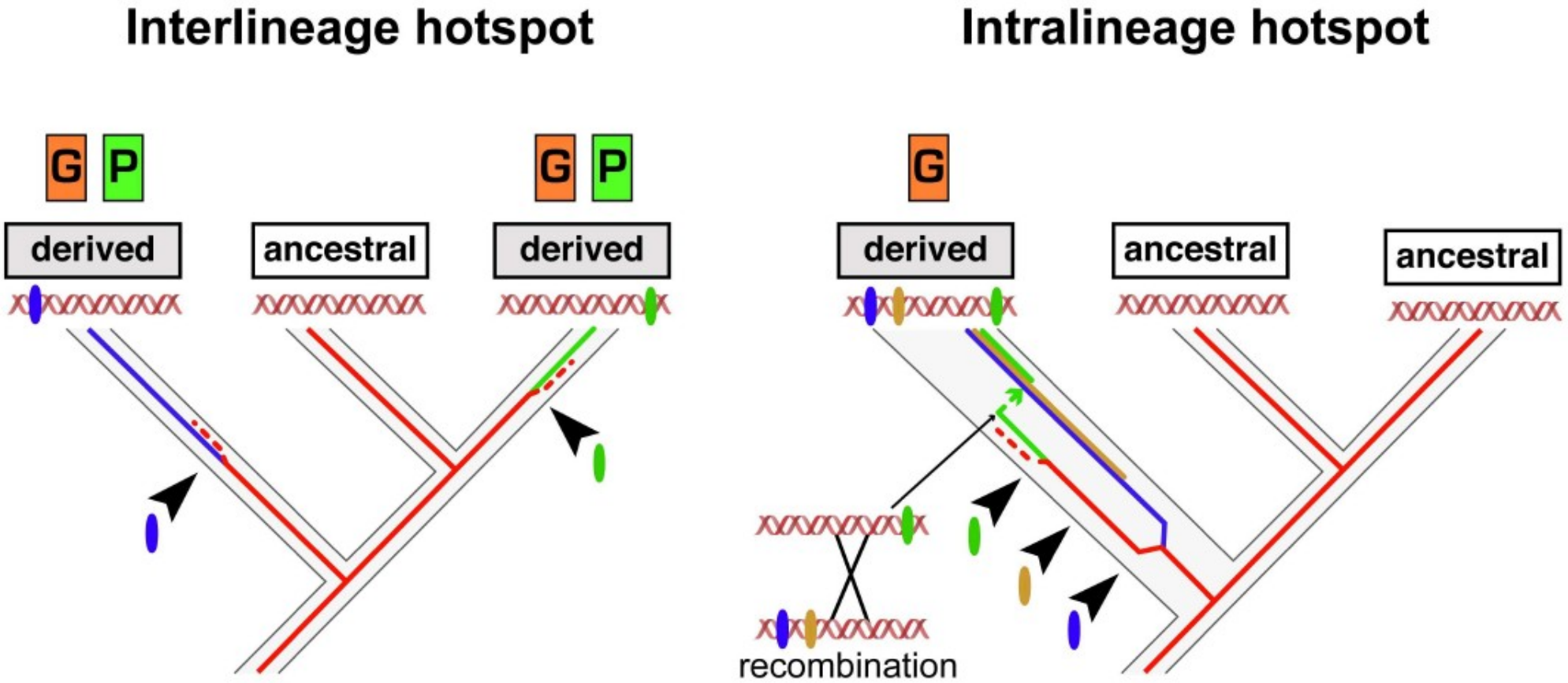


(Shirangi et al., 2009 PloS Biol)

Intralineage hotspot



Hotspot genes: preferred targets of evolution



Martin and Orgogozo,2013

Repeats in..

.. the genes responsible for natural evolution

Ex : *hemoglobin* in dogs and humans in Tibet
(Wang et al 2014 GBE)

.. the genes responsible for experimental evolution

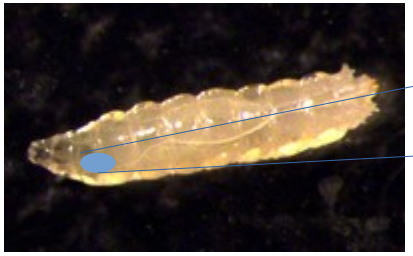
Ex : *sulfate transporter SUL1* in yeasts in low sulfate
(Gresham et al 2008 PloS Genetics)

Orgogozo 2014 Interface Focus

Why is the set of genetic paths limited?

There are specialized genes in a genome

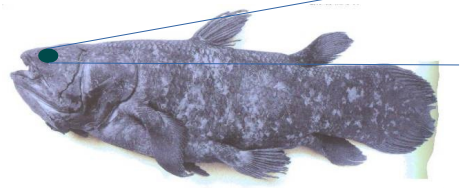
Steroid hormone biosynthesis



a specialized tissue
specialized enzymes

2-4 mutations in *nvd*

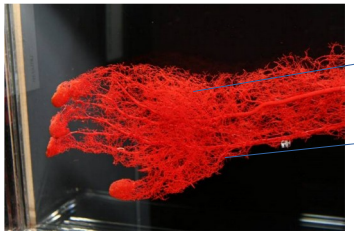
Color vision



a specialized tissue
specialized molecules

mutations in *opsin* genes

Hypoxia resistance



a specialized tissue
specialized molecules

mutations in *haemoglobin* genes

McCracken
2009

Specialized genes are usually genes that interact with external parameters

Why is the set of genetic paths limited?

genes with specialized functions

But what about phenotypes involving multifunctional genes?

