Interactions between several loci, Epistasis, Super Genes, Pleiotropy, Interactions Genes x Environment

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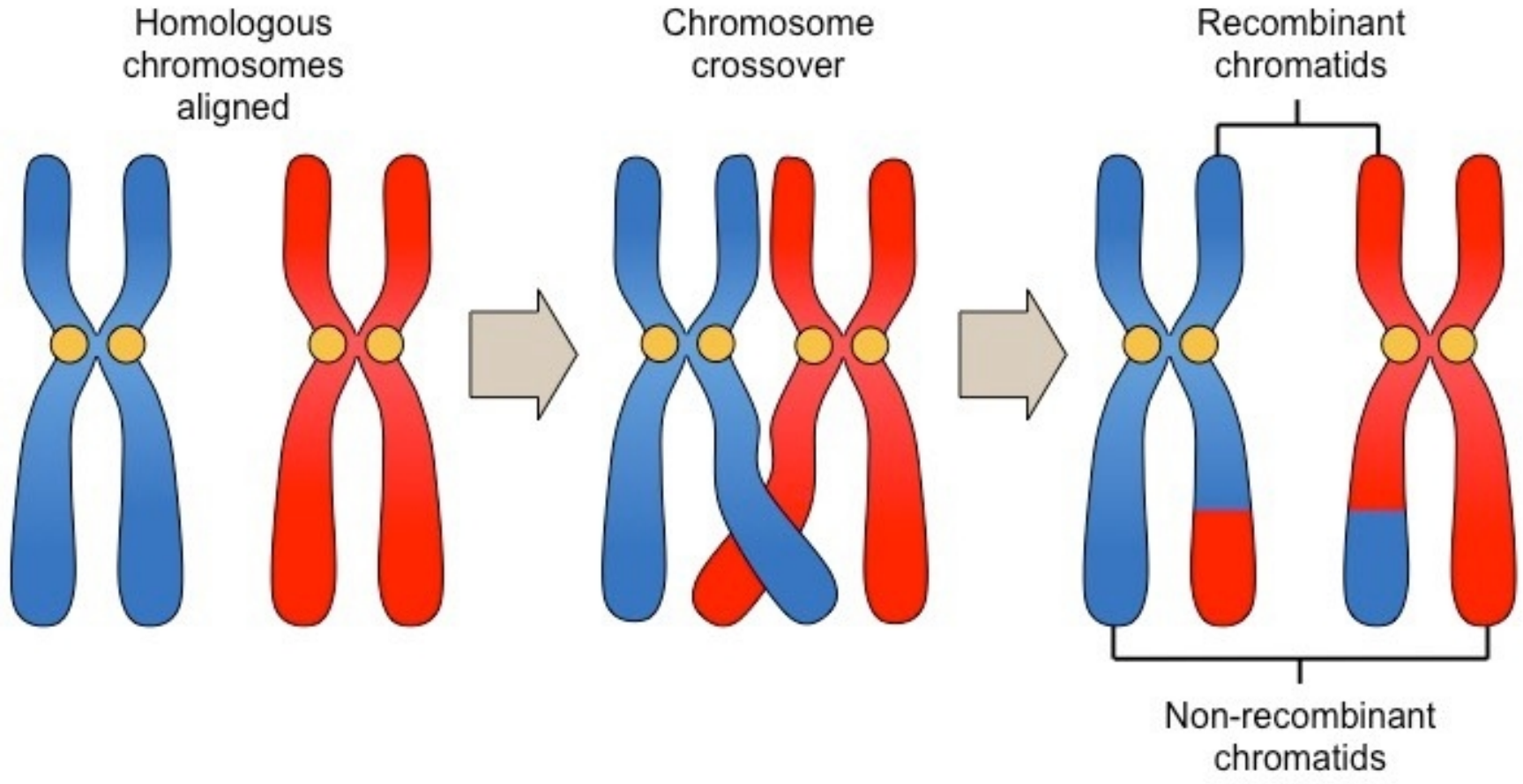
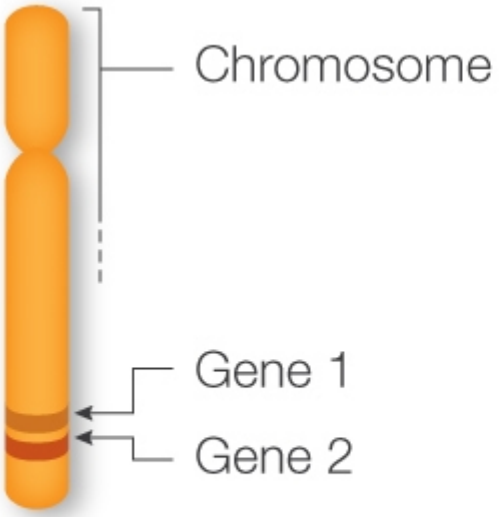
Genetic Linkage

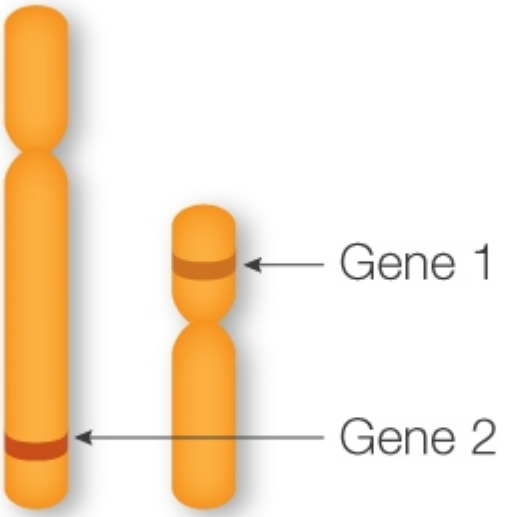
Crossing overs



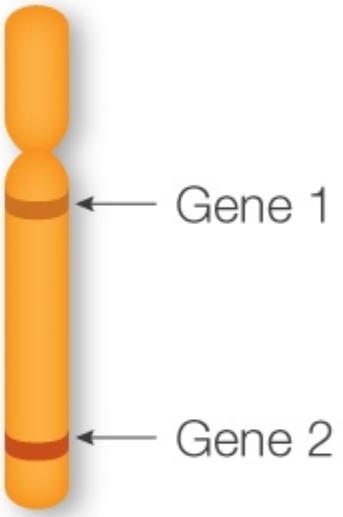
About one recombination event per chromosome arm



Linked



Not Linked

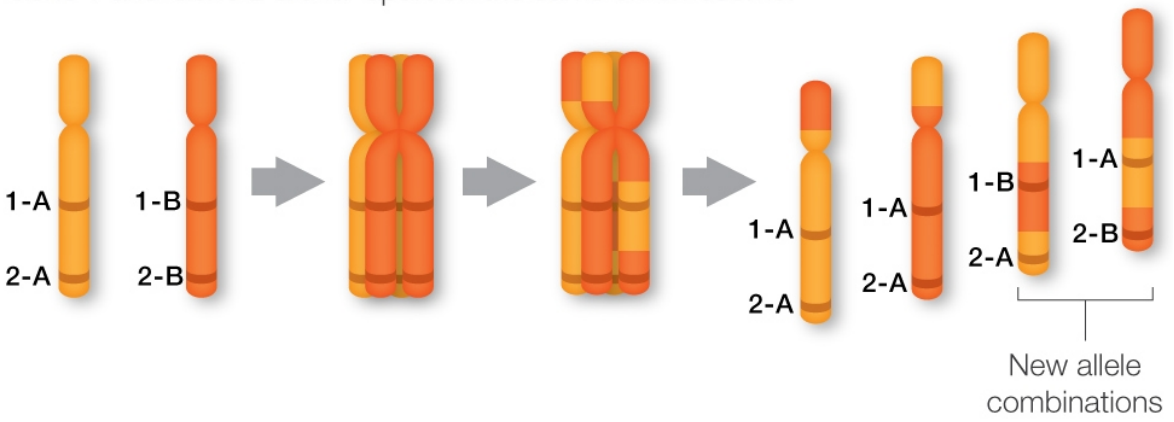


Not Linked

https://learn.genetics.utah.edu/content/pigeons/geneticlinkage/

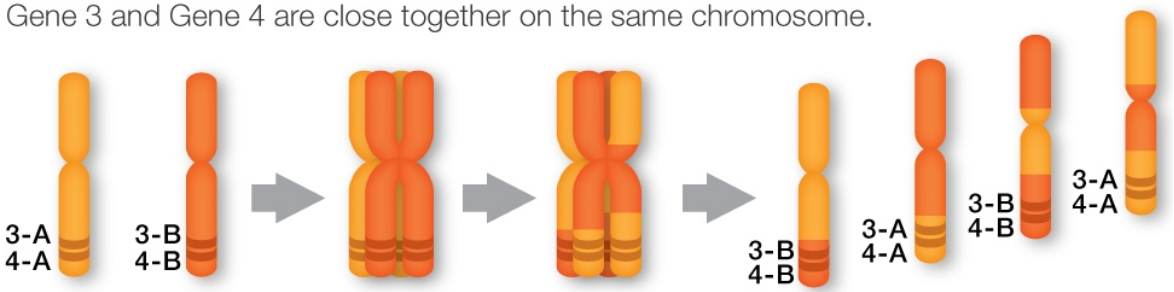
Not Linked

Gene 1 and Gene 2 are far apart on the same chromosome.



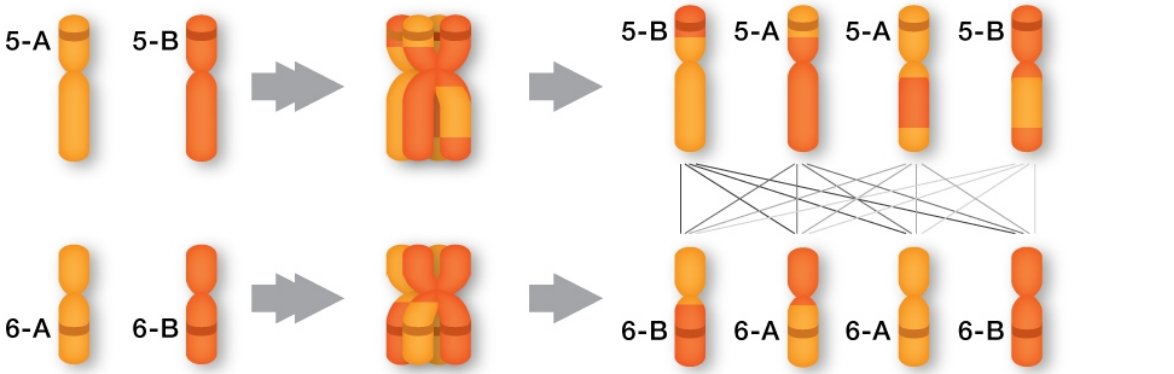
Linked

Gene 3 and Gene 4 are close together on the same chromosome.



Not Linked

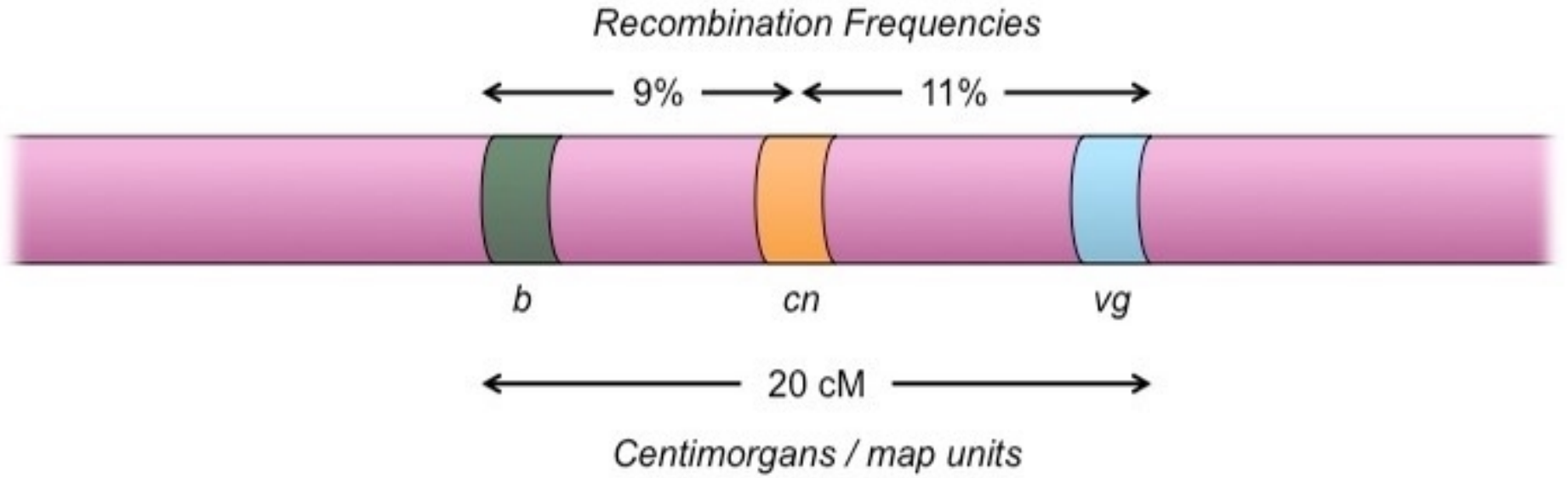
Gene 5 and Gene 6 are on separate chromosomes.



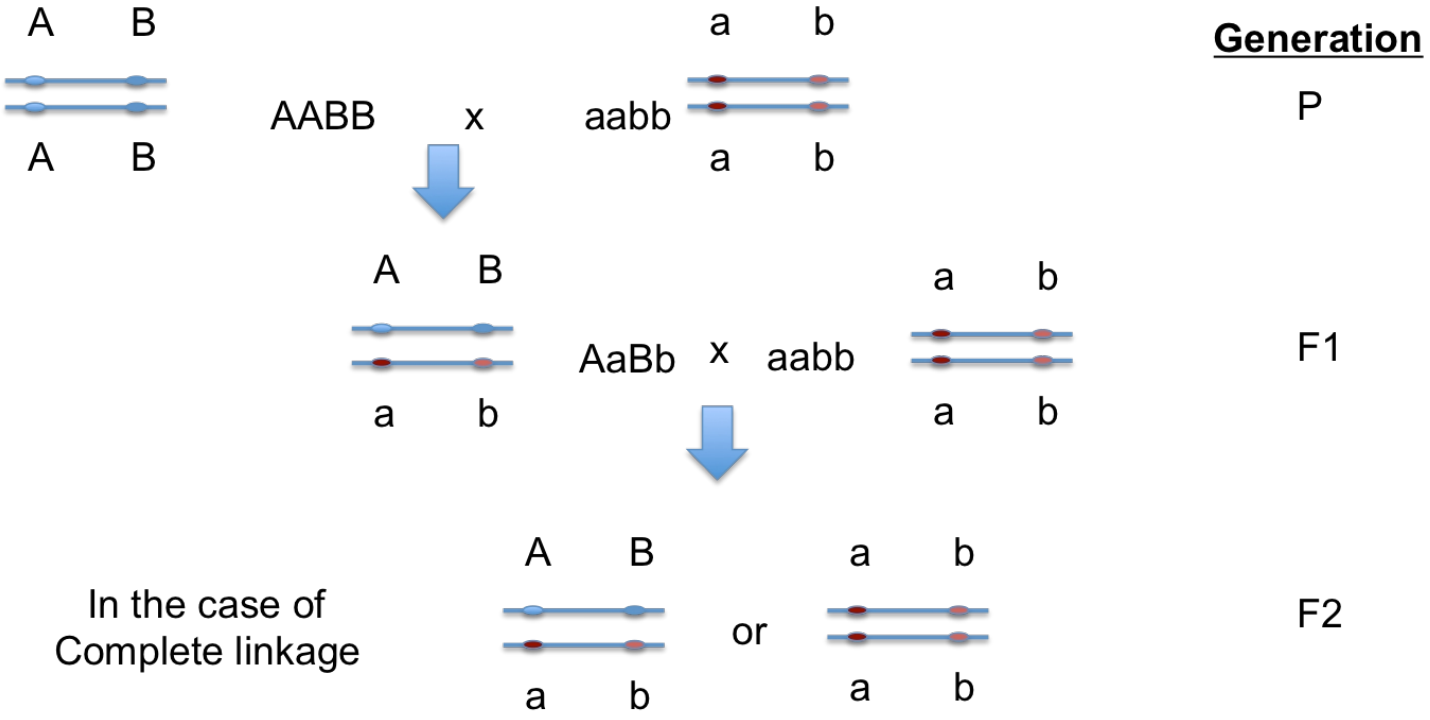
One “centiMorgan”
= genetic distance that produces a recombination frequency of 1%

Genetic distance (in cM)

