1) Identifying the mutations responsible for phenotypic differences

2) Gephe : thinking in terms of differences

3) Genetic hotspots of evolution

How do genotypes map onto phenotypes ?

DEVELOPMENTAL BIOLOGY

EVOLUTIONARY GENETICS

Both are direct descendants of Morgan's school. Emphasis on genes.

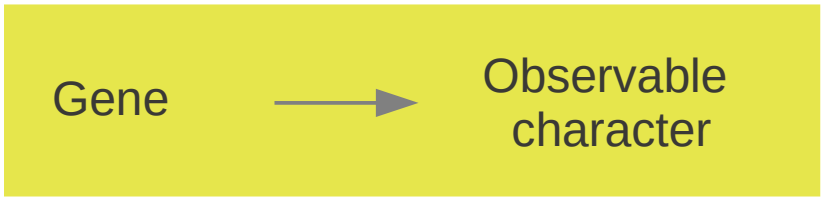
How does an organism form from a single cell?

What makes one organism different from another one?

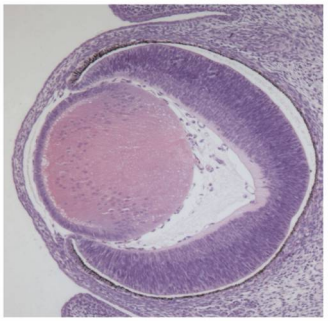
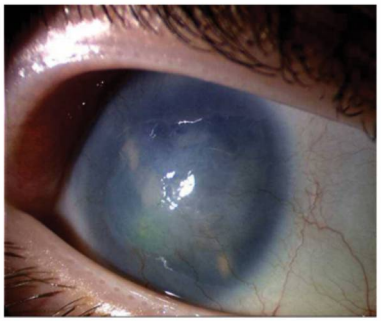
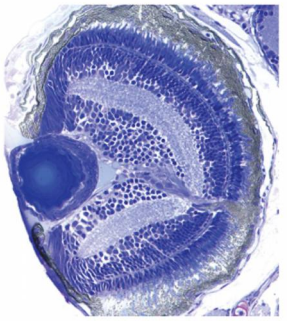
One of the central problems of biology is that of differentiation - how does an egg develop into a complex many-celled organism? That is, of course, the traditional major problem of embryology; but it also appears in genetics in the form of the question,
"How do genes produce their effects?

Sturtevant, 1932

How do genes produce observable traits?



Pax6 : an eye gene ?

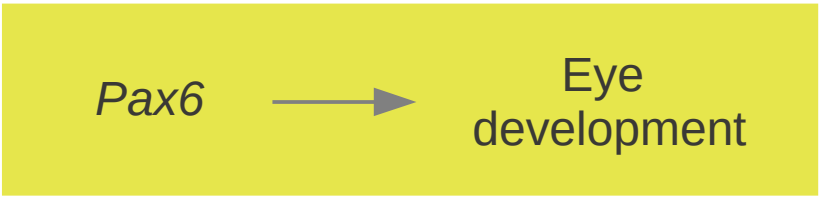
	Human	Mouse	Zebrafish	*Drosophila*
WT				
mut				
	***PAX6*$^{+/-}$**	***Pax6*$^{-/-}$**	***pax6b*$^{-/-}$**	***ey*$^{-/-}$**
EQs	cornea opaque iris absent retina degenerate lens opaque aqueous humor of eyeball increased pressure	eye decreased size lens fused_to cornea iris morphology anterior chamber absent	eye decreased size lens decreased size retina malformed	eye absent