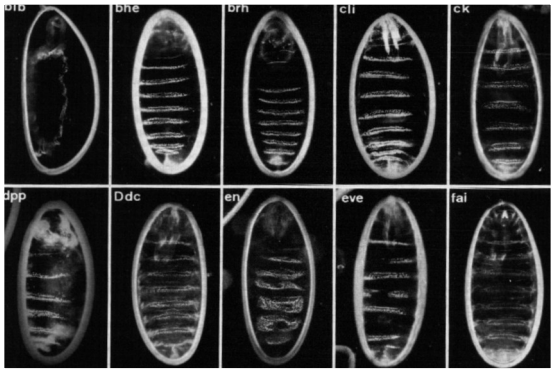
Evolution appears to use a restricted set of all possible paths

Changes in trichome pattern

EVOLUTION

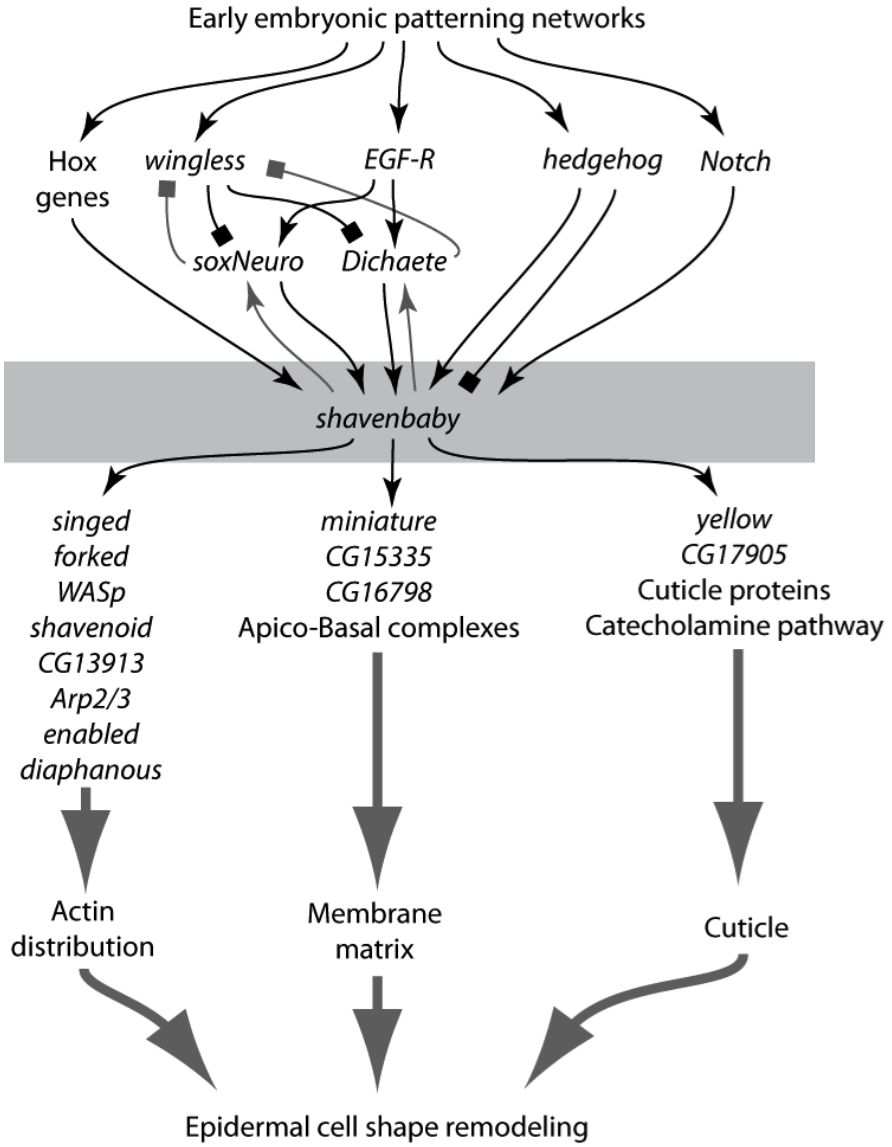
A single gene

MUTAGENESIS



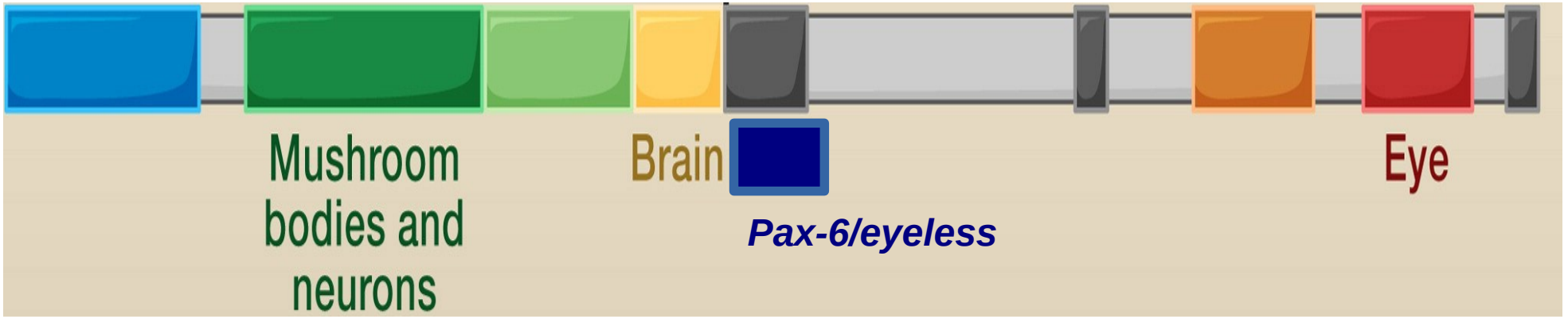
(Nüsslein-Volhard et Weischaus)