= (# Recombinant gametes) X 100
Total gametes



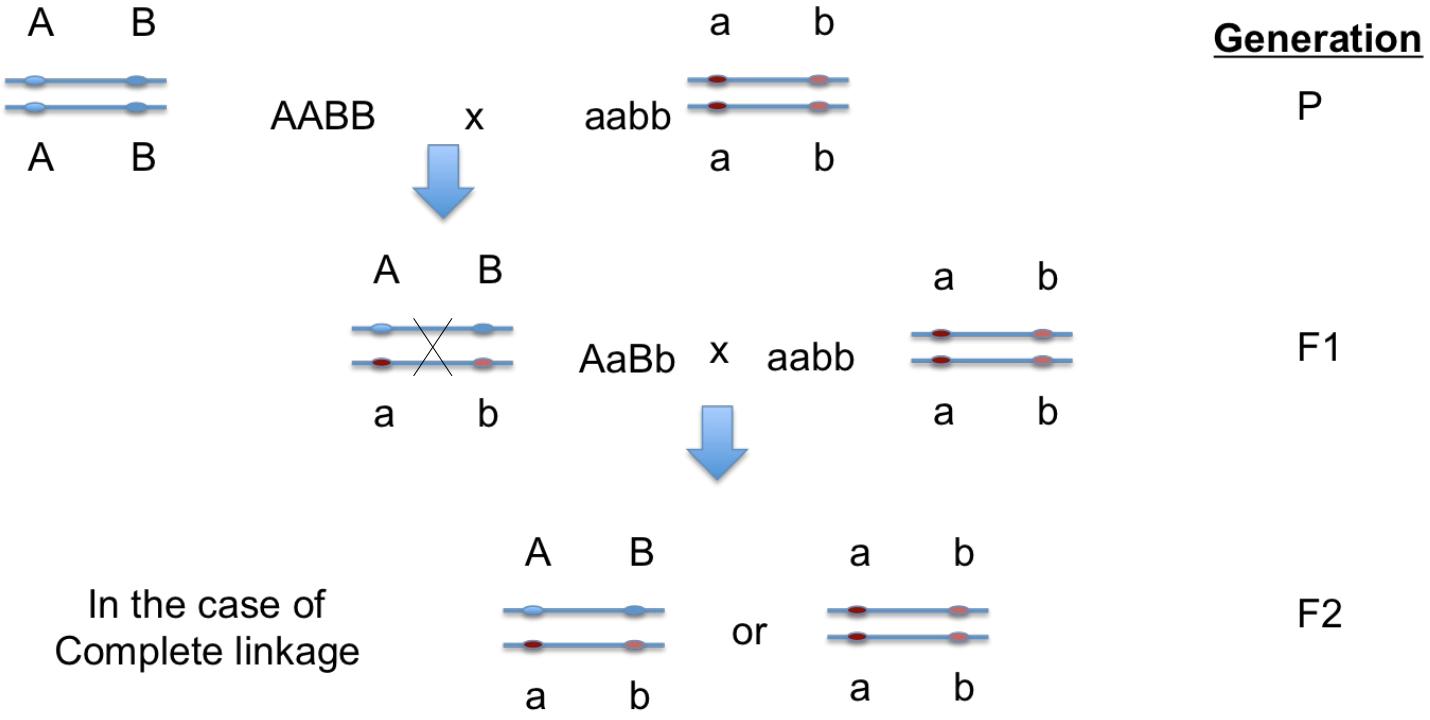
Measure of genetic linkage



Complete Linkage

50% AaBb
50% aabb

Measure of genetic linkage



Complete Linkage

50% AaBb
50% aabb

Genetic Linkage

40% AaBb
10% Aabb
10% aaBb
40% aabb

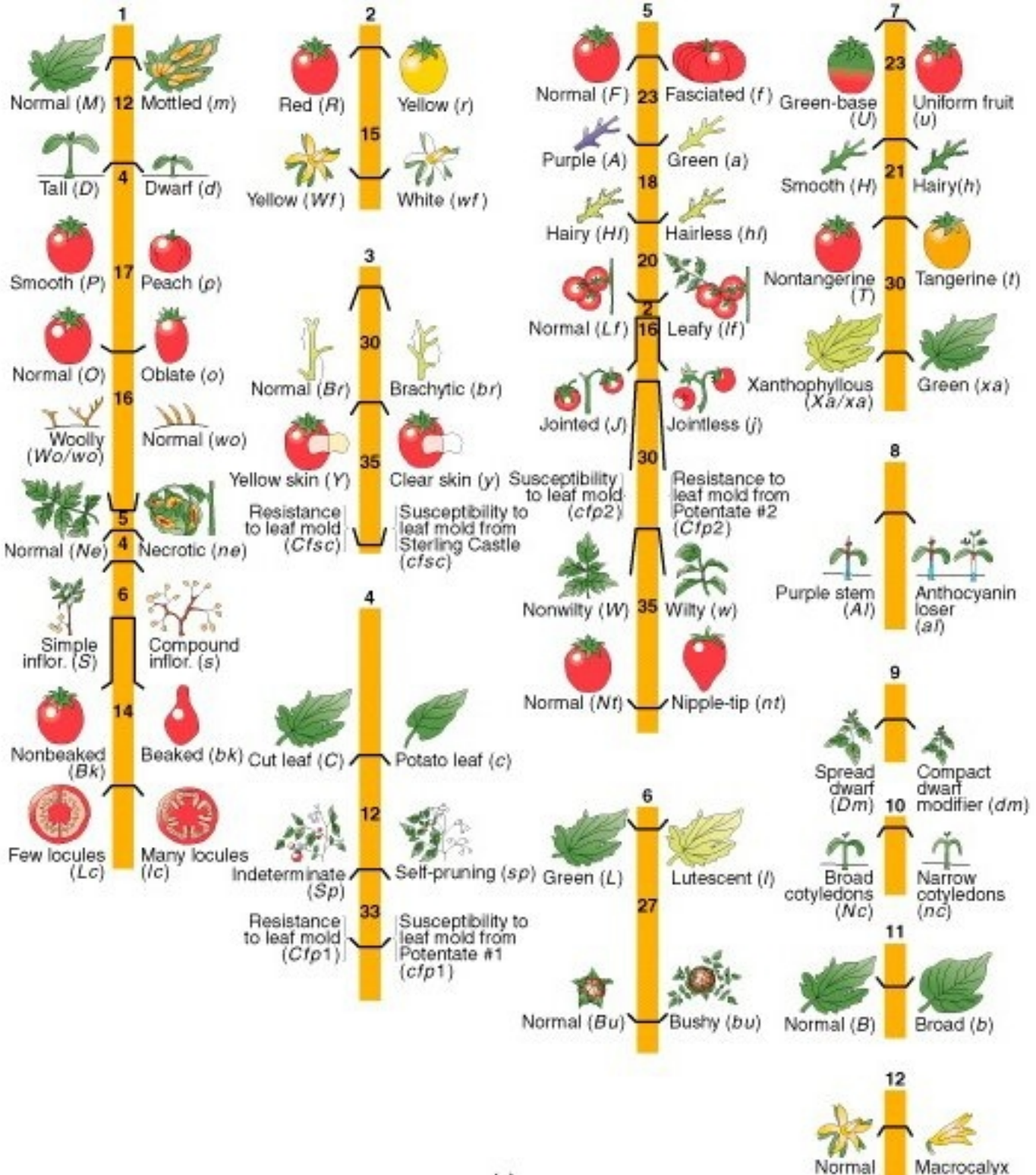
20% of recombinants so 20cM

Measure of genetic linkage

If y % recombinant gametes and y < 50% => y cM apart

Due to double cross-overs and cross-over interference,
genetic distances need corrections when long and are not fully additive

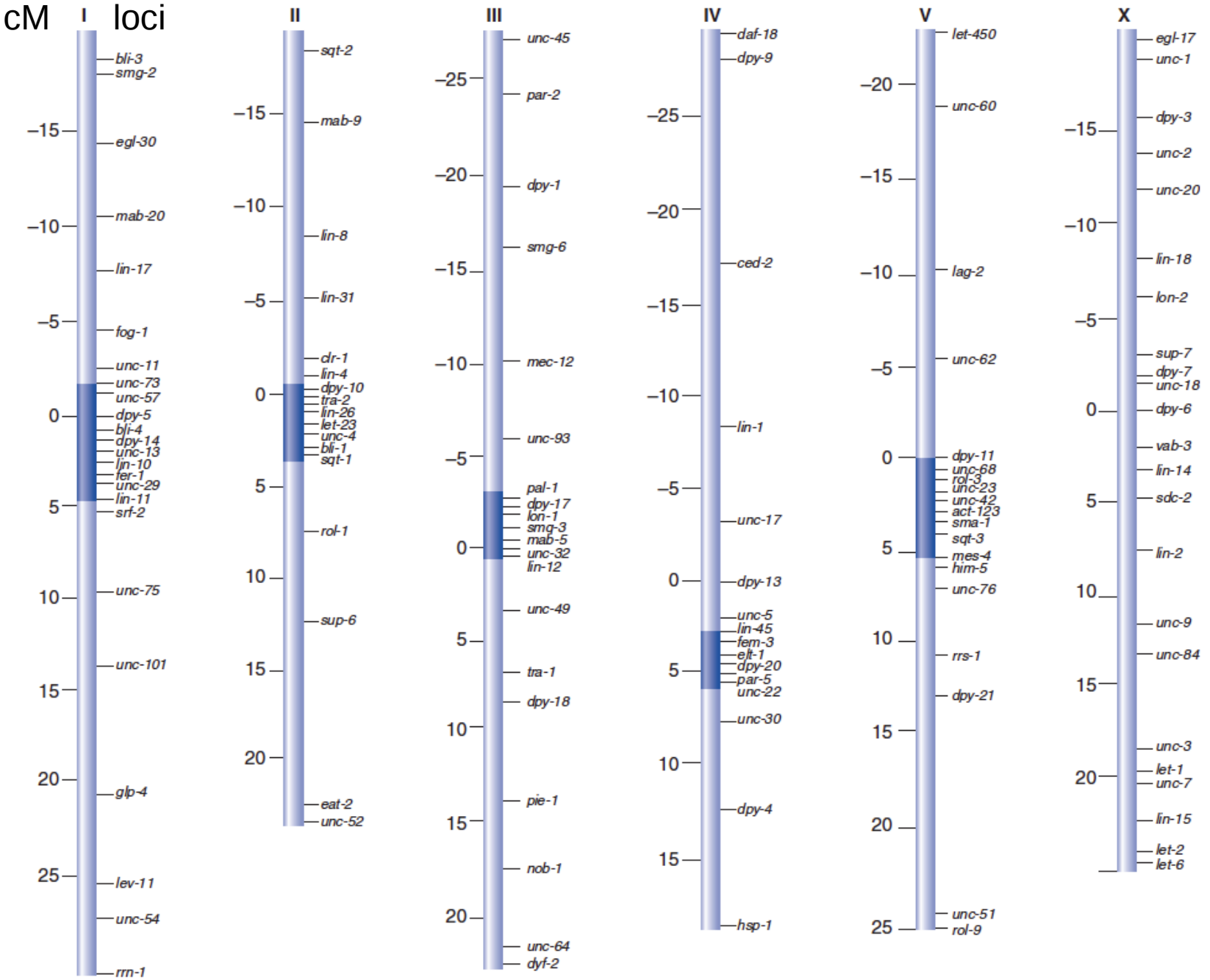
If the linkage group is longer than 50 cM, mutations at the two extremities are operationally unlinked


1
Normal (M)
12
Mottled (m)
Tall (D)
4
Dwarf (d)
Smooth (P)
17
Peach (p)
Normal (O)
Oblate (o)
16
Woolly (Wo/wo)
Normal (wo)
Normal (Ne)
5
4
Necrotic (ne)
6
Simple inflor. (S)
Compound inflor. (s)
14
Nonbeaked (Bk)
Beaked (bk)
Few locules (Lc)
Many locules (lc)
2
Red (R)
Yellow (r)
15
Yellow (Wf)
White (wf)
3
30
Normal (Br)
Brachytic (br)
35
Yellow skin (Y)
Clear skin (y)
Resistance to leaf mold (Cfsc)
Susceptibility to leaf mold from Sterling Castle (cfsc)
4
Cut leaf (C)
Potato leaf (c)
12
Indeterminate (Sp)
Self-pruning (sp)
33
Resistance to leaf mold (Cfp1)
Susceptibility to leaf mold from Potentate #1 (cfp1)
5
Normal (F)
23
Fasciated (f)
Purple (A)
Green (a)
18
Hairy (Hl)
Hairless (hl)
20
Normal (Lf)
2
16
Leafy (lf)
Jointed (J)
Jointless (j)
30
Susceptibility to leaf mold (cfp2)
Resistance to leaf mold from Potentate #2 (Cfp2)
Nonwilty (W)
35
Wilty (w)
Normal (Nt)
Nipple-tip (nt)
6
Green (L)
Lutescent (l)
27
Normal (Bu)
Bushy (bu)
7
23
Green-base (U)
Uniform fruit (u)
21
Smooth (H)
Hairy(h)
Nontangerine (T)
30
Tangerine (t)
Xanthophyllous (Xa/xa)
Green (xa)
8
Purple stem (Al)
Anthocyanin loser (al)
9
Spread dwarf (Dm)
Compact dwarf modifier (dm)
10
Broad cotyledons (Nc)
Narrow cotyledons (nc)
11
Normal (B)
Broad (b)
12
Normal
Macrocalyx

Genetic map

in units of recombination

1 centiMorgan (cM)
= 1% recombinants



Genetic Markers

Mark the region of interest through genetic linkage

Are not causal (or only rarely) for variation in the phenotype of interest

Detected:

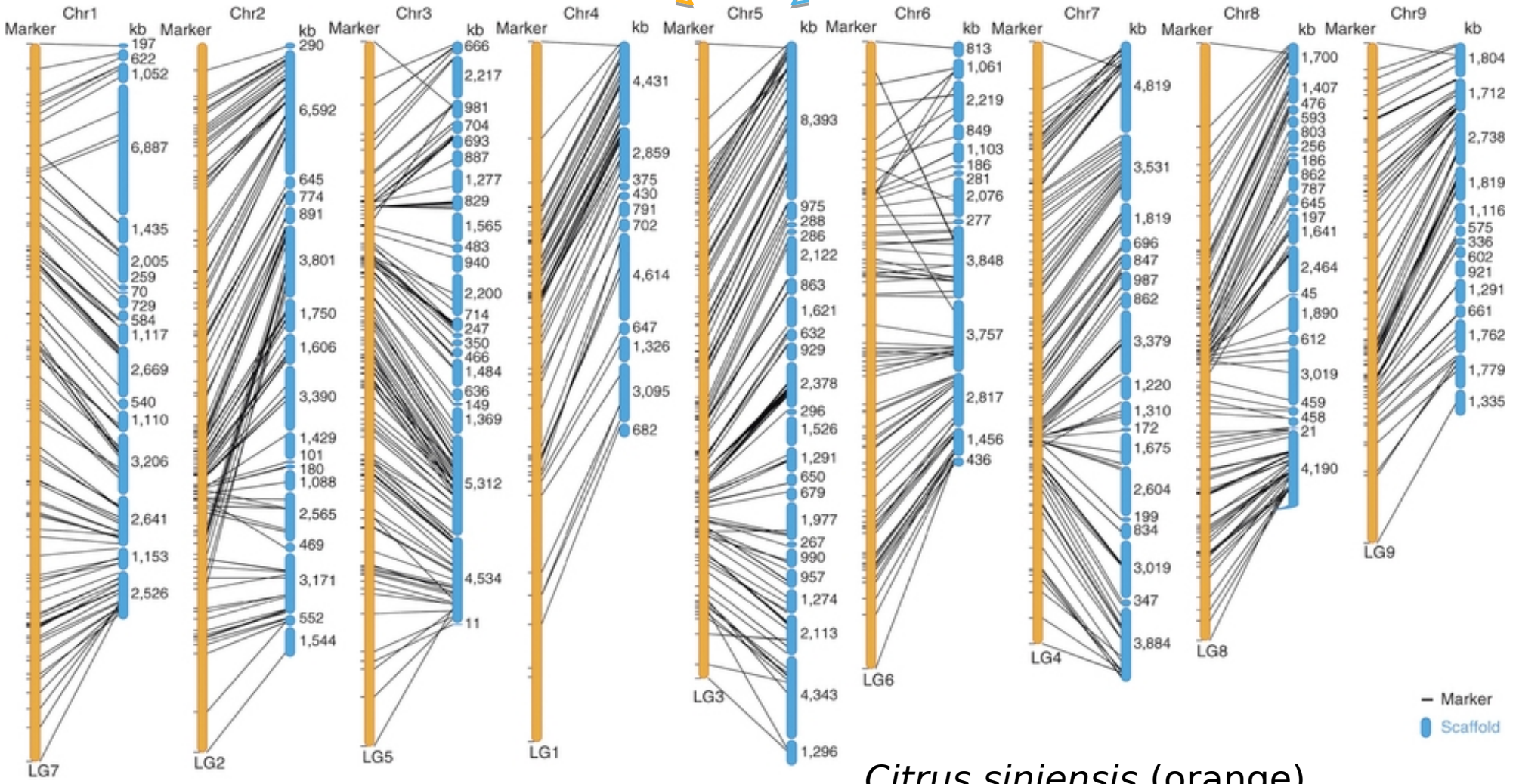
- through their phenotypic effect:
  white eyes, dumpy shape, GFP marker

- molecularly: PCR, sequencing
transposon insertion, single-nucleotide polymorphism (SNP), indel

Alignment of genetic and physical maps

Genetic map in units of recombination
1 centiMorgan (cM) = 1% recombinants

Physical map in base pair units

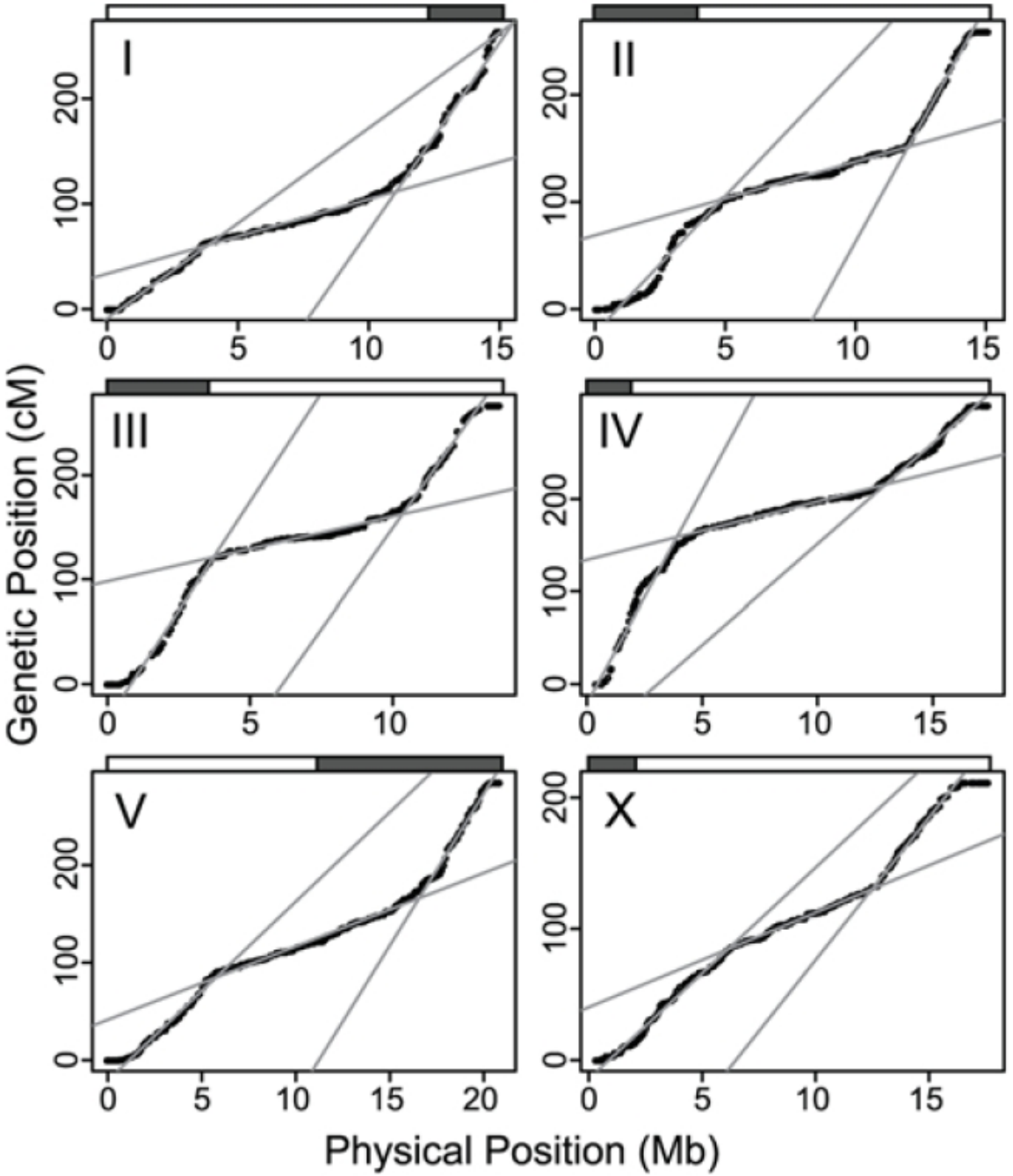


Citrus siniensis (orange)