Drosophila

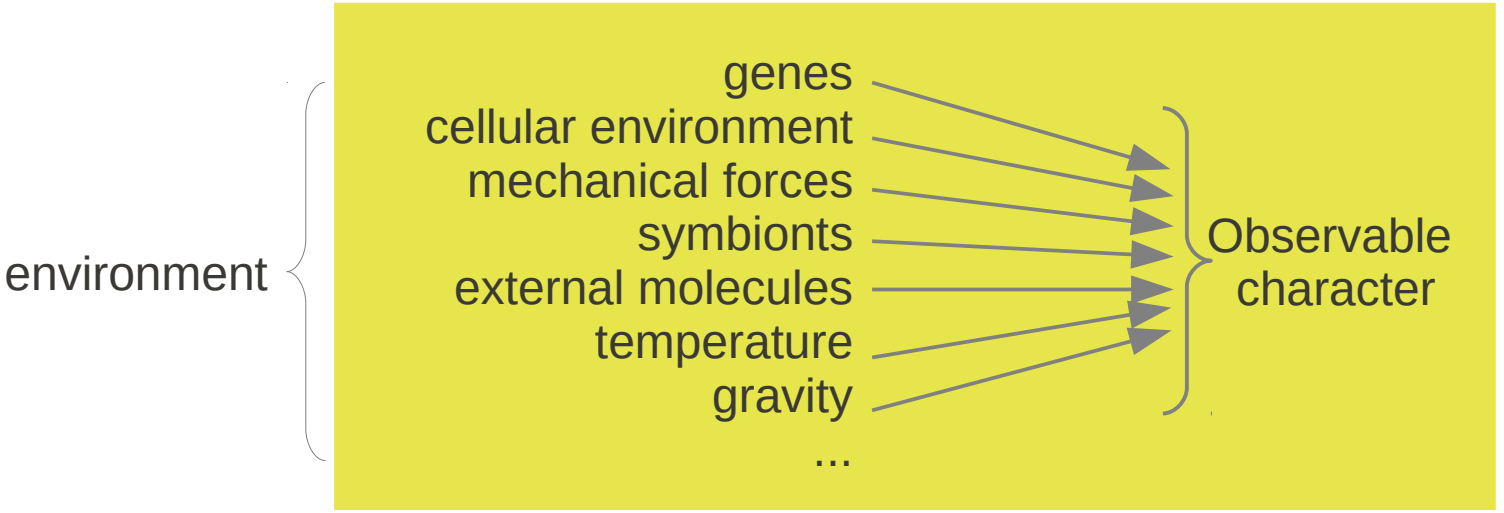
Ectopic expression of Pax6

Gene → Observable character

Pax6 → Eye development

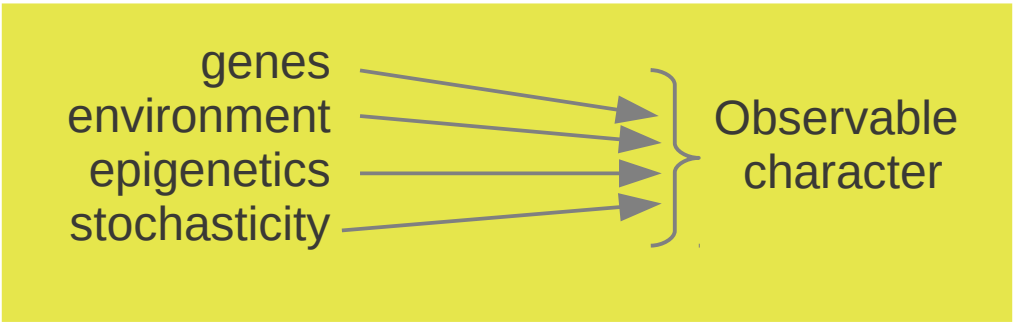


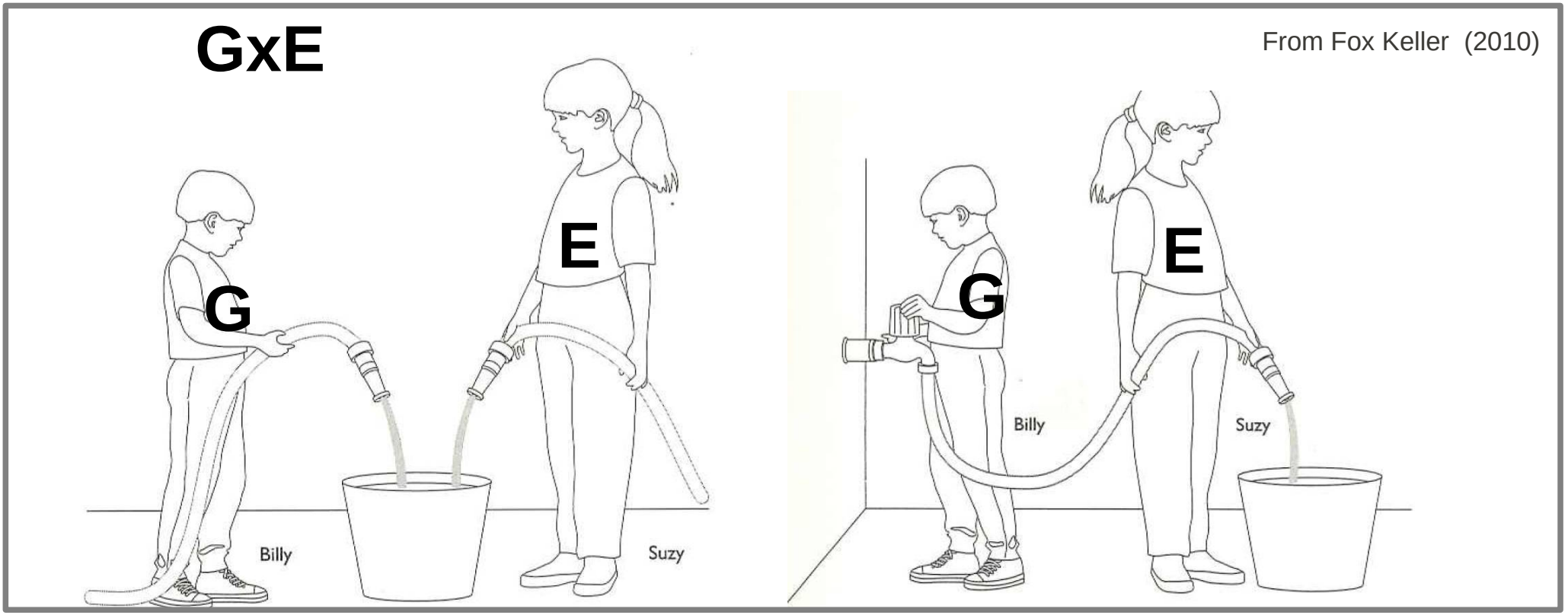
Too simplistic

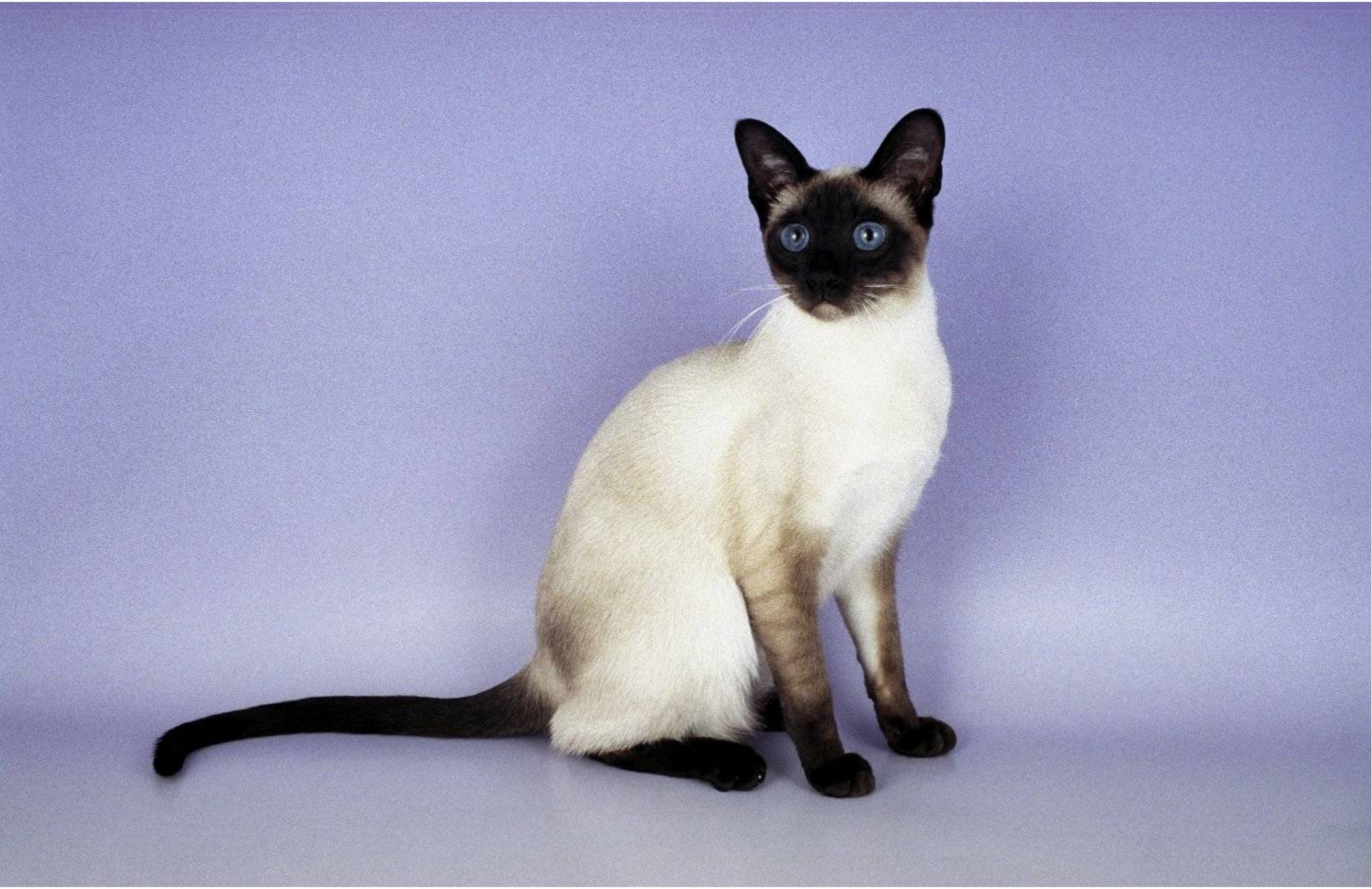


Better, but difficult to disentangle the effects

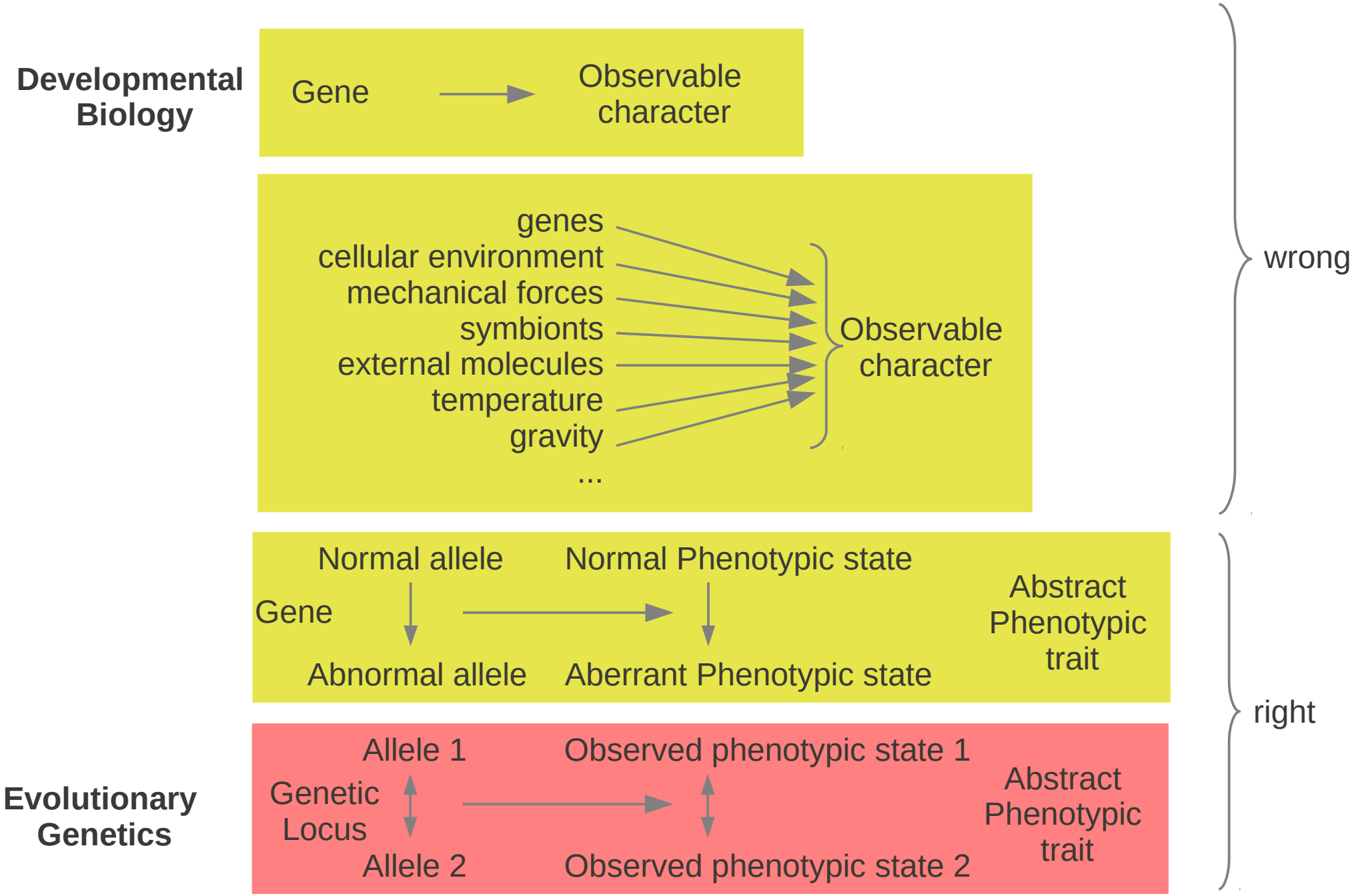
Difficulty in disentangling the various effects







The wrong and the right perspectives



Ex : hair color

Incorrect

gènes
présence de l'organisme
présence de la tête
âge
coloration des cheveux
exposition solaire
...

→ couleur des cheveux

Correct

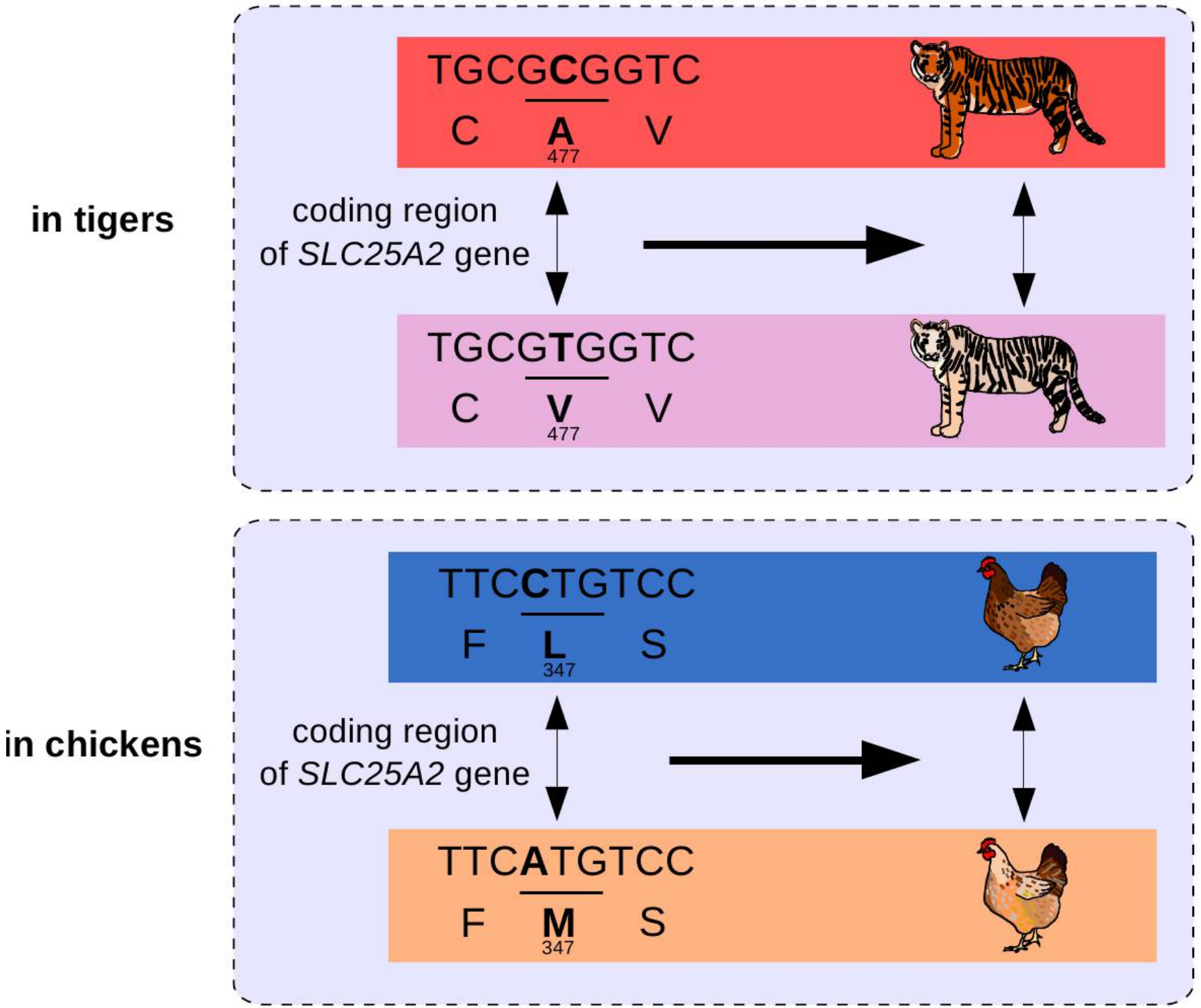
Allèle 1
Locus génétique
Allèle 2

→ Couleur des cheveux de l'individu 1
→ Couleur des cheveux de l'individu 2

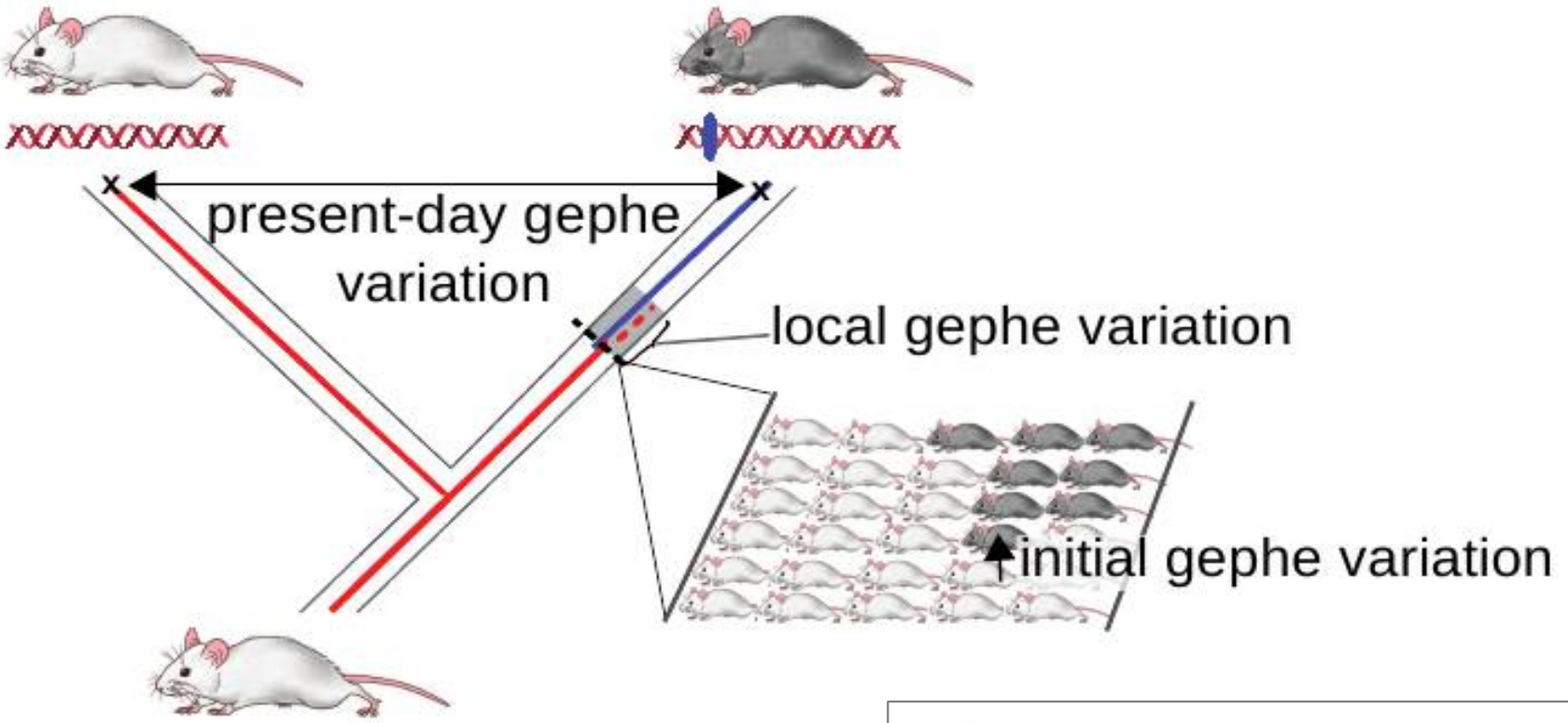
Exposition solaire longue
Exposition solaire courte

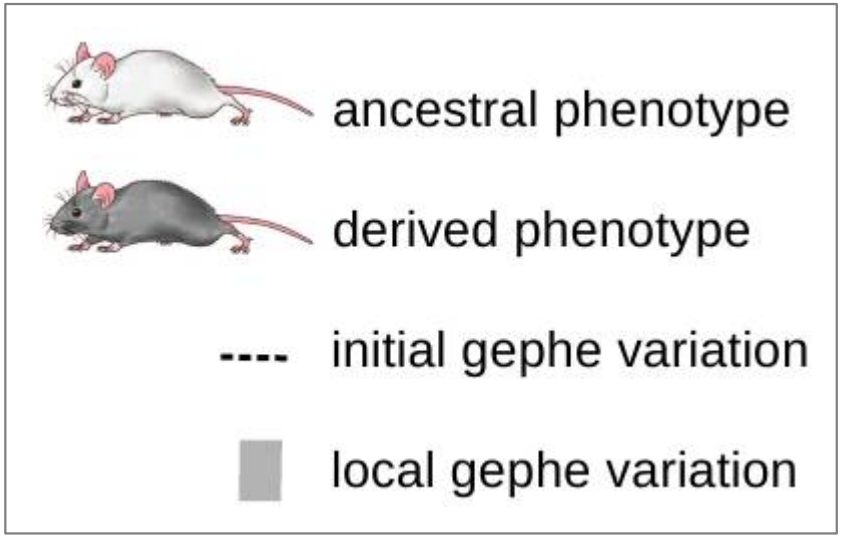
→ Couleur des cheveux de l'individu 1
→ Couleur des cheveux de l'individu 2

Coloration
Age
...