~100 genes



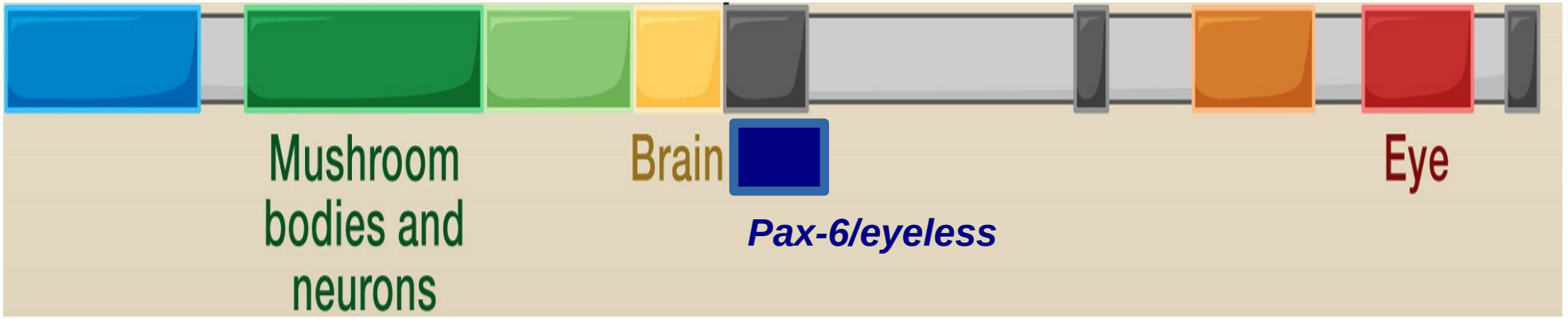
(Stern et Orgogozo, 2008 Evolution – Stern et Orgogozo, 2009 Science)

Specialized loci within multifunctional genes



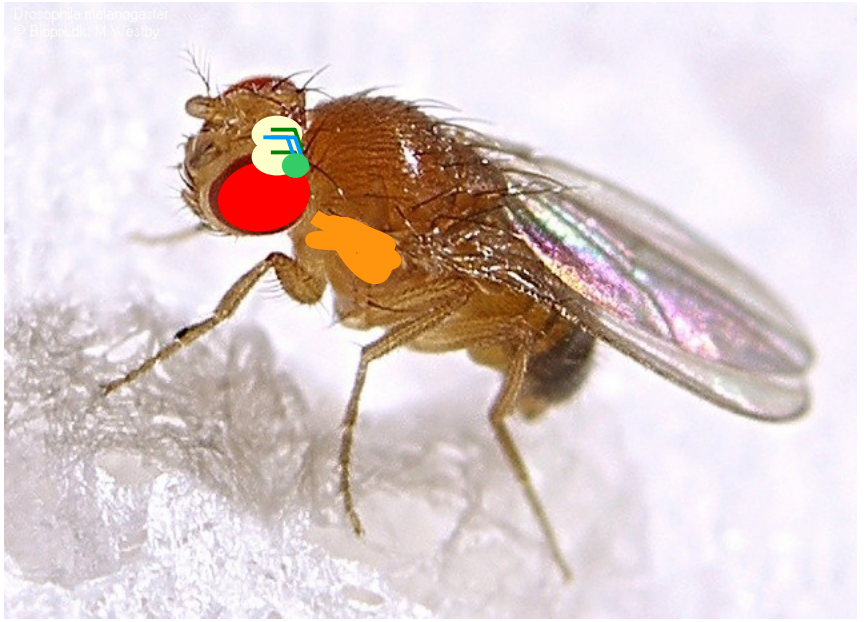
Carroll 2008

Specialized loci within multifunctional genes



Carroll 2008

Modularity of cis-regulatory elements is reflected in modularity of body parts



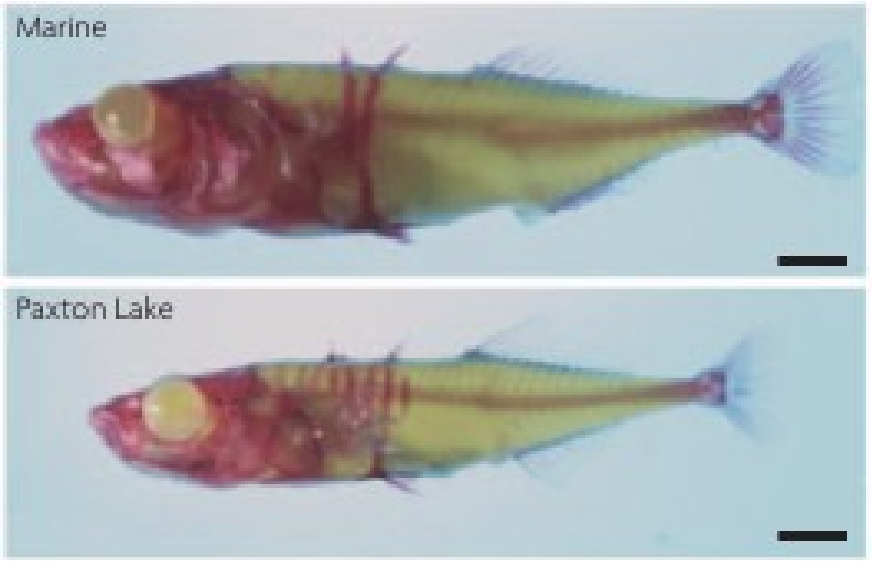
Why is the set of genetic paths limited?

