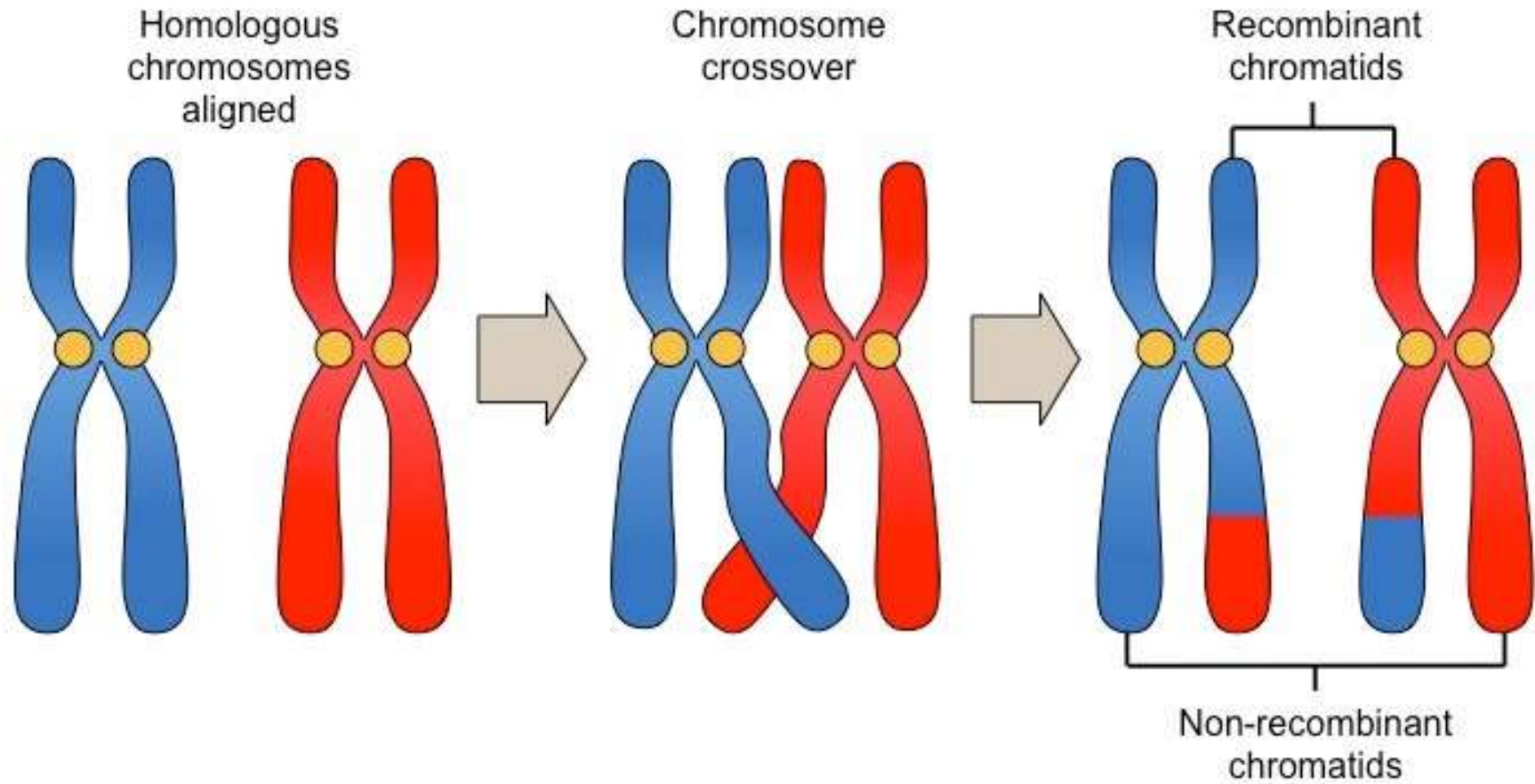


**Interactions between several loci,
Epistasis, Super Genes,
Pleiotropy,
Interactions Genes x Environment**

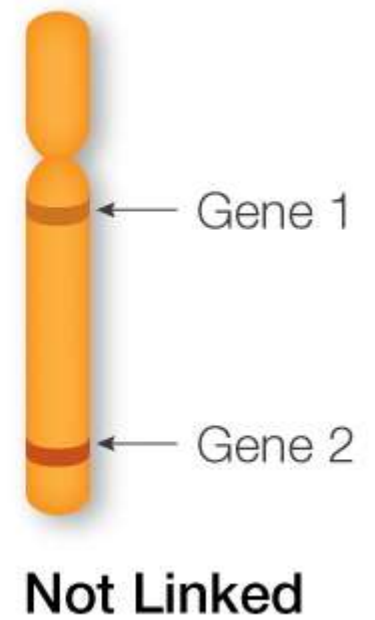
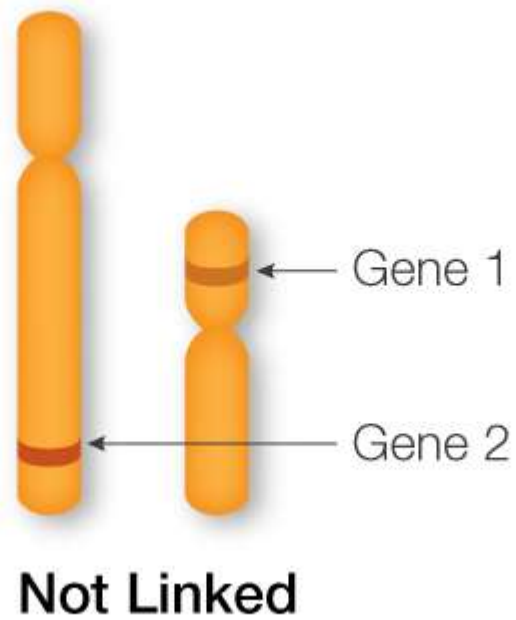
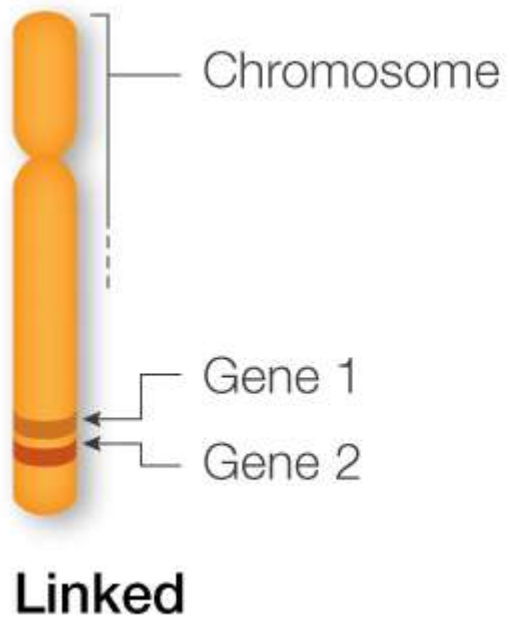
**Virginie Courtier-Orgogozo
Institut Jacques Monod, Paris**

Genetic Linkage

Crossing overs

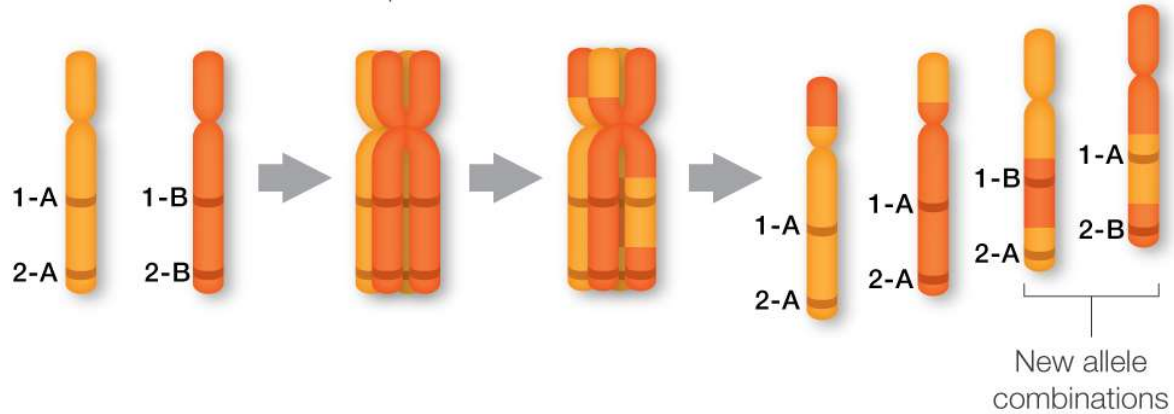


About one recombination event per chromosome arm



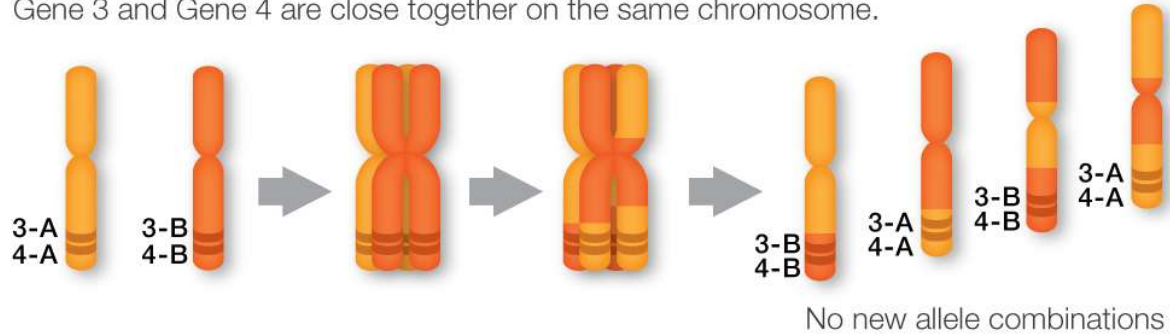
Not Linked

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



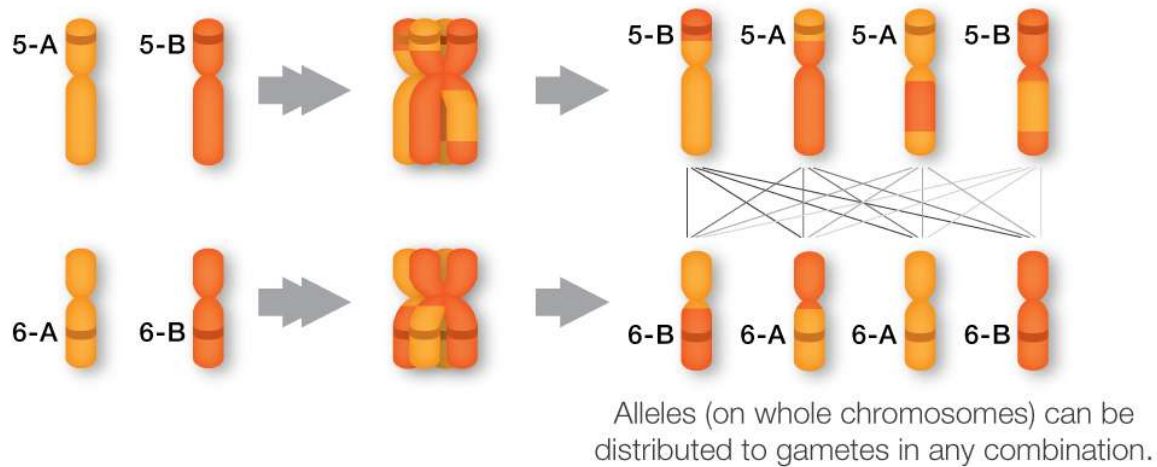
Linked

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



Not Linked

Gene 5 and Gene 6 are on separate chromosomes.

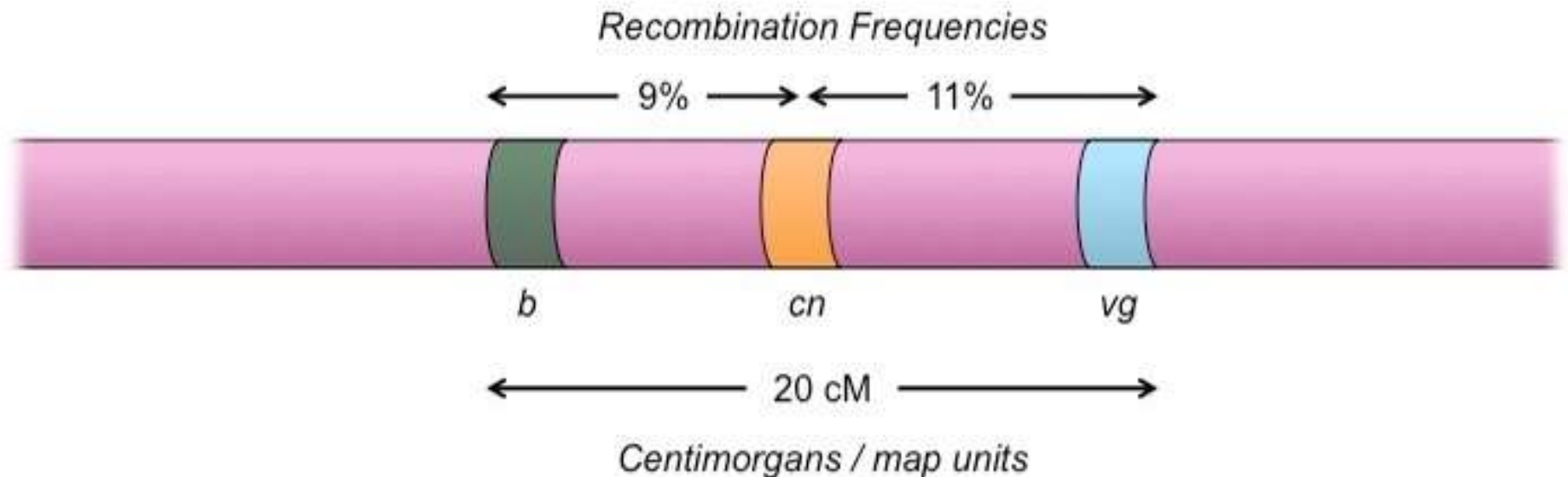


One “centiMorgan”

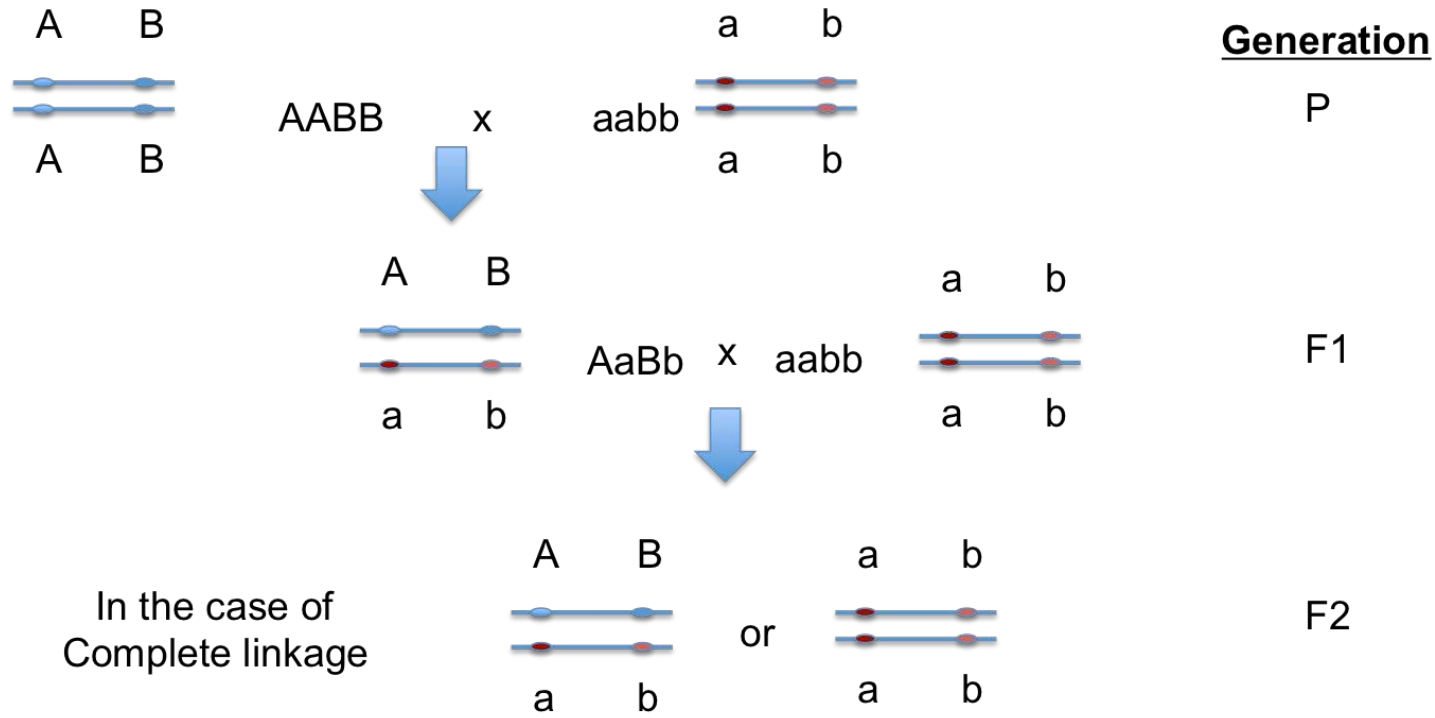
= genetic distance that produces a recombination frequency of 1%

Genetic distance (in cM)

$$= \frac{(\# \text{ Recombinant gametes}) \times 100}{\text{Total gametes}}$$



Measure of genetic linkage

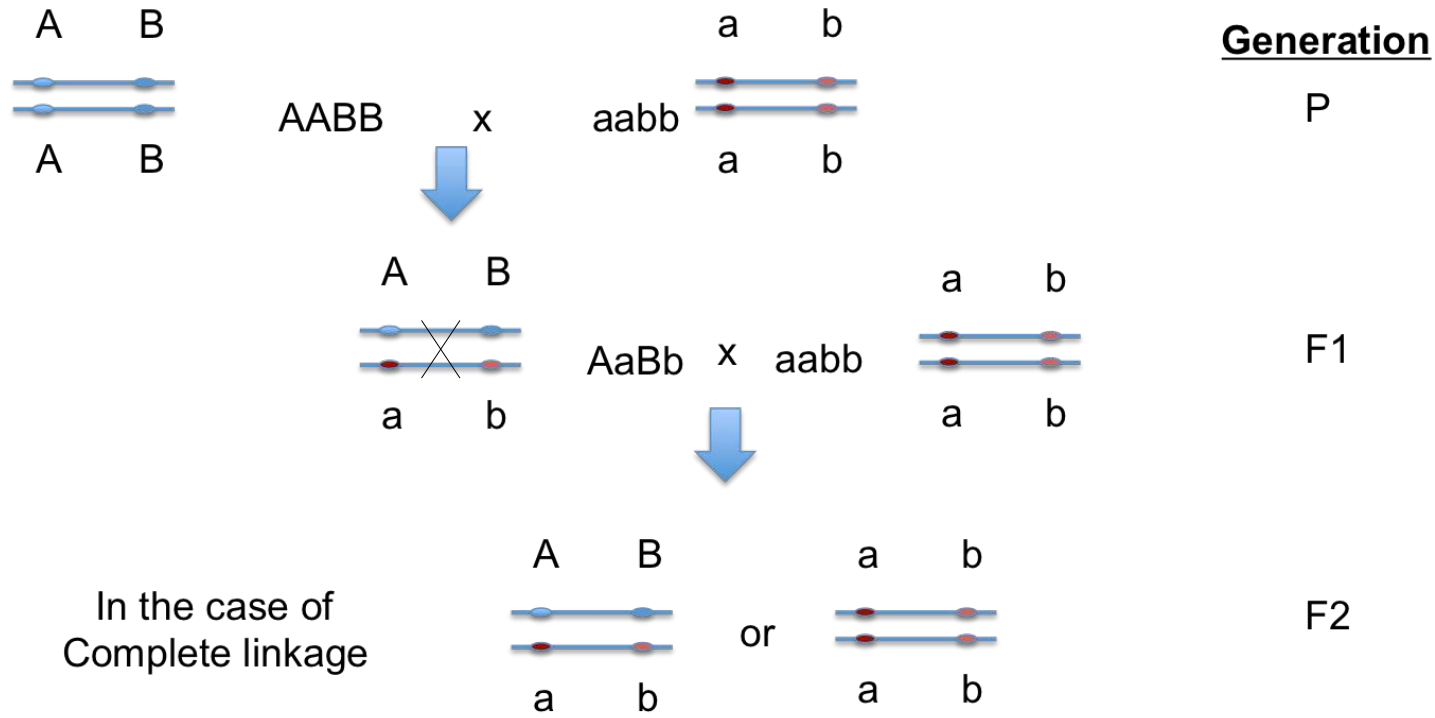


Complete Linkage

50% AaBb

50% aabb

Measure of genetic linkage



Complete Linkage

50% AaBb
50% aabb

Genetic Linkage

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

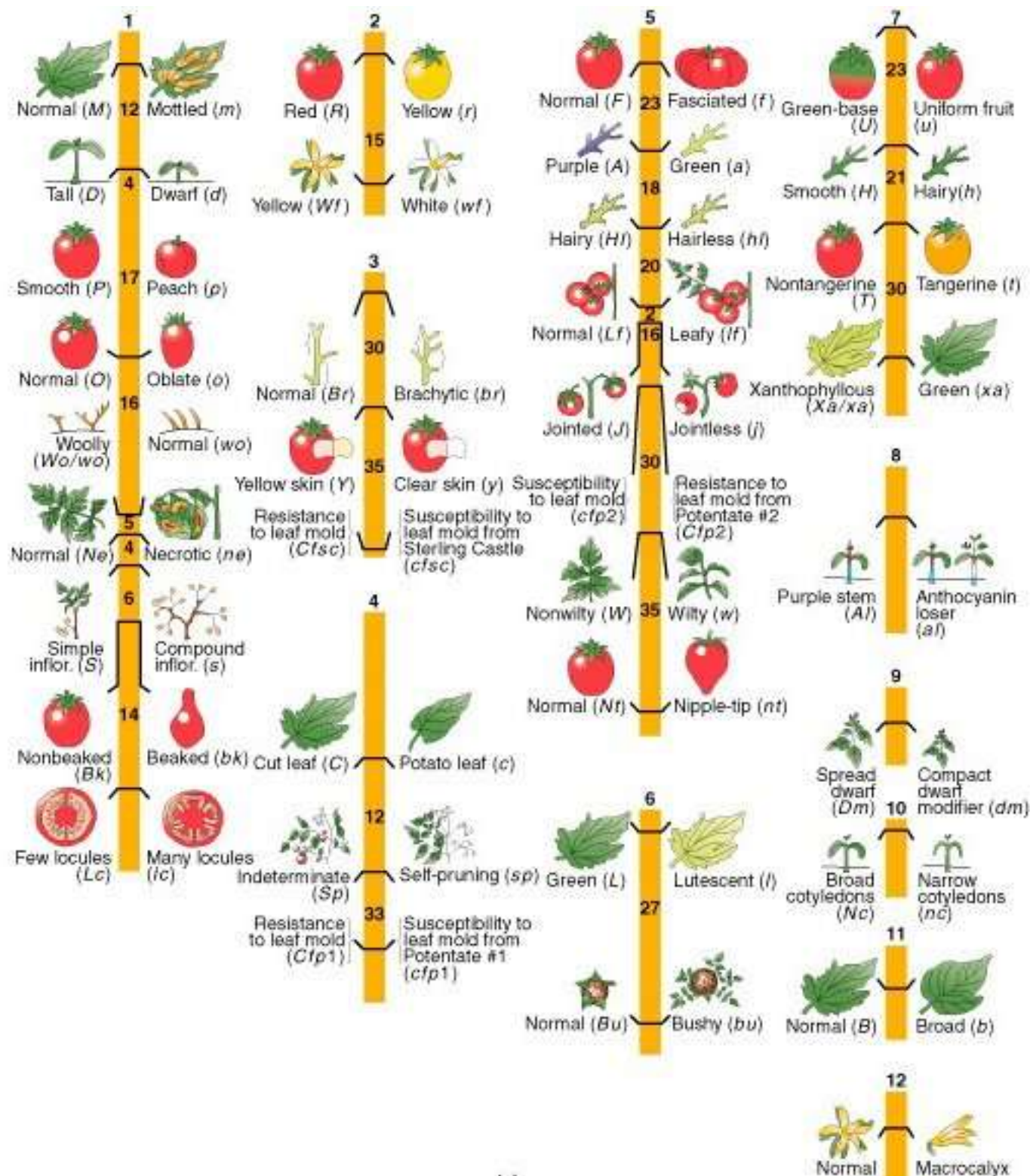
20% of recombinants so 20cM

Measure of genetic linkage

If y % recombinant gametes and $y < 50\%$ $\Rightarrow y$ cM apart

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

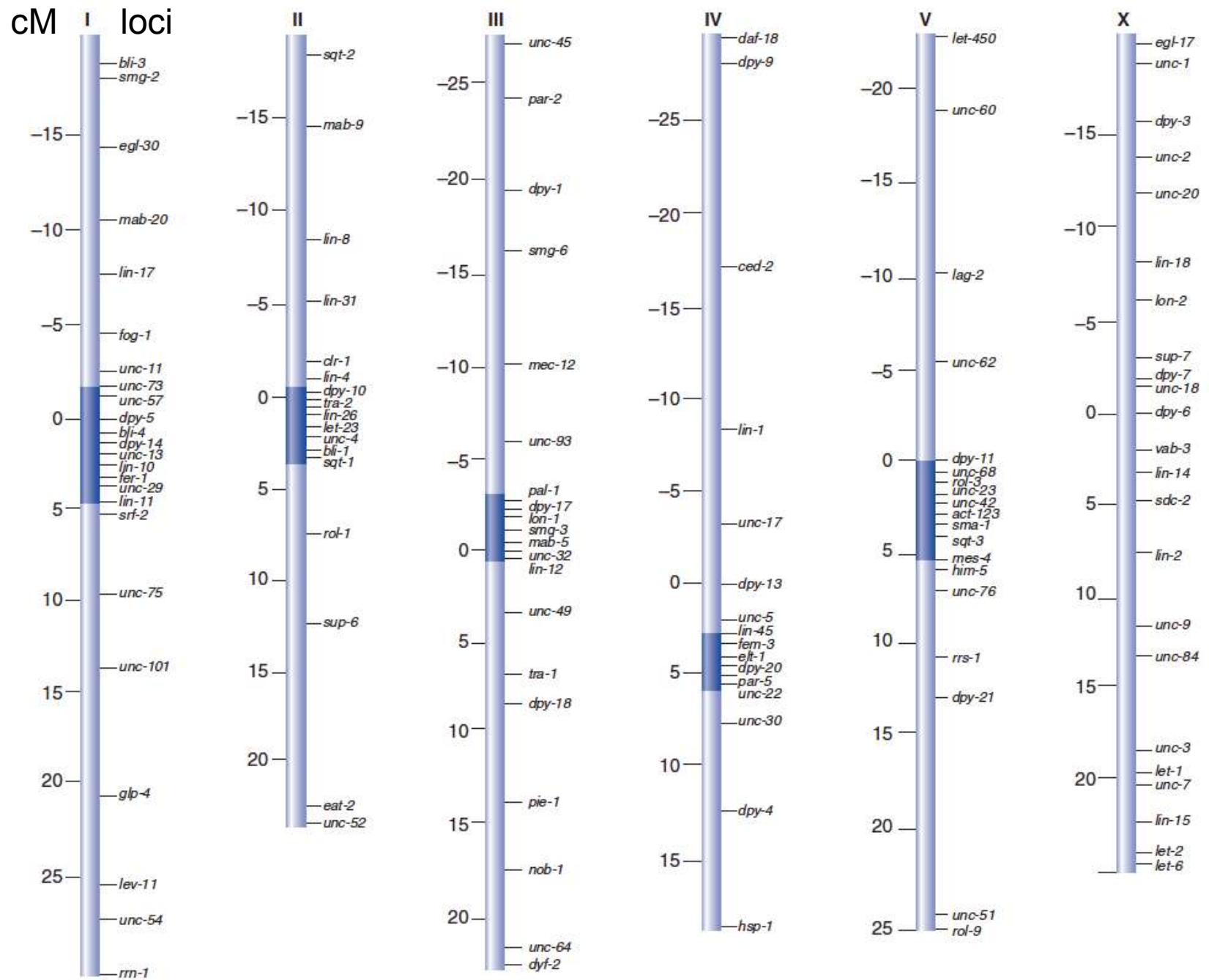
If the linkage group is longer than 50 cM, mutations at the two extremities are operationally unlinked



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



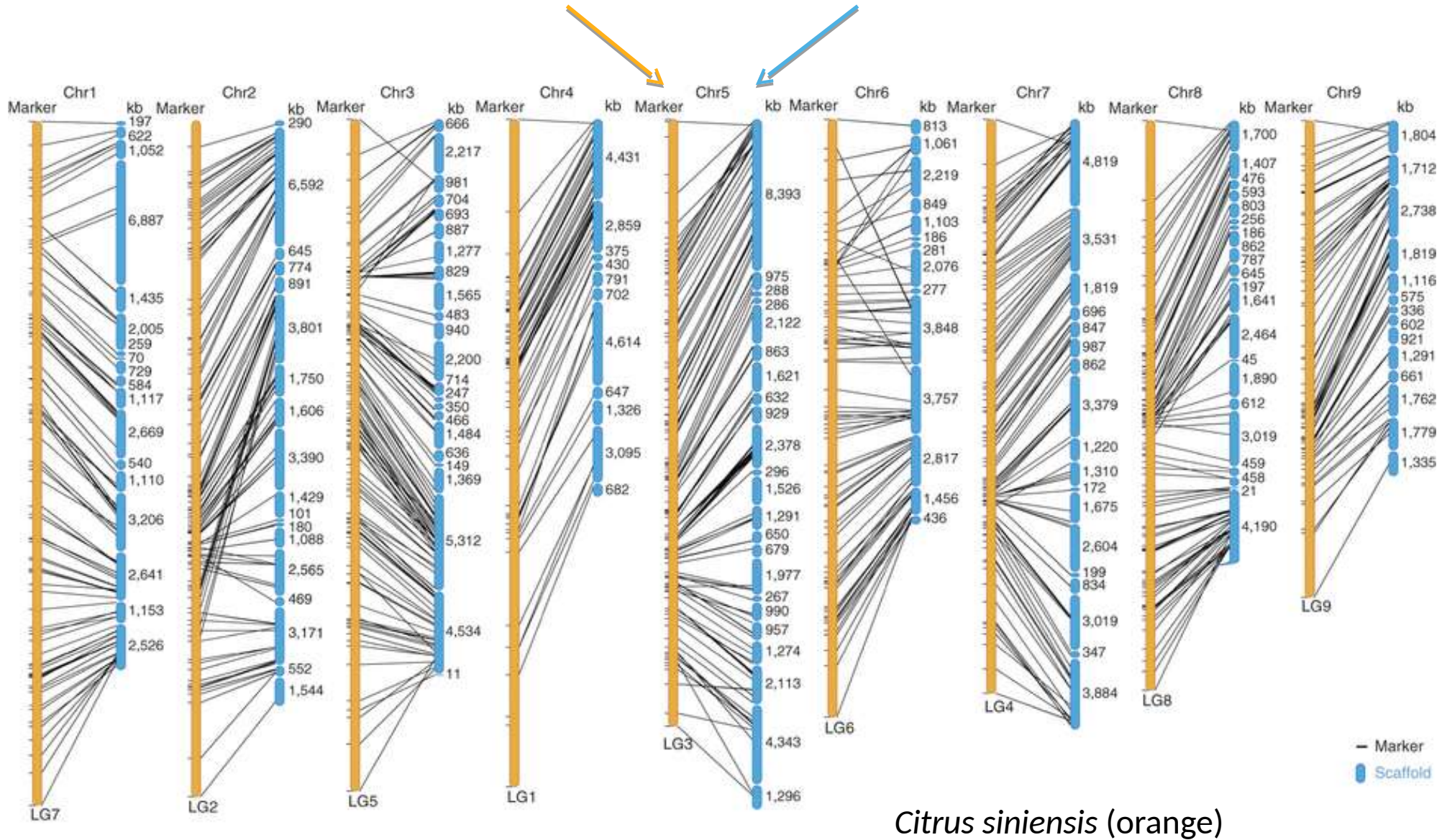
Detected:

- 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

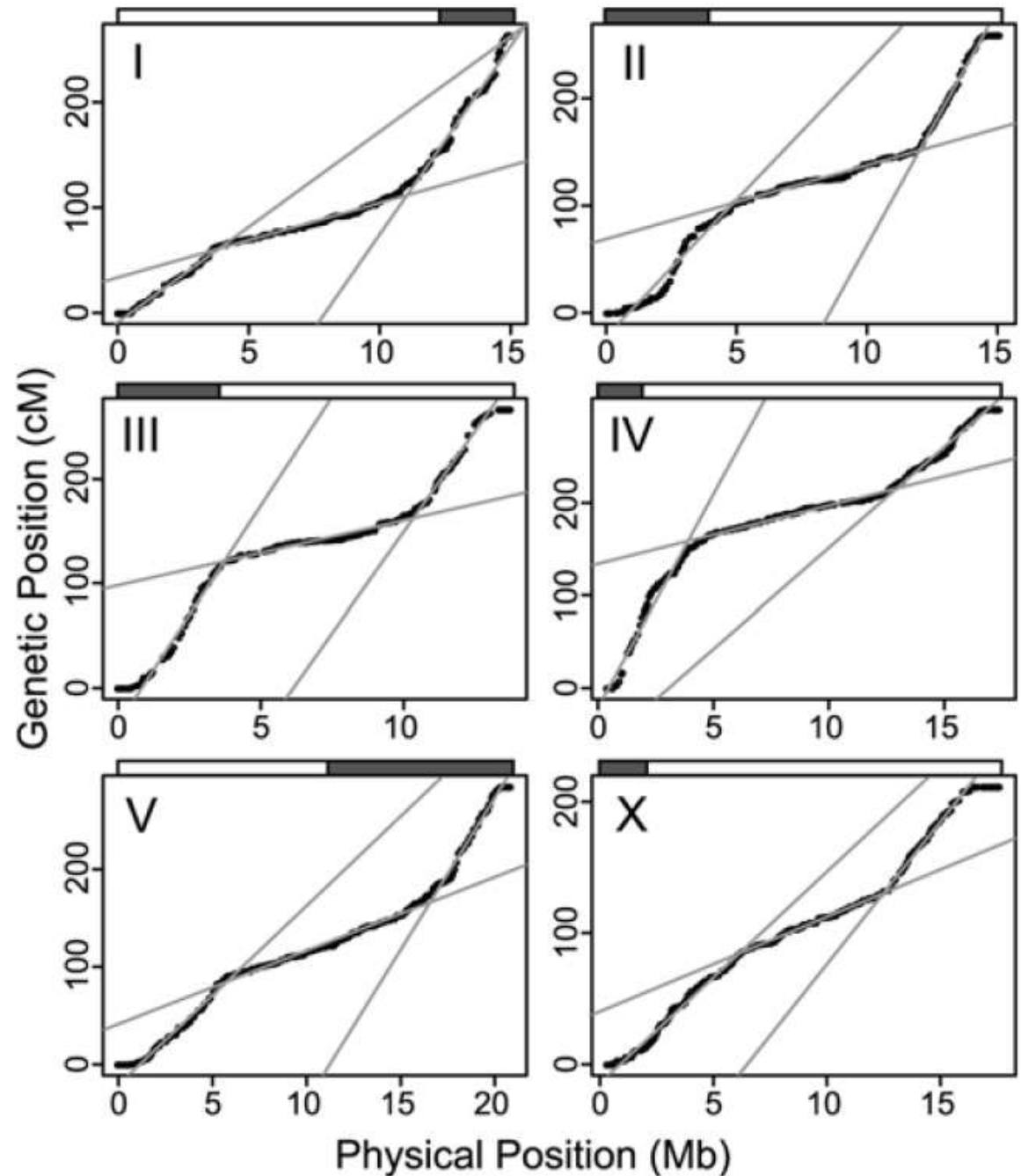
Physical map in base pair units



Alignment of genetic and physical maps

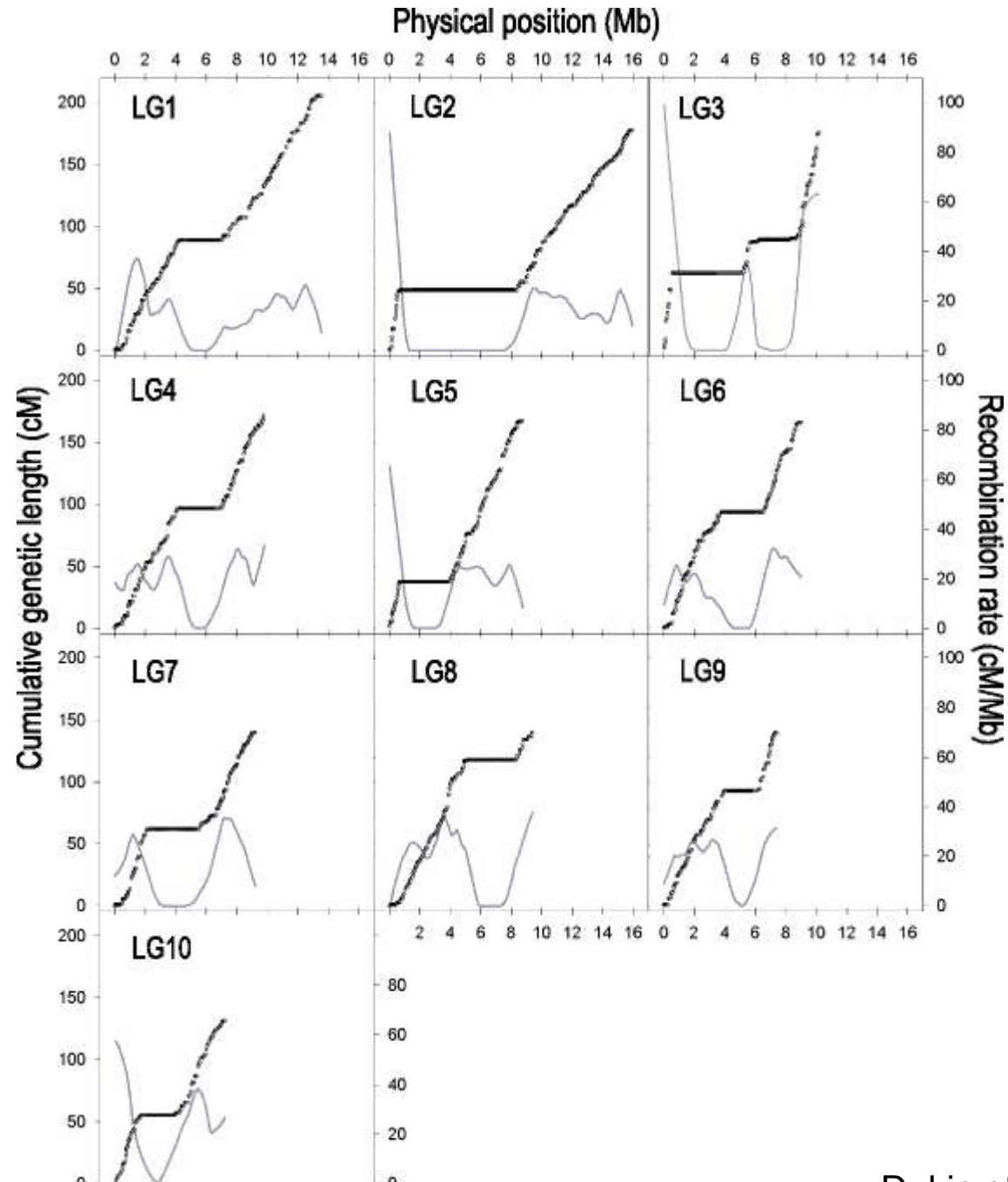
Marey map

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



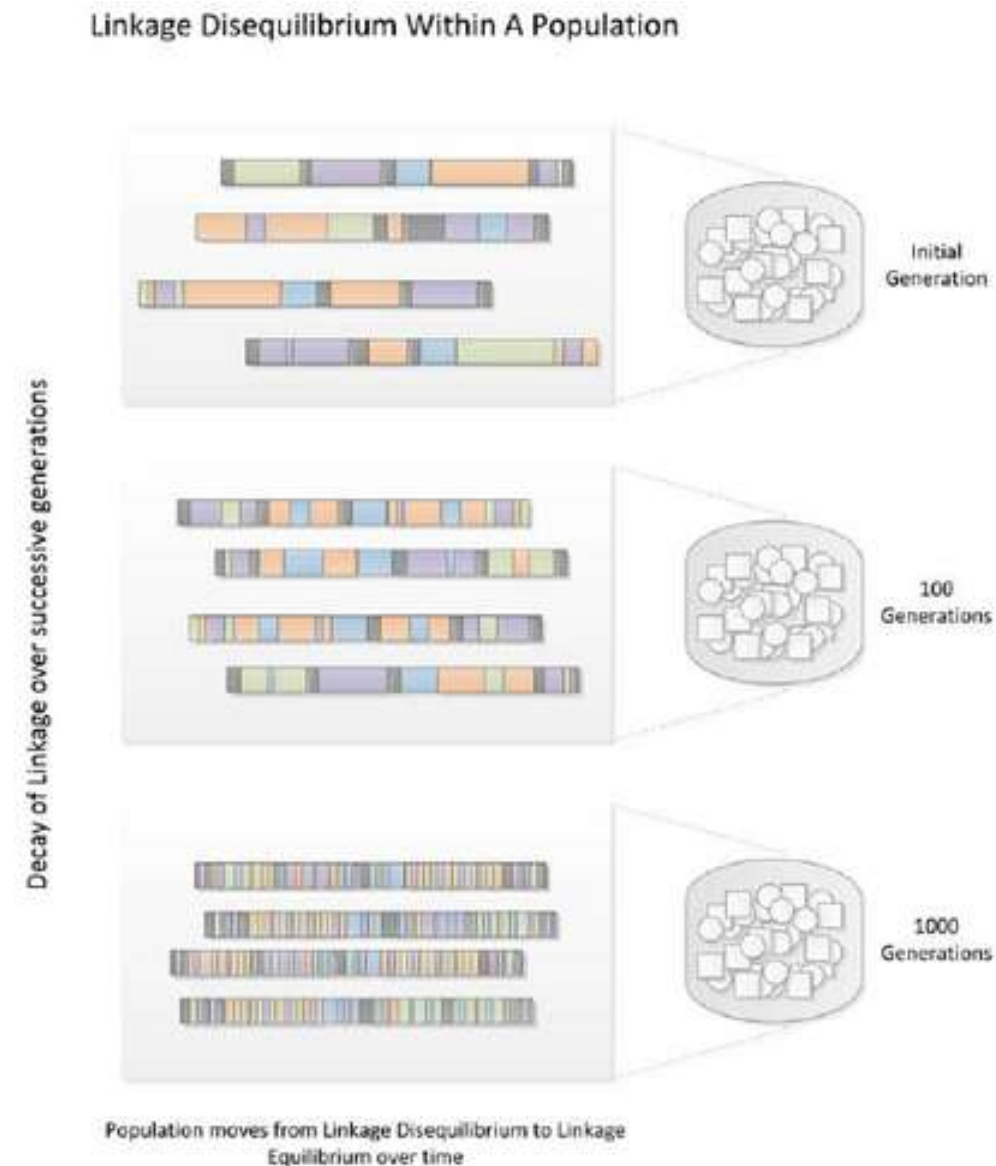
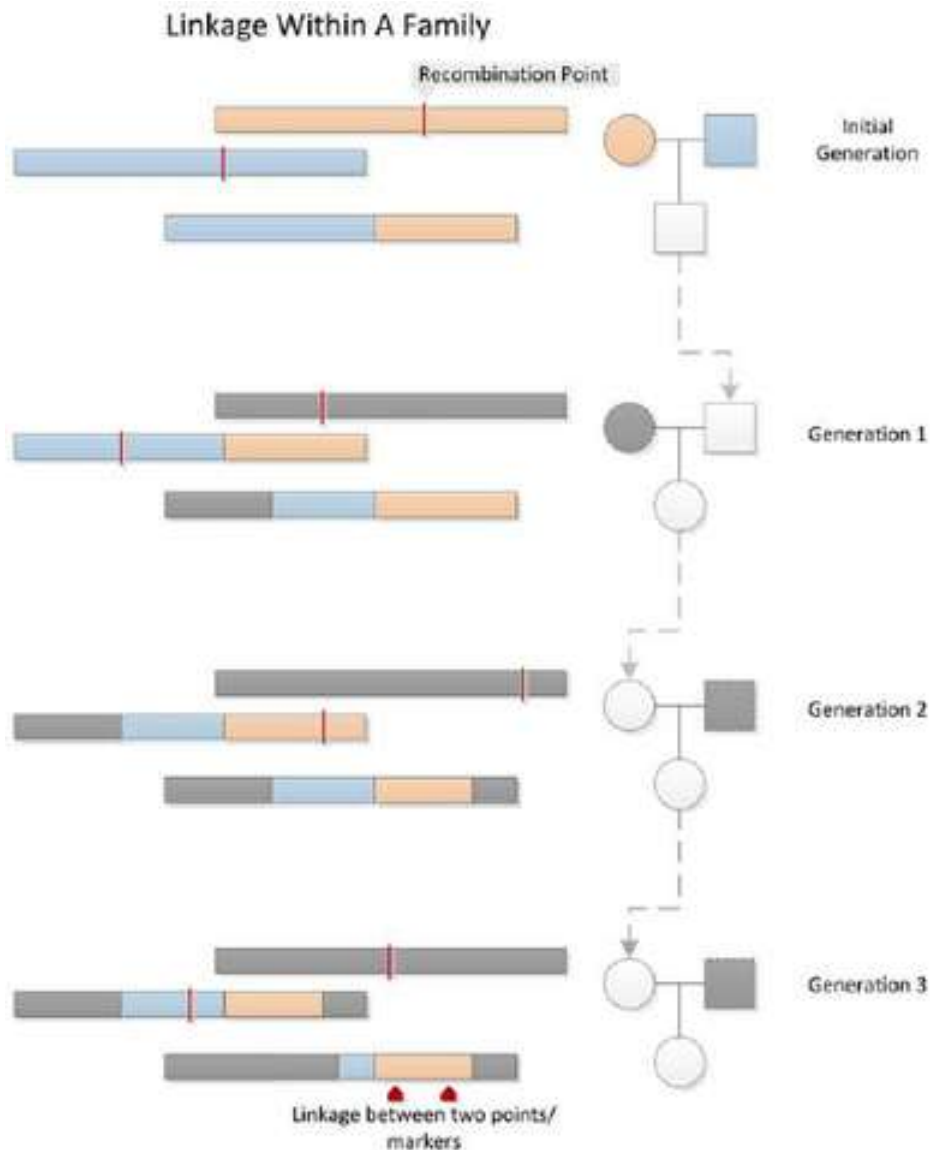
Recombination rate varies along the chromosome

Marey maps in *Daphnia*

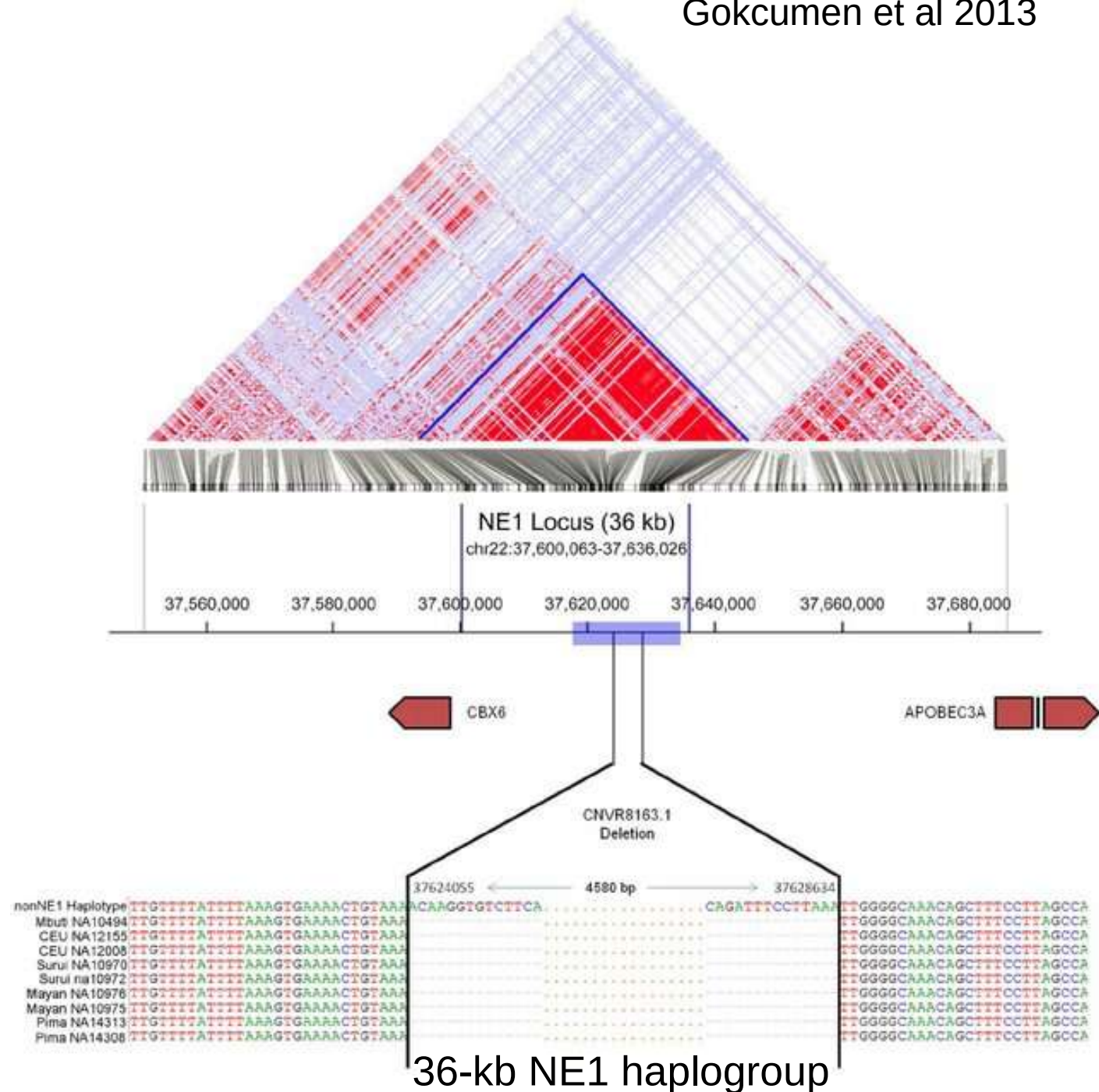


Linkage disequilibrium (LD)

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



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*

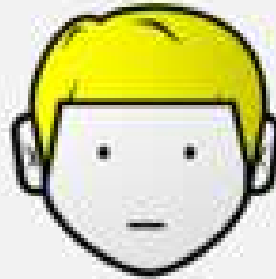
medium-range = a few kb: *Homo sapiens*, *Arabidopsis thaliana*

long-range = Mb: *Caenorhabditis elegans*

Epistasis

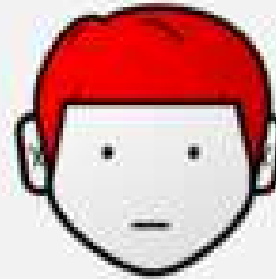
= Non-additive interaction of alleles at different loci
for a given phenotype

**Allele for
blond hair**



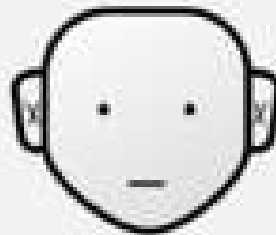
Blond hair

**Allele for
red hair**

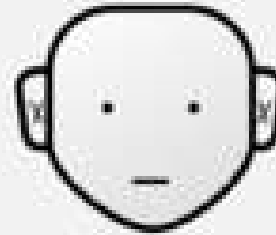


Red hair

**Allele for
baldness**

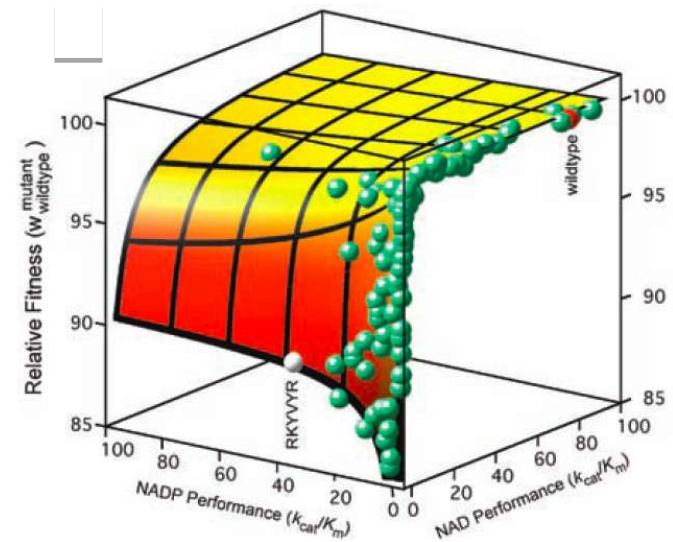
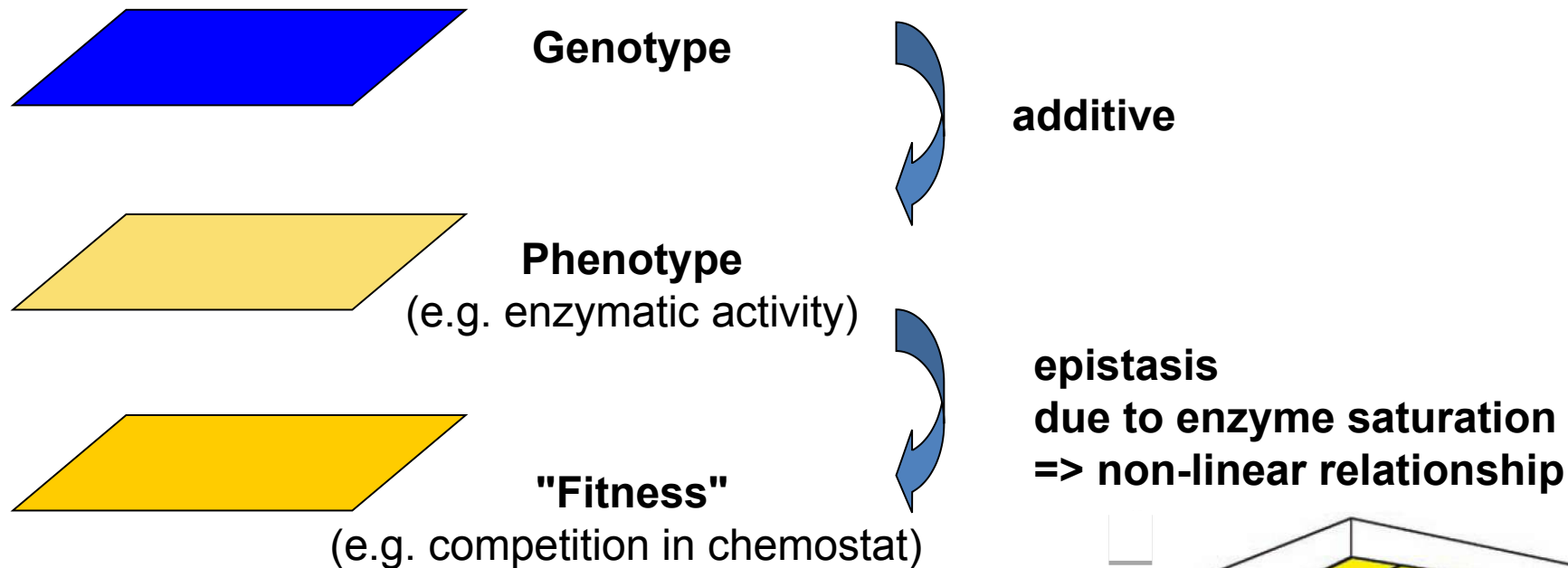


Bald



Bald

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



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)

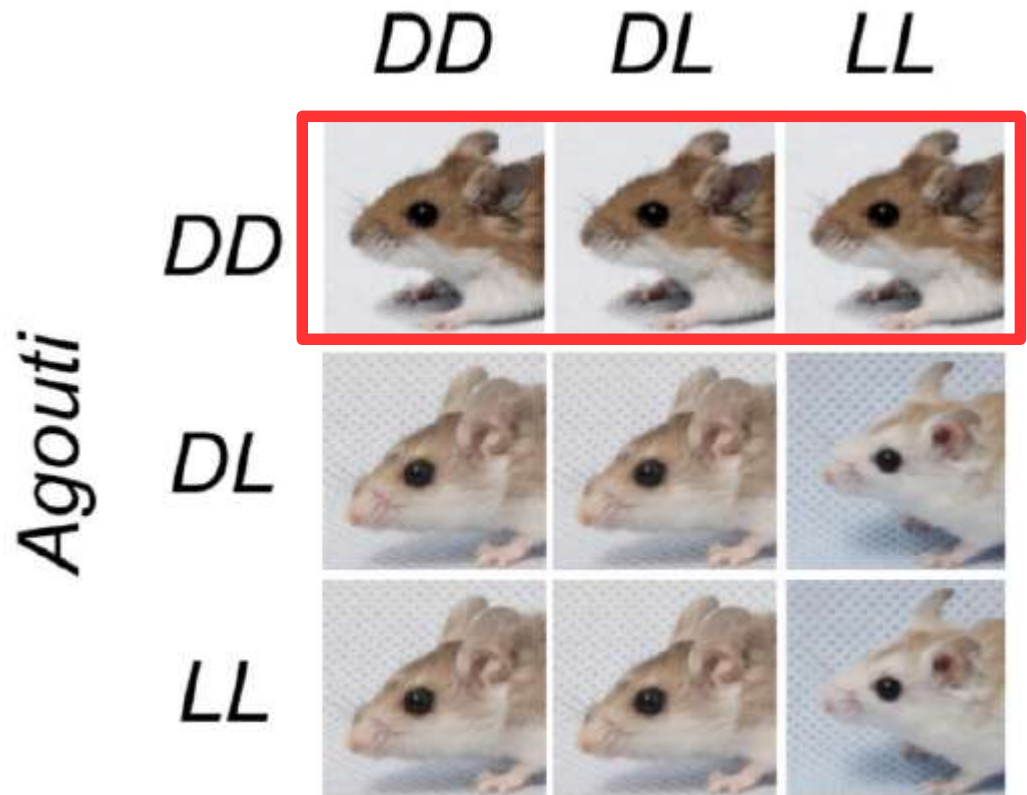
non-additive mapping of genotype space to phenotype space

=> confusion between lab geneticists and evolutionary geneticists

Meaning of "epistasis" depends on the scientific context!

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

Natural alleles
3 phenotypes



***Agouti*^D is epistatic
over *Mc1R* alleles**

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

Laboratory mutants
3 phenotypes



Agouti

AA

Aa

aa

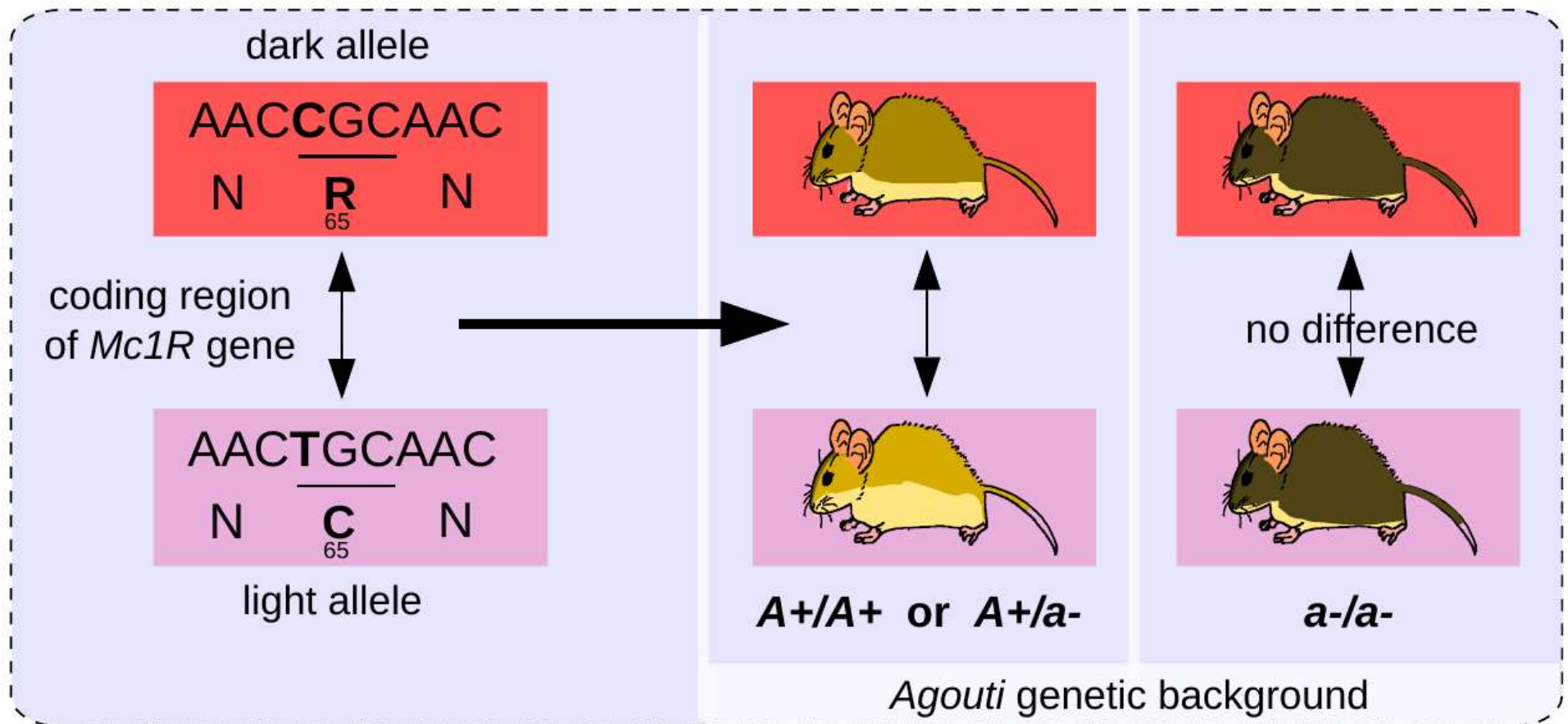
EE

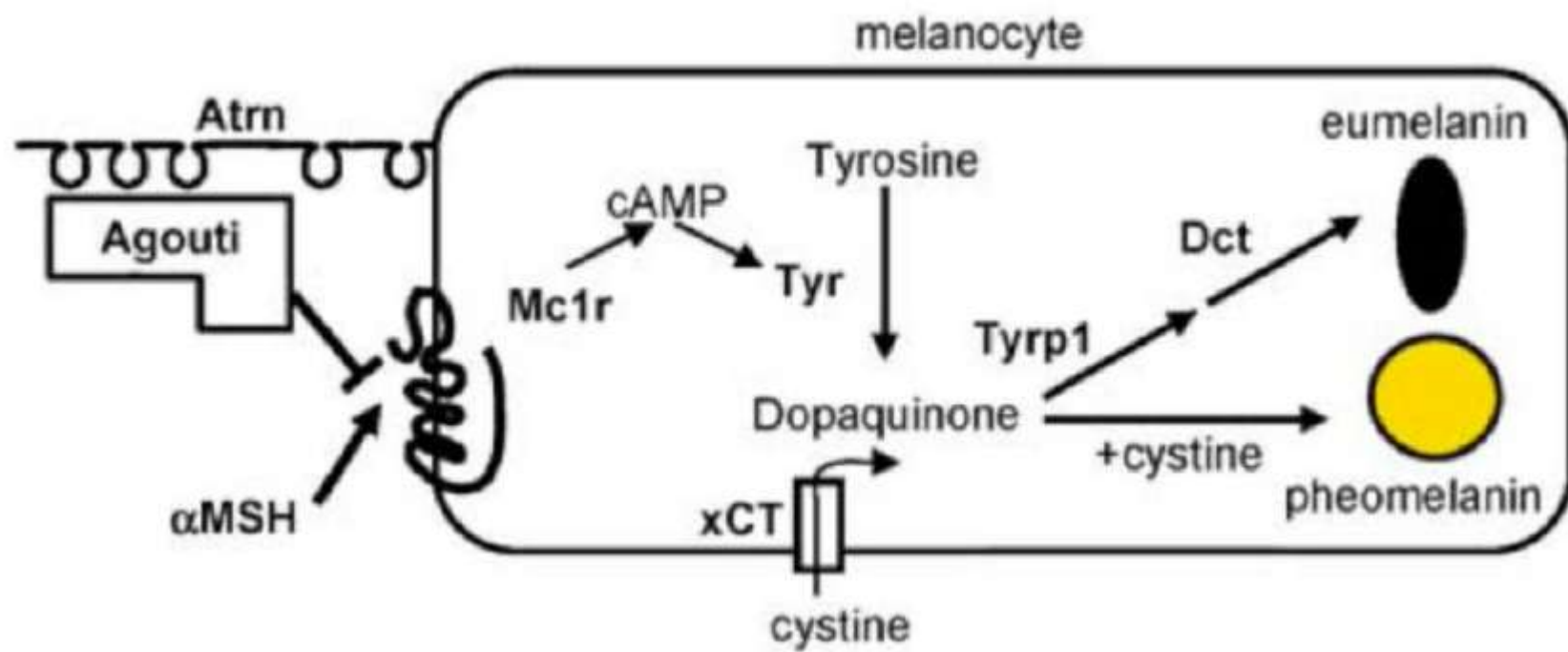
Ee

ee

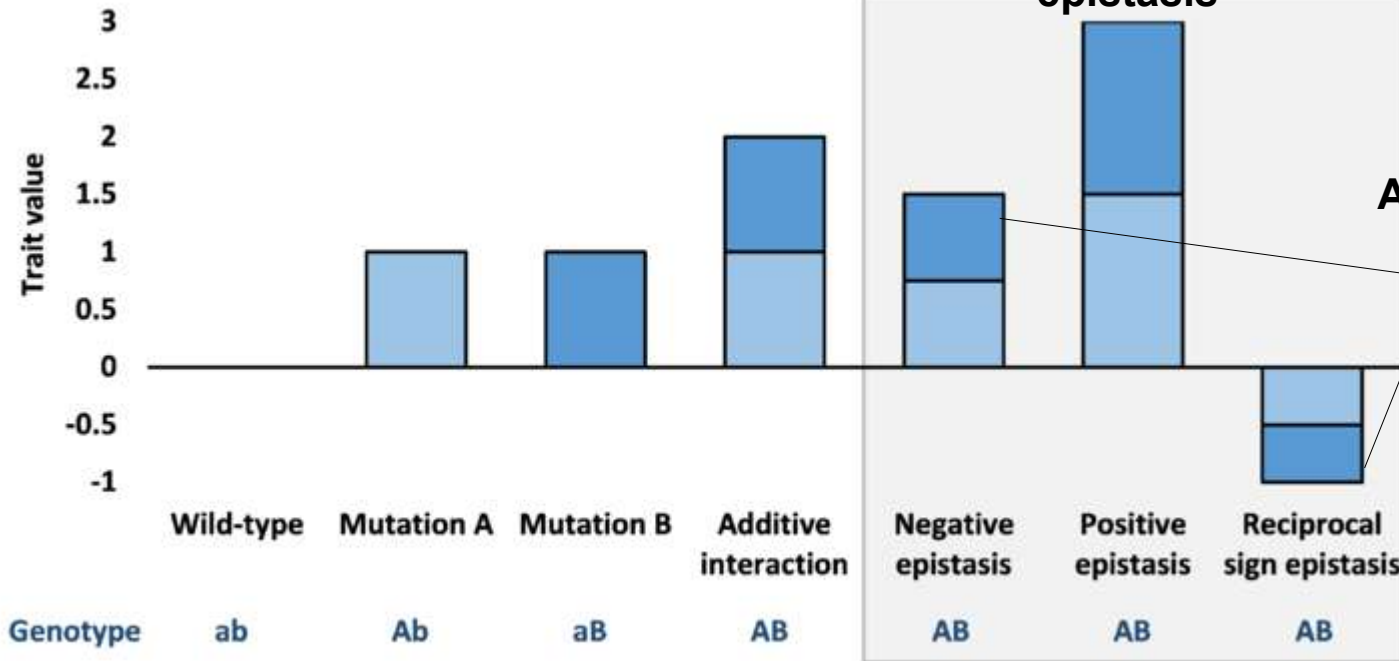


***Mc1R^e is epistatic
over *Agouti* alleles***

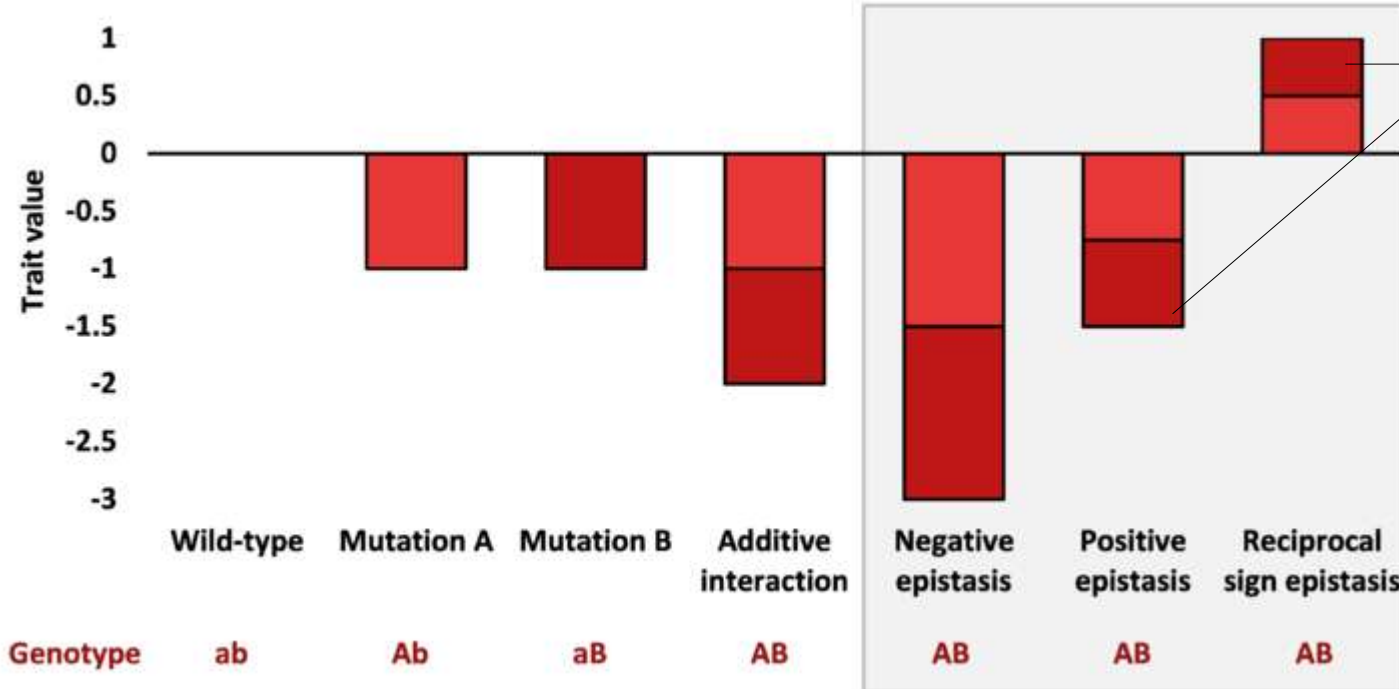




Epistasis between
beneficial mutations



Epistasis between
deleterious mutations



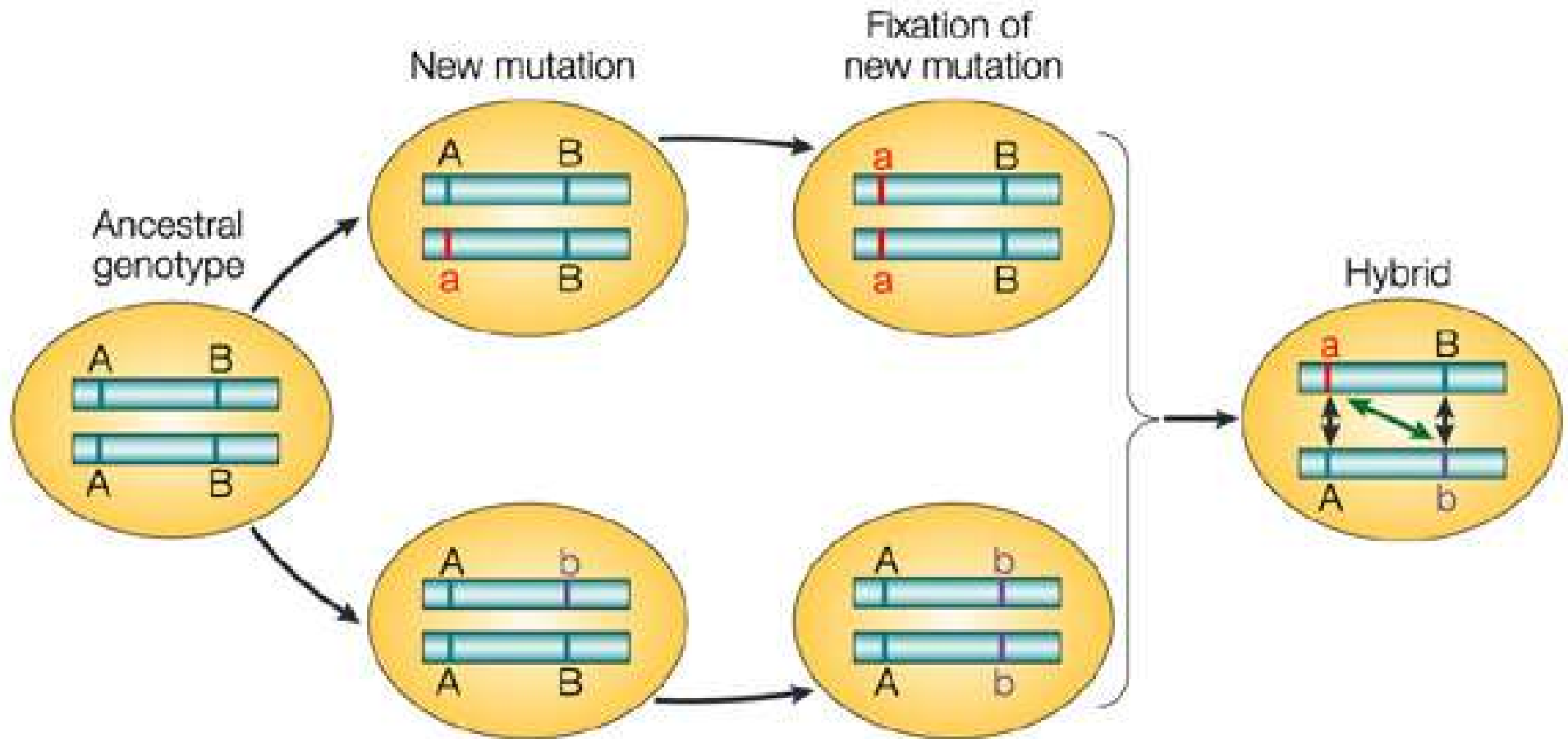
Synergistic
epistasis

"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 a^2 , b^2)

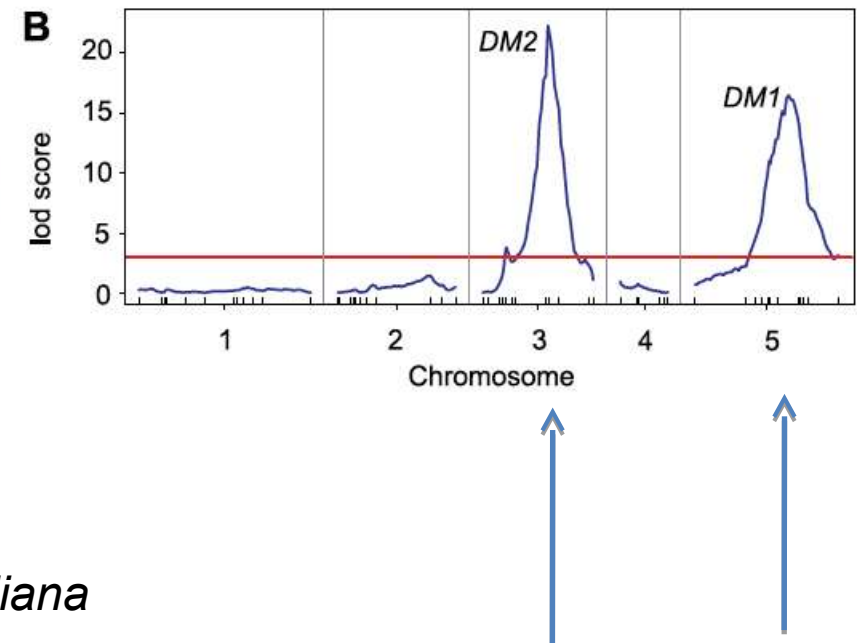
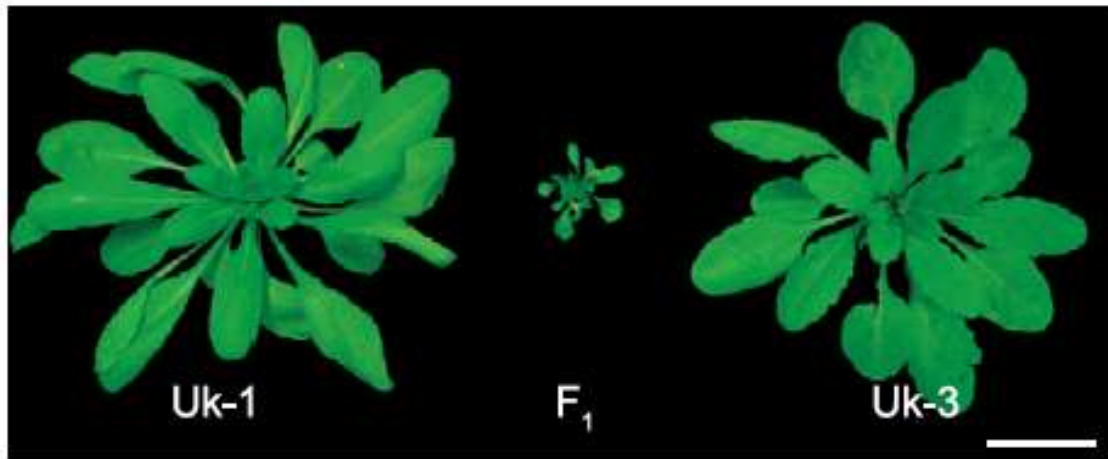
"Positive or negative epistasis": the phenotypic value
is either increased or decreased relative to additivity

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



possible mechanism of speciation

Hybrid incompatibility in *A. thaliana*



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

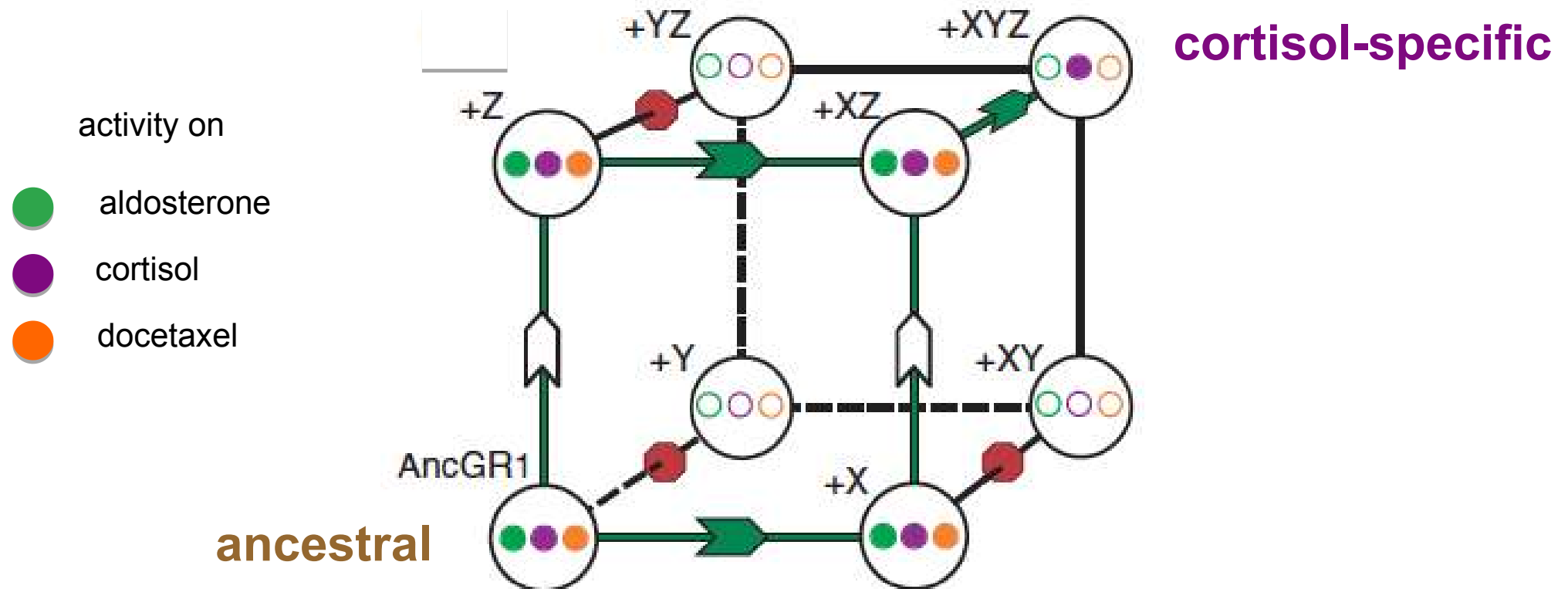
Dangerous Mix 2: RPP1 gene
resistance against oomycete

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

Intramolecular epistasis

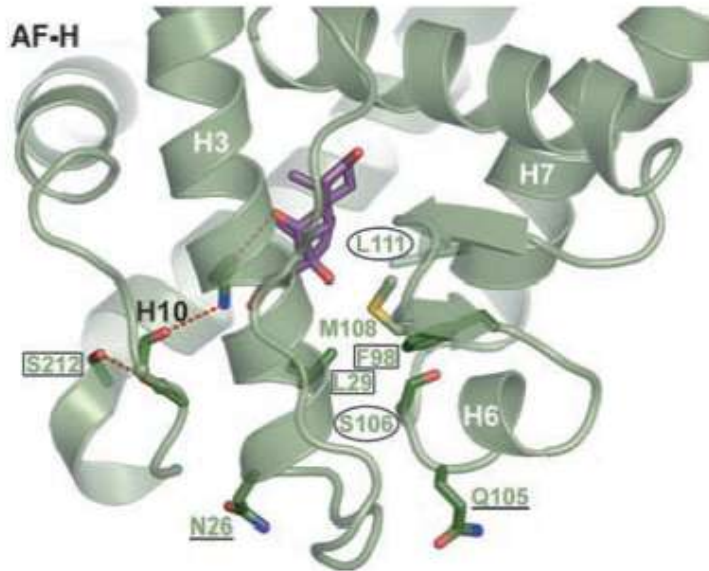
Reconstruction of ancestral protein sequence
from phylogenetic analysis of extant family in databases

Vertebrate corticoid receptor family

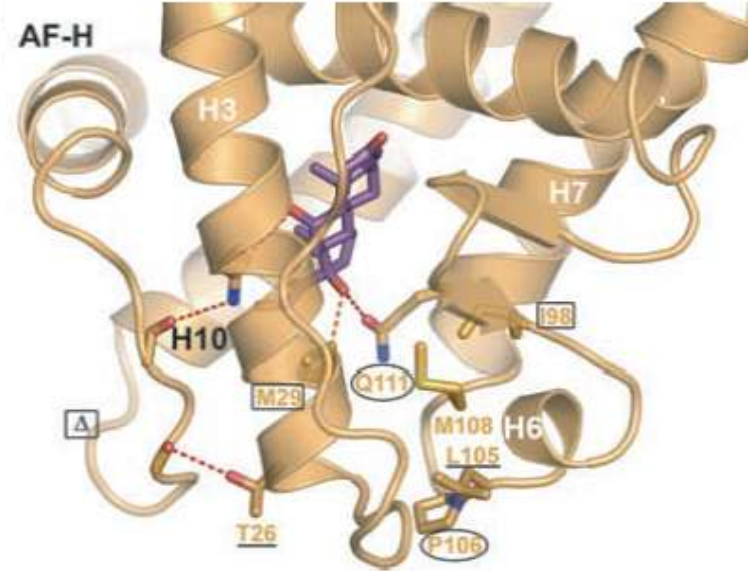


permissive substitutions

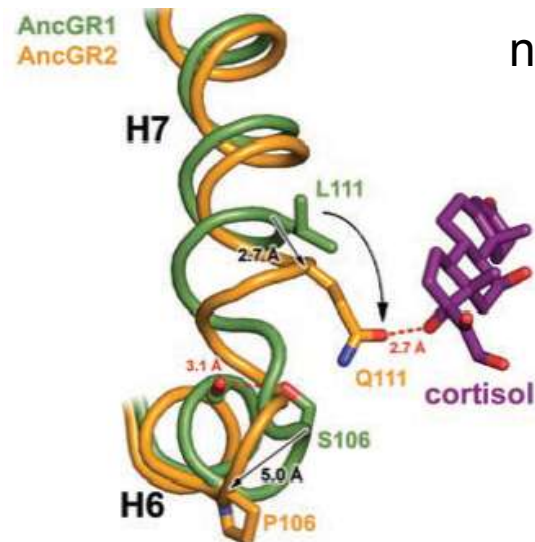
AncGR1



AncGR2

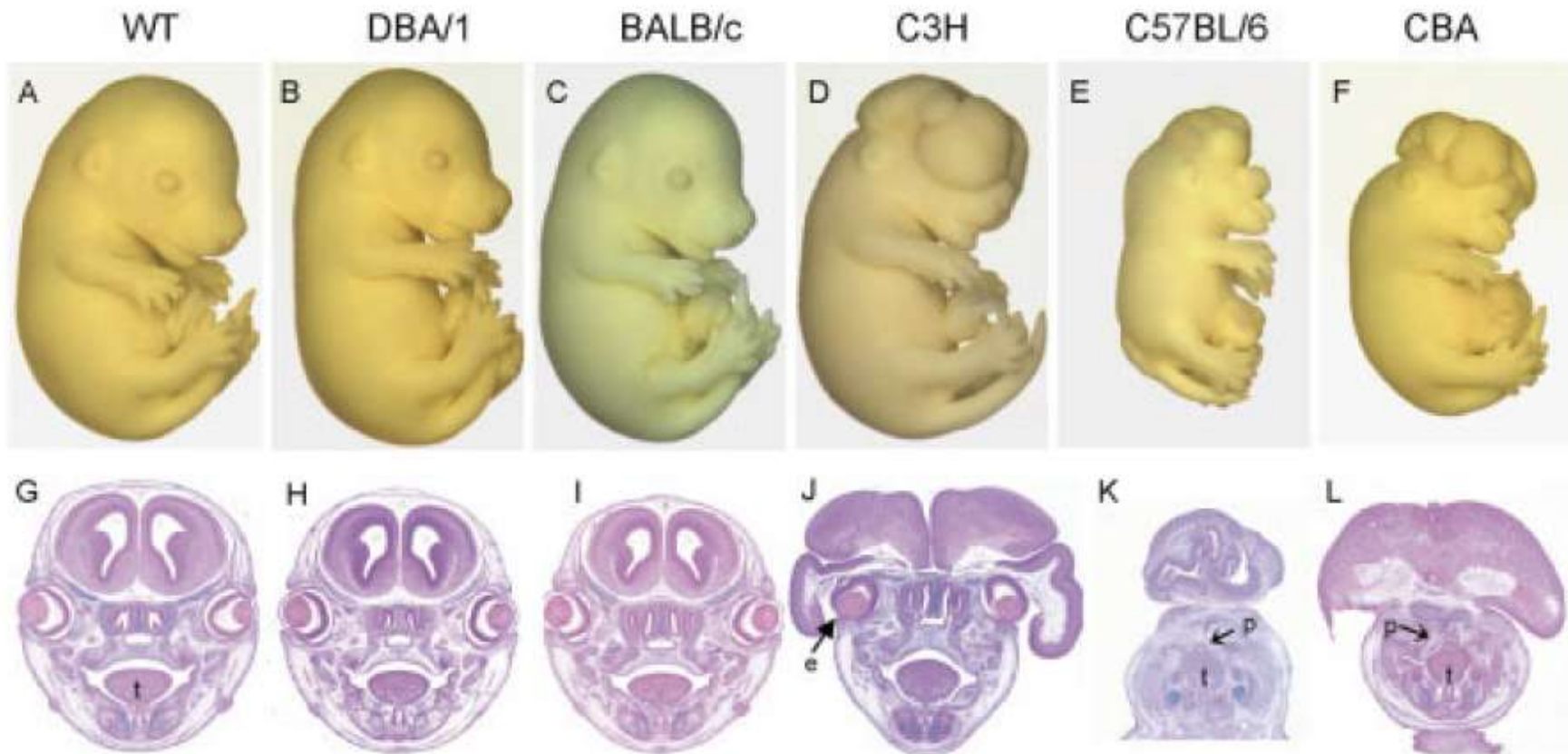


new interactions with cortisol



Expressivity of one mutation varies with wild genetic background

Tcof1^{-/-} heterozygote mice



Different kinds of GxG interactions

$\underset{m1}{G}$ x $\underset{m2}{G}$ between 2 laboratory mutations

$\underset{a1/a2}{G}$ x $\underset{b1/b2}{G}$ between 2 natural alleles

$\underset{m}{G1}$ x $\underset{m}{G2}$ one mutation
in different wild genetic backgrounds
“cryptic” variation

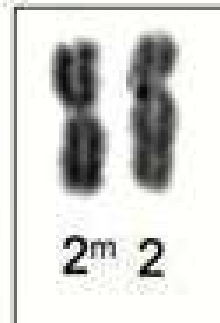
$\underset{a1/a2}{G}$ x $\underset{b1/b2}{G}$ x $\underset{c1/c2}{G}$ >2 loci

Gerke et al. 2010

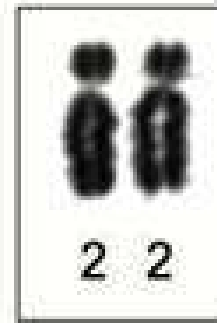
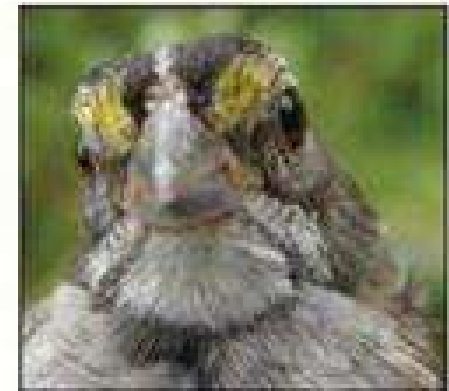
Super genes

White throated sparrow

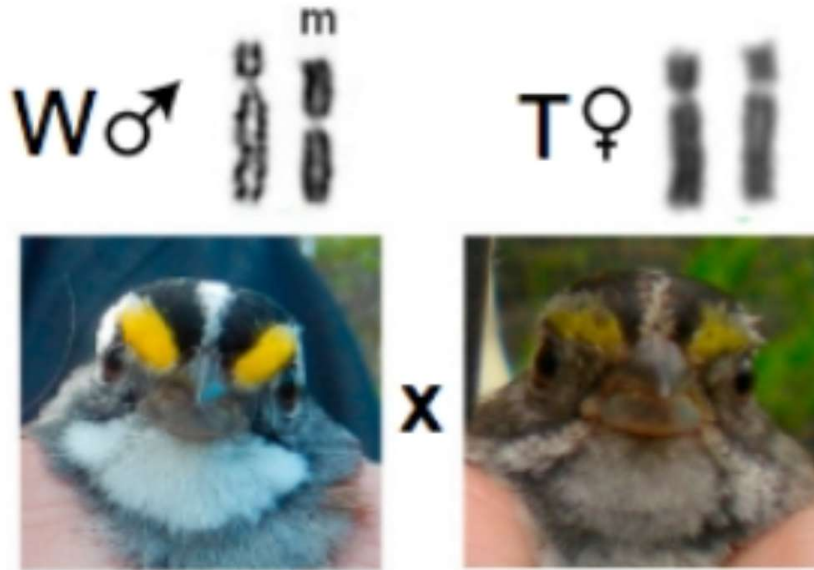
White morph



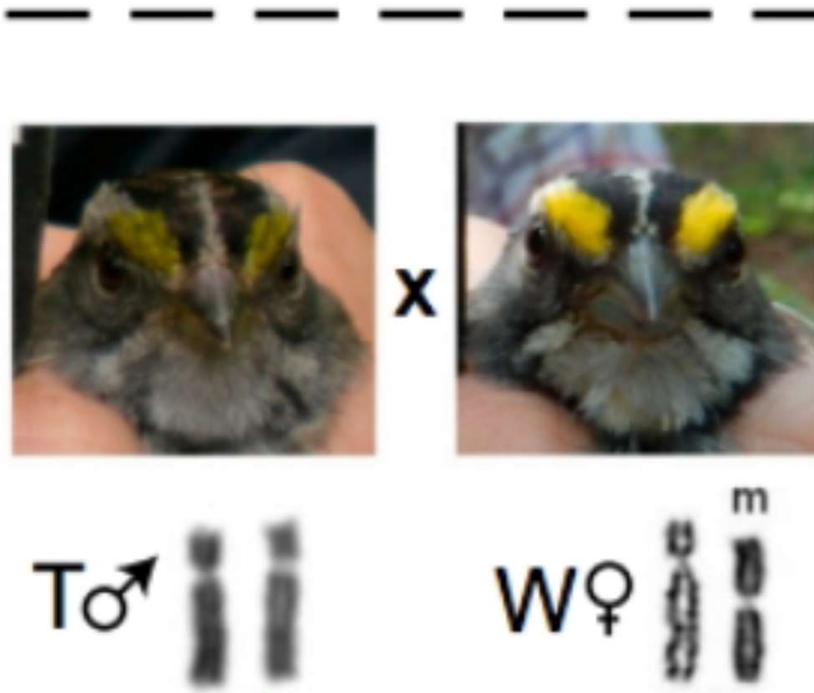
Tan morph



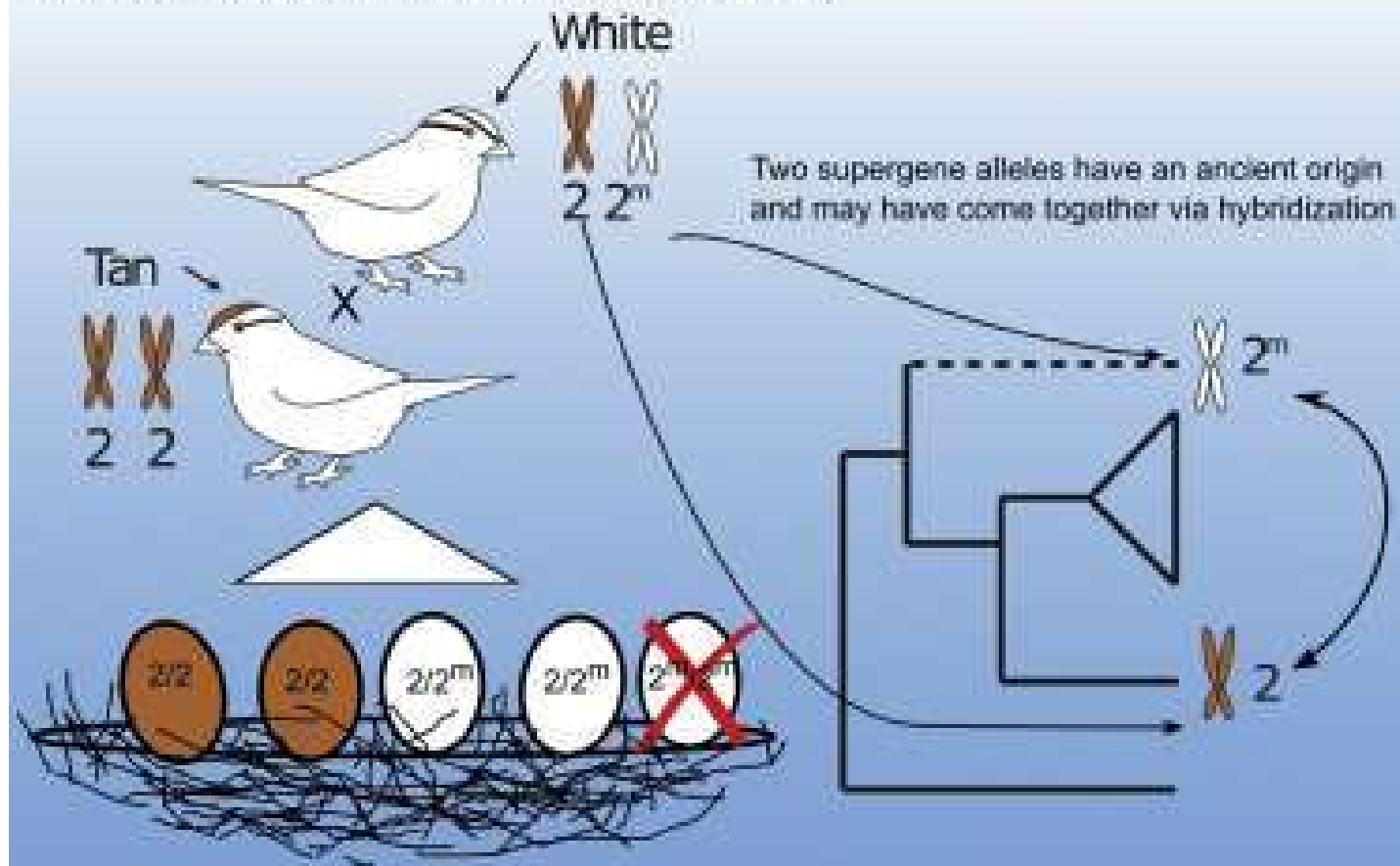
Disassortative mating



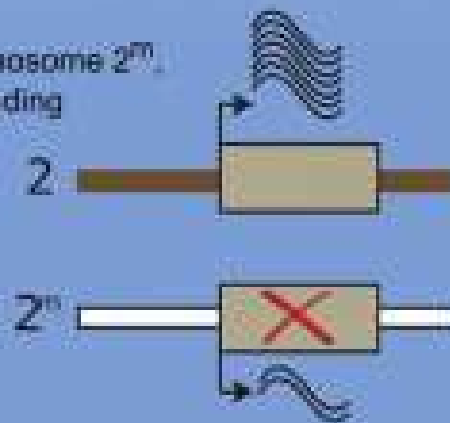
Never W male x W female
Never T male x T female



Two sparrow morphs are determined by a supergene
Alternative alleles are maintained by disassortative mating



Due to a lack of recombination on chromosome 2^m ,
that version of the chromosome is degrading



Rest of Genome

**White-throated
Sparrow***

--- Harris' Sparrow*

Golden-crowned
Sparrow*

--- White-crowned Sparrow

--- Rufous-collared Sparrow

--- Dark-eyed Junco

--- Song Sparrow

white: 2^m

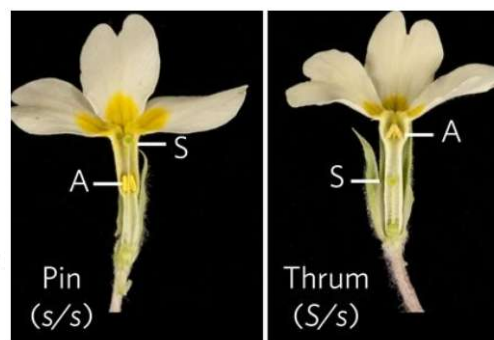
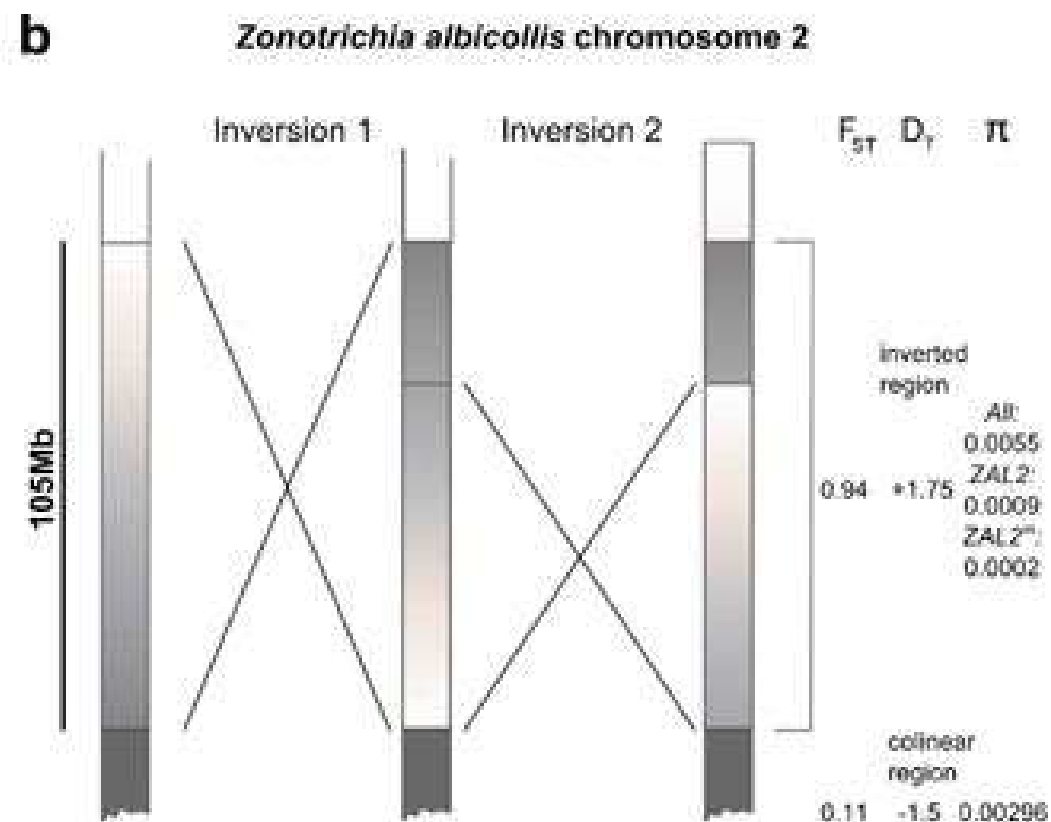
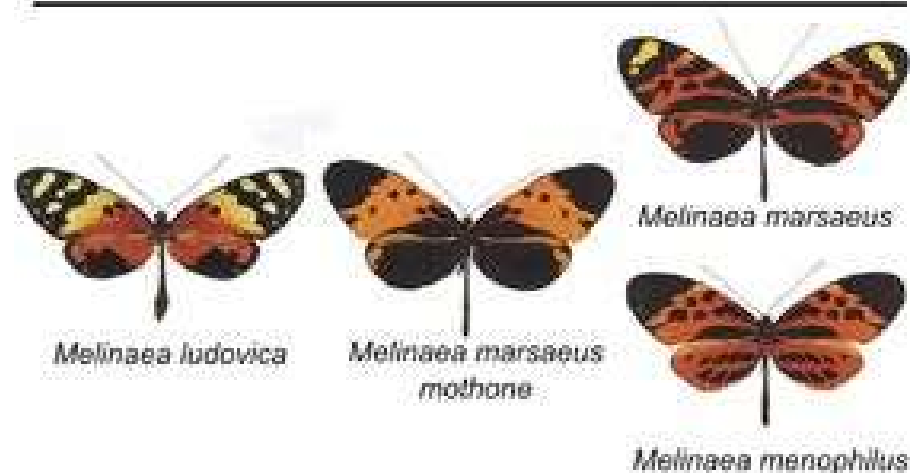
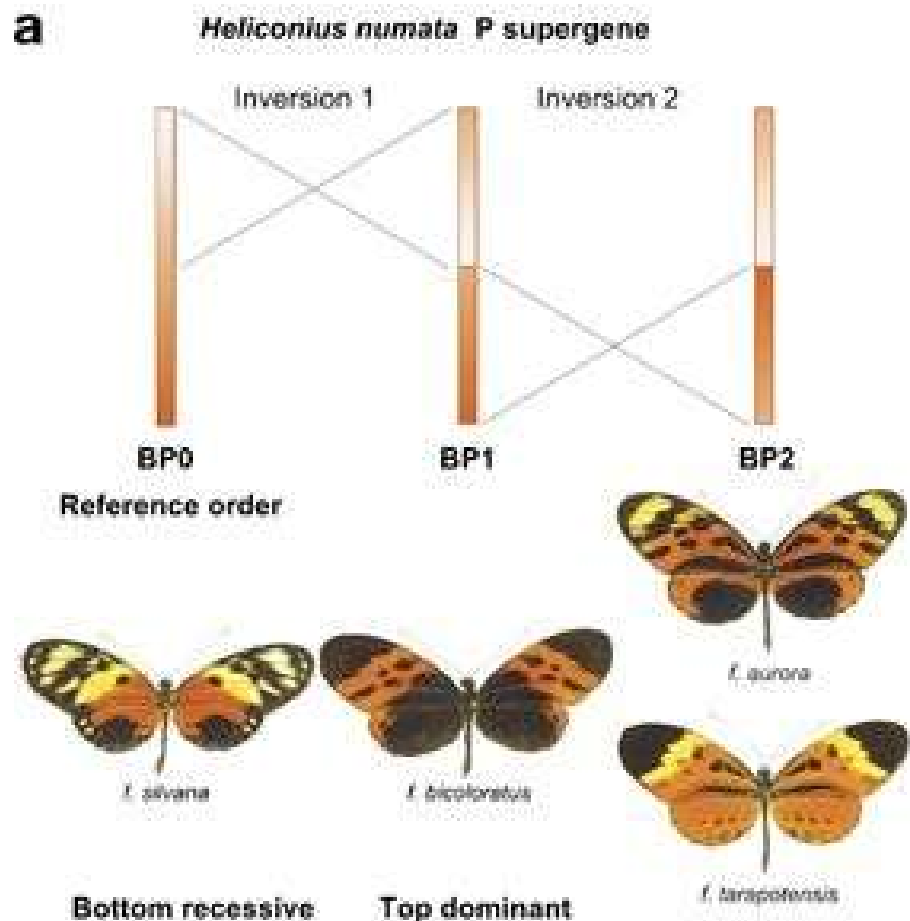
tan: 2

Inverted Region

0.03

0.03





Pleiotropy

= when a genetic change affects several phenotypes

Various meanings for Pleiotropy

Pleiotropy of a gene

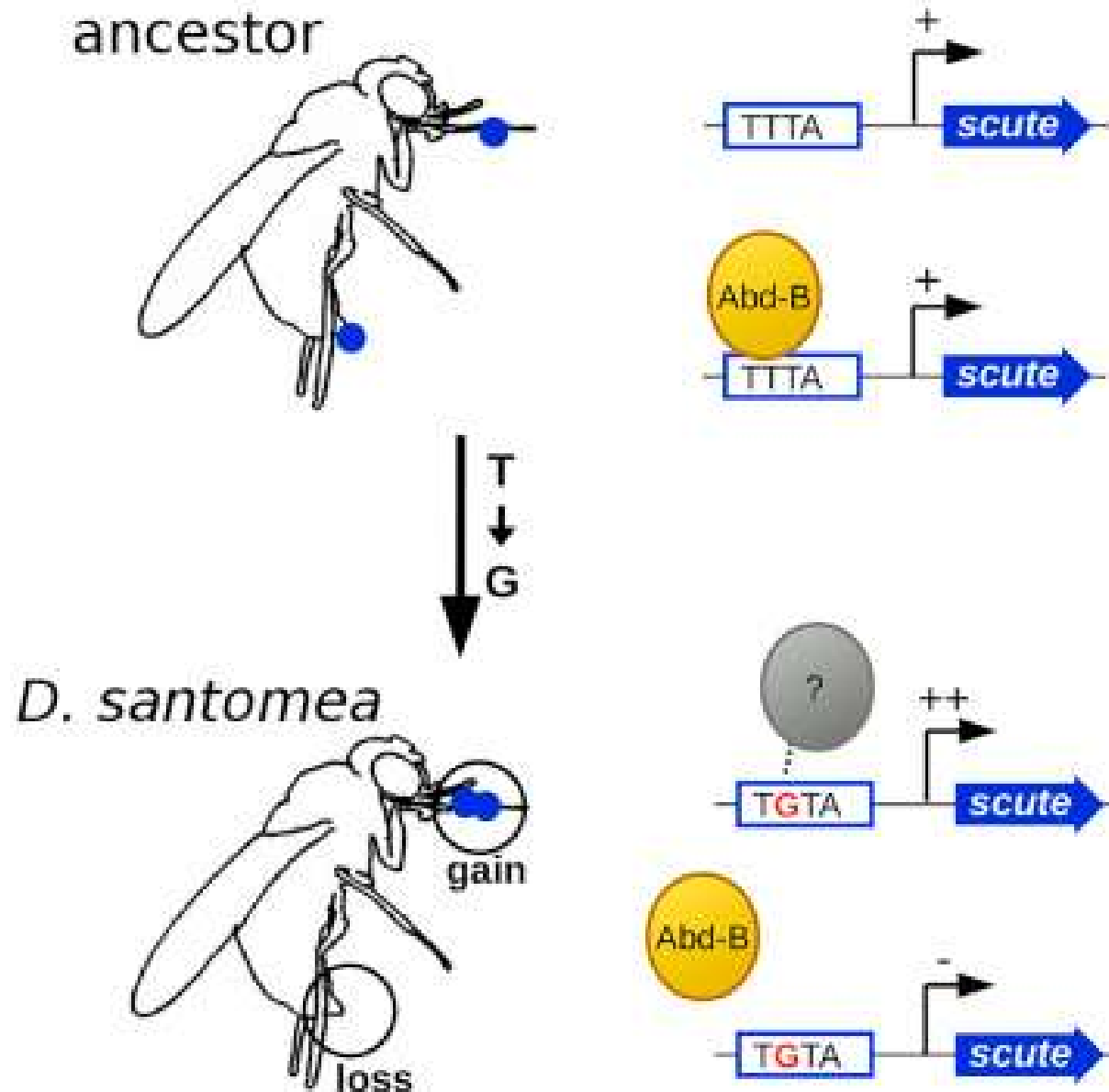
(means pleiotropy of the *null* mutation)

Pleiotropy of a cis-regulatory region

(means pleiotropy of the *deletion* of the region)

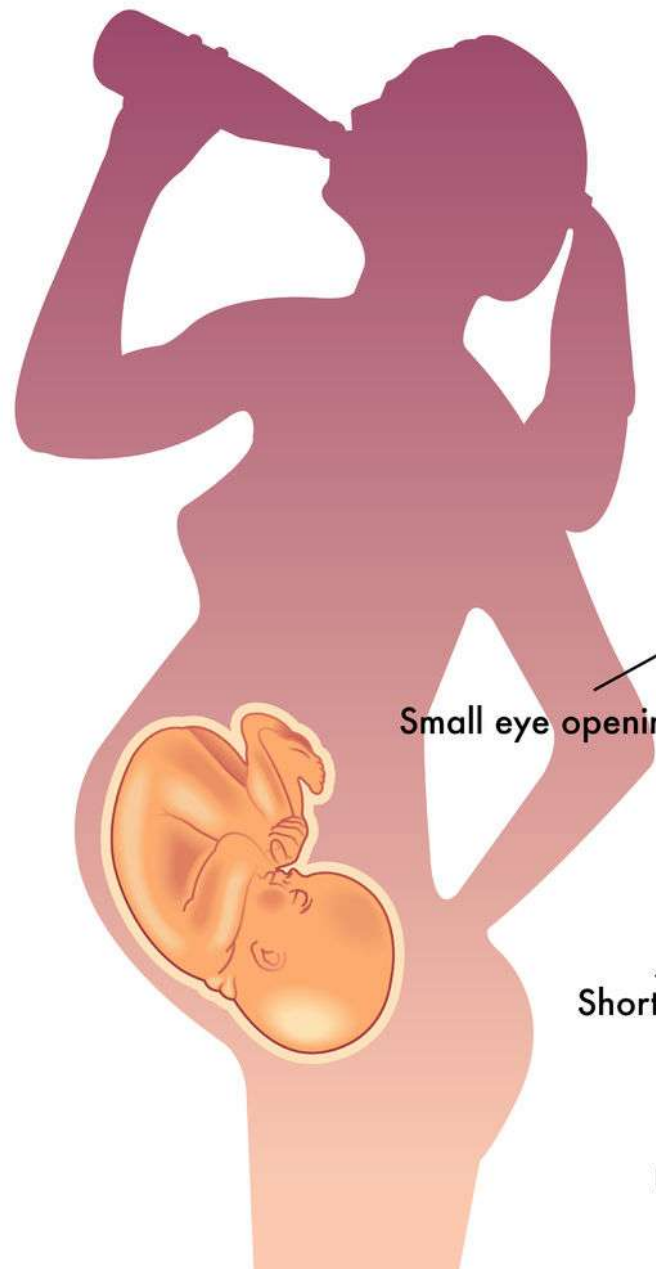
Pleiotropy of a mutation

A pleiotropic cis-regulatory mutation responsible for species difference



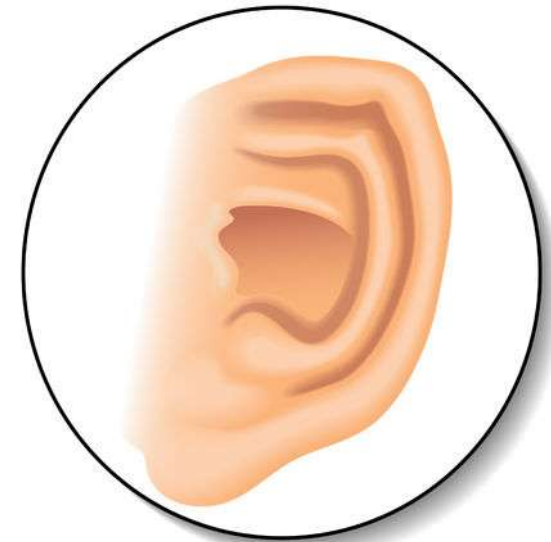
G x E

(FAS) Fetal Alcohol Syndrome



Small eye openings

Low nasal bridge



Top of the ear underdeveloped

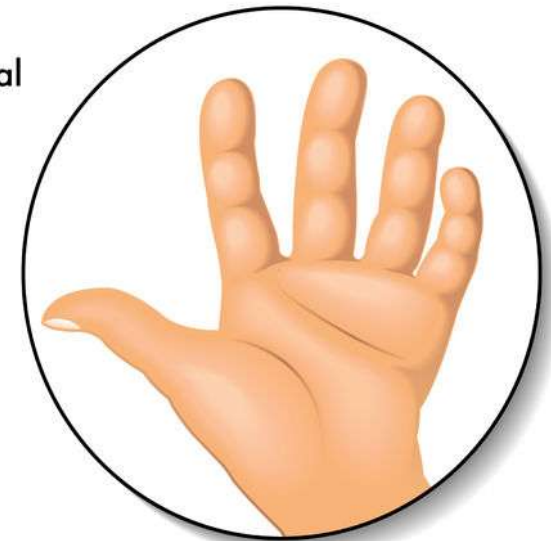
Epicanthal folds

Indistinct philtrum

Short nose

Thin upper lip

Underdeveloped jaw



Curved fifth finger (clinodactyly)

Causes of skin color differences

Genetic



Environment



$$\text{Phenotype} = G + E + G \times E$$

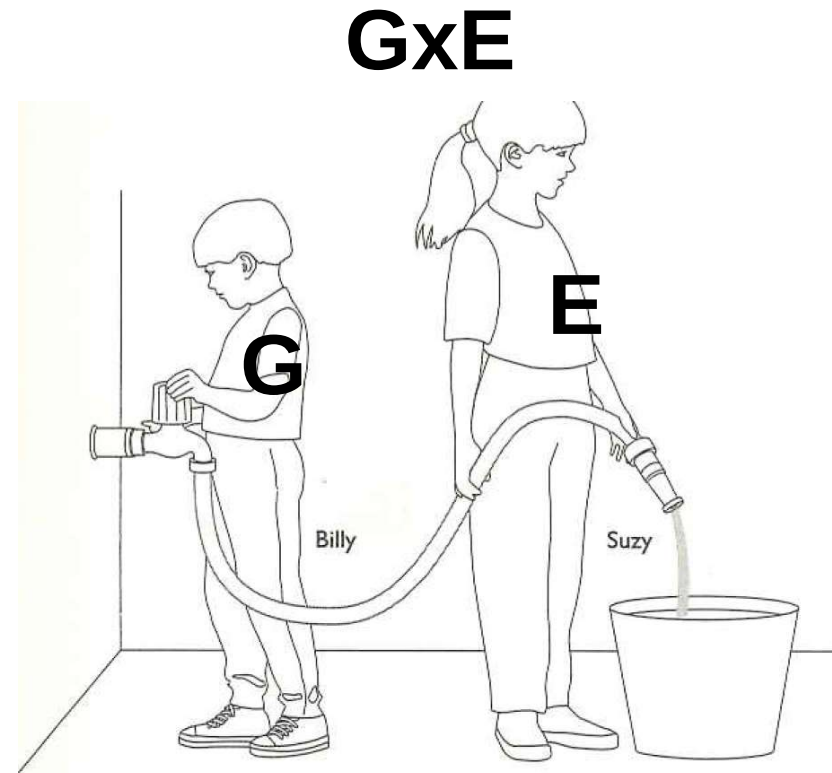
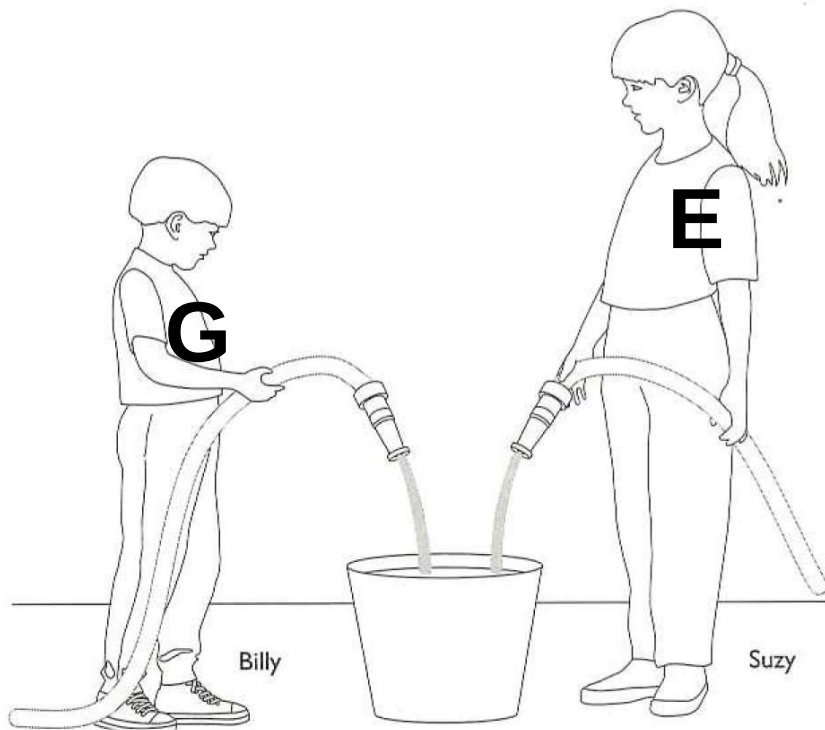
The Siamese cat

An example of GxE

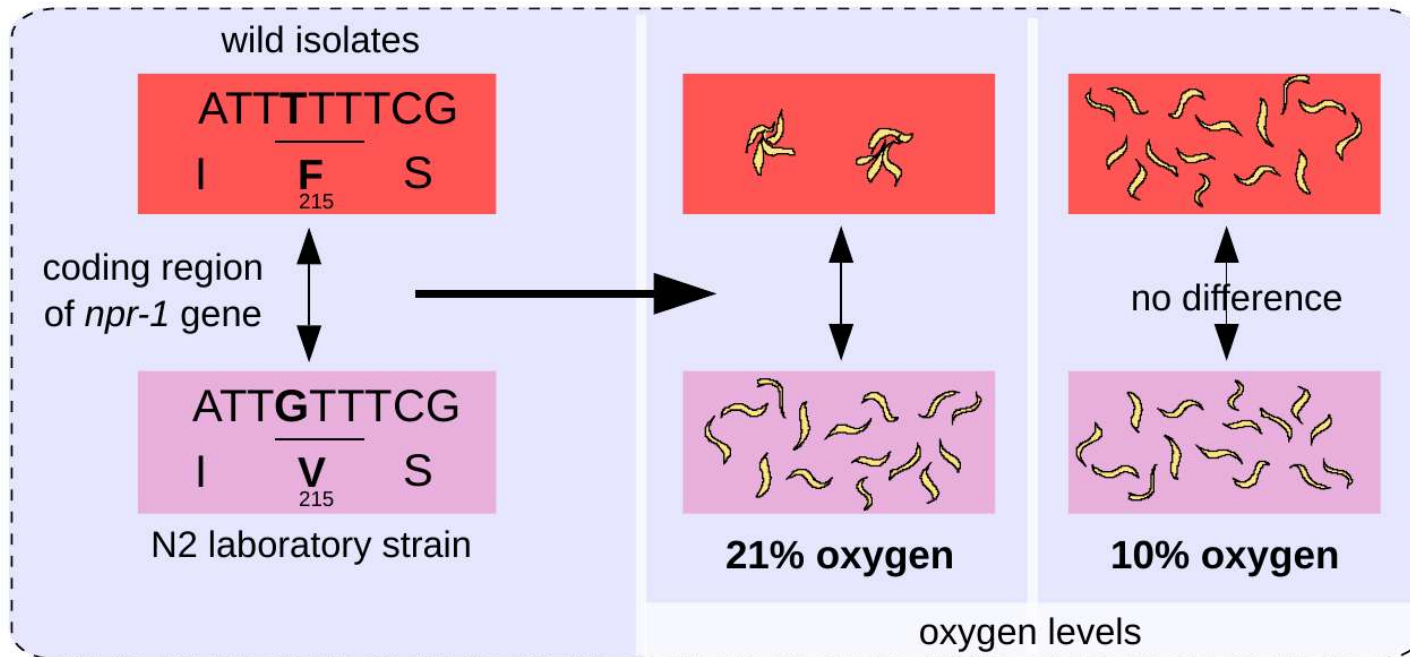


Mutation in *tyrosinase*
Heat-sensitive
enzyme
No production of
melanin in warm body
parts

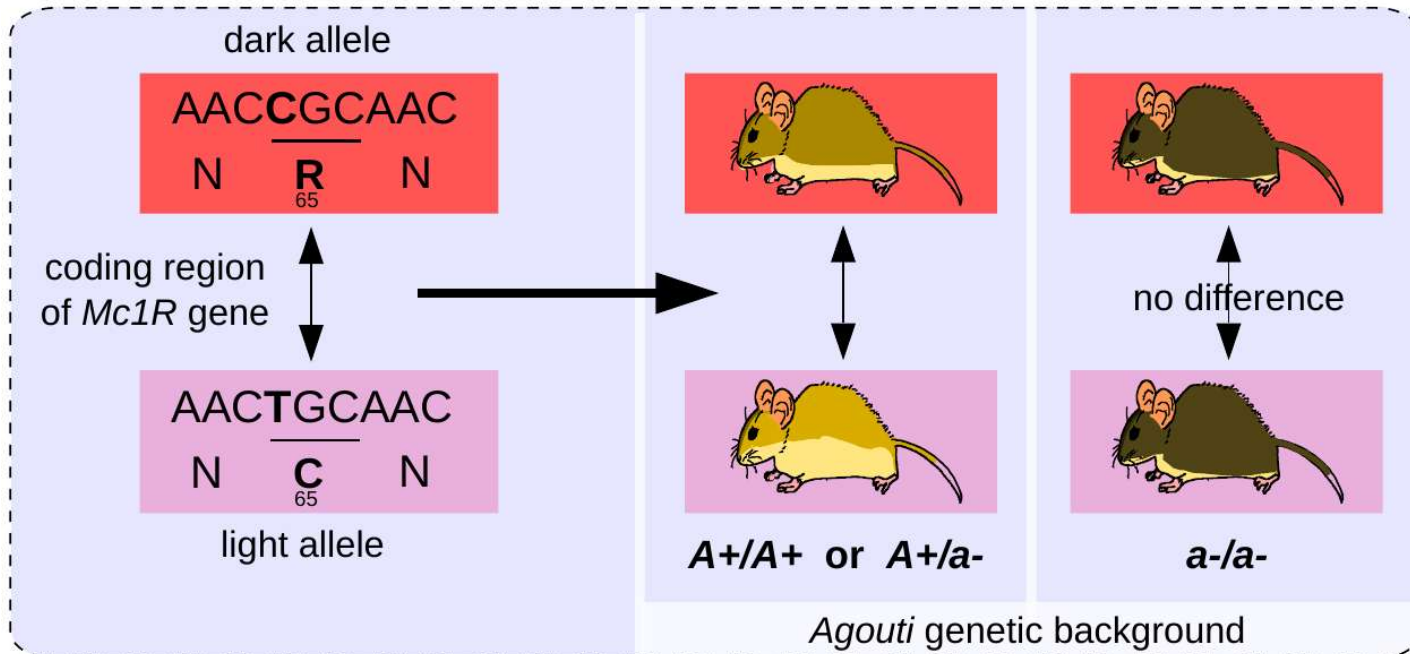
Contributions of the genotype (G) and the environment (E) to phenotypic variation



A GxE interaction

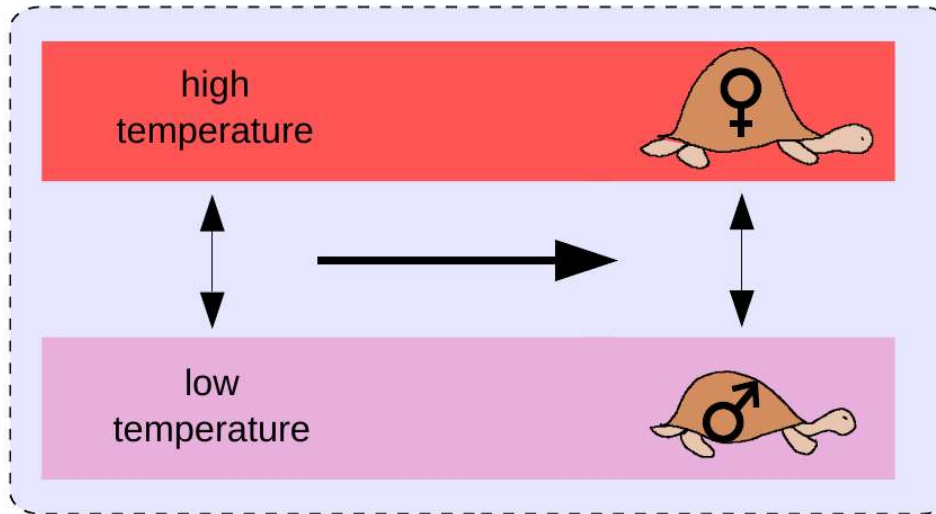


B GxG interaction

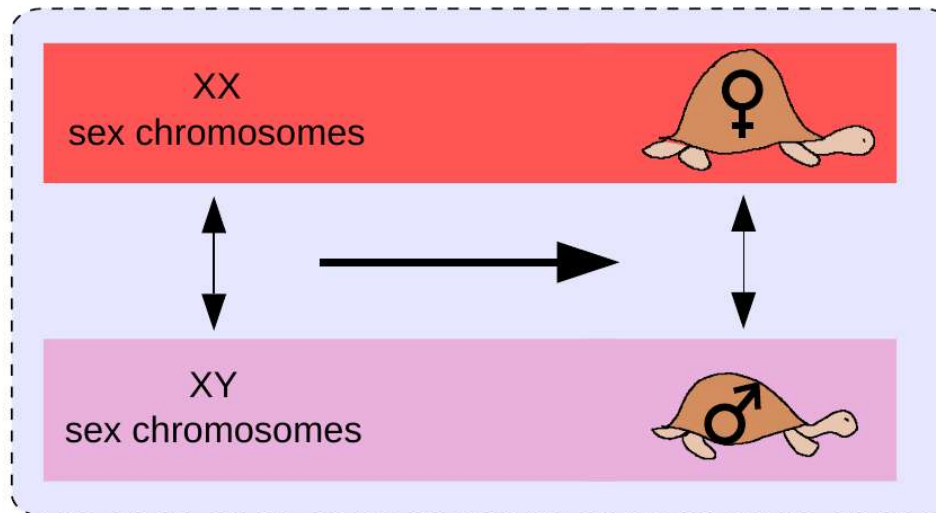


Comparing G and E effects

A enphe



B gephe

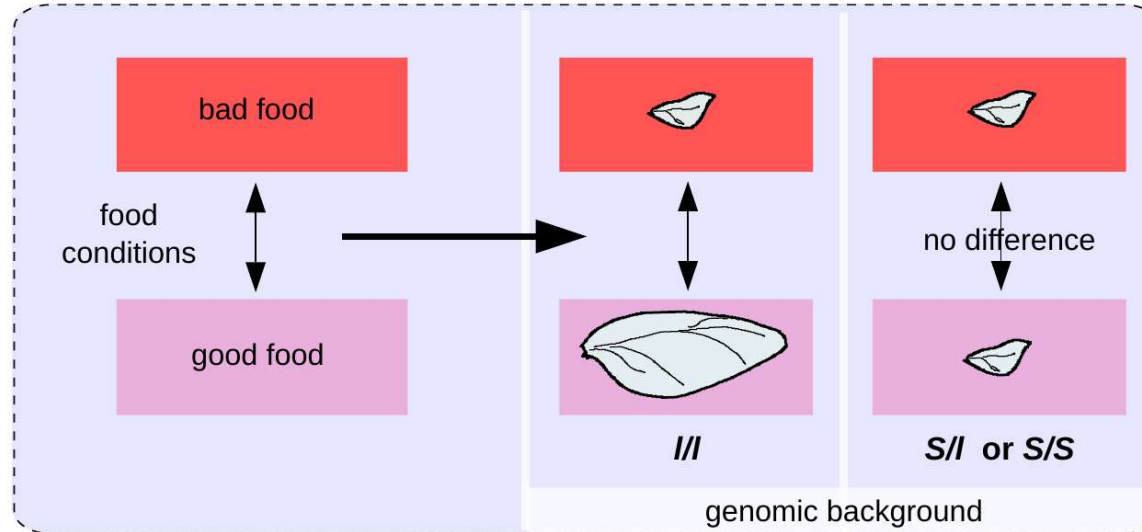


Intermingled G and E effects

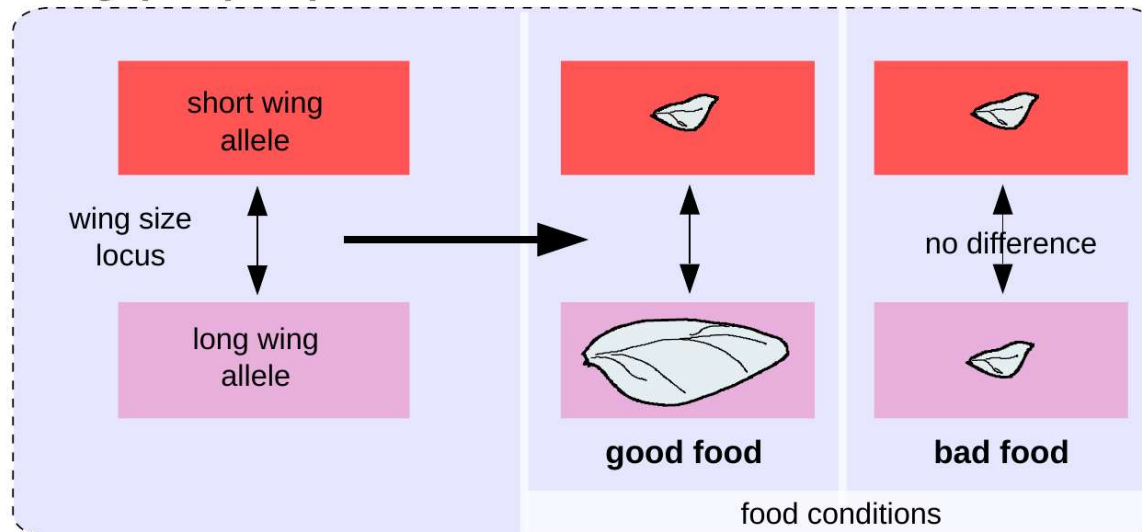
Calathus melanocephalus



A enphe perspective

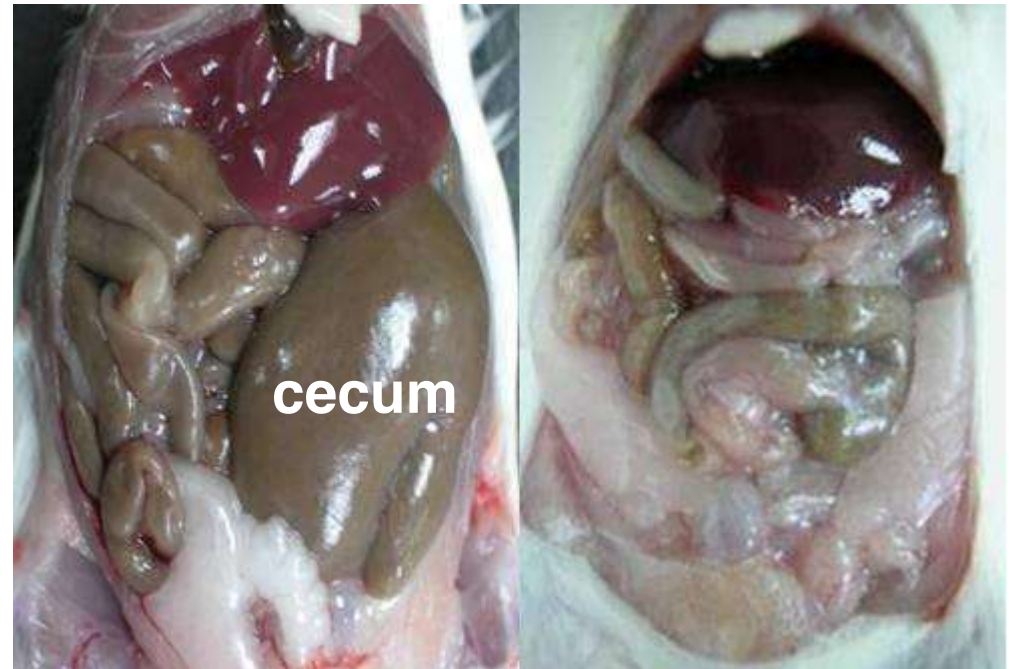