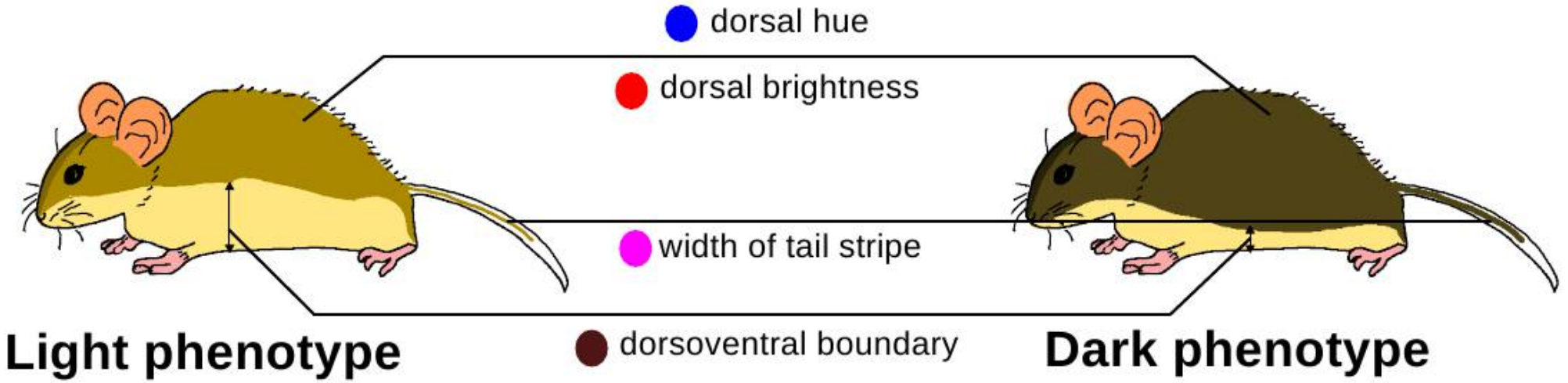

in tigers
TGCGCGGTC
C A V
477
coding region
of SLC25A2 gene
TGCGTGGTC
C V V
477
in chickens
TTCCTGTCC
F L S
347
coding region
of SLC25A2 gene
TTCATGTCC
F M S
347

Gephe: a difference at various levels

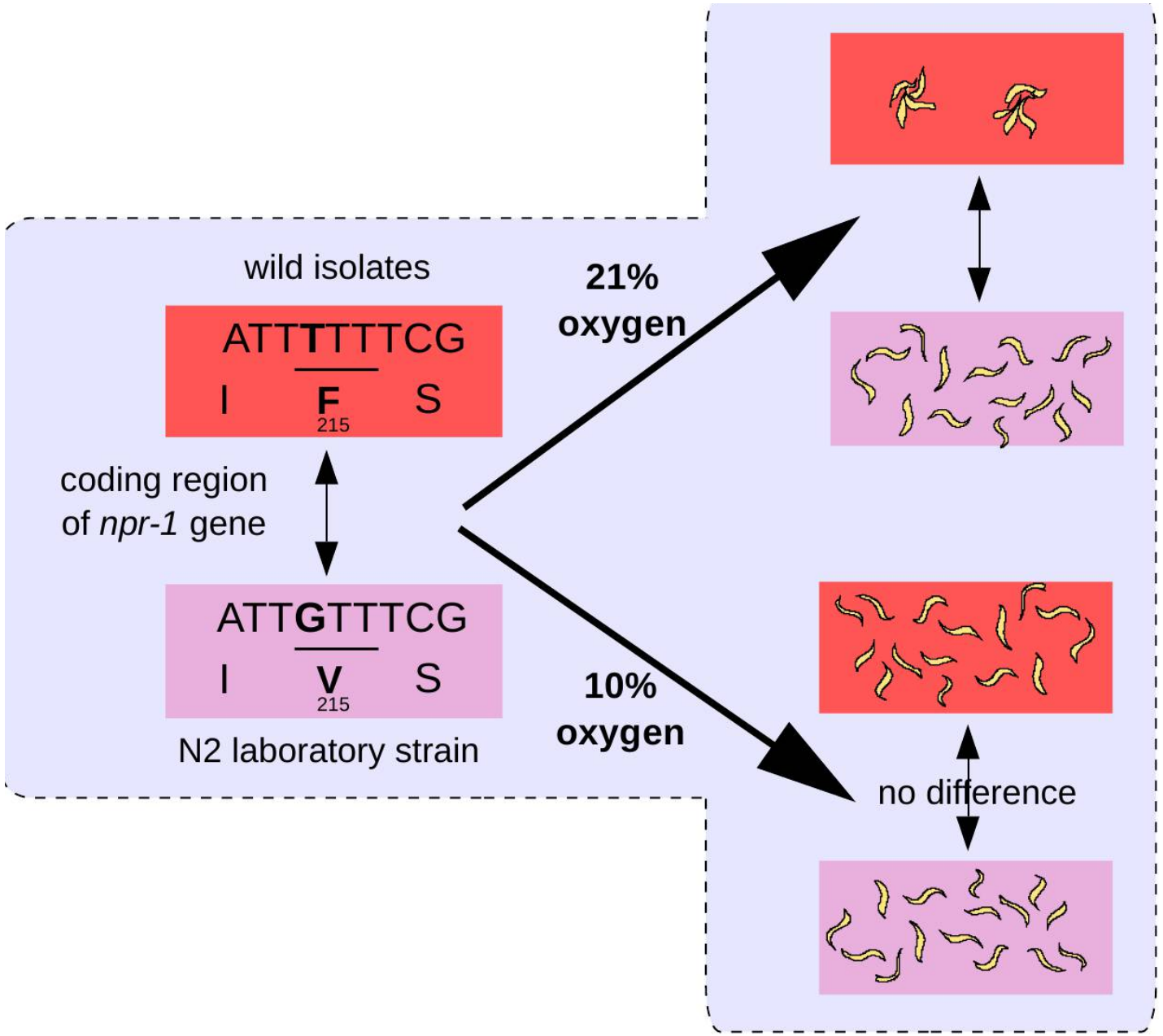




A hierarchy of gephe
Different loci within the same gene



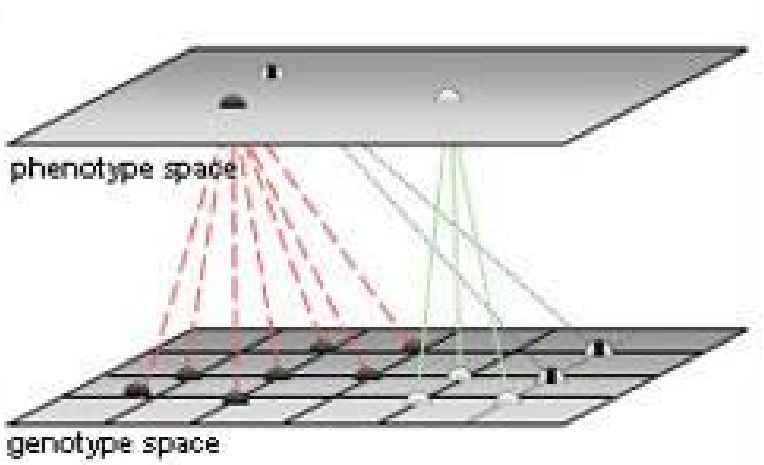
Integrating GxE and GxG into the gephe concept

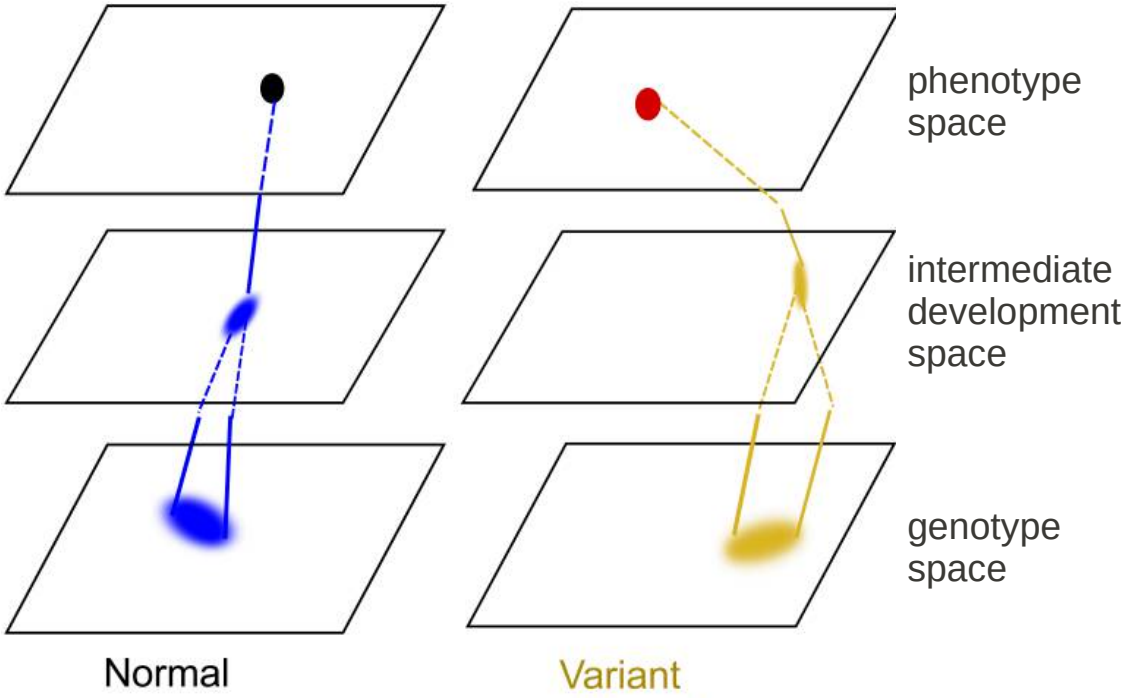


Andersen 2014

How do genotypes map onto phenotypes ?

Phenotype = observable attributes of an individual
Genotype = inheritable genetic material = DNA or RNA





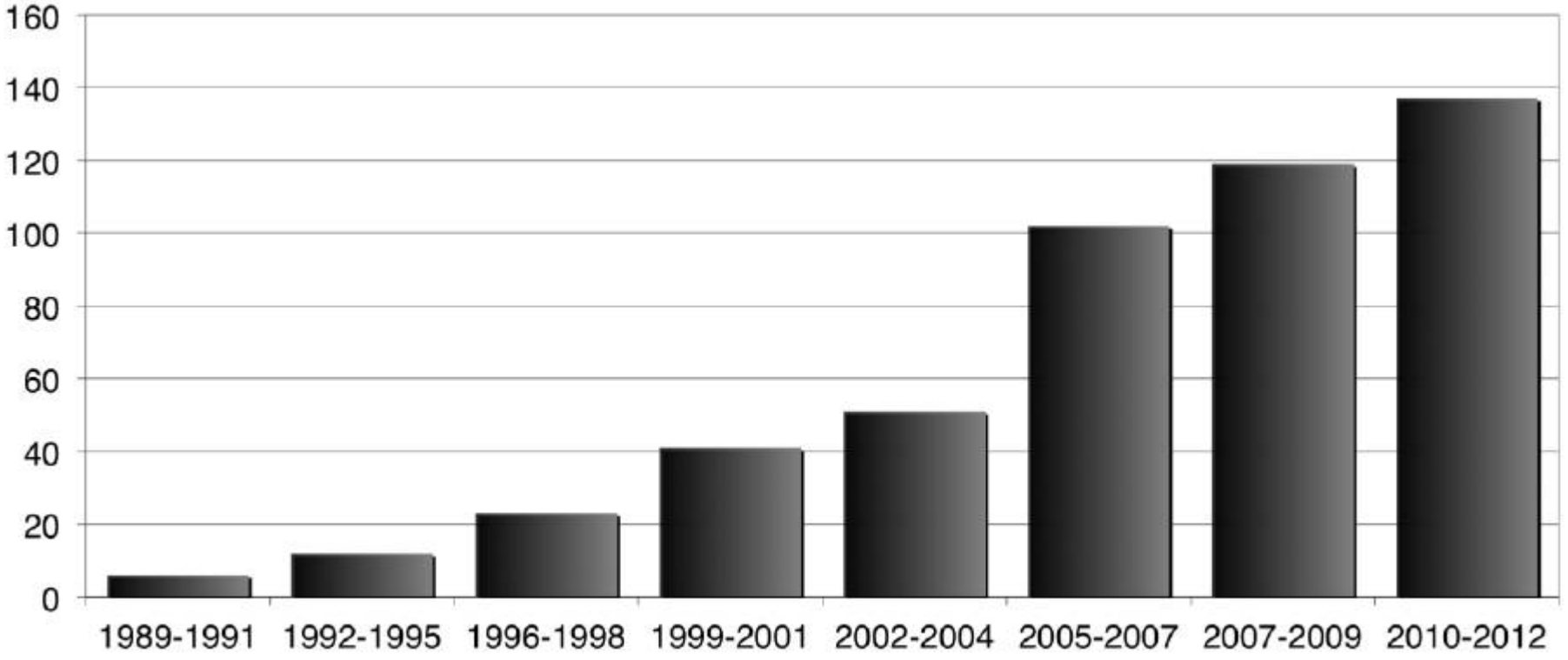
Can we imagine spaces of differences ?