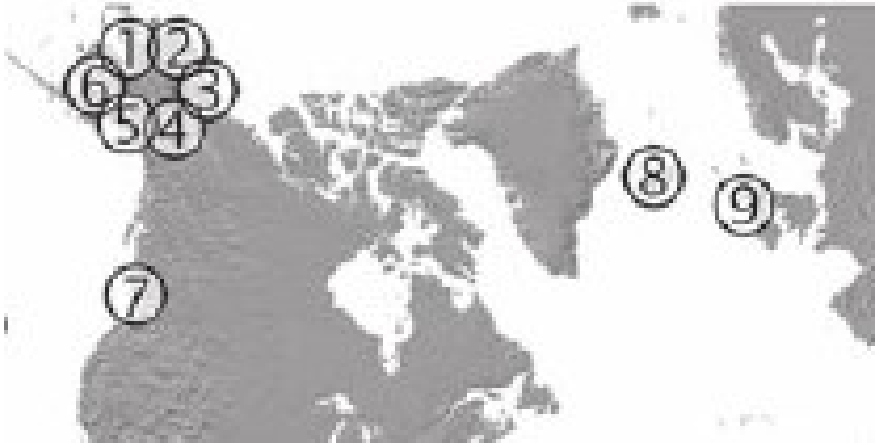
genes with specialized functions

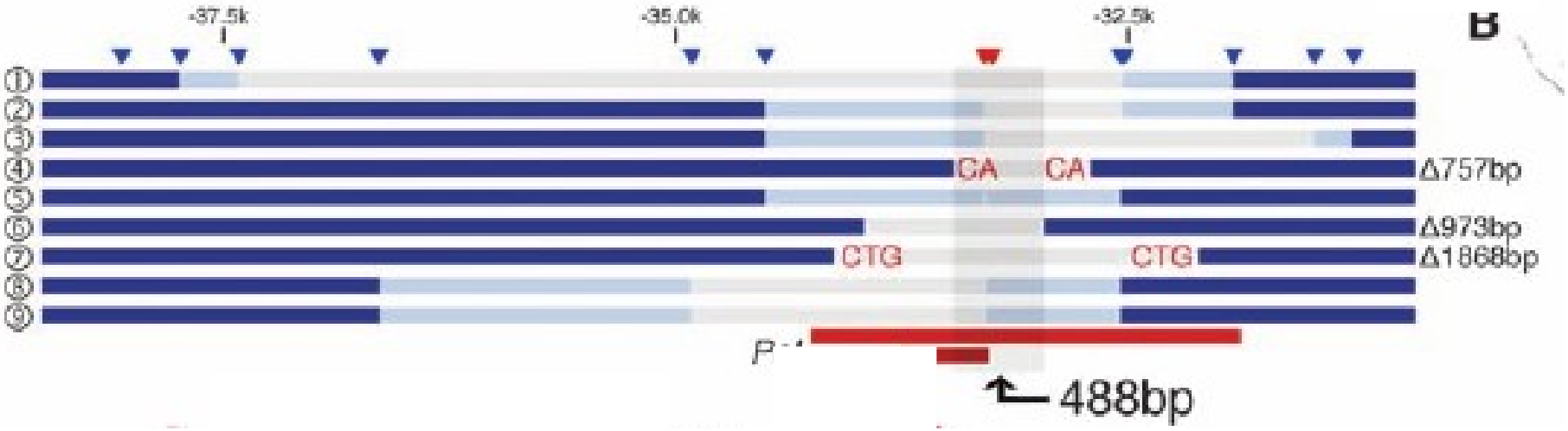
multifunctional genes with specialized regions

mutational bias

9 deletions in the cis-regulatory region of *Pitx1* *due to region sensitive to chromosome breaks*







Why is the set of genetic paths limited?

genes with specialized functions

multifunctional genes with specialized regions

mutational bias

Classical Darwinian Evolution

1

Variation

UNPREDICTABLE

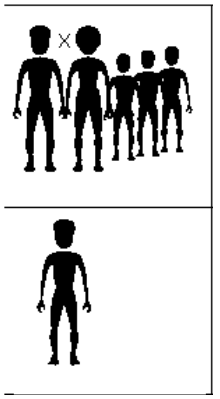
Mutations in DNA

2

Transmission to the next generation

3

Reproduction
Variability between individuals



Selection

Genetic Drift

UNPREDICTABLE

http://evolution.berkeley.edu

Many unpredictable processes
at a low level

?