Alignment of genetic and physical maps

Marey map

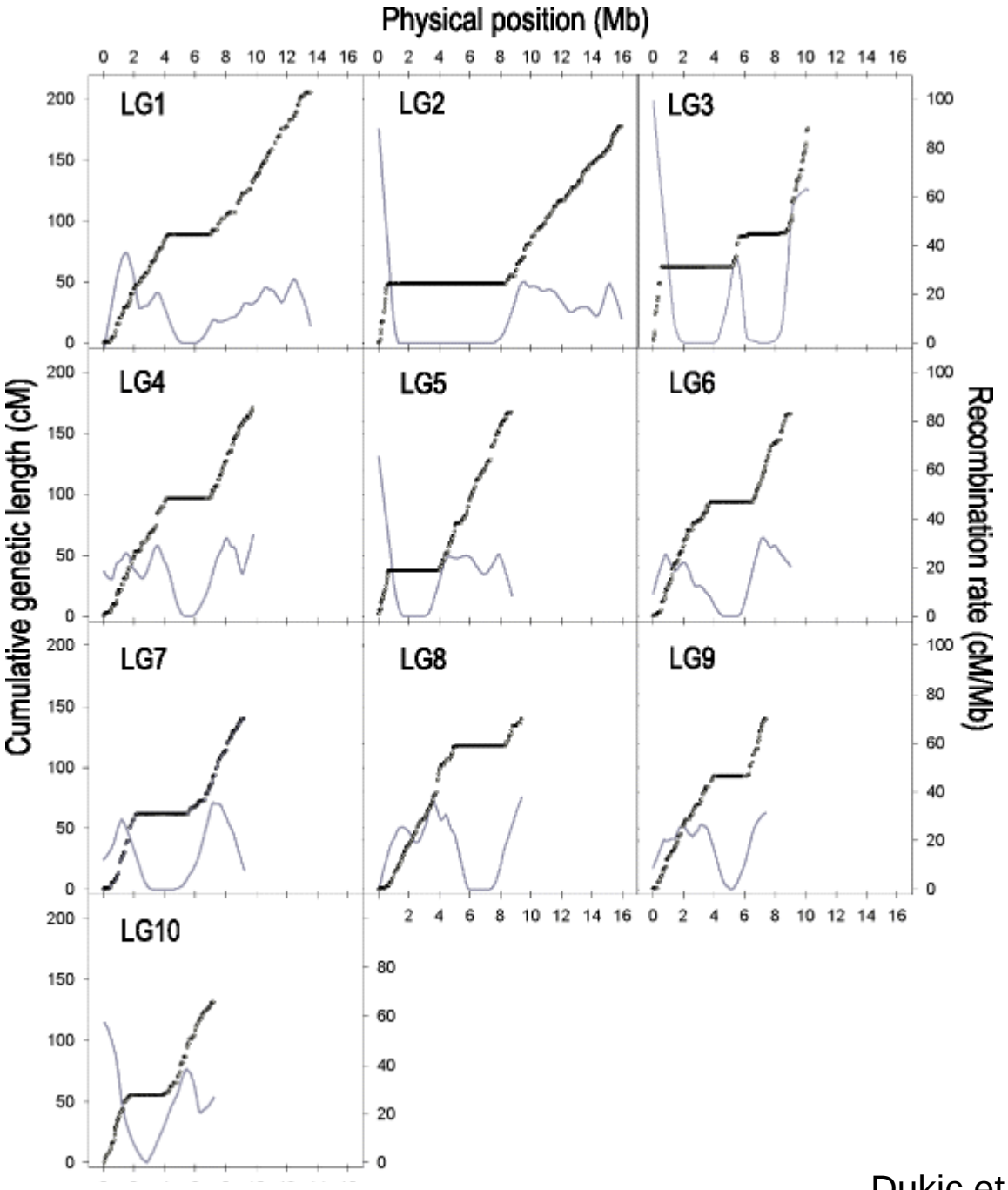
Genetic position was measured in centiMorgansbased on a recombinant inbred advanced intercross line population, and not based on meiotic distances.



Recombination rate varies along the chromosome

C. elegans
Rockman & Kruglyak
PLoS Gen 2009

Marey maps in Daphnia



Dukic et al. 2016 BMC Genetics

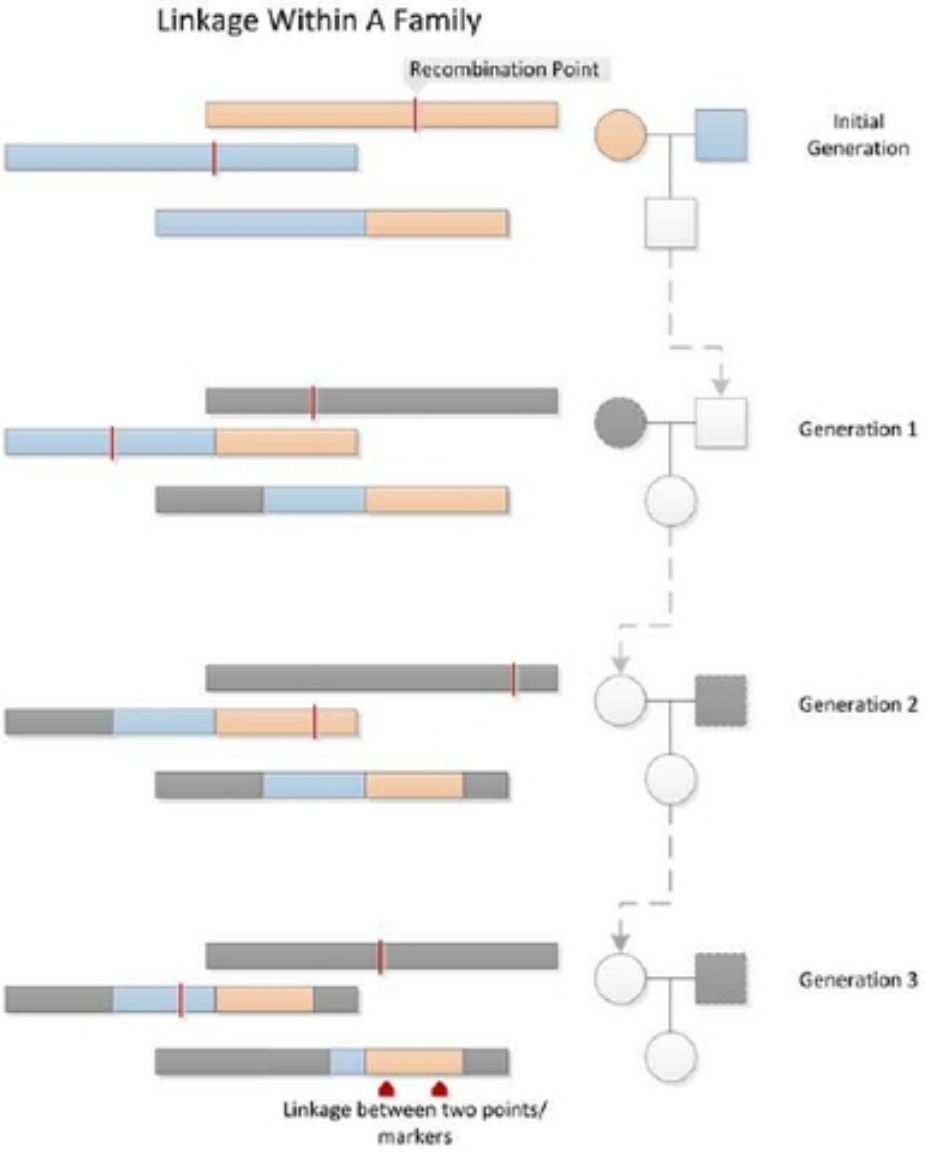
Linkage disequilibrium range of a species is a function of **age of alleles, outcrossing and recombination rates**

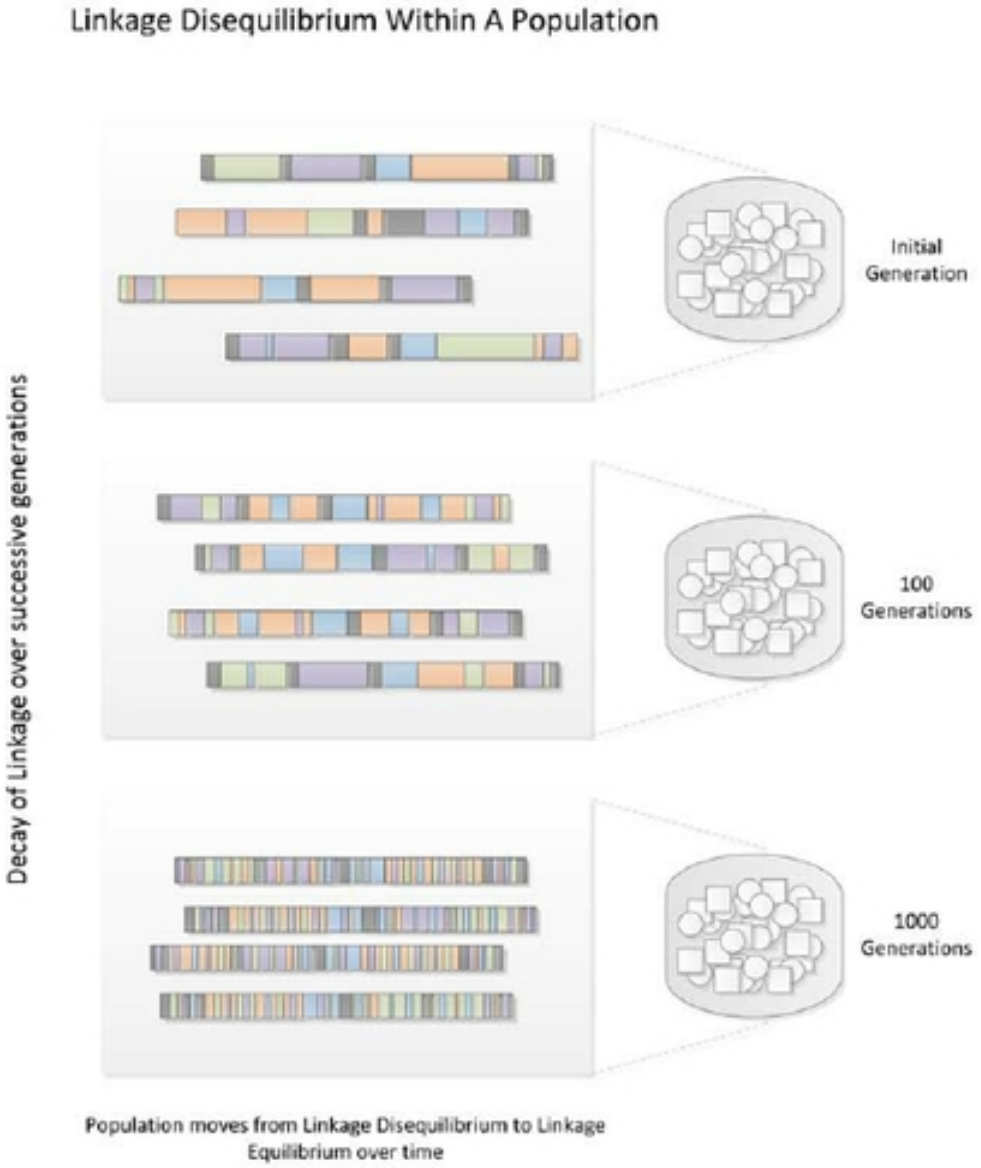
Depends on organism and genome region

short-range = 100 bp *Drosophila melanogaster*, *Caenorhabditis remanei*
medium-range = a few kb: *Homo sapiens*, *Arabidopsis thaliana*
long-range = Mb: *Caenorhabditis elegans*

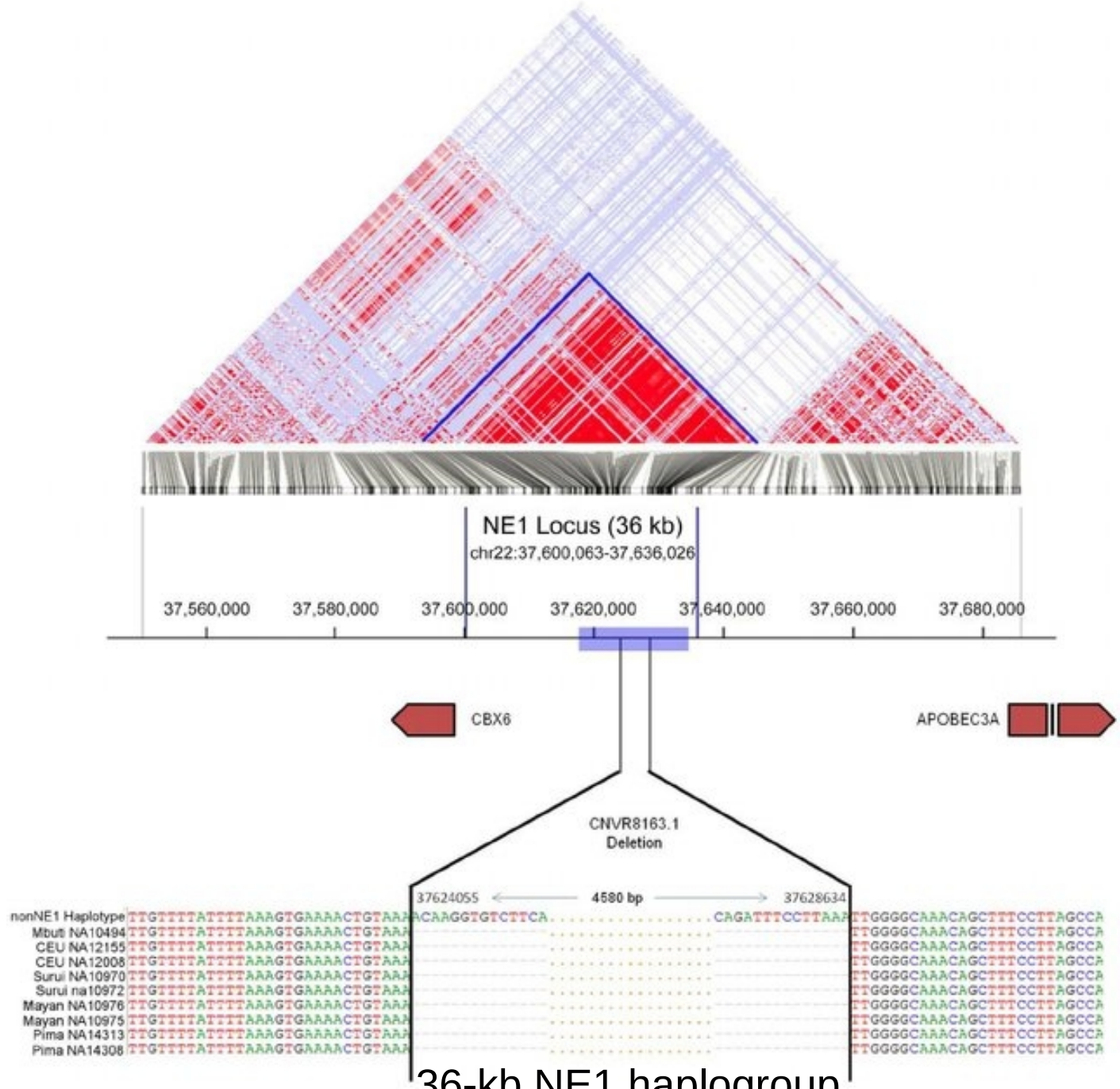
Linkage disequilibrium (LD)

non-random association of alleles at different loci in a given population





The Linkage Disequilibrium (LD) block was determined using SNP data of the CEU population from 1000 human Genomes



36-kb NE1 haplogroup contains a 4.6-kb deletion in perfect linkage disequilibrium with 12 SNP aligns with Neandertal haplotype

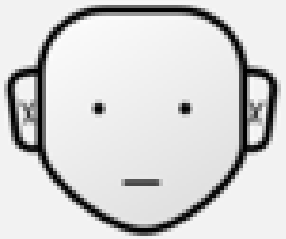
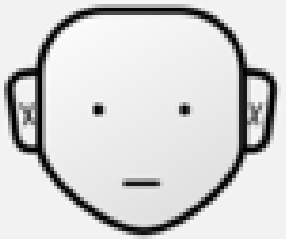
Variation in Linkage disequilibrium (LD)

LD is a function of
age of alleles, outcrossing and recombination rates

Depends on organism and genome region
short-range = 100 bp *D. melanogaster*, *Caenorhabditis remanei*
medium-range = a few kb: *Homo sapiens*, *Arabidopsis thaliana*
long-range = Mb: *Caenorhabditis elegans*

Epistasis

= Non-additive interactions of alleles at different loci for a given phenotype

	Allele for blond hair	Allele for red hair
	 Blond hair	 Red hair
Allele for baldness	 Bald	 Bald

Various meanings for Epistasis

Laboratory genetics, with null alleles

m1 is epistatic to *m2*
if *m1 m2* displays the M1 phenotype
=> genetic pathway

Quantitative / evolutionary genetics

"epistasis" used for **"gene interaction"**
= non-*additive* effect for any combination (heterozygote, homozygote)
non-additive mapping of genotype space to phenotype space

=> confusion between lab geneticists and evolutionary geneticists

Meaning of "epistasis" depends on the scientific context!