1) Identifying the mutations responsible for phenotypic differences

2) Gephe : thinking in terms of differences

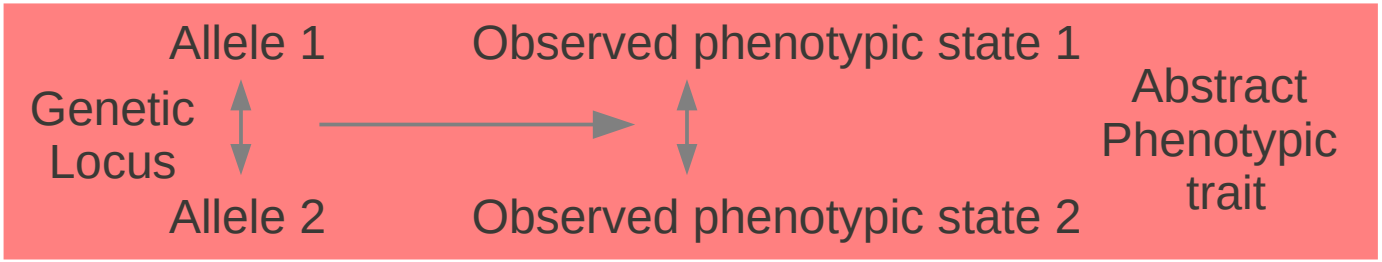
3) Genetic hotspots of evolution

Number of alleles identified as responsible for a phenotypic difference in animals and plants
(including domestication)



Martin and Orgogozo 2013

Gephes widespread across species



Genetic locus	Phenotypic trait
One particular coding site in the *Nav1.4* gene	Resistance to tetrodotoxin or saxotoxin
Various coding sites in *opsin* genes	Color vision
SLC45A2 coding region	Pigmentation of eye, hair and skin
Mc1R coding region	Pigmentation of hair and skin, but not eye
Cis-regulatory element in the *lactase* gene	Ability to digest milk
Cis-regulatory element in the *pitx1* gene	Pelvis morphology
Cis-regulatory elements in the *optix* gene	Red color pattern on butterfly wings
Cis-regulatory and coding regions of the *FRIGIDA* gene	Flowering time

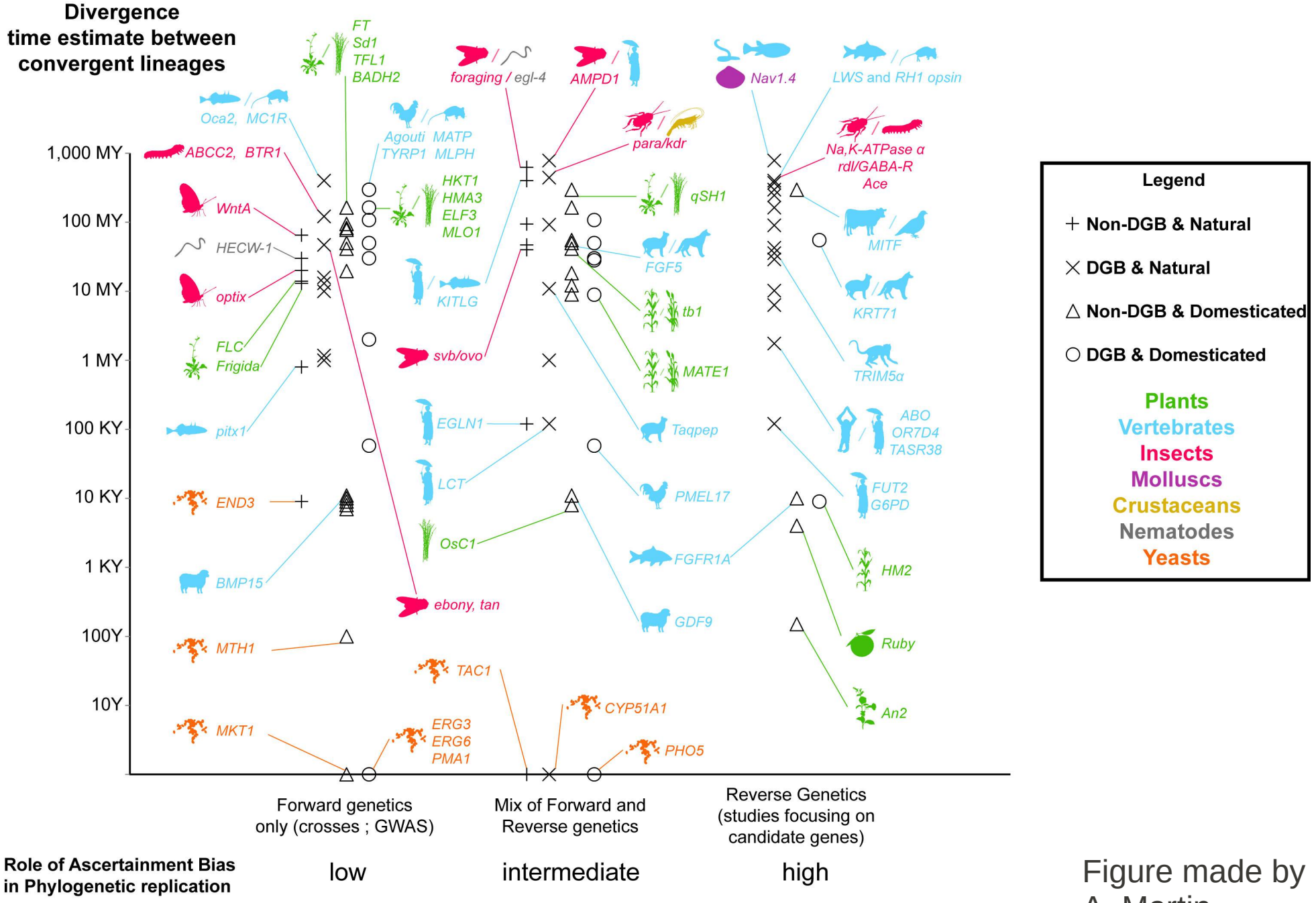
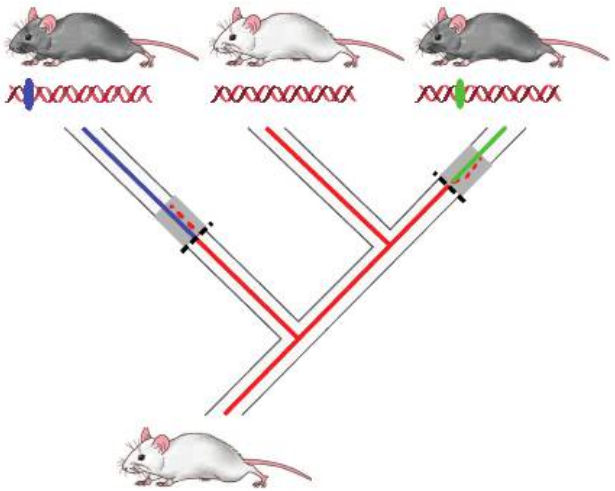
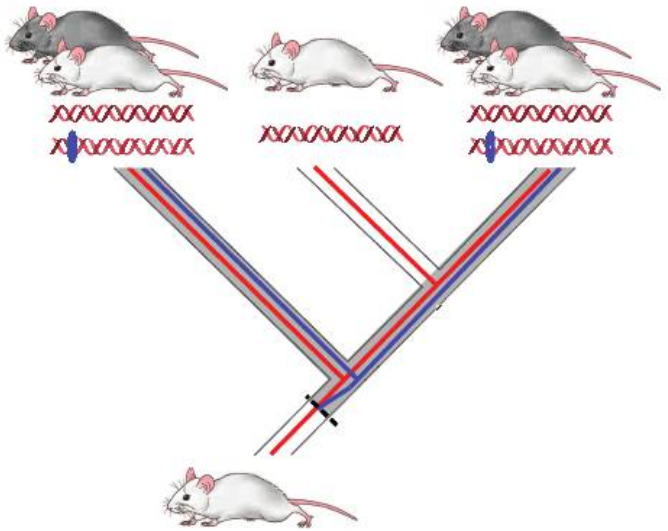


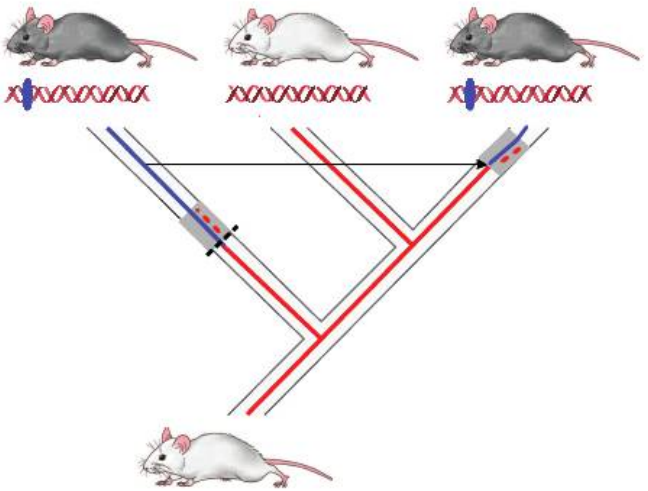
Figure made by A. Martin



Genetic convergence

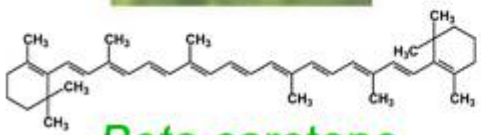


Ancestral polymorphism

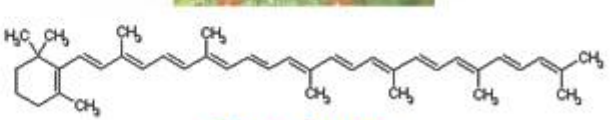


Lateral transfer

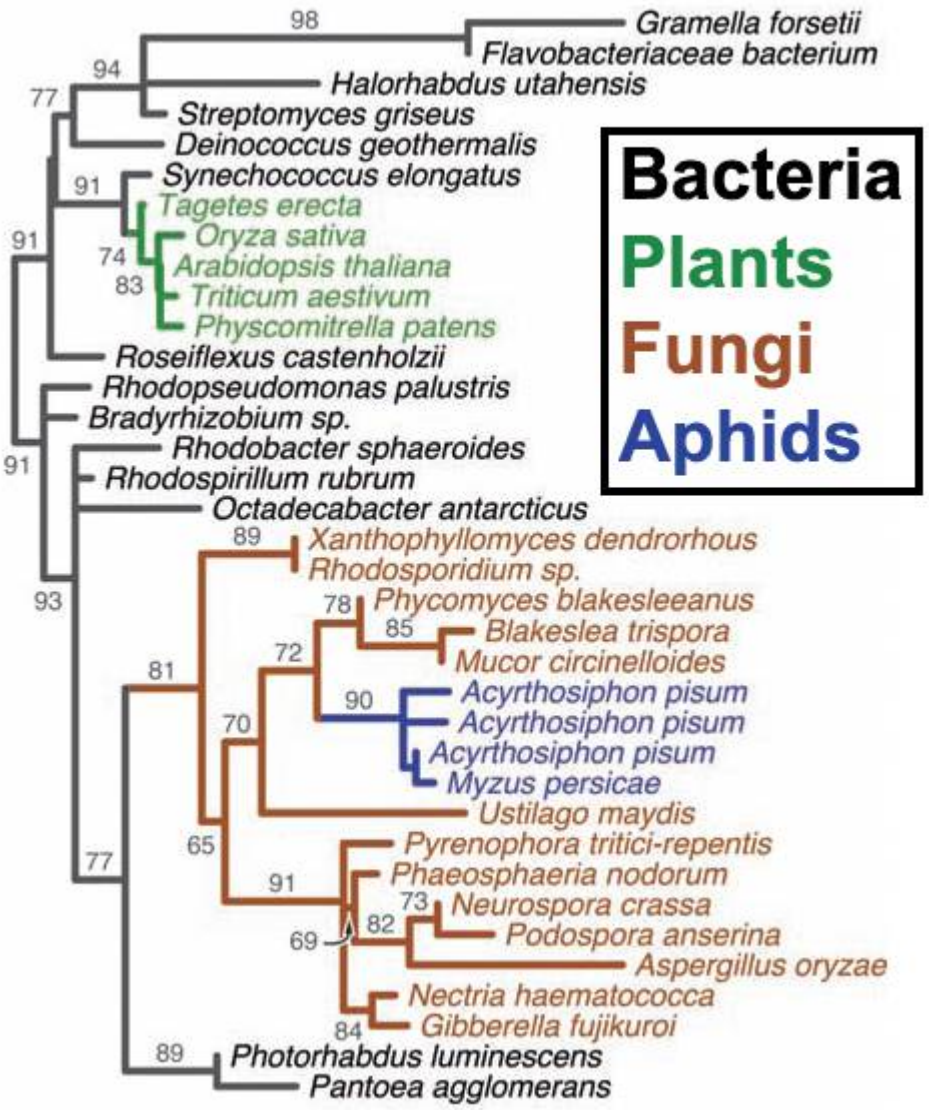
Genetic plagiarism of body color in aphids