Predictable Evolution
at the genetic level

Mutations in DNA
Chromosome segregation during meiosis
Assortative mating
Gamete competition during fecondation
Life history traits
Genetic linkage
Environmental changes (meteorite, etc.)
...

From random processes can emerge predictability

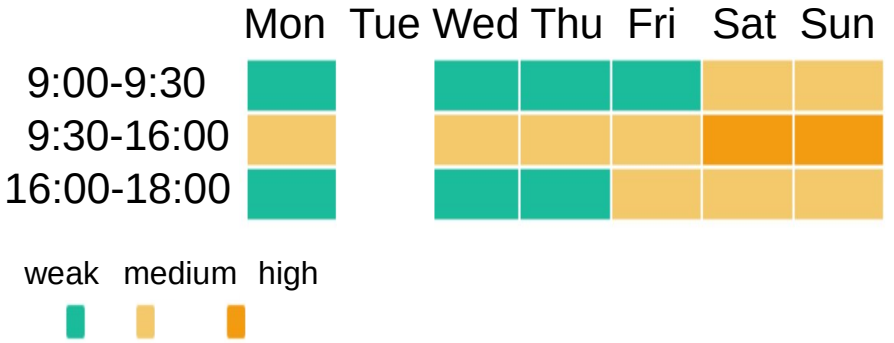
Many unpredictable processes
at a low level