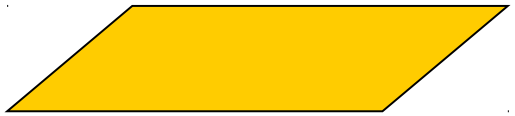
Additivity at one phenotypic level does not imply additivity to another level

Genotype

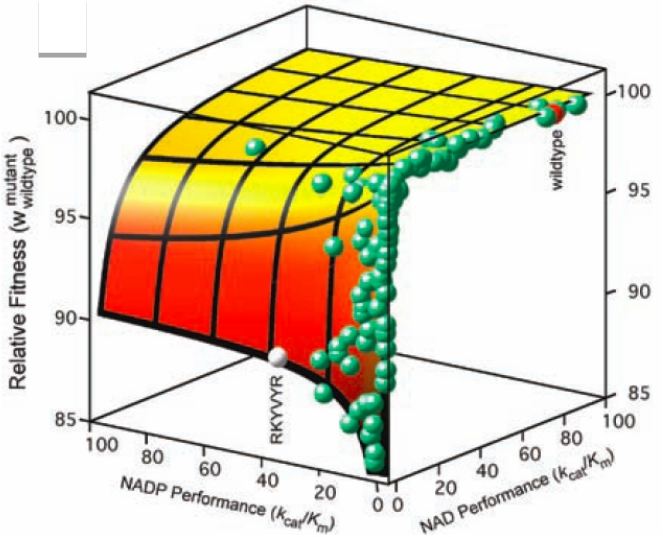
additive

Phenotype
(e.g. enzymatic activity)

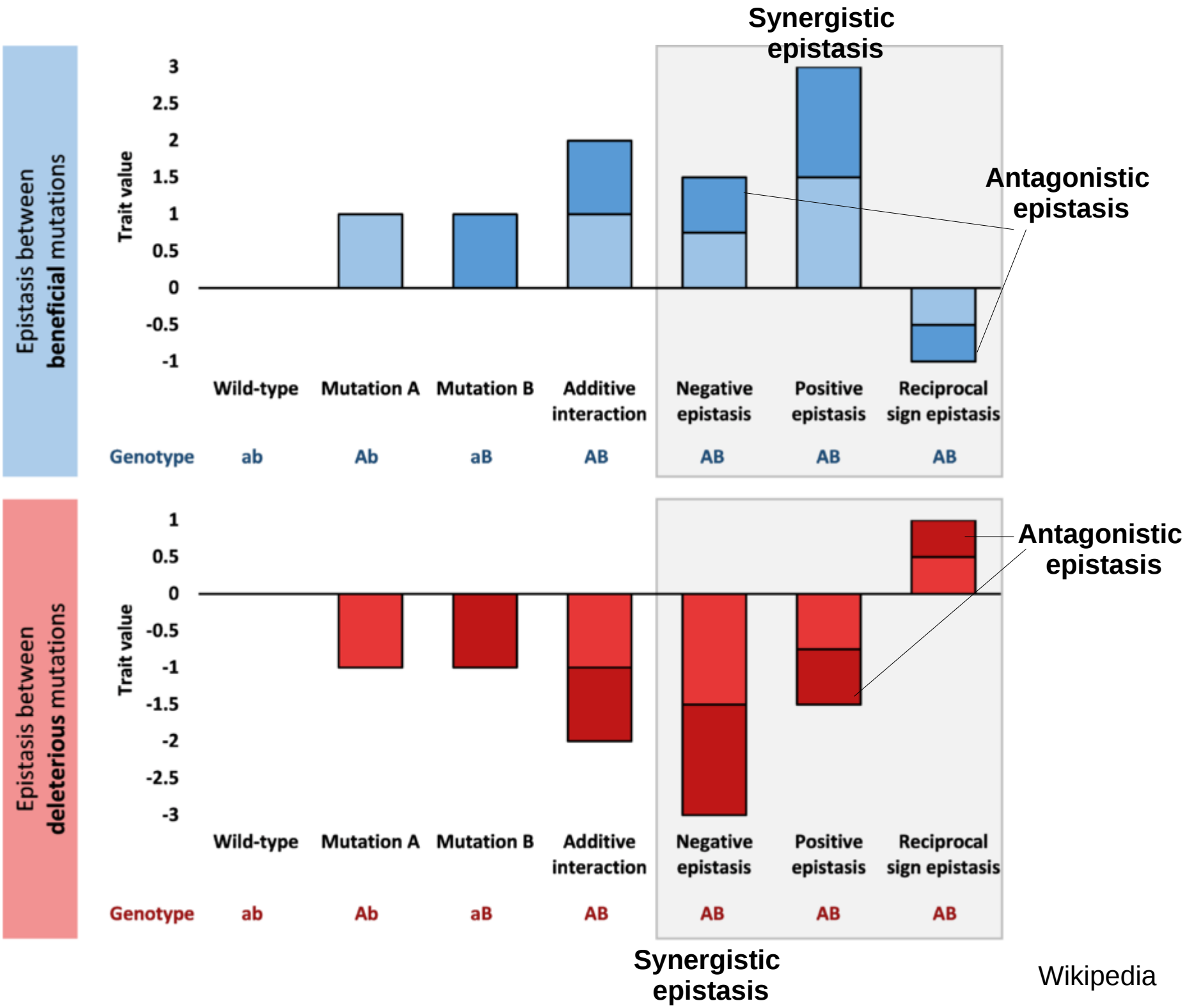
epistasis
due to enzyme saturation
=> non-linear relationship



"Fitness"
(e.g. competition in chemostat)



Lunzer et al. *Science* 2005

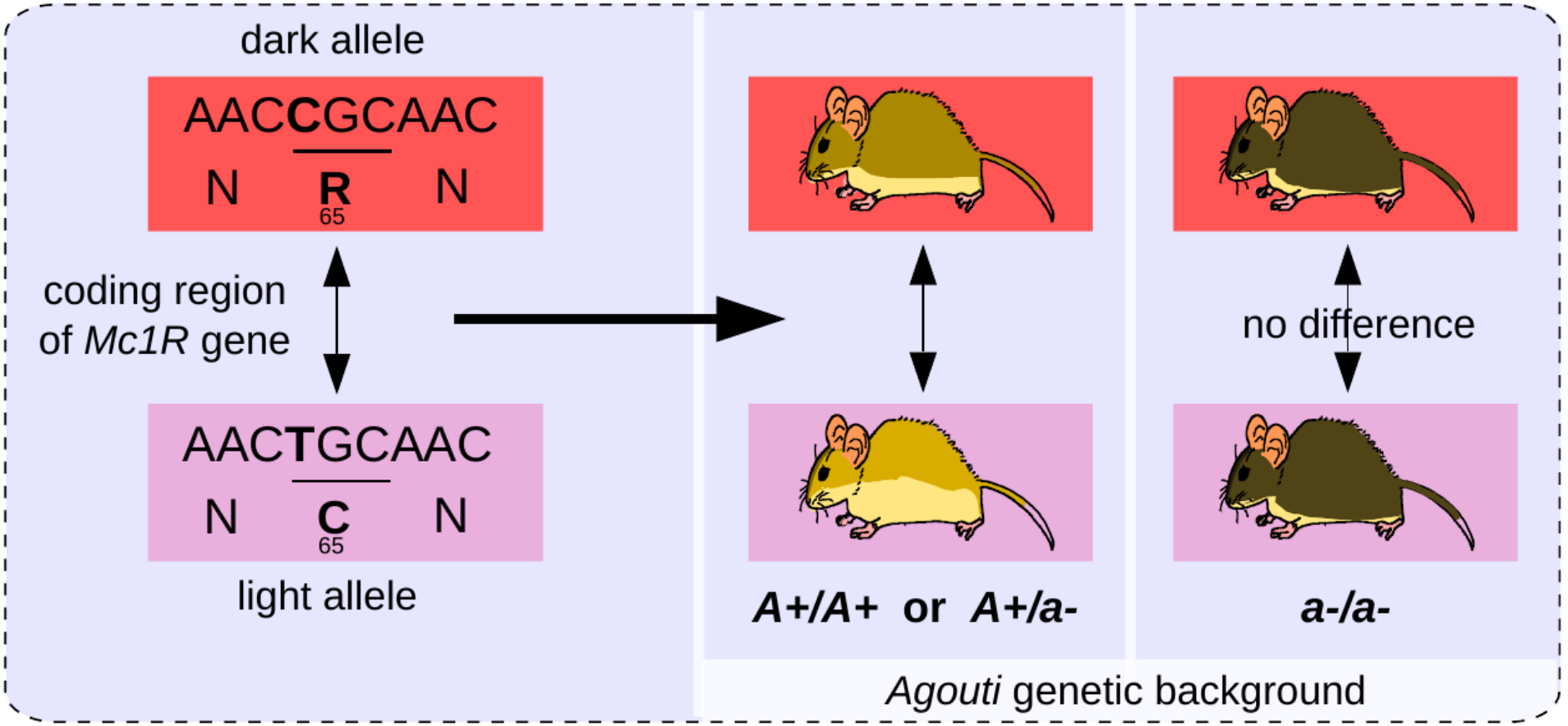

Synergistic epistasis
Antagonistic epistasis
Epistasis between beneficial mutations
Trait value
3
2.5
2
1.5
1
0.5
0
-0.5
-1
Wild-type
Mutation A
Mutation B
Additive interaction
Negative epistasis
Positive epistasis
Reciprocal sign epistasis
Genotype
ab
Ab
aB
AB
AB
AB
AB
Antagonistic epistasis
Epistasis between deleterious mutations
Trait value
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
Wild-type
Mutation A
Mutation B
Additive interaction
Negative epistasis
Positive epistasis
Reciprocal sign epistasis
Genotype
ab
Ab
aB
AB
AB
AB
AB
Synergistic epistasis

Wikipedia

"**Synergistic epistasis**": the effects of both alleles
reinforce each other (more than the sum of their individual effects);
extreme case: synthetic phenotype (new phenotype)

"**Antagonistic epistasis**": the effects of the two alleles
partially **compensate** (less than the sum of effects of *a2, b2*)

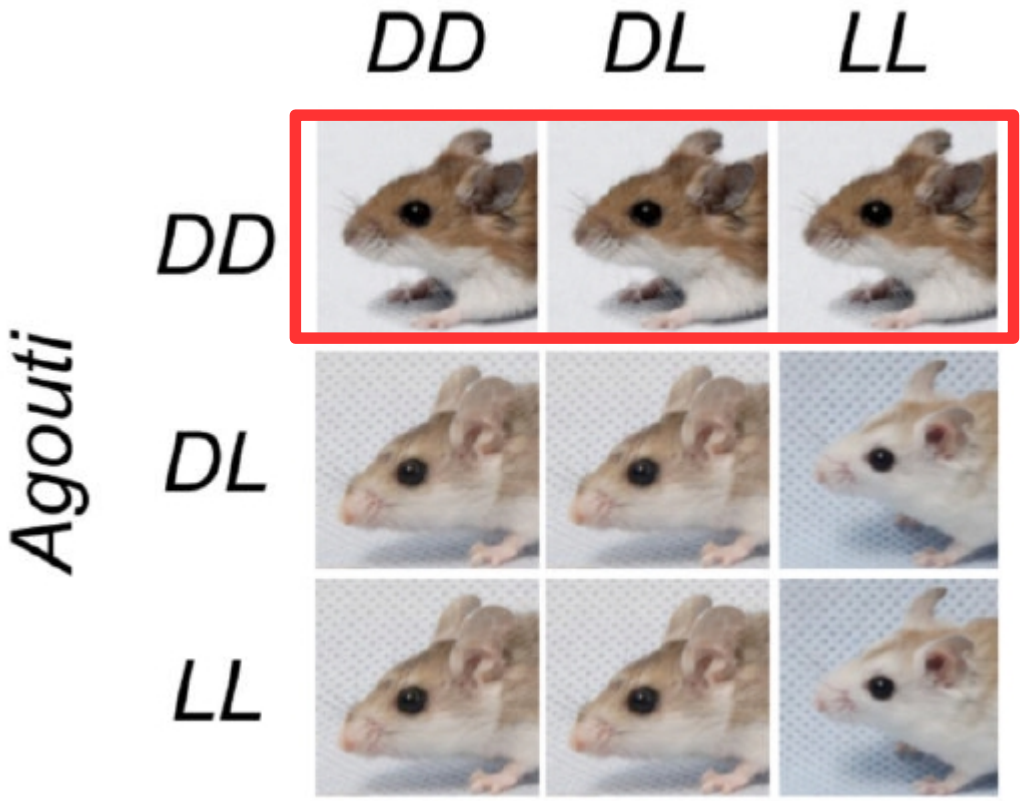
"**Positive or negative epistasis**": the phenotypic value
is either increased or decreased relative to additivity



Orgogozo, Morizot, Martin 2015

Agouti (D, L) and *Mc1R* (D,L)

Natural alleles
3 phenotypes

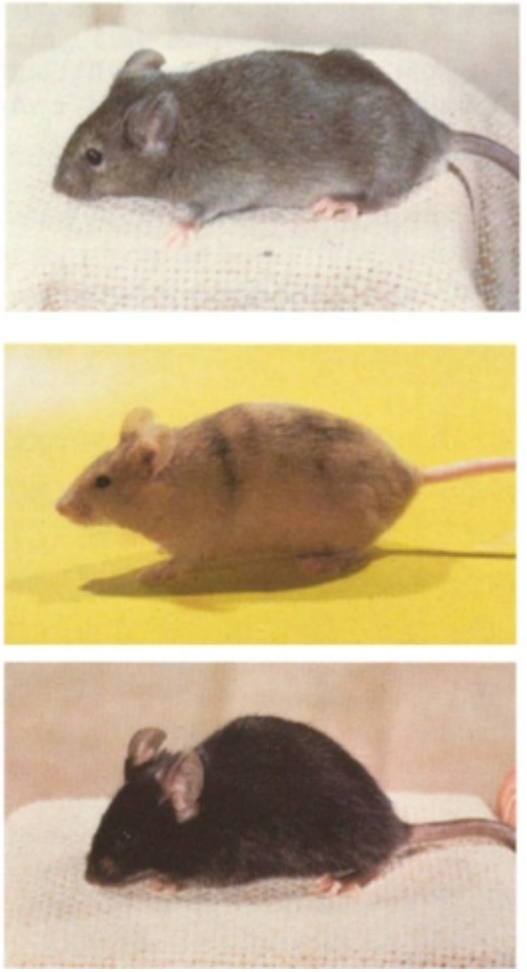


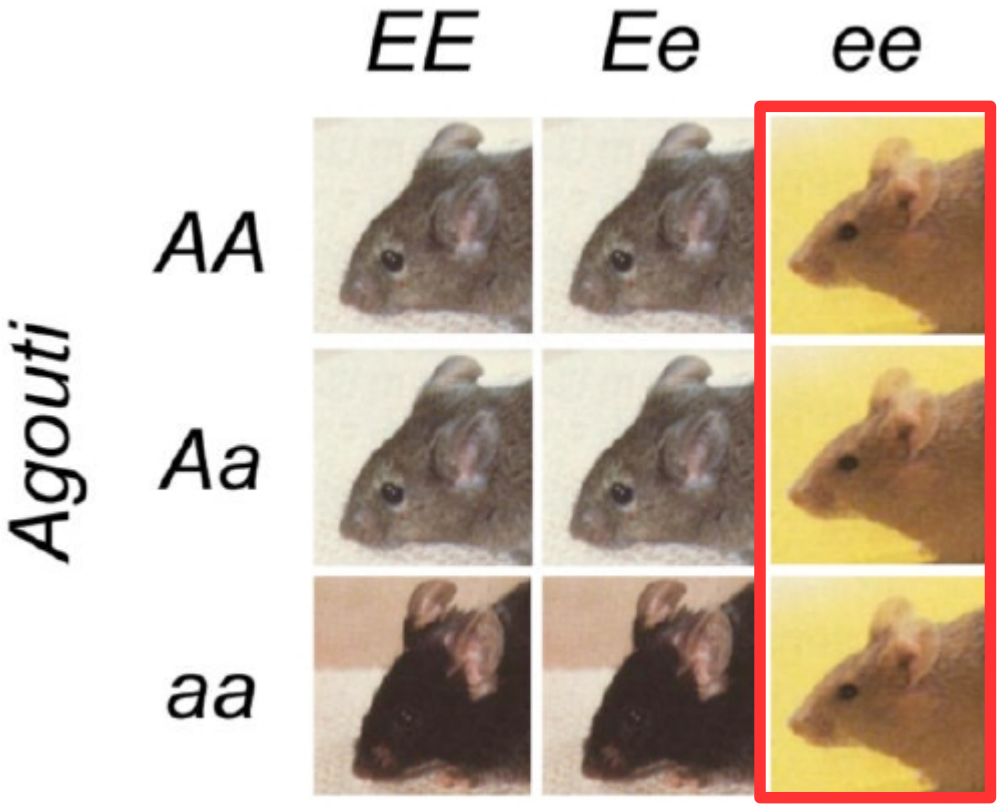
Agouti^{D} is epistatic over Mc1R alleles

Philipps 2008

Agouti (A, a) and *Mc1R* (E,e)

Laboratory mutants
3 phenotypes

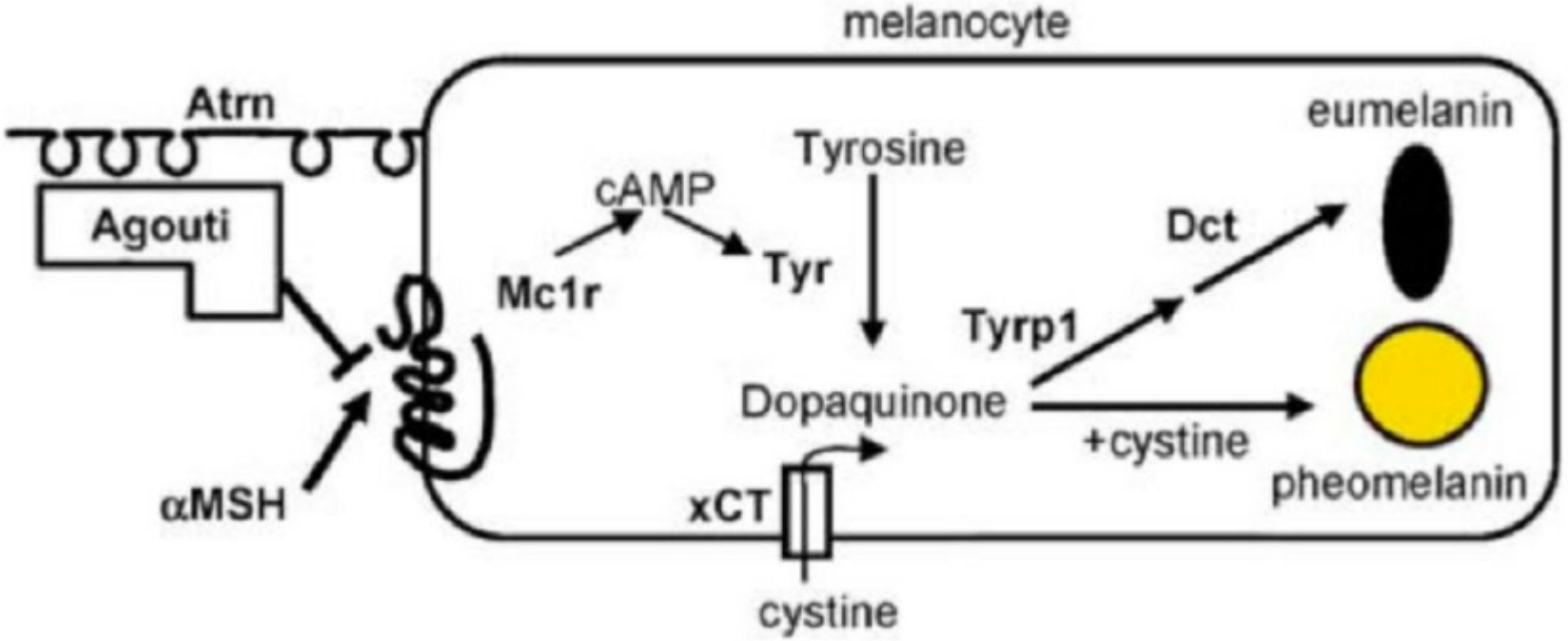




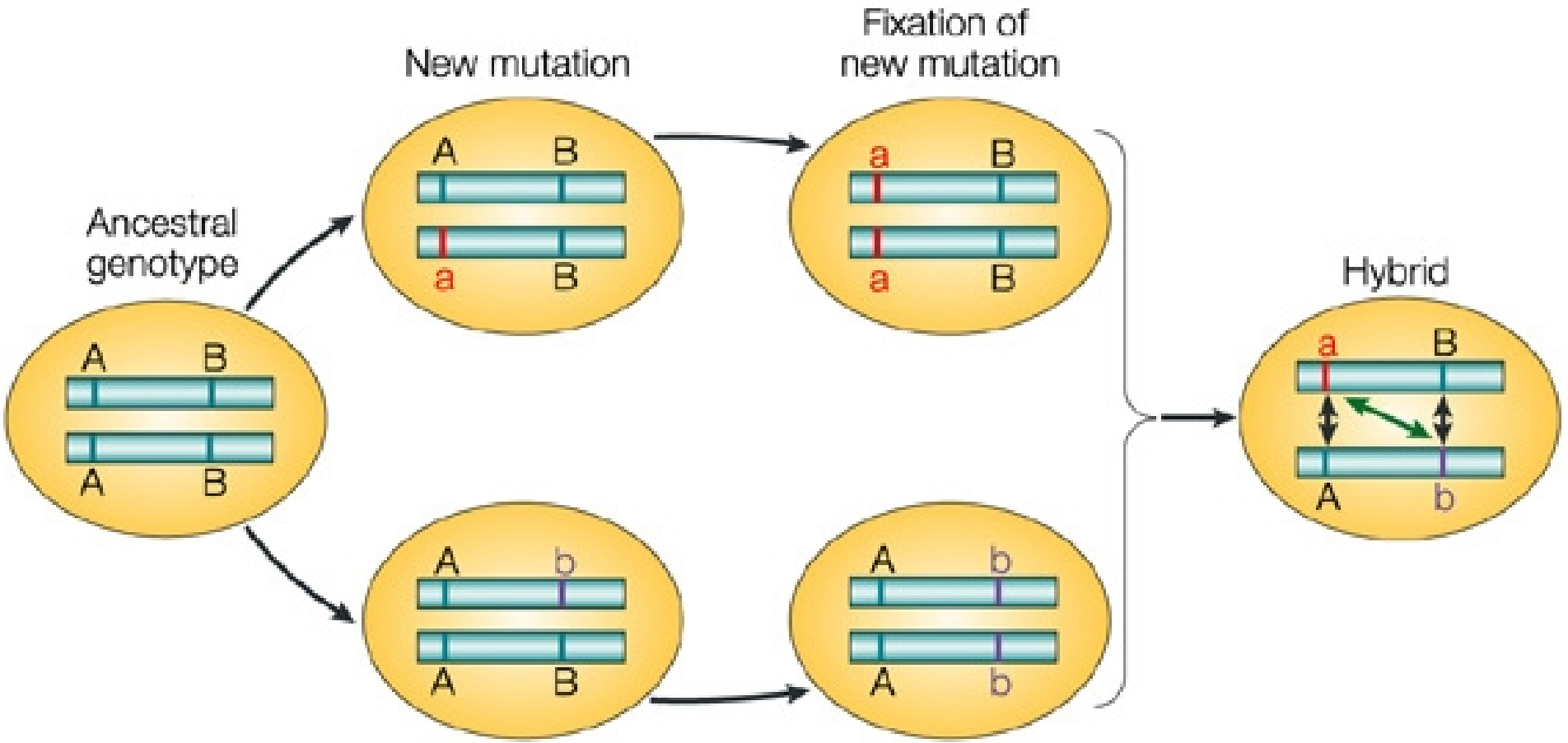
Mc1R^{e} is epistatic over Agouti alleles