Beta-carotene



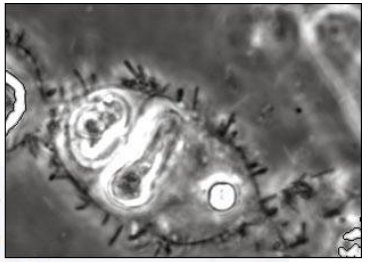
Torulene



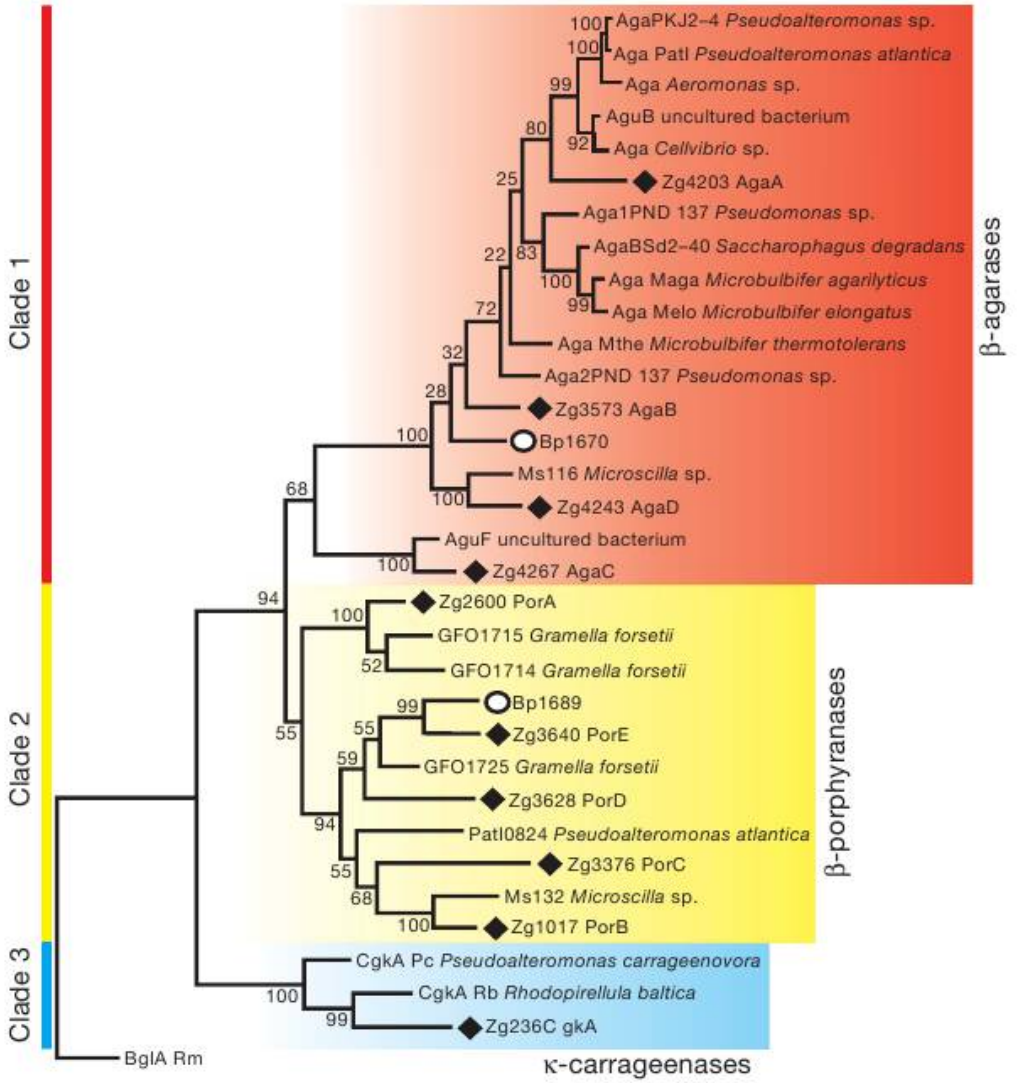
Moran and Jarvik 2010 Science

We are what we eat
Seaweed digestion in Japanese people

◆ *Zobellia galactanivorans*



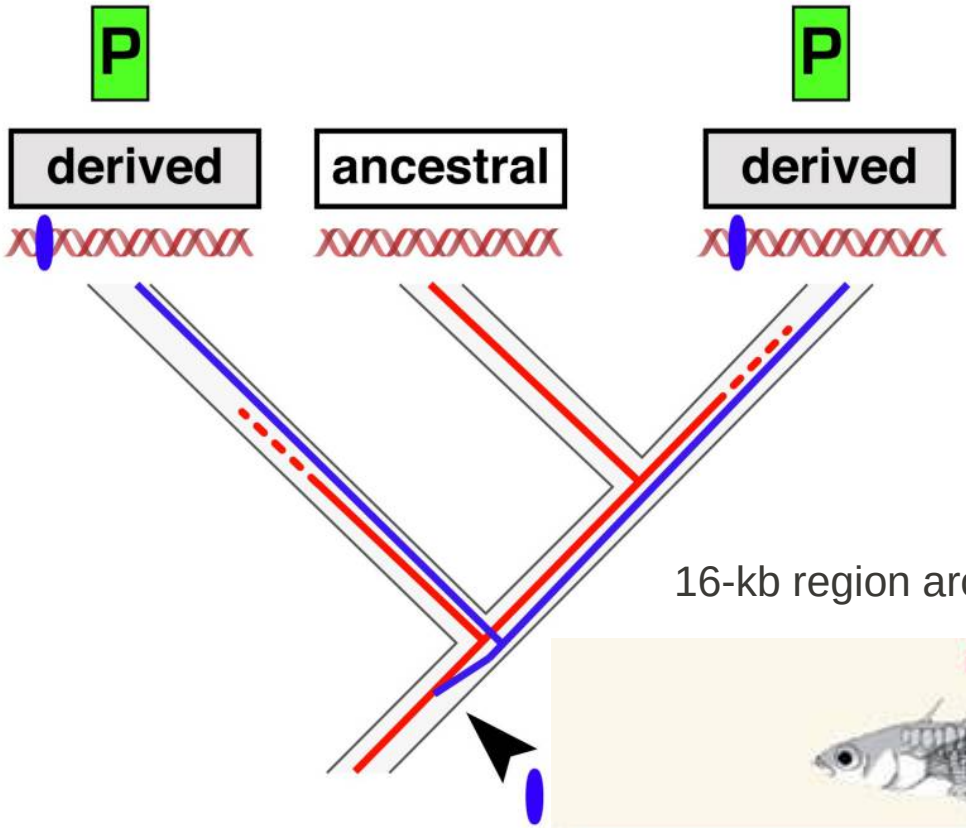
seaweed



○ *Bacteroides plebeius*
from Japanese microbiome only!

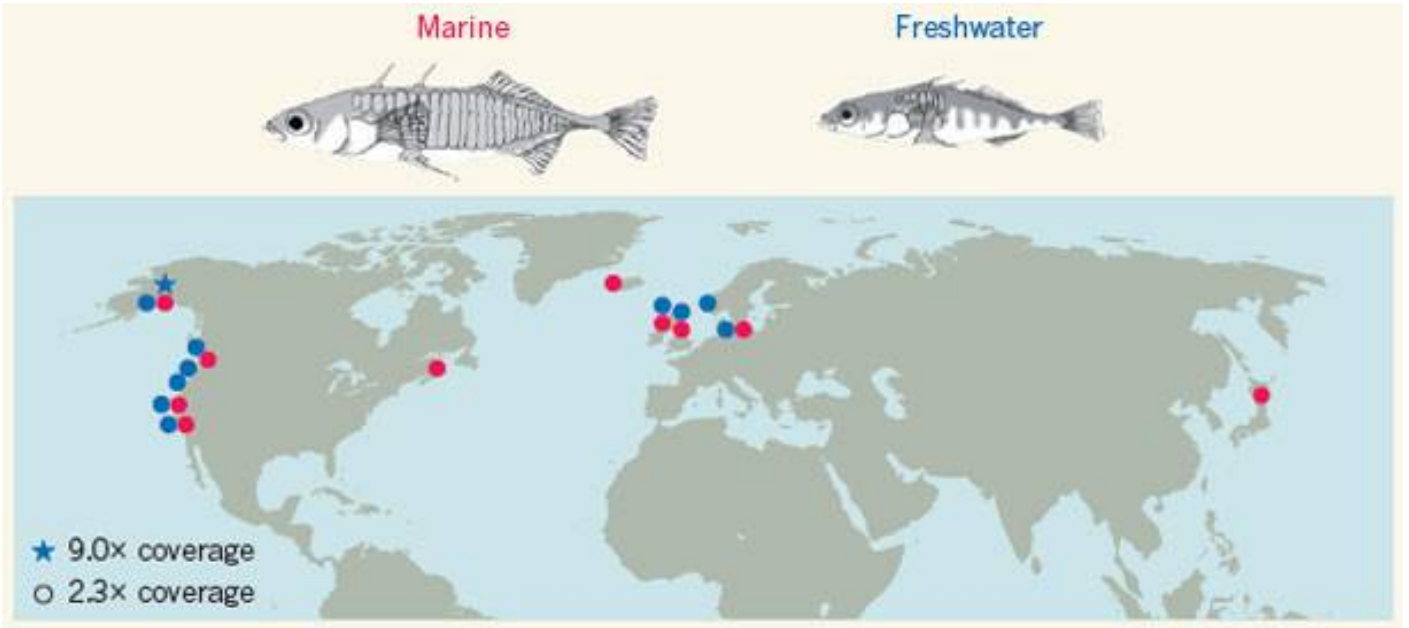
Hehemann et al 2010 Nature

Repeated evolution via ancestral polymorphisms



Incomplete lineage sorting
Standing genetic variation

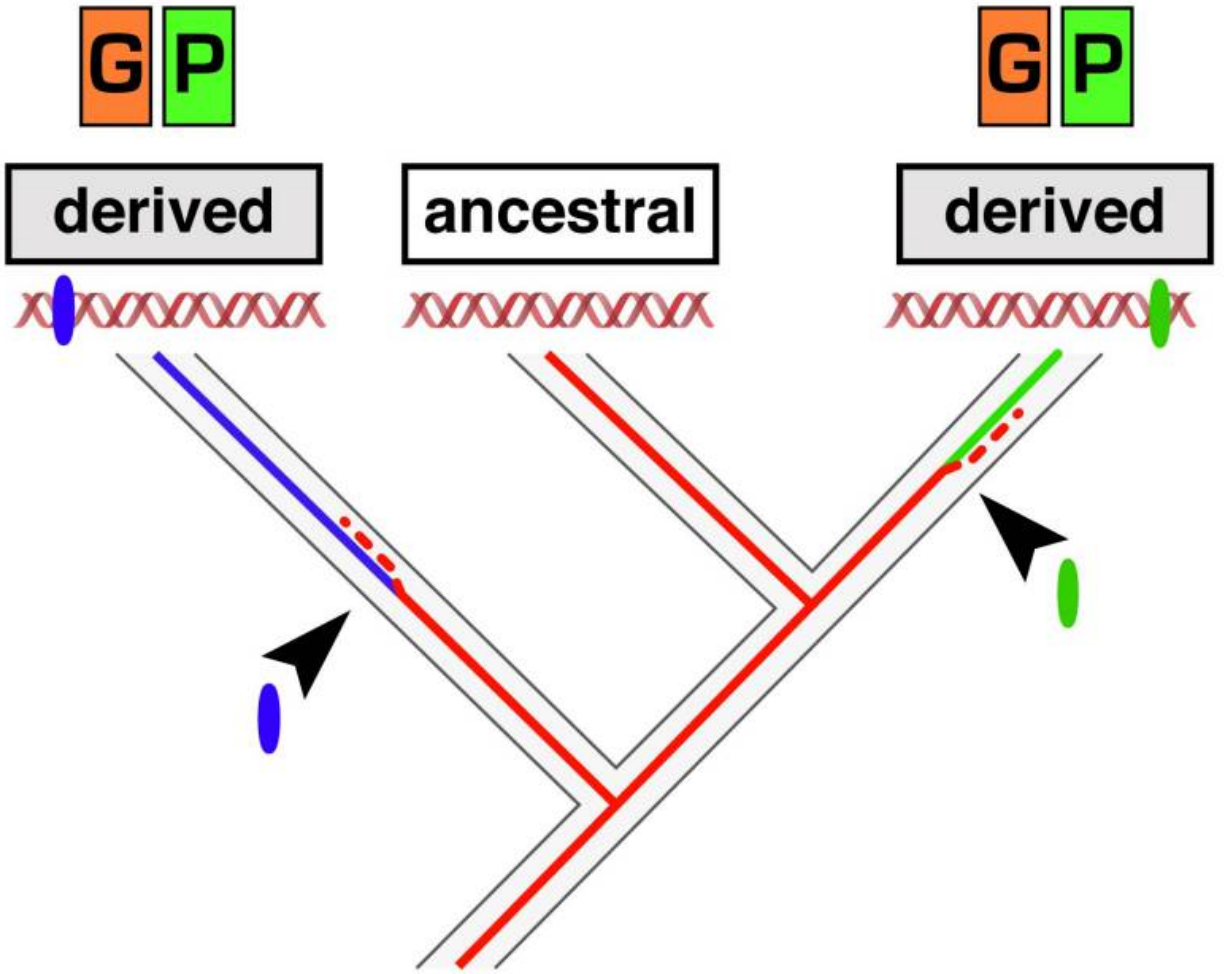
16-kb region around *Eda* shared by all freshwater fishes