→

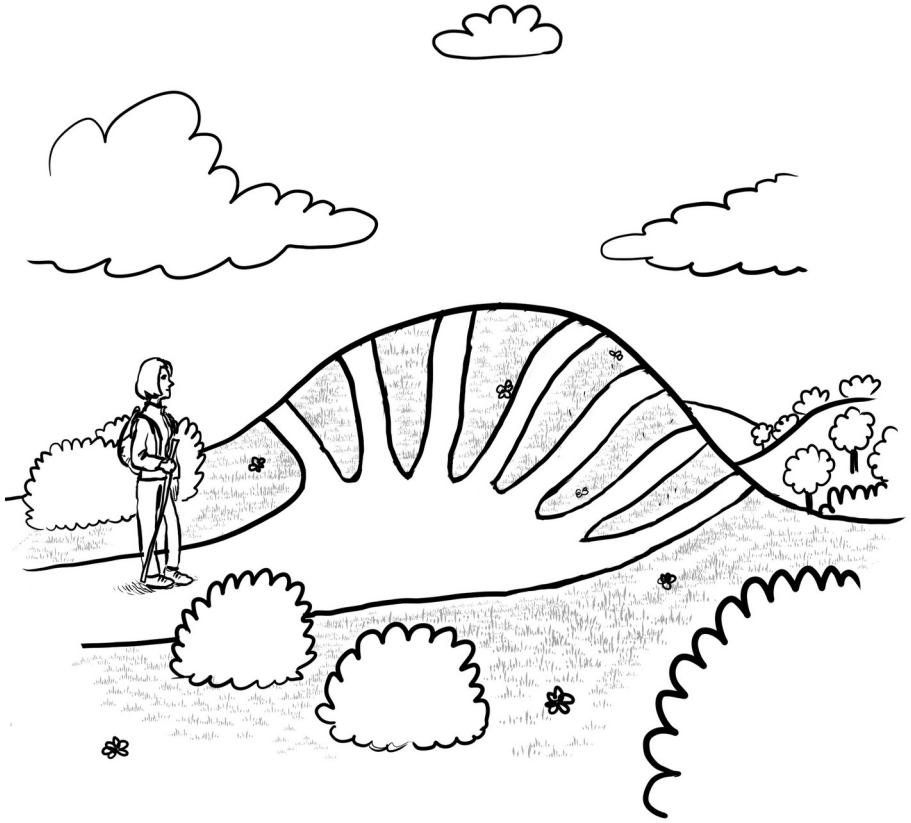
Predictable
at a higher level

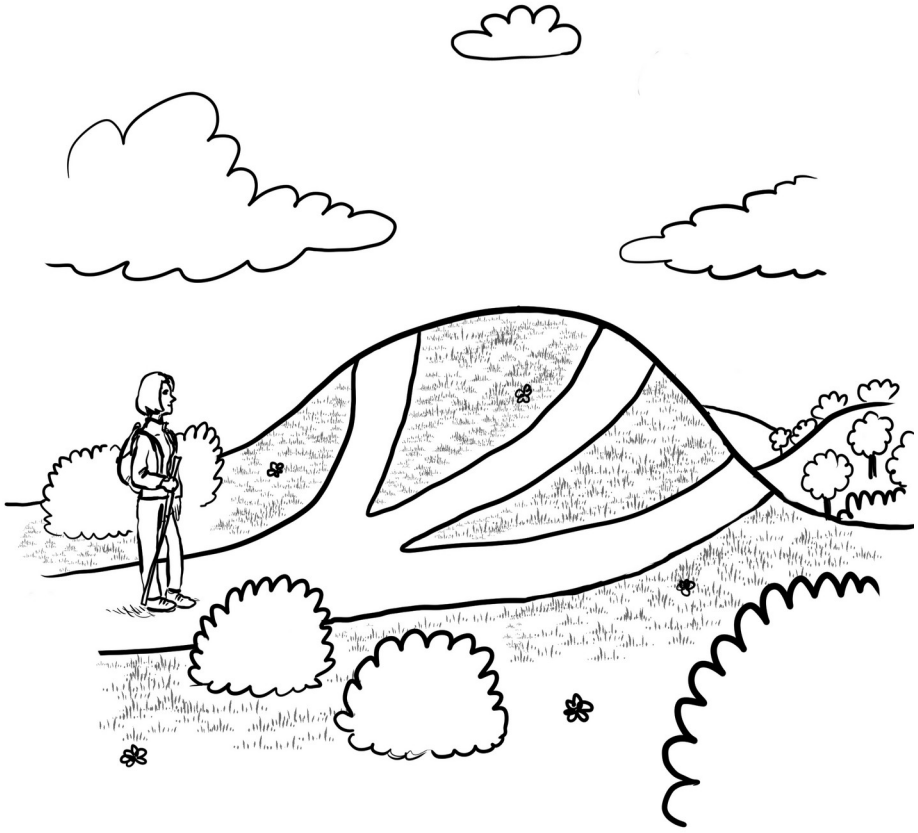
Trajectory of single individuals

Estimated waiting time for Louvre museum

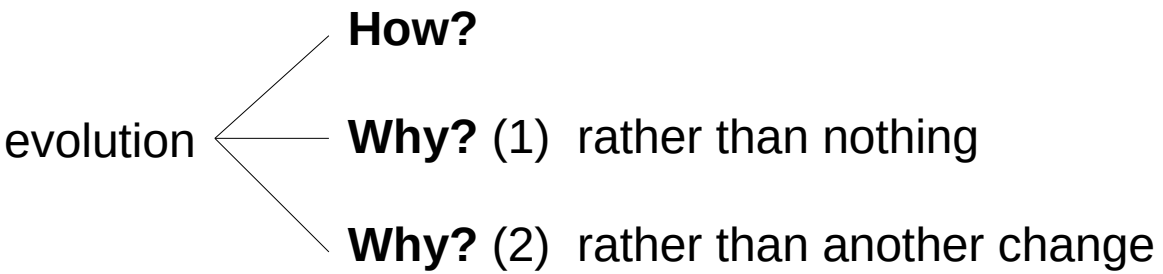


The number of possible paths for evolution is smaller than previously thought





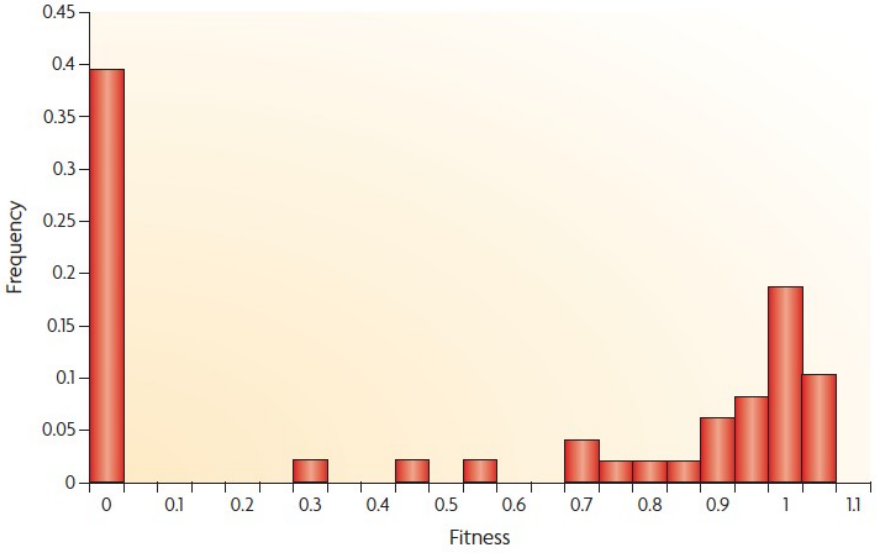
What are all the possible evolutionary paths?



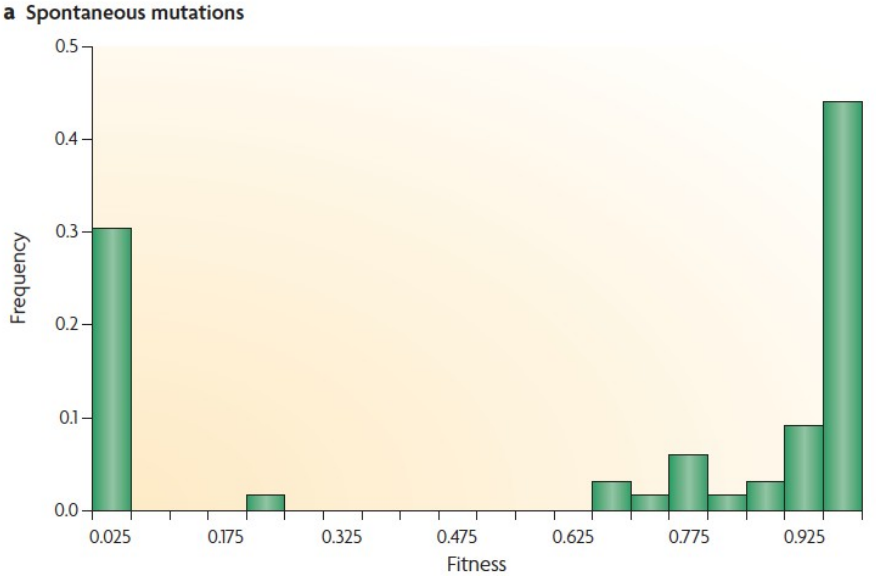
Test all possible paths:

Examine all possible mutations in a protein sequence, in a cis-regulatory sequence, etc.