Philipps 2008


Agouti
Mc1r
Eumelanin
(black/brown pigment)
Pheomelanin
(red/yellow pigment)


melanocyte
Atrn
Agouti
αMSH
Mc1r
cAMP
Tyr
Tyrosine
Dopaquinone
xCT
cystine
Tyrp1
Dct
+cystine
eumelanin
pheomelanin

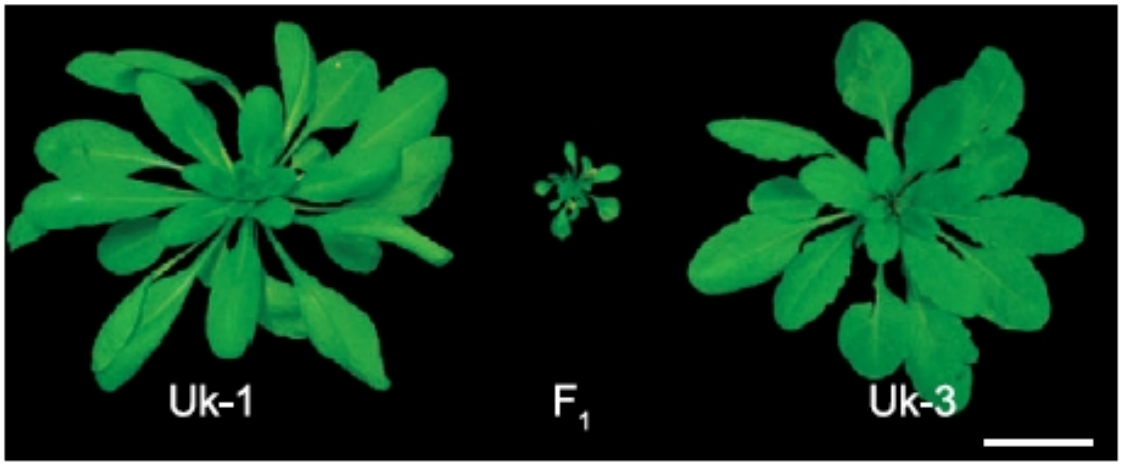
Dobzhansky-Muller model of hybrid incompatibility A special case of epistasis

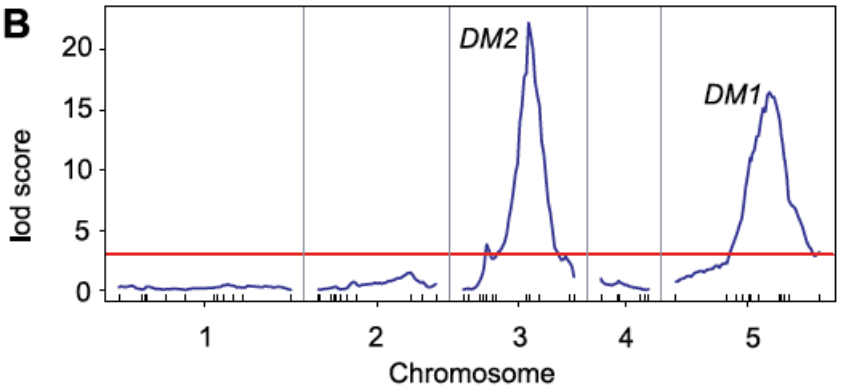


possible mechanism of speciation

Nature Reviews | Genetics

Hybrid incompatibility in *A. thaliana*





necrosis by auto-immune response at 16°C
in 2% of crosses among wild isolates of *A. thaliana*

Dangerous Mix 2: RPP1 gene
resistance against oomycete

Dangerous Mix 1: member of a large family
of pathogen resistance gene *NB-LRR*

Bomblies et al. *PLoS Biology* 2007, Chae et al. *Cell* 2015

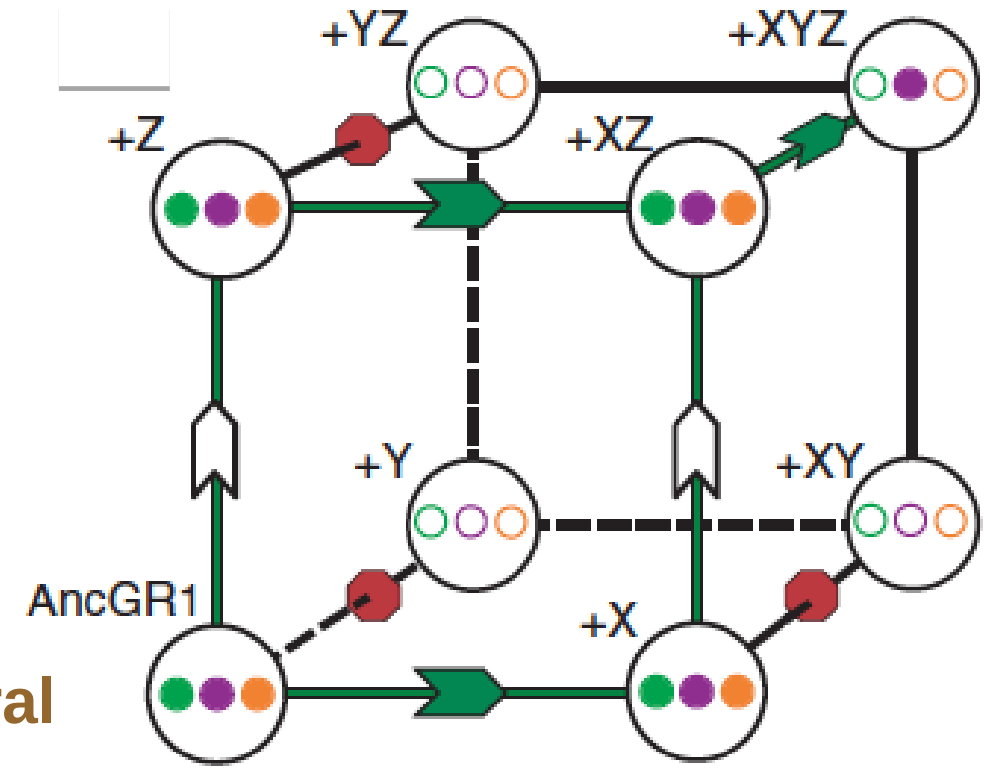
Intramolecular epistasis

Reconstruction of ancestral protein sequence
from phylogenetic analysis of extant family in databases

Vertebrate corticoid receptor family

activity on

- aldosterone
- cortisol
- docetaxel



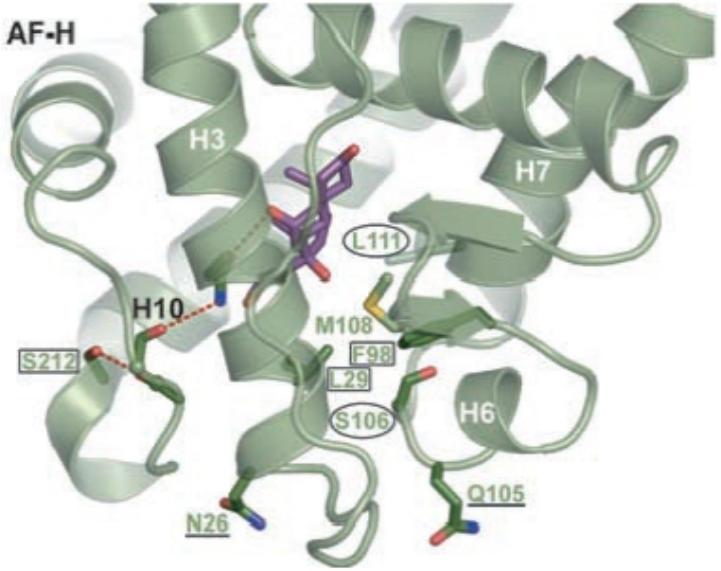
cortisol-specific

ancestral

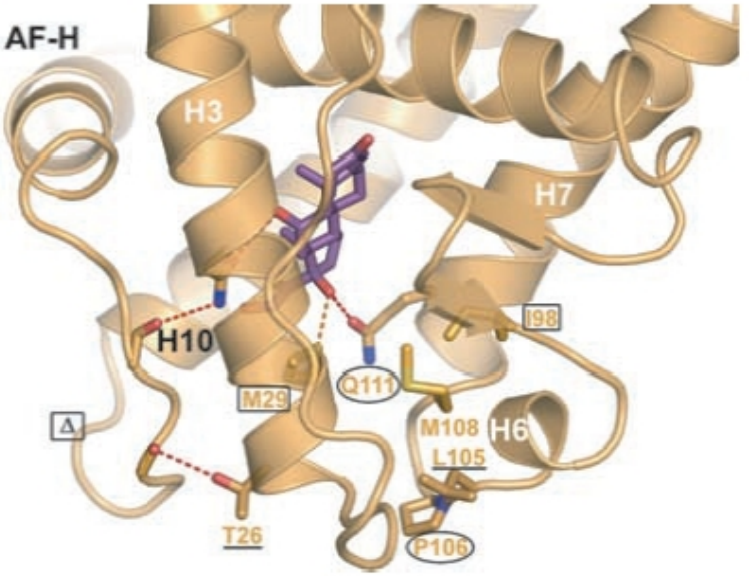
Ortlund et al. *Science* 2007

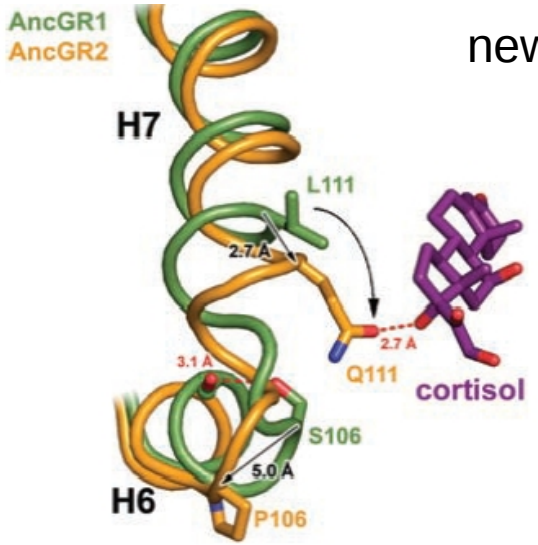
permissive substitutions

AncGR1



AncGR2

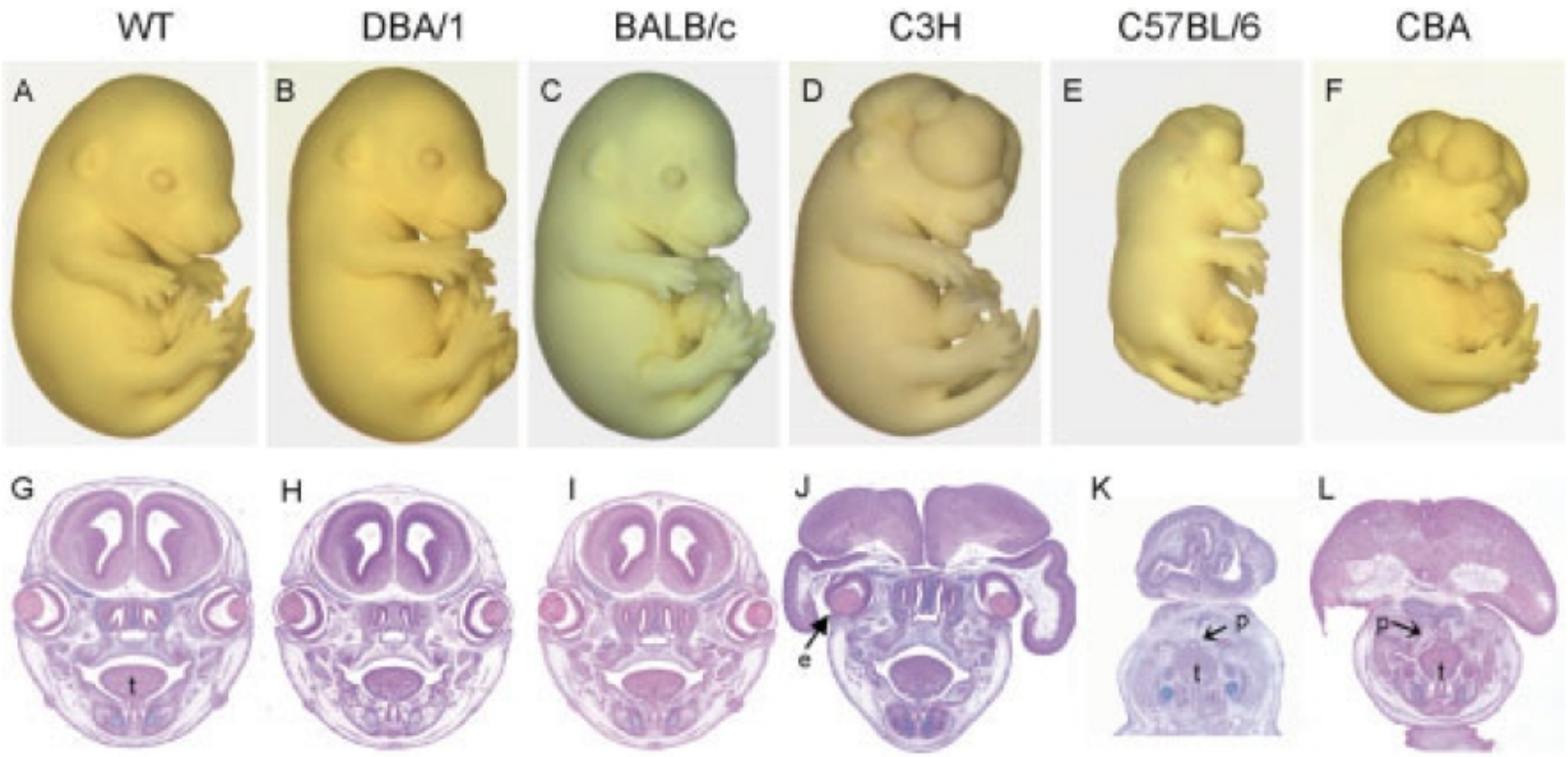




new interactions with cortisol

Expressivity of one mutation varies with wild genetic gackground

Tcof1/- heterozygote mice



Dixon & Dixon *Dev Dyn* 2004

Different kinds of GxG interactions

G *m1* x G *m2* between 2 laboratory mutations

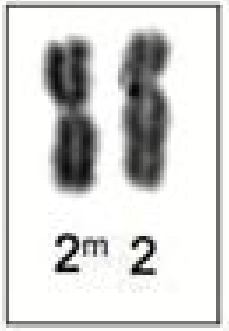
G *a1/a2* x G *b1/b2* between 2 natural alleles

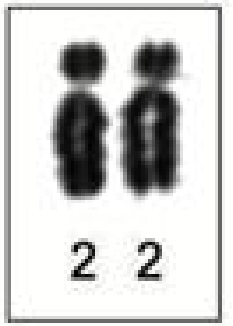
G1 *m* x G2 *m*
one mutation
in different wild genetic backgrounds
“cryptic” variation