Armor plate
(Colosimo 2005
Jones 2012)

There is a limited set of genetic paths to evolution

Repeated evolution sensu stricto



Legend

G — repetition observed at genotypic level

P — repetition observed at phenotypic level

derived — derived phenotype

ancestral — ancestral phenotype

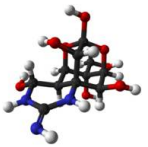
ancestral allele

Repeated evolution

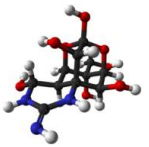
clam

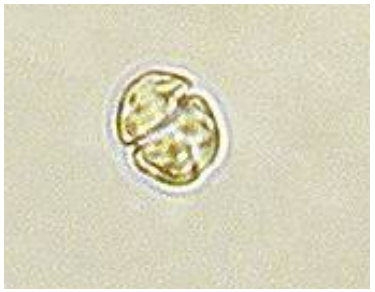
garter snake

Saxitoxin



Tetrodotoxin





toxic plancton

toxic newt

pufferfish (fugu)

Bricelj 2005
Geffeney 2005
Venkatesh 2005

Repeated evolution
via the same amino acid change

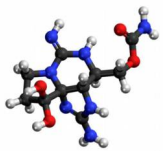
clam

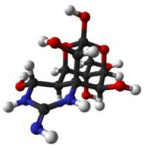
garter snake

Nav1.4
X E945D

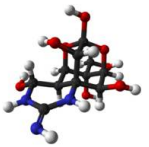
Nav1.4 sodium channel
X E945D

Saxitoxin

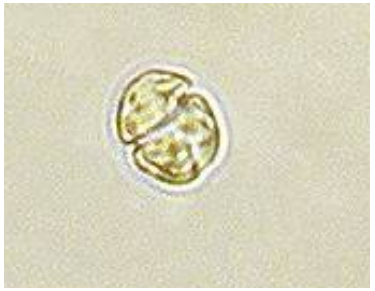




Tetrodotoxin



Nav1.4
E945D
X



toxic plancton

toxic newt

pufferfish (fugu)

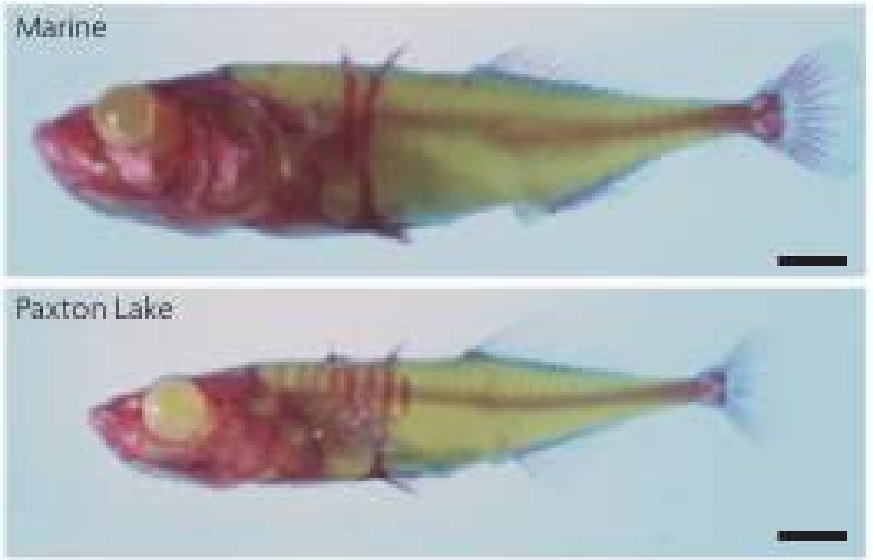
Bricelj 2005
Geffeney 2005
Venkatesh 2005

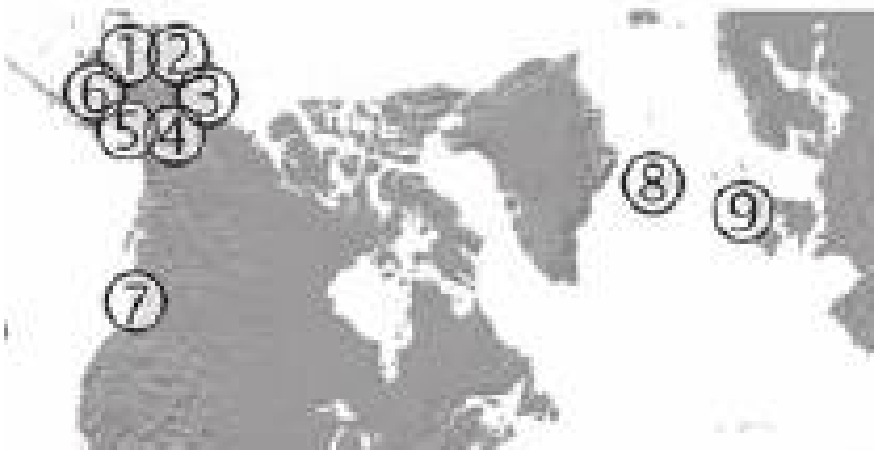
Repeated evolution via the same amino acid change

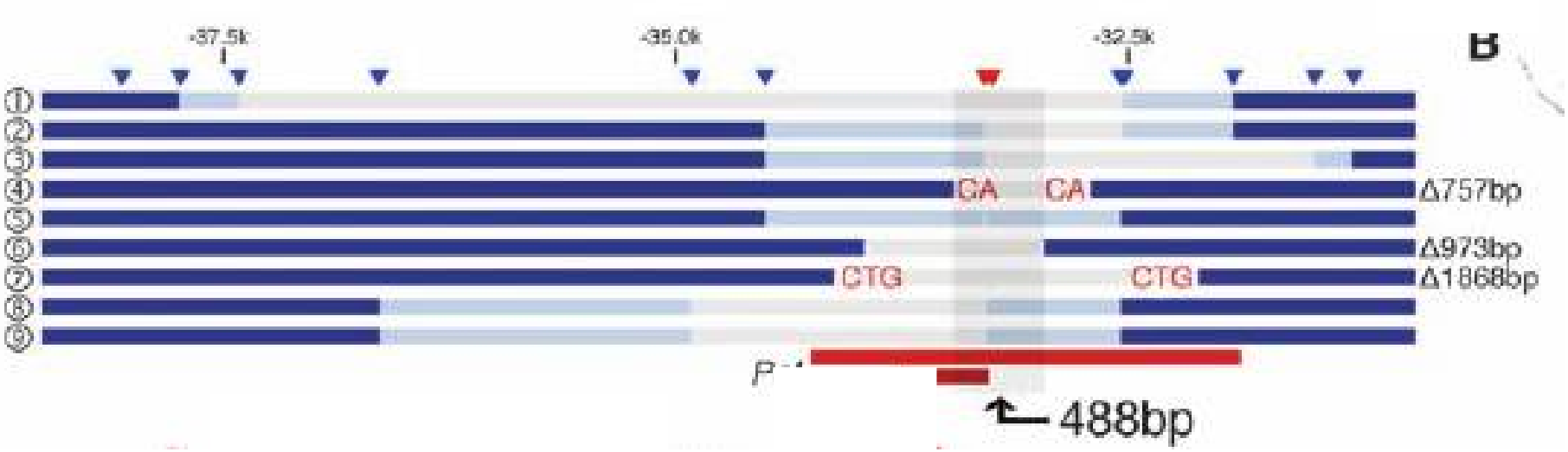
Locus	Mutation	Homoplastic lineages	Variation	Xenobiotic
Ace-1	Gly119Ser	5 (insects)	Intraspecific	Insecticides (organophosphorus)
ERG3	Trp205Stop	4 (yeast lines)	Experimental	Fungicide (nystatin)
ERG6	Gln44Stop Gly127Arg Tyr223Stop	3 (yeast lines) 4 (yeast lines) 4 (yeast lines)	Experimental	Fungicide (nystatin)
Esterase E3	Gly137Asp Trp251Leu/Ser	3 (flies) 2 (blowflies)	Intraspecific	Insecticides (diazinon) Insecticides (malathion)
Na,K-ATPase α	Asn122His Glu111Val Glu111Leu Iso315Val Thr797Ala	5 (insects) 3 (insects) 3 (insects) 2 (insects) 2 (insects)	Interspecific	Host plant toxins (cardenolides)
Nav1.4 channel	Glu945Asp Glu945Asp Glu945Asp	1 (pufferfish) 1 (snake) 1 (bivalve mollusk)	Interspecific Interspecific Intraspecific	Endogenous toxin (tetrodoxin) Salamander toxin (tetrodoxin) Plankton toxin (saxitoxin)
para (kdr)	Leu1014His Leu1014Phe Leu1014Ser Met918Thr Thr929Ile	2 (insects) 11 (insects) 2 (mosquitoes) 5 (insects) 3 (2 moths, 1 louse)	Intraspecific	Insecticides (pyrethroids)
Rdl	Ala302Gly Ala302Ser	3 (insects) 11 (insects)	Intraspecific	Insecticides (cyclodienes)
Vkorc1	Leu128Ser/Gln Tyr139Cys	3 (rodents) 2 (rodents)	Intraspecific	Pesticide (warfarin)

Resistance to xenobiotics

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

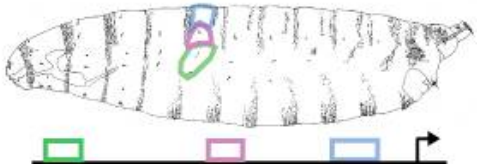






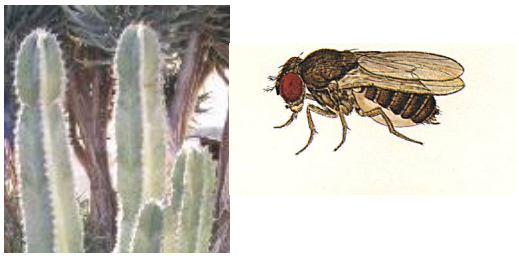
Accumulation of evolutionary-relevant mutations at the same locus

≥ 6 mutations in *svb*



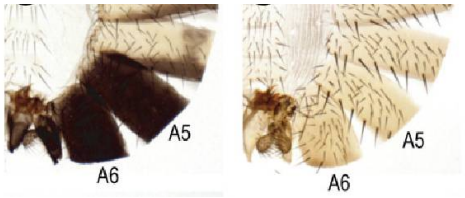
(McGregor, Orgogozo et al. 2007 Nature)

2-4 mutations in *nvd*



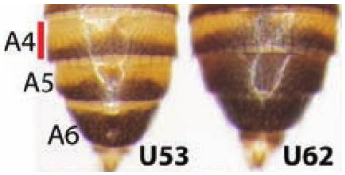
(Lang et al. 2012 Science)

3 mutations in *tan*



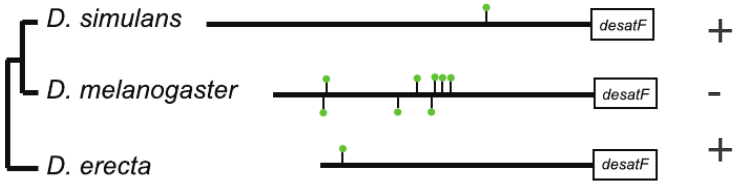
(Jeong et al., 2008 Cell)