Mostly deleterious and neutral mutations



Vesicular Stomatitis Virus



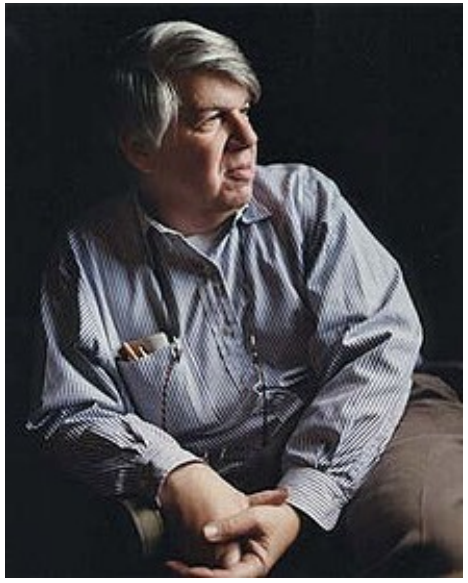
Saccharomyces cerevisiae diploids

Eyre-Walker and Keightley *NRG* 2007

Evolution:
unconstrained and unpredictable?

[past and present organisms are]
a subset of workable, but basically fortuitous, survivals among a much larger set that could have functioned just as well, but either never arose, or lost their opportunities, by historical happenstance.

Stephen Jay Gould, 2002

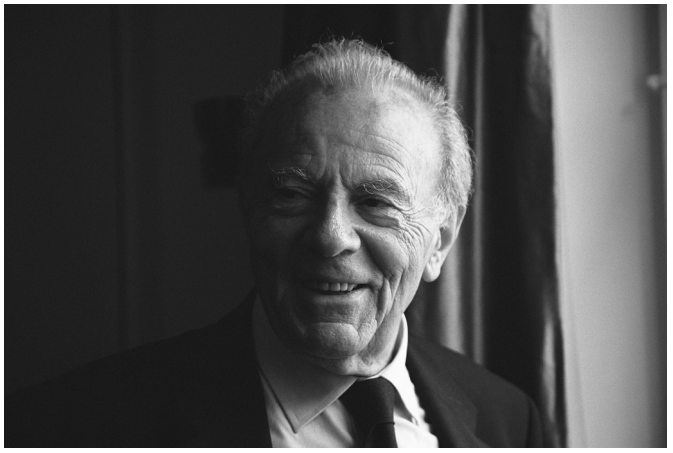


It is hard to realize that the living world as we know it is just one among many possibilities; that its actual structure results from the history of the earth.

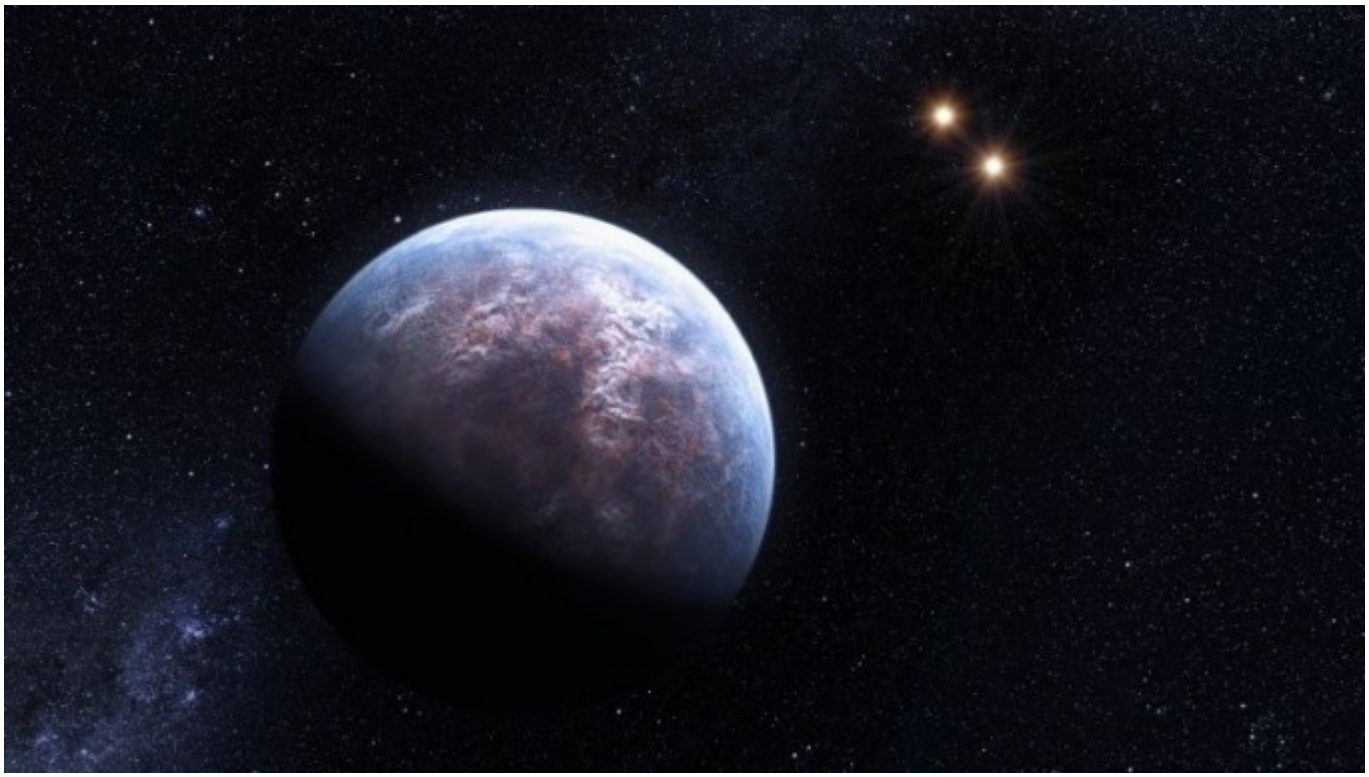
1977

Evolution and Tinkering

François Jacob



Would life evolve again, would it produce similar living beings?