G *a1/a2* x G *b1/b2* x G *c1/c2* >2 loci

Gerke et al. 2010

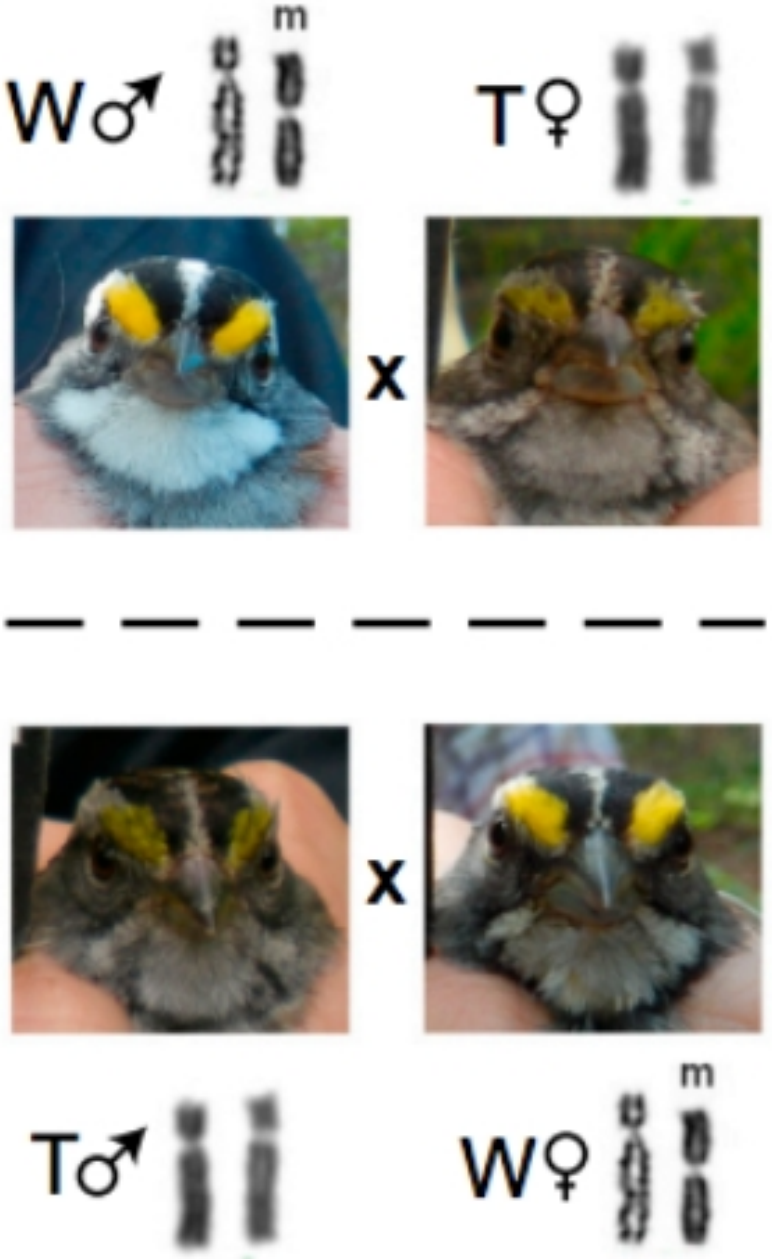
Super genes



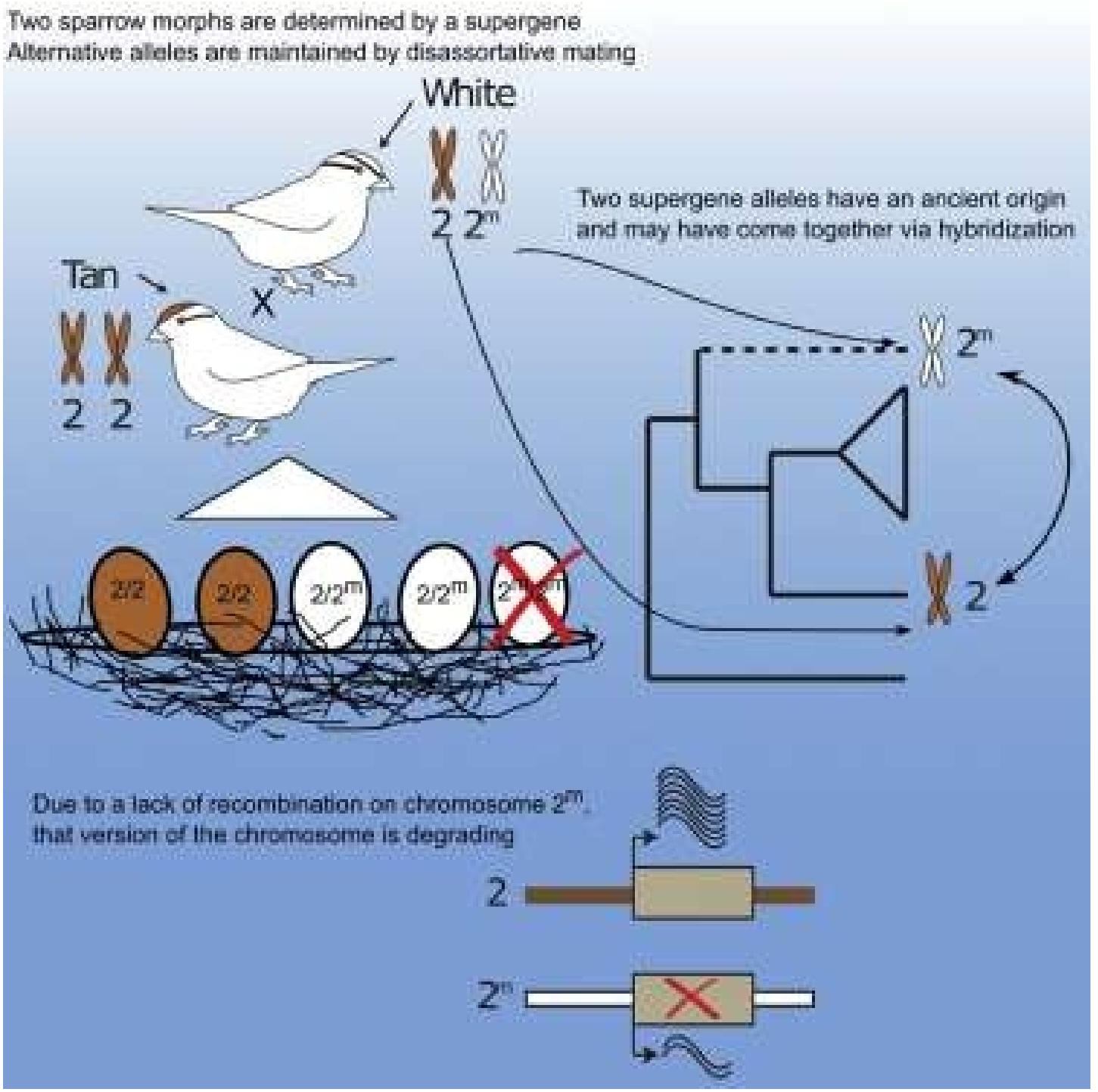


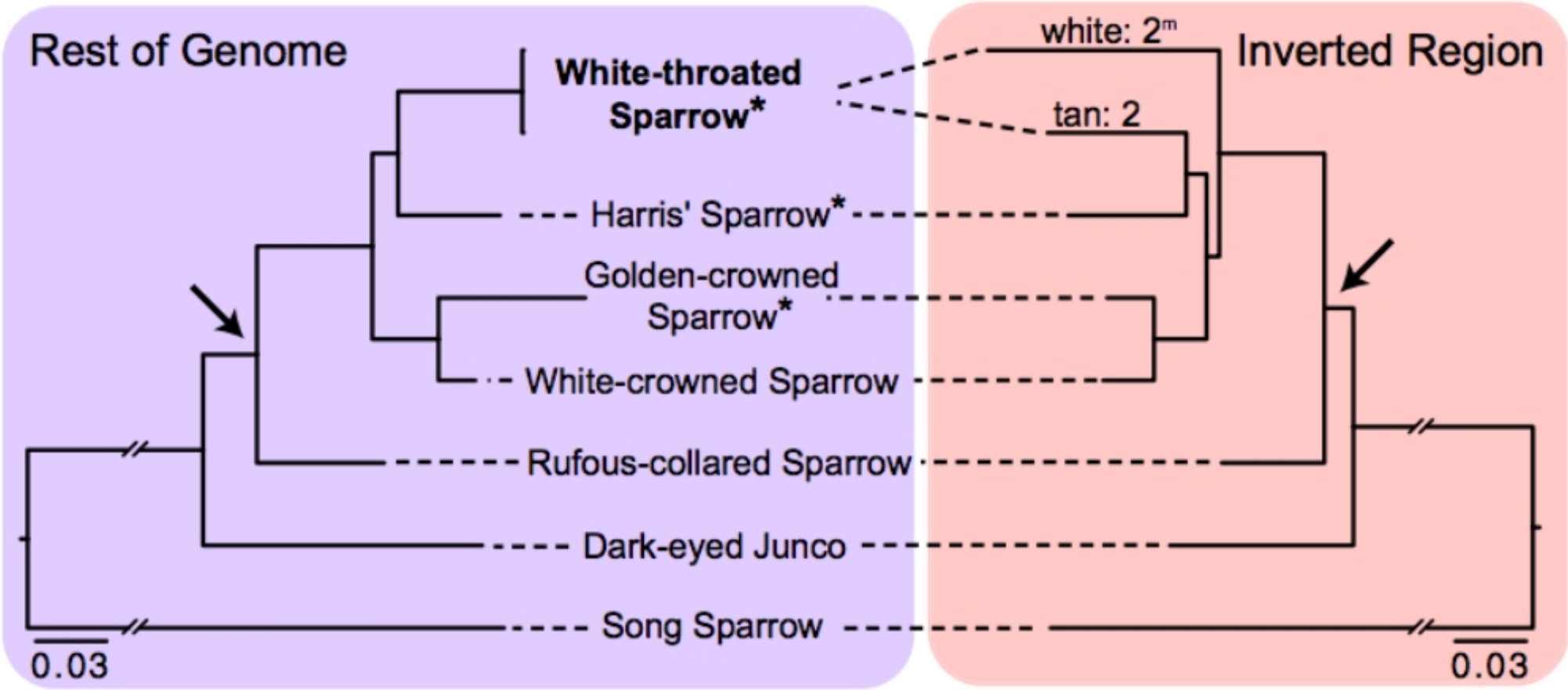
Tuttle et al. 2016 Curr Biol

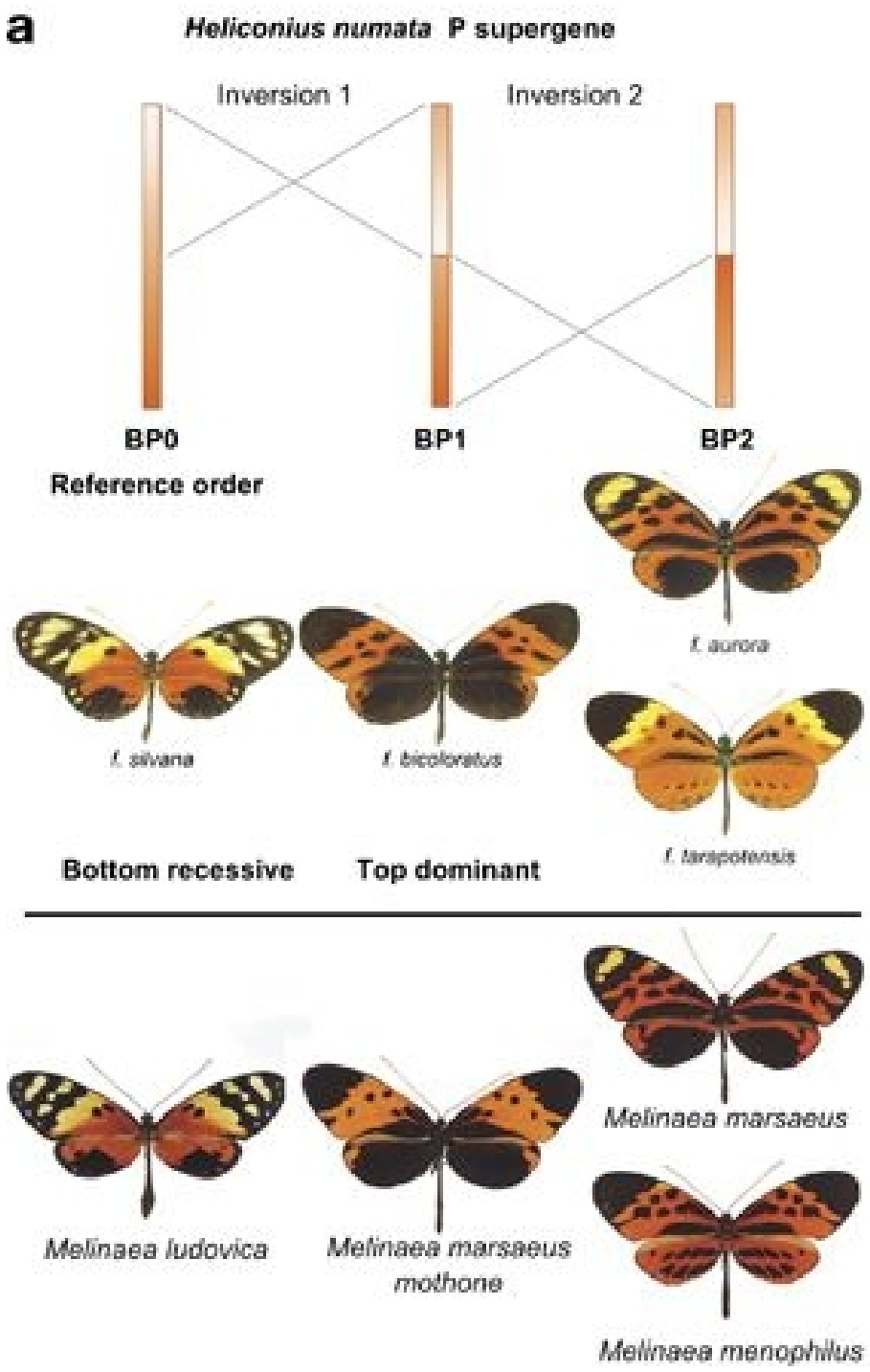
Disassortative mating

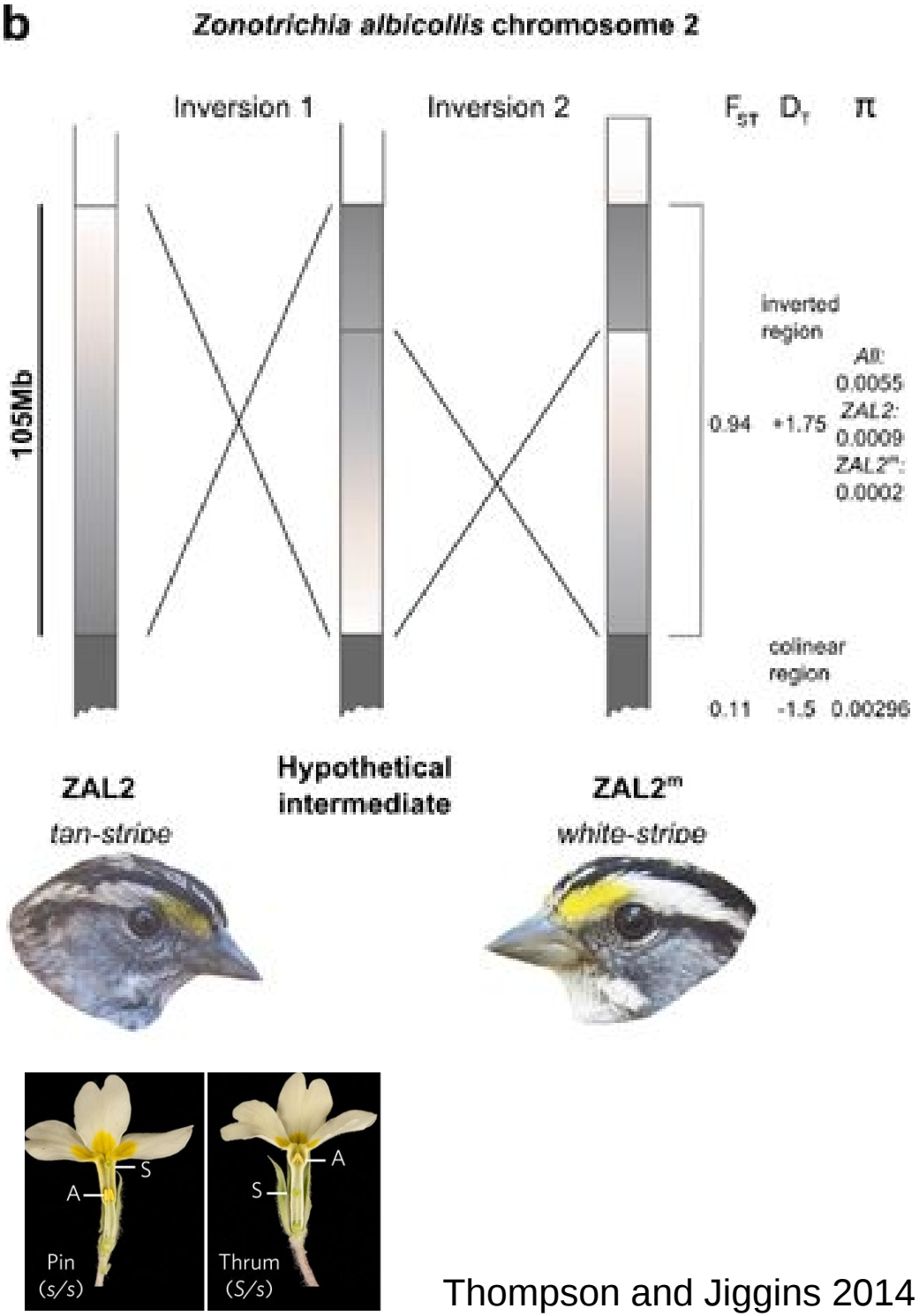


Never W male x W female
Never T male x T female


Two sparrow morphs are determined by a supergene
Alternative alleles are maintained by disassortative mating
White
Tan
X
2 2
2 2m
Two supergene alleles have an ancient origin
and may have come together via hybridization
2m
2
2/2
2/2
2/2m
2/2m
Due to a lack of recombination on chromosome 2m,
that version of the chromosome is degrading
2
2m


Rest of Genome
Inverted Region
White-throated Sparrow*
white: 2m
tan: 2
Harris' Sparrow*
Golden-crowned Sparrow*
White-crowned Sparrow
Rufous-collared Sparrow
Dark-eyed Junco
Song Sparrow
0.03
0.03





Thompson and Jiggins 2014

Pleiotropy

= when a genetic change affects several phenotypes

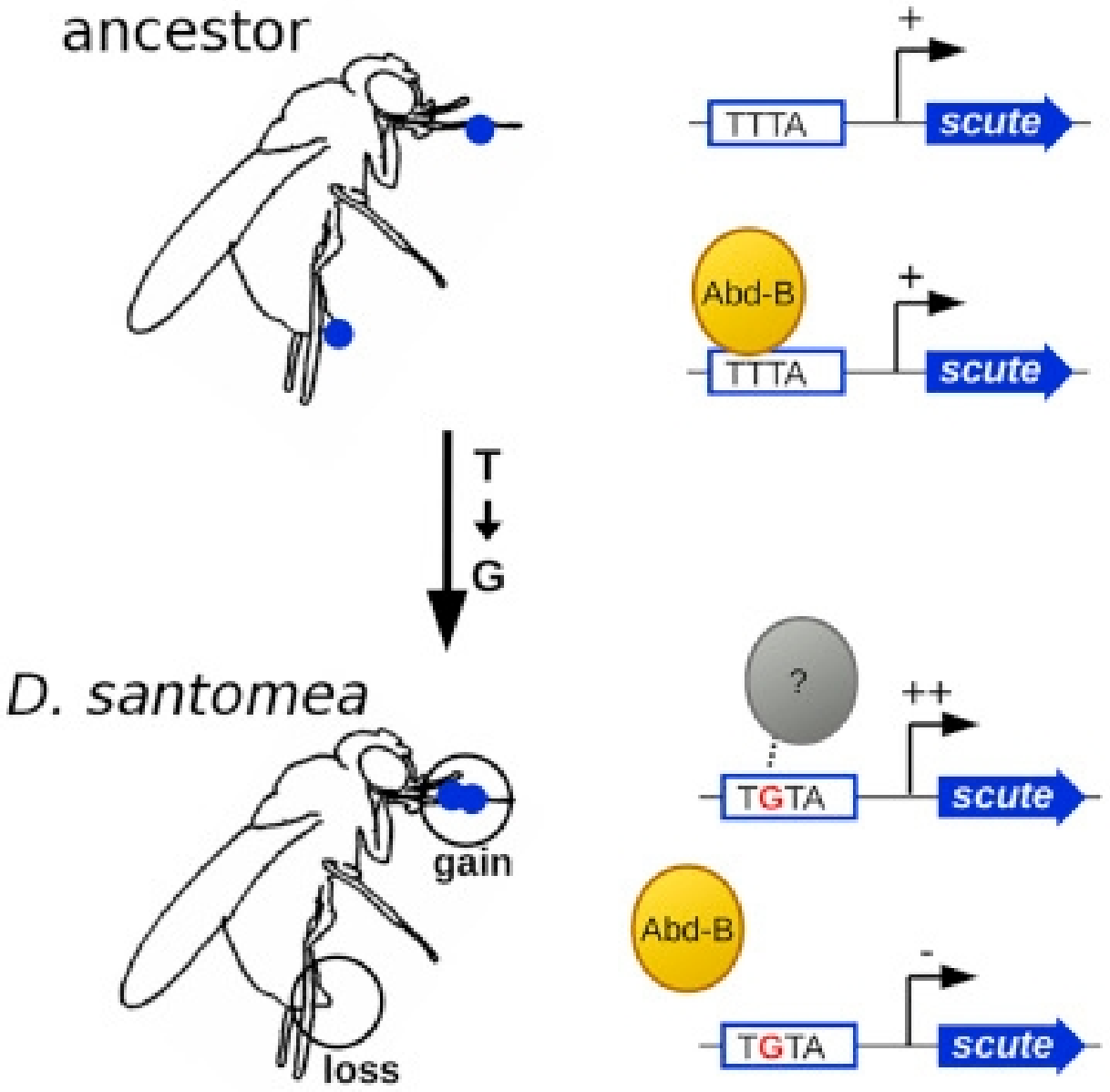
Various meanings for Pleiotropy

Pleiotropy of a gene
(means pleiotropy of the *null* mutation)

Pleiotropy of a cis-regulatory region
(means pleiotropy of the *deletion* of the region)

Pleiotropy of a mutation

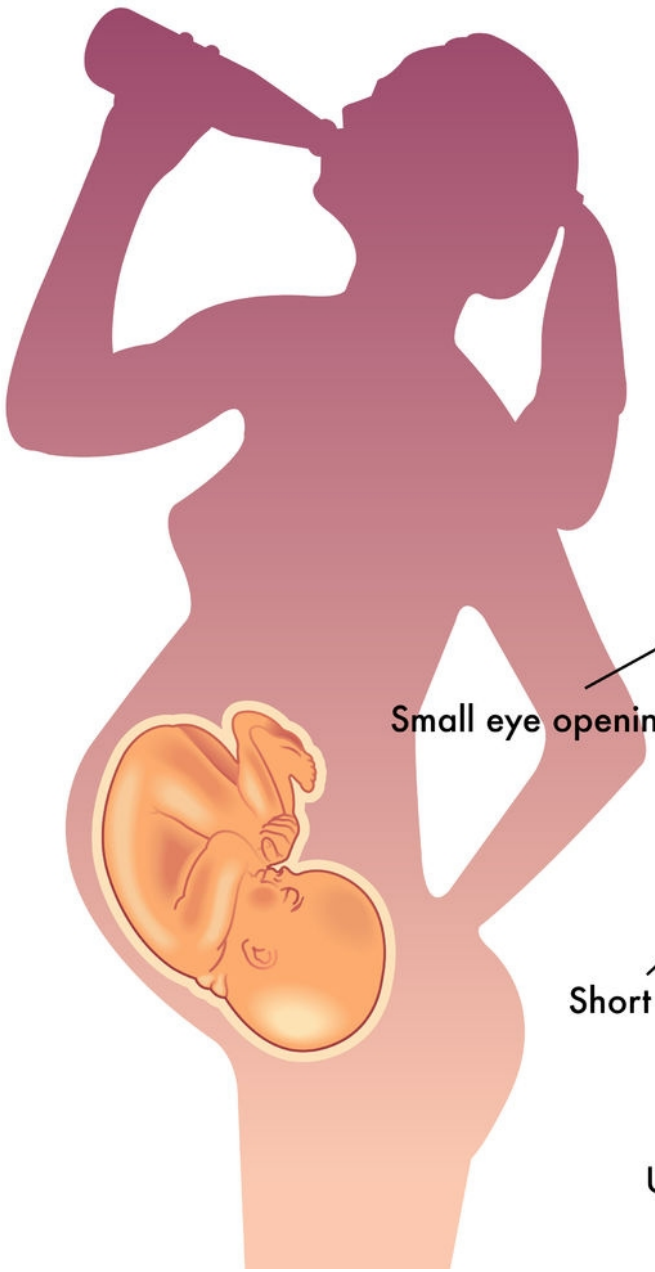
A pleiotropic cis-regulatory mutation responsible for species difference

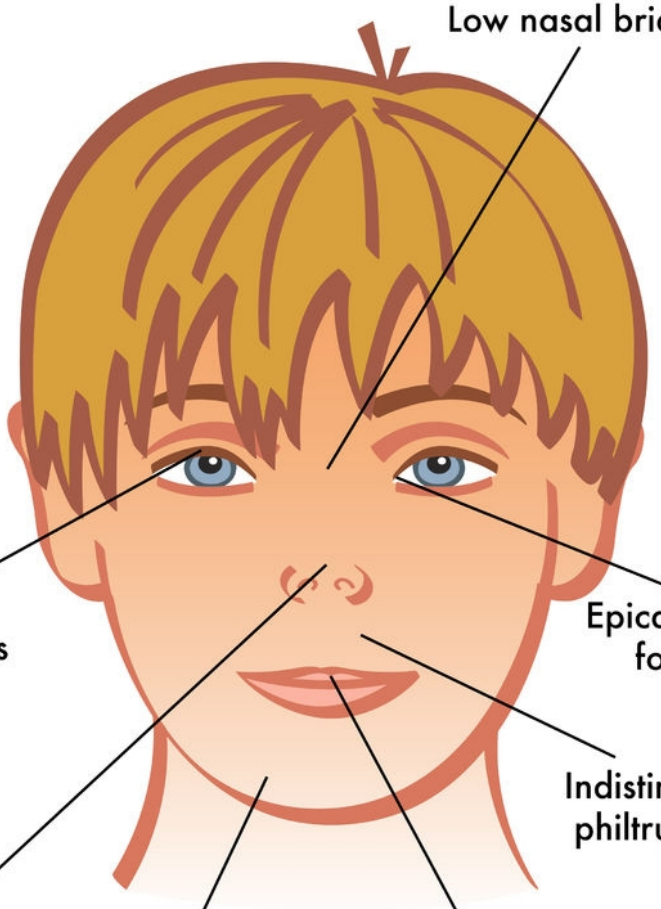


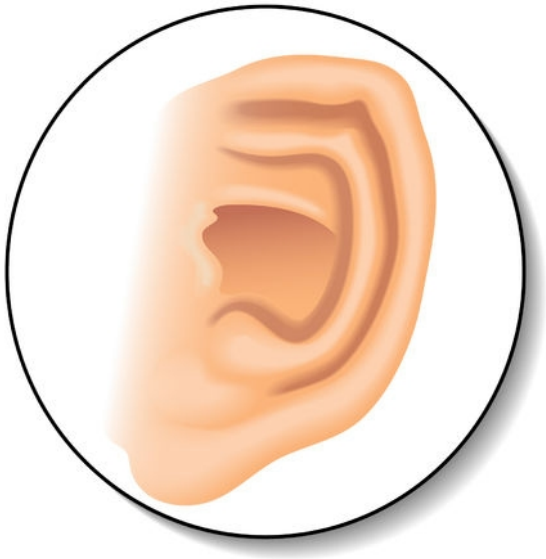
Nagy et al 2019

G x E

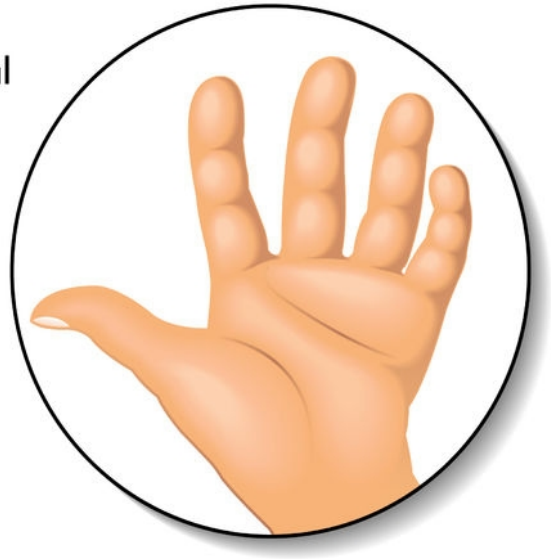
(FAS)
Fetal Alcohol Syndrome







Top of the ear underdeveloped

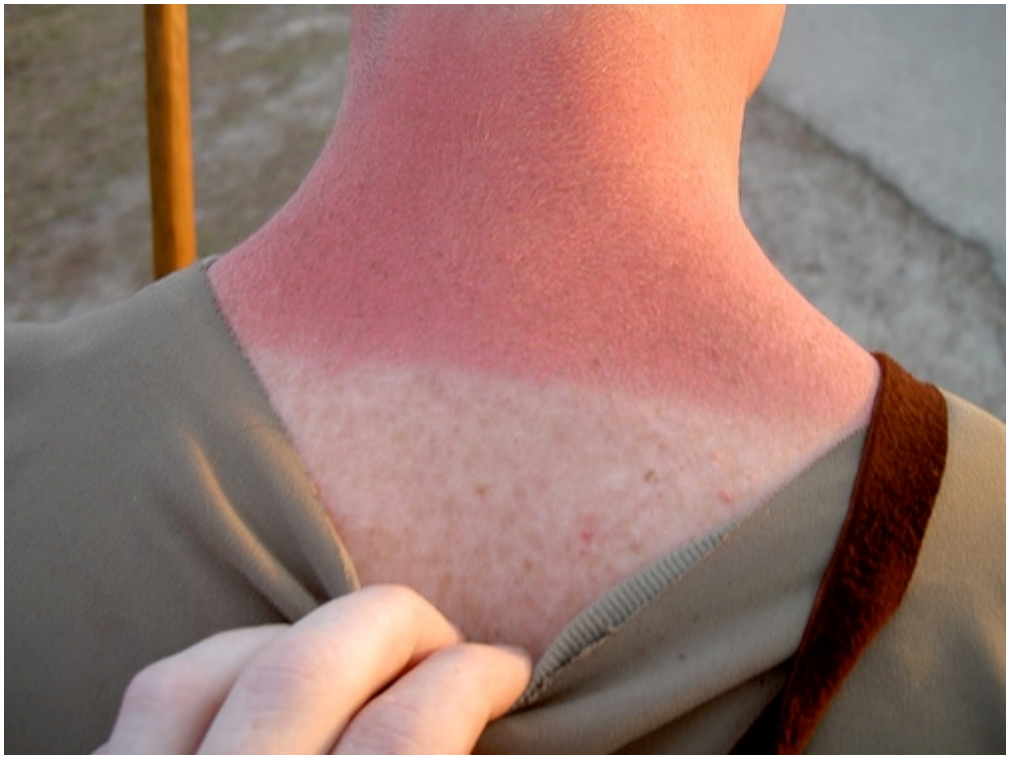


Curved fifth finger (clinodactyly)

Causes of skin color differences

Genetic

Environment

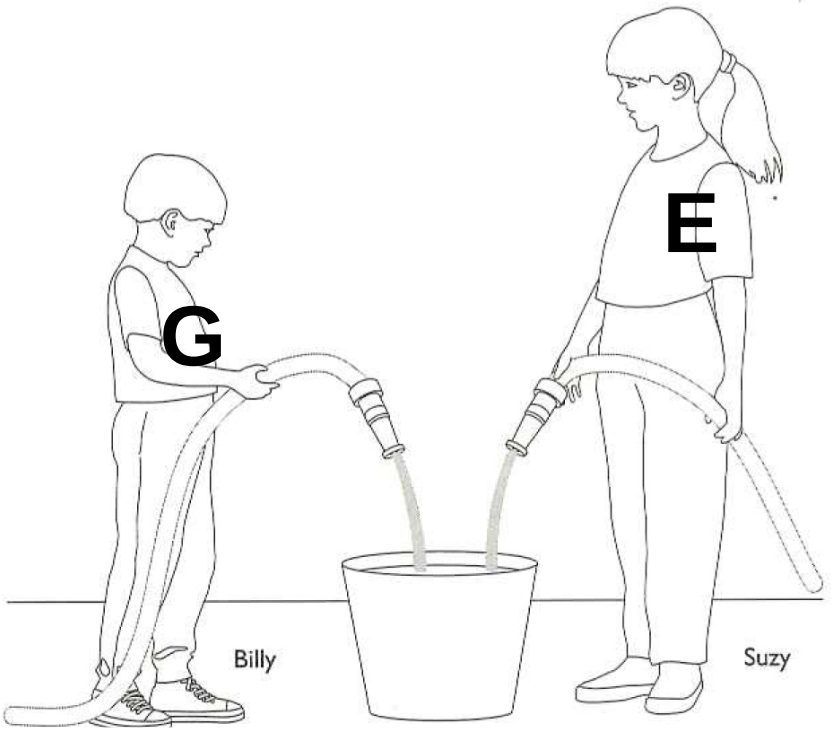


Phenotype = G + E + GxE

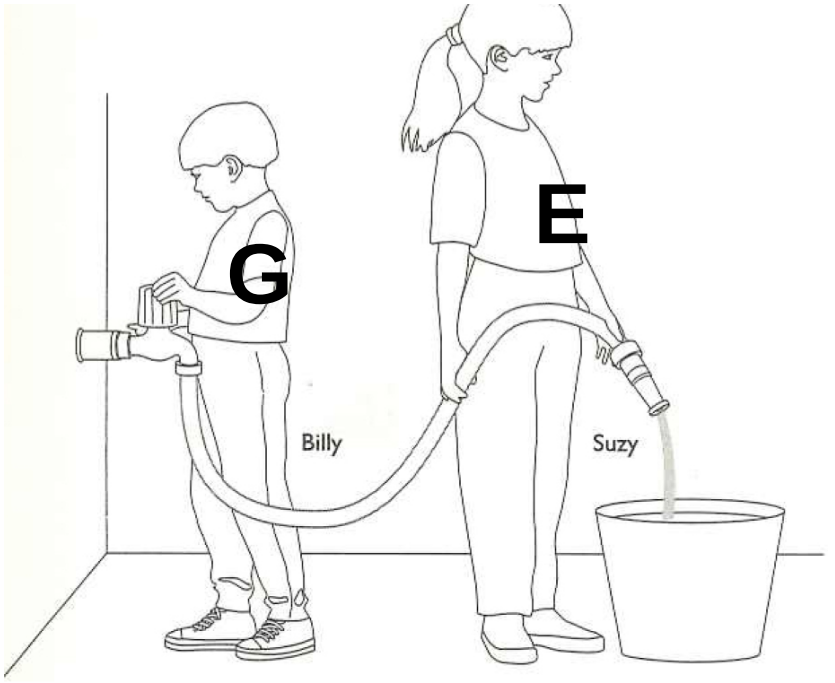
The Siamese cat
An example of GxE

Mutation in *tyrosinase*
Heat-sensitive enzyme
No production of melanin in warm body parts

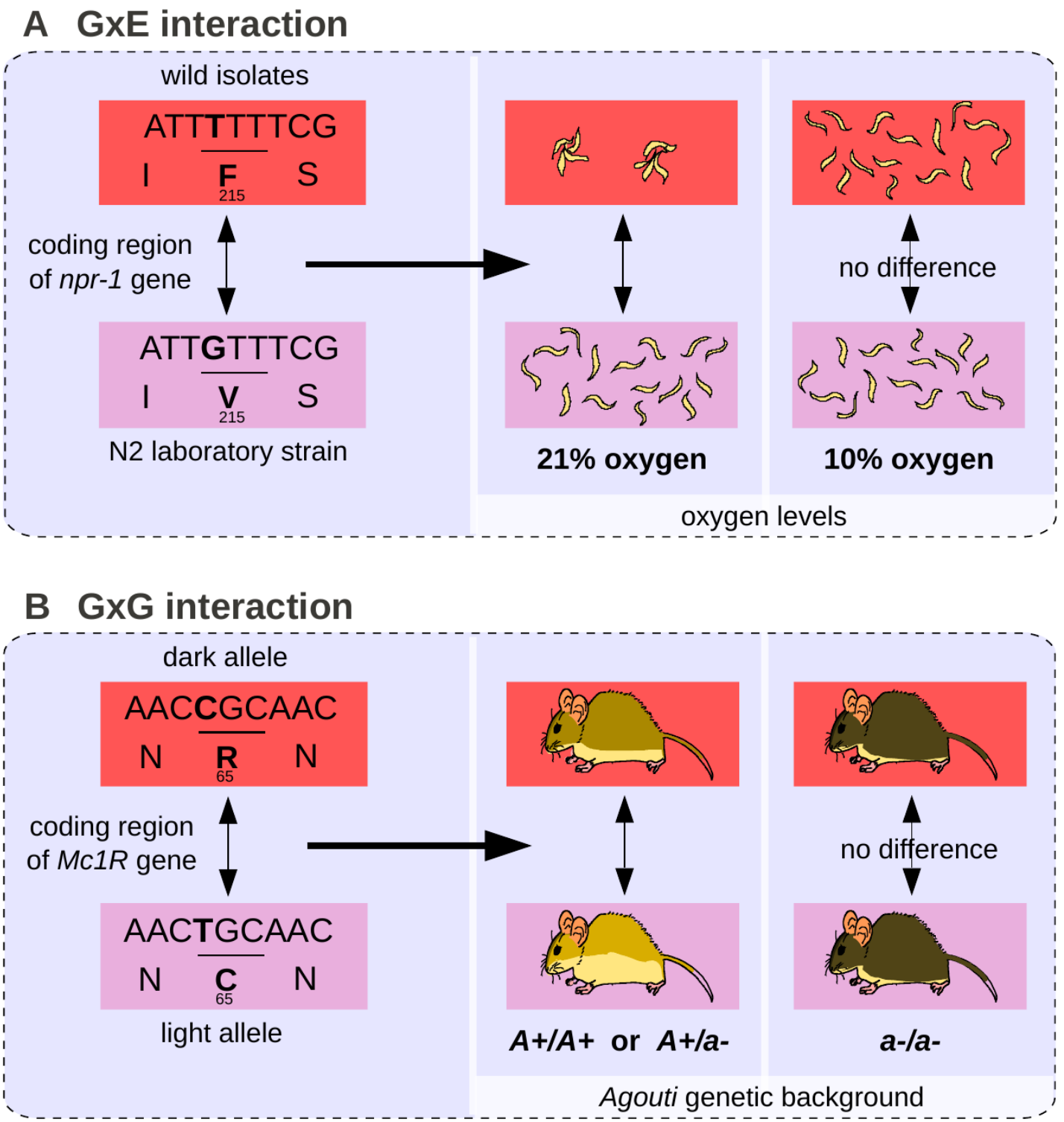
Contributions of the genotype (G) and the environment (E) to phenotypic variation



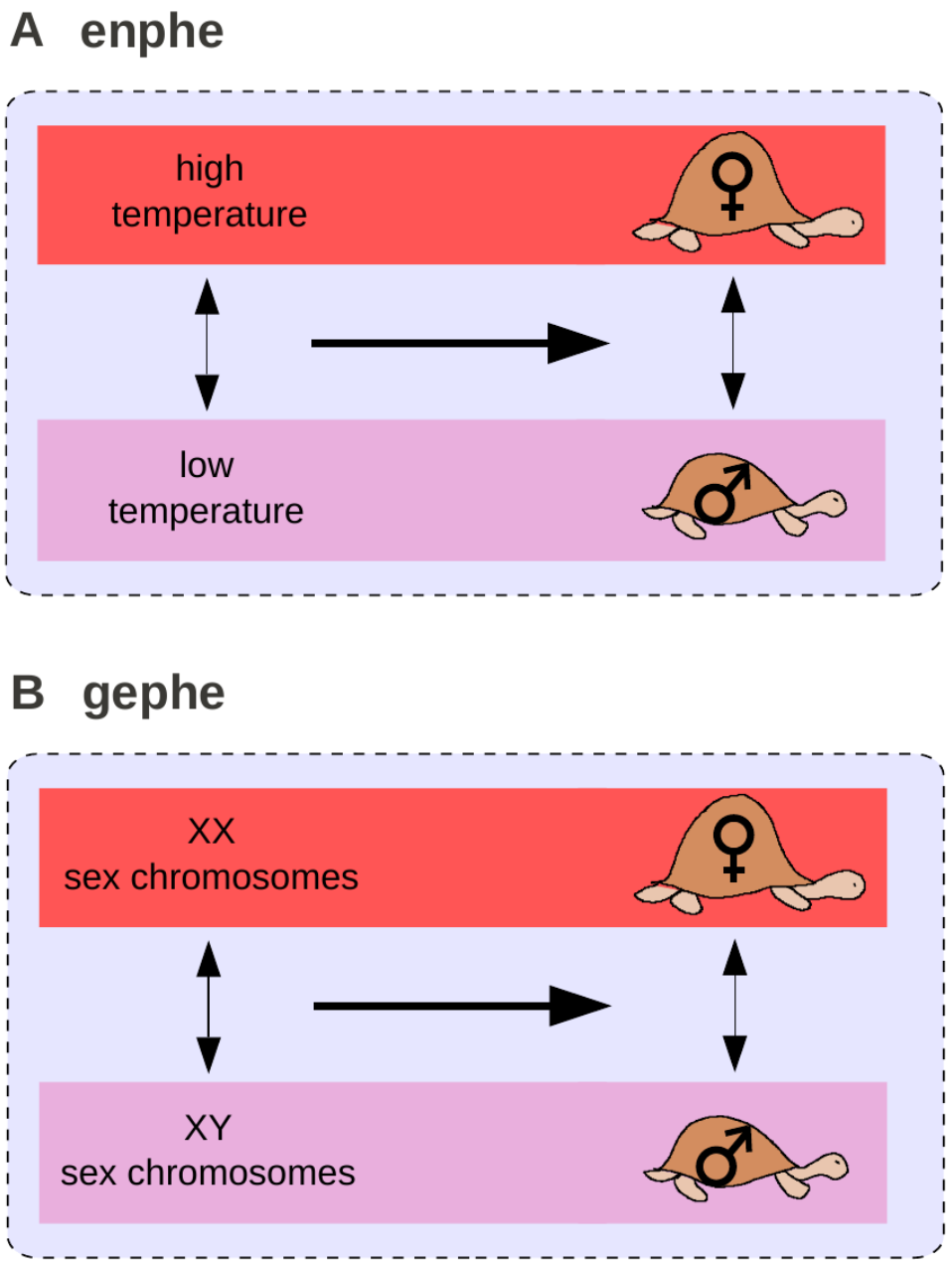
GxE



From Fox Keller (2010)

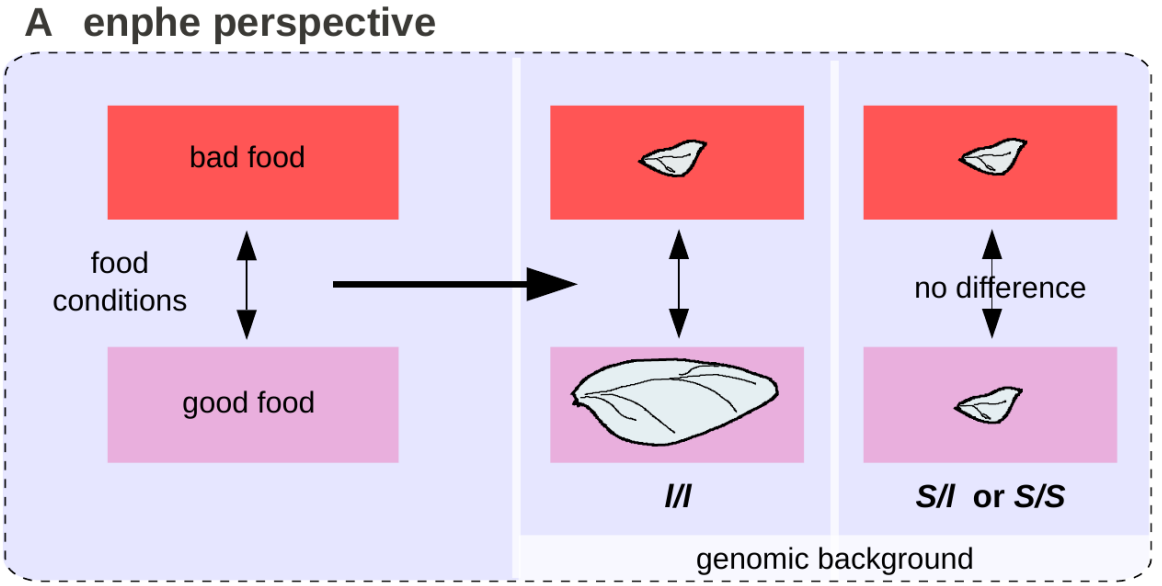

A GxE interaction
wild isolates
ATTTTTTCG
I F S
215
coding region
of npr-1 gene
ATTGTTTCG
I V S
215
N2 laboratory strain
21% oxygen
10% oxygen
no difference
oxygen levels
B GxG interaction
dark allele
AACCGCAAC
N R N
65
coding region
of Mc1R gene
AACTGCAAC
N C N
65
light allele
A+/A+ or A+/a-
a-/a-
no difference
Agouti genetic background

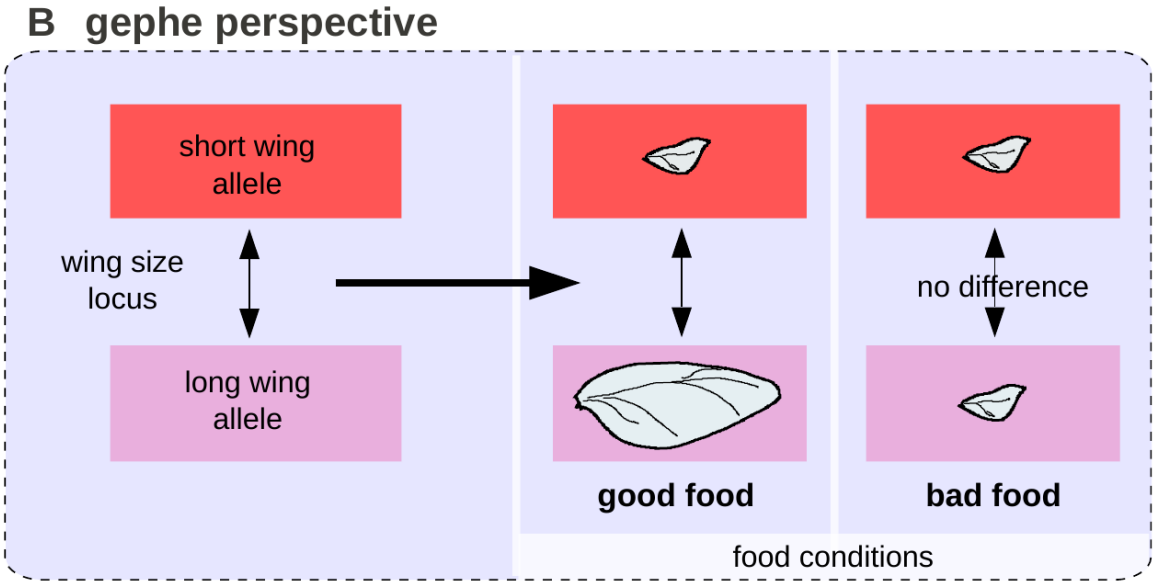
Comparing G and E effects



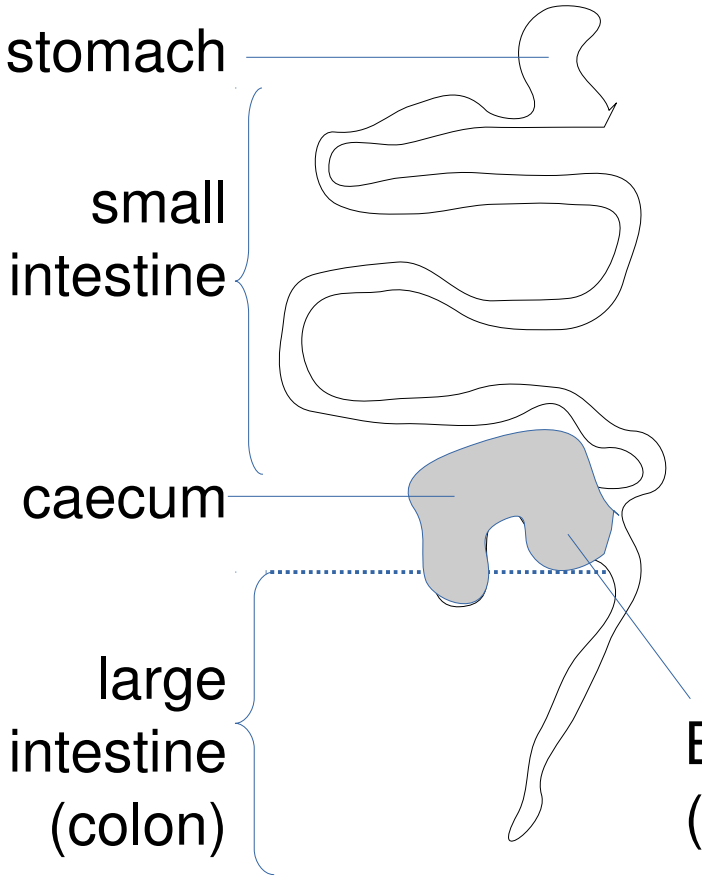
Intermingled G and E effects

Calathus melanocephalus

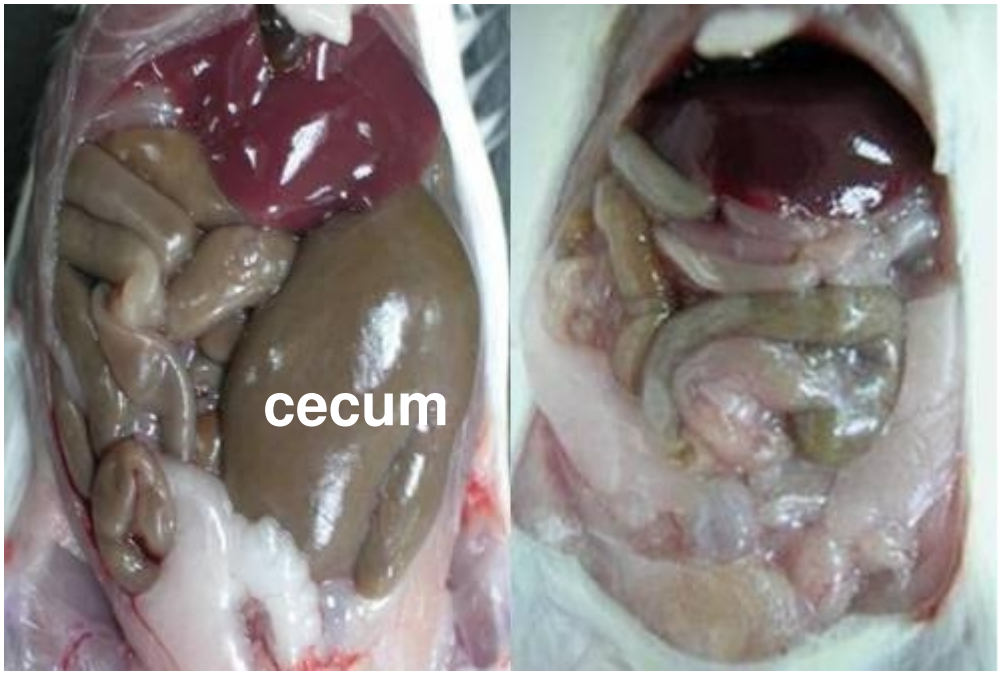




Mouse caecum development
An other example of GxE



Bacteria (digest cellulose, produce vitamine K)



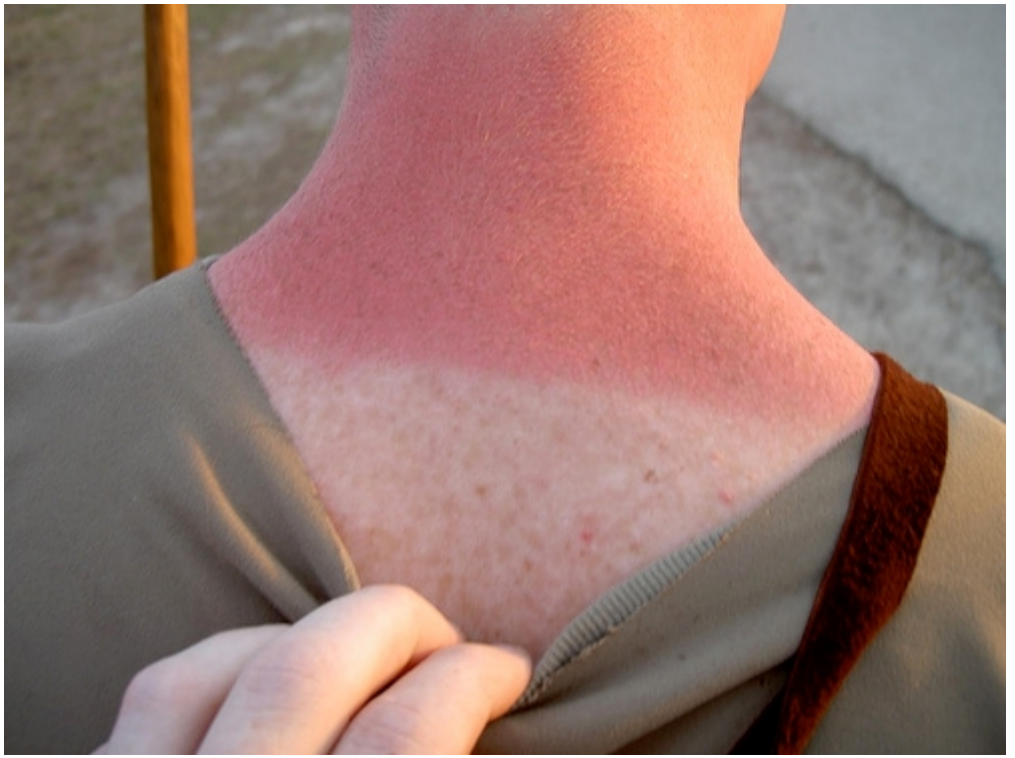
germfree

normal

Causes of phenotypic differences?

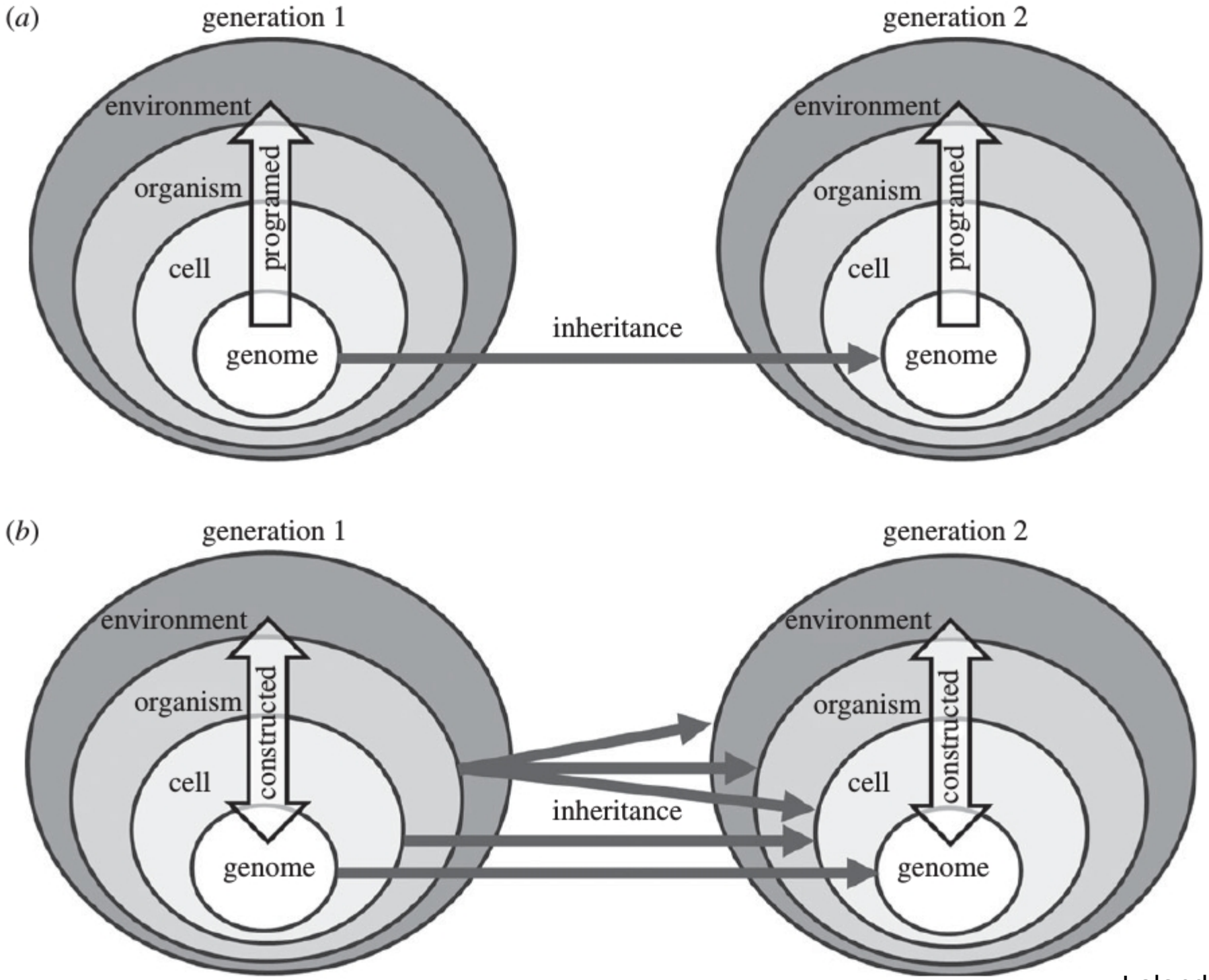
Heritable

Non heritable



Phenotype = H + NH + HxNH

Like GxE but not always (Exceptions: DNA methylation, microbiome, langage, accent, culture, life style, parental care, maternal effet...)


(a)
generation 1
generation 2
environment
organism
cell
genome
programed
inheritance
environment
organism
cell
genome
programed
(b)
generation 1
generation 2
environment
organism
cell
genome
constructed
inheritance
environment
organism
cell
genome
constructed

Laland 2015

Complexifications of the G-P map

Genetic Linkage

Epistasis

Supergene

Pleiotropy

GxE (introduction)