5 mutations in *ebony*



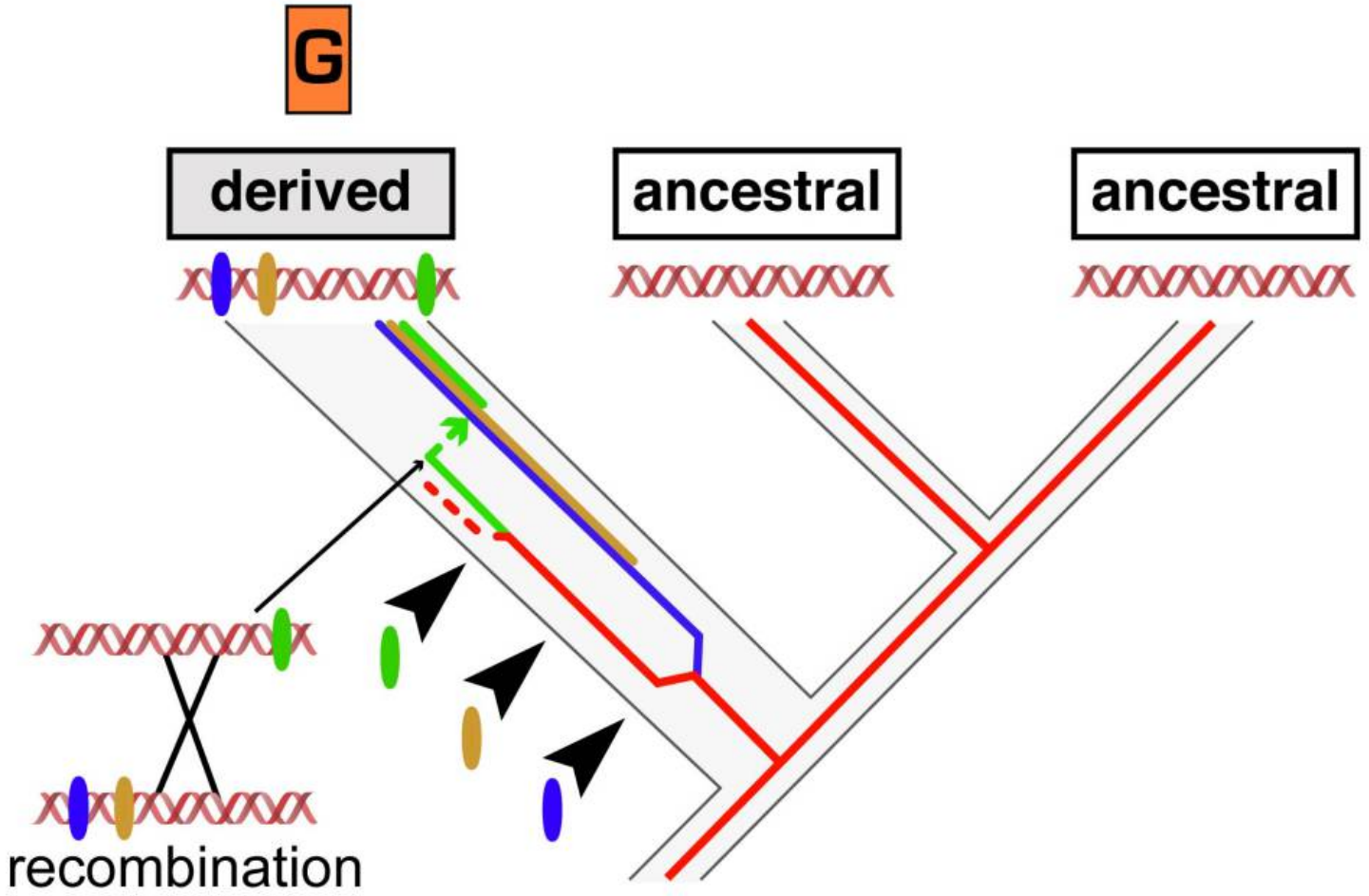
(Rebeiz et al., 2009 Cell)

3 deletions in *desatF*



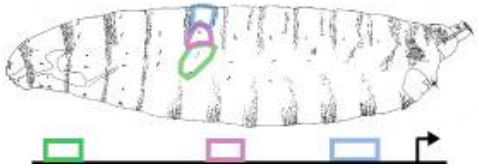
(Shirangi et al., 2009 PloS Biol)

Intralineage hotspot



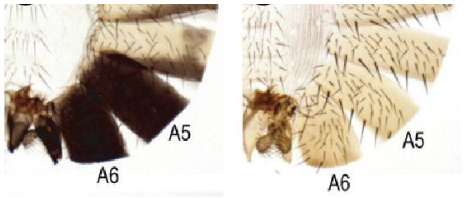
Accumulation of evolutionary-relevant mutations at the same locus

≥ 6 mutations in *svb*



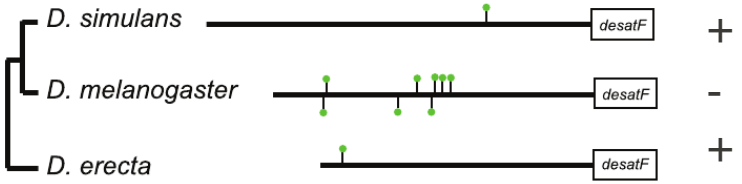
(McGregor, Orgogozo et al. 2007 Nature)

3 mutations in *tan*



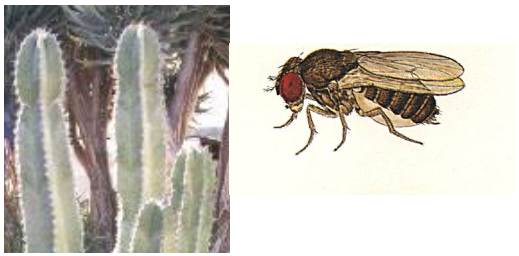
(Jeong et al., 2008 Cell)

3 deletions in *desatF*



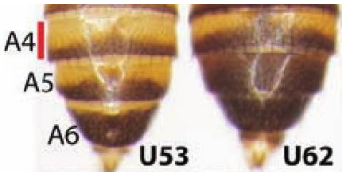
(Shirangi et al., 2009 PloS Biol)

2-4 mutations in *nvd*



(Lang et al. 2012 Science)

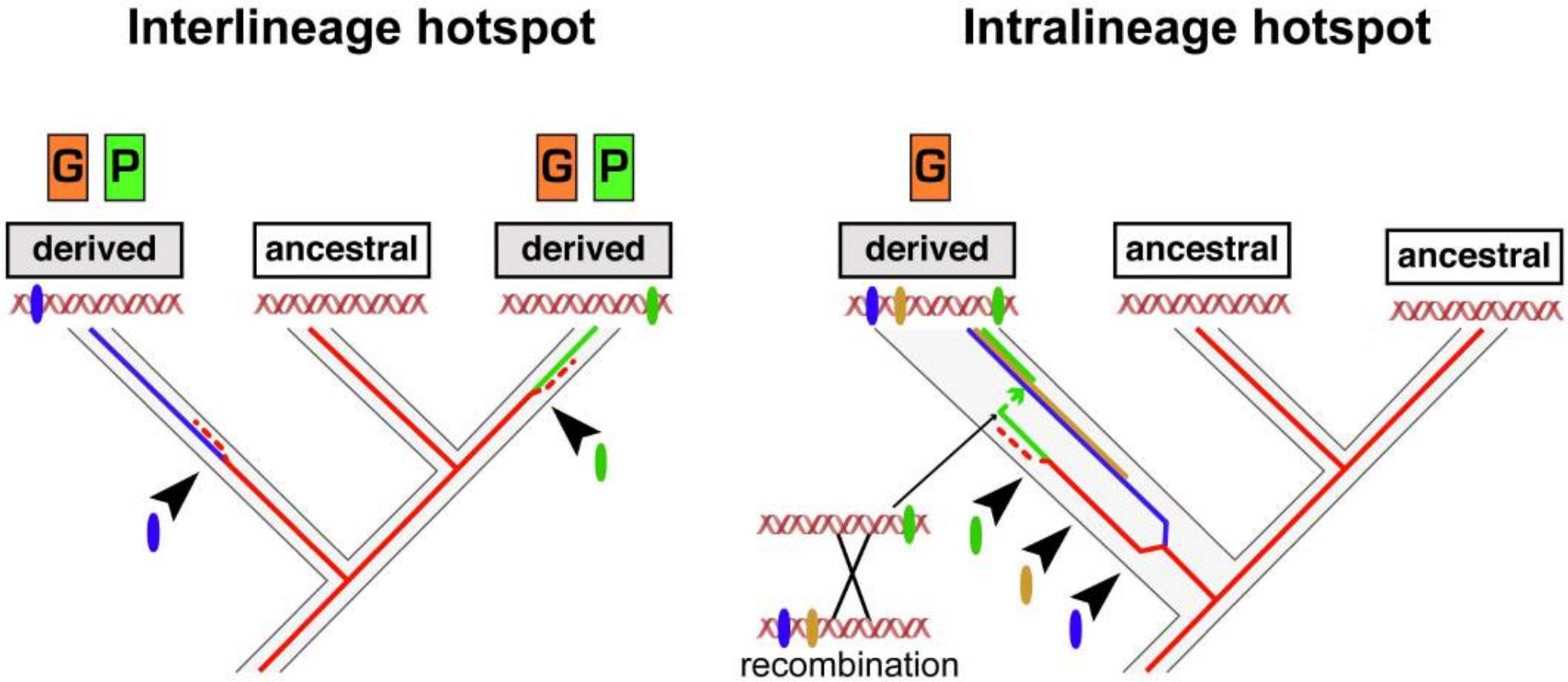
5 mutations in *ebony*



(Rebeiz et al., 2009 Cell)

Can we detect signatures of multiple neighboring sweeps?

Hotspot genes: preferred targets of evolution

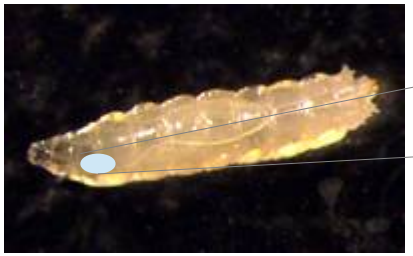


Martin and Orgogozo,2013

Why is the set of genetic paths limited?

There are specialized genes in a genome

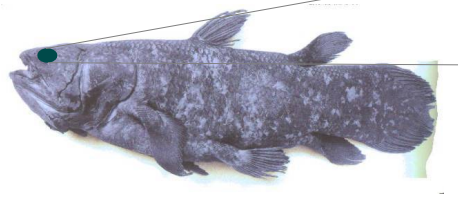
Steroid hormone biosynthesis



a specialized tissue
specialized enzymes

2-4 mutations in *nvd*

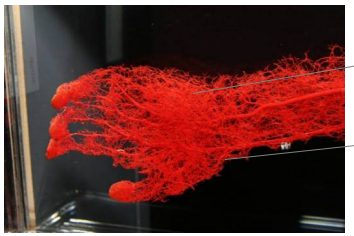
Color vision



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?***

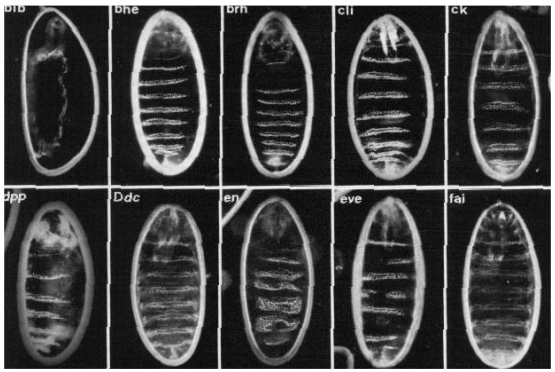
Evolution appears to use a restricted set of all possible paths

Changes in trichome pattern

EVOLUTION

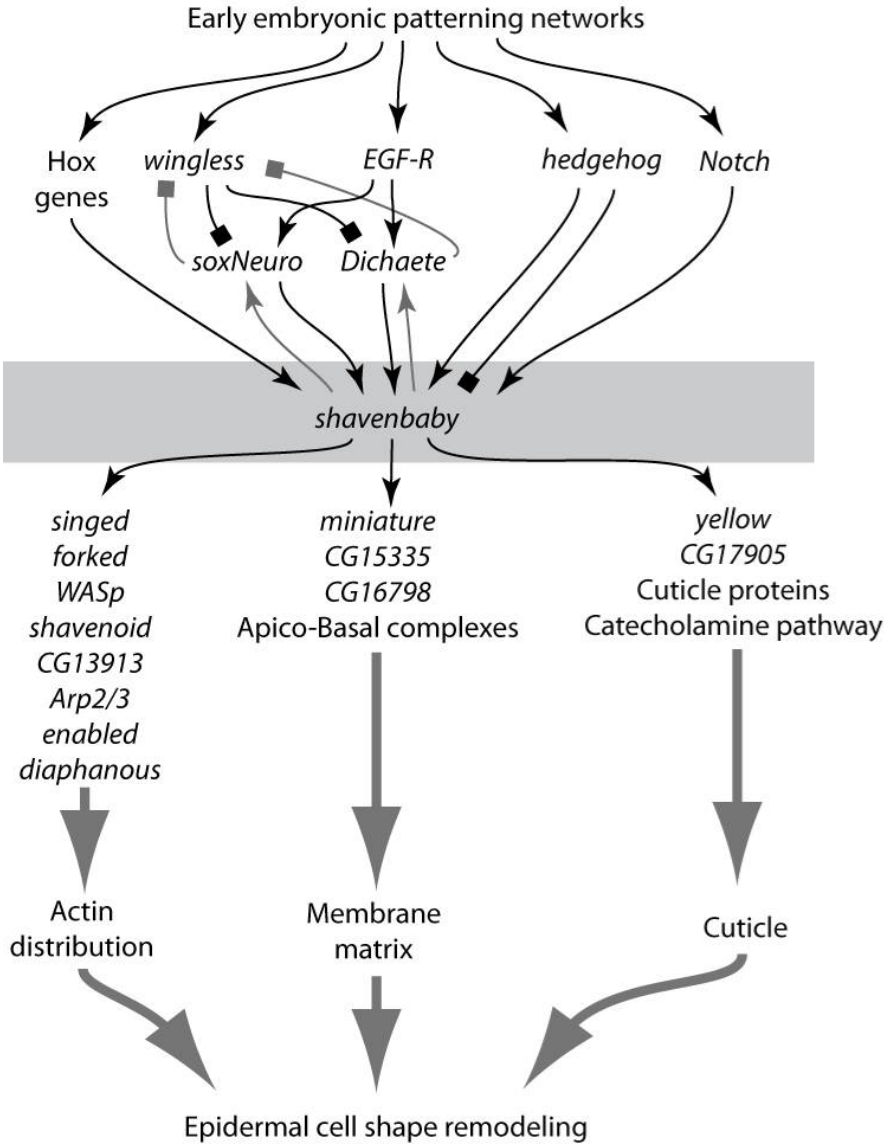
A single gene

MUTAGENESIS



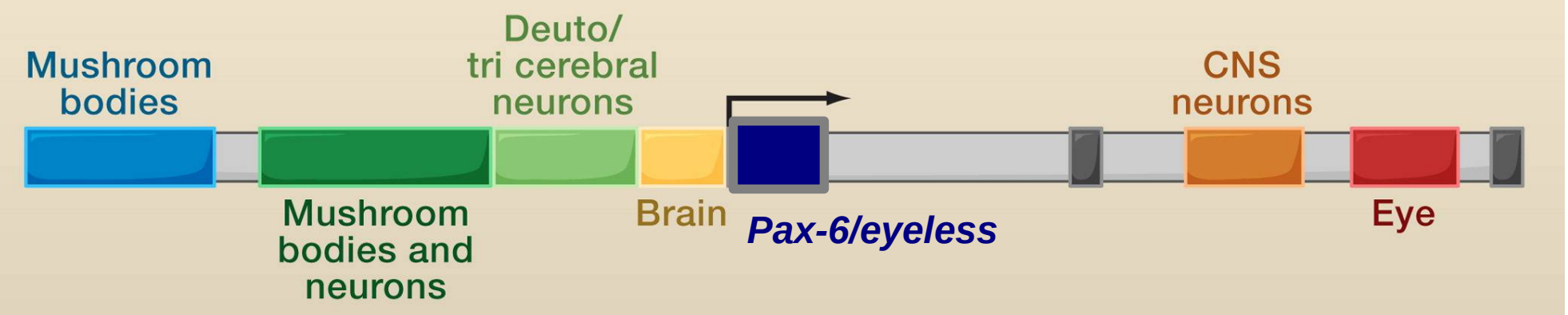
(Nüsslein-Volhard et Weischaus)

~100 genes



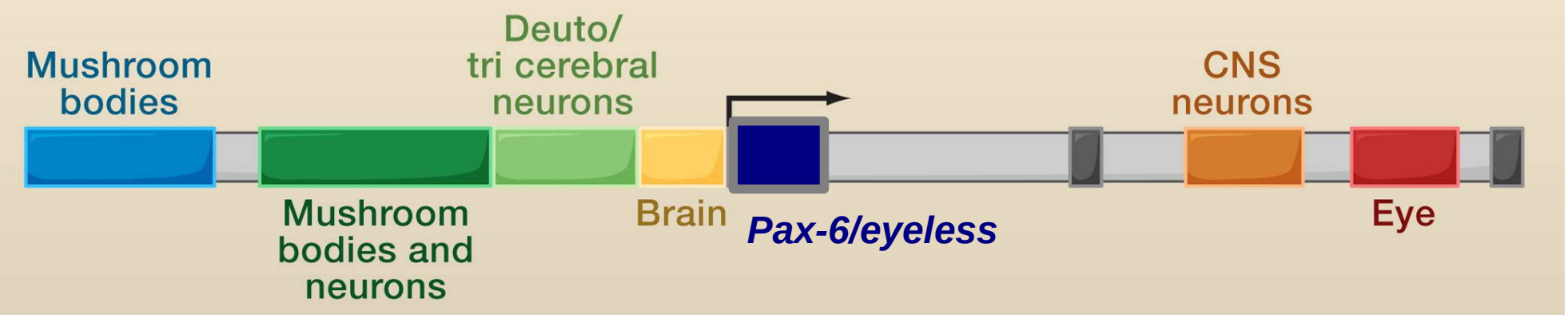
(Stern et Orgogozo, 2008 Evolution – Stern et Orgogozo, 2009 Science)

There are specialized loci within multifunctional genes in a genome



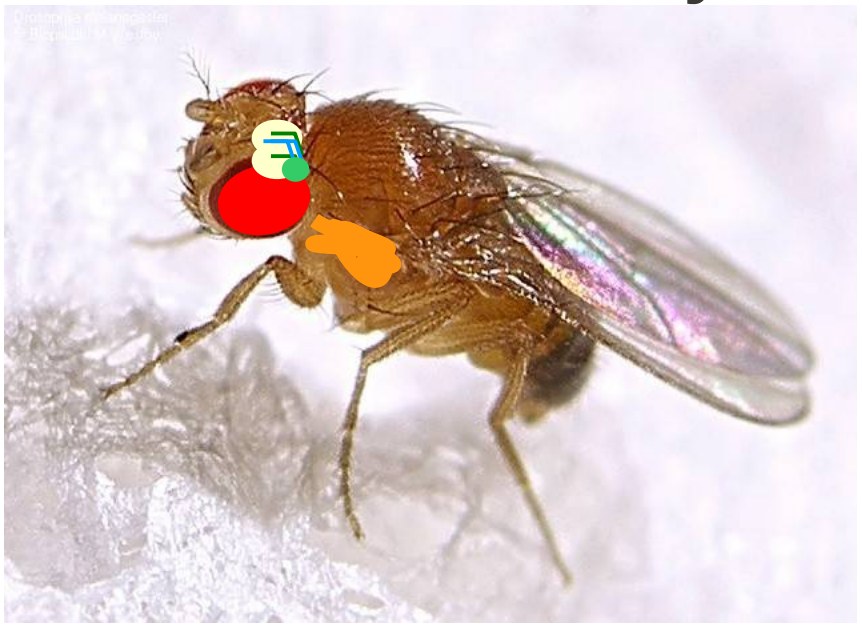
Carroll 2008

There are specialized loci within multifunctional genes in a genome



Carroll 2008

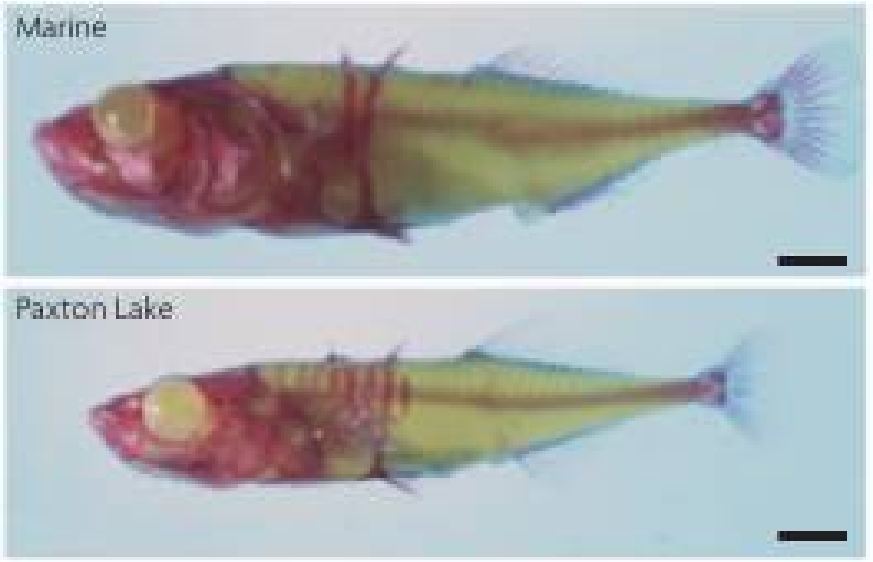
The modularity of cis-regulatory elements is reflected in the modularity of body parts

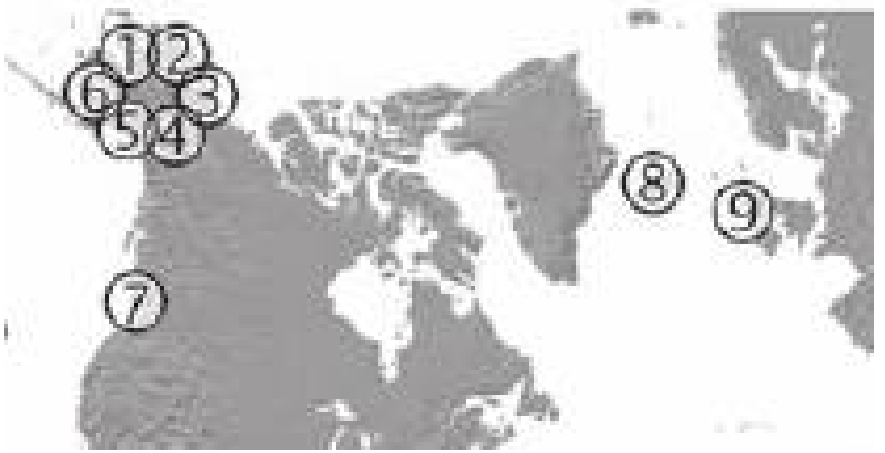


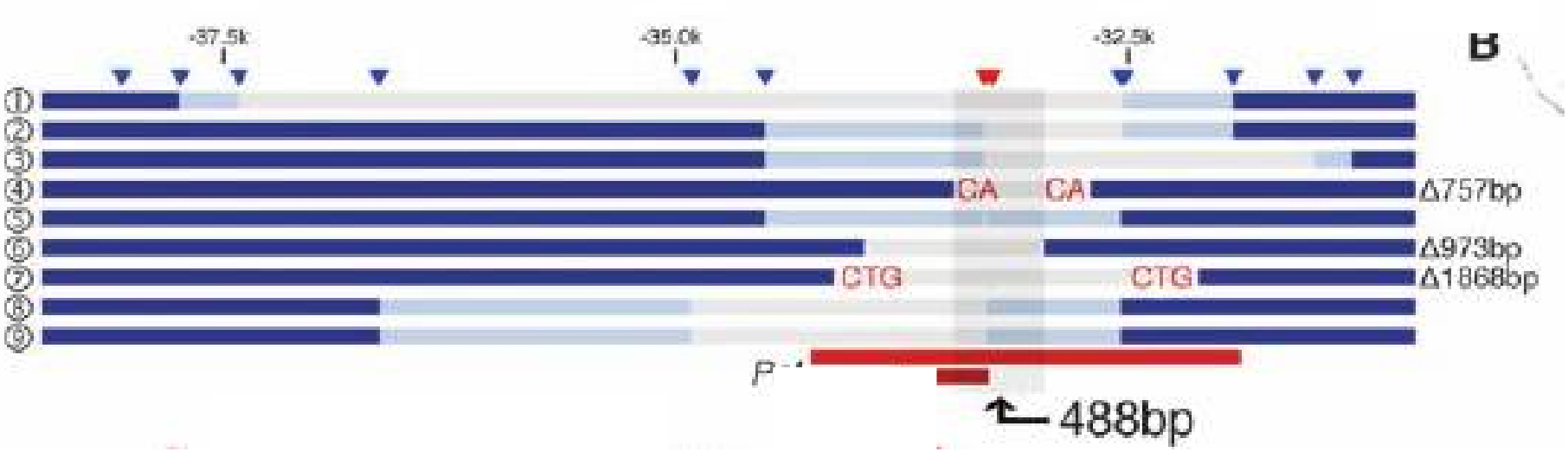
Why is the set of genetic paths limited?

- → **genes with specialized functions**
- → **multifunctional genes with specialized regions**
- → **mutational bias**

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







Conclusion

1) Identifying the mutations responsible for phenotypic differences

Pitx1

nvd

2) Gephe : thinking in terms of differences

can we find a new repesentation of gephe spaces?

3) Genetic hotspots of evolution

can we detect signatures of multipe neighboring sweeps?