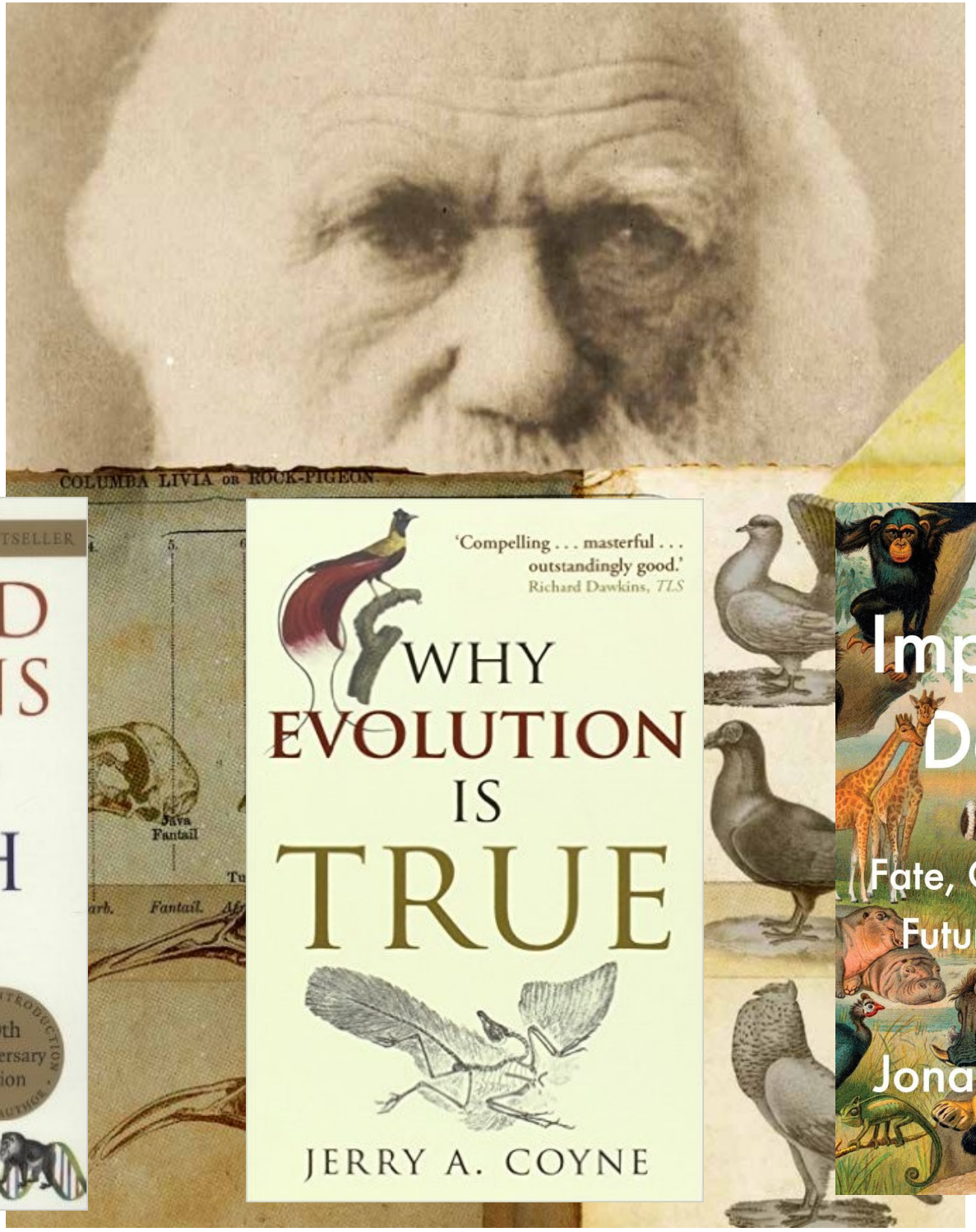


evolution

How?

Why? (1) rather than nothing

Why? (2) rather than another change



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Richard Dawkins, *TLS*

WHY EVOLUTION IS TRUE

JERRY A. COYNE

Improbable Destinies

Fate, Chance, and the Future of Evolution

Jonathan B. Losos

Diverse conclusions from Gephebase

More known cases of coding than cis-regulatory mutations

Bias towards certain species

Bias towards certain traits

Long-term versus short-term evolution: fewer null mutations, more cis-regulatory mutations

Hotspot genes

Nucleic Acids Research, 2019 **1**
doi: 10.1093/nar/gkz796

Gephebase, a database of genotype–phenotype relationships for natural and domesticated variation in Eukaryotes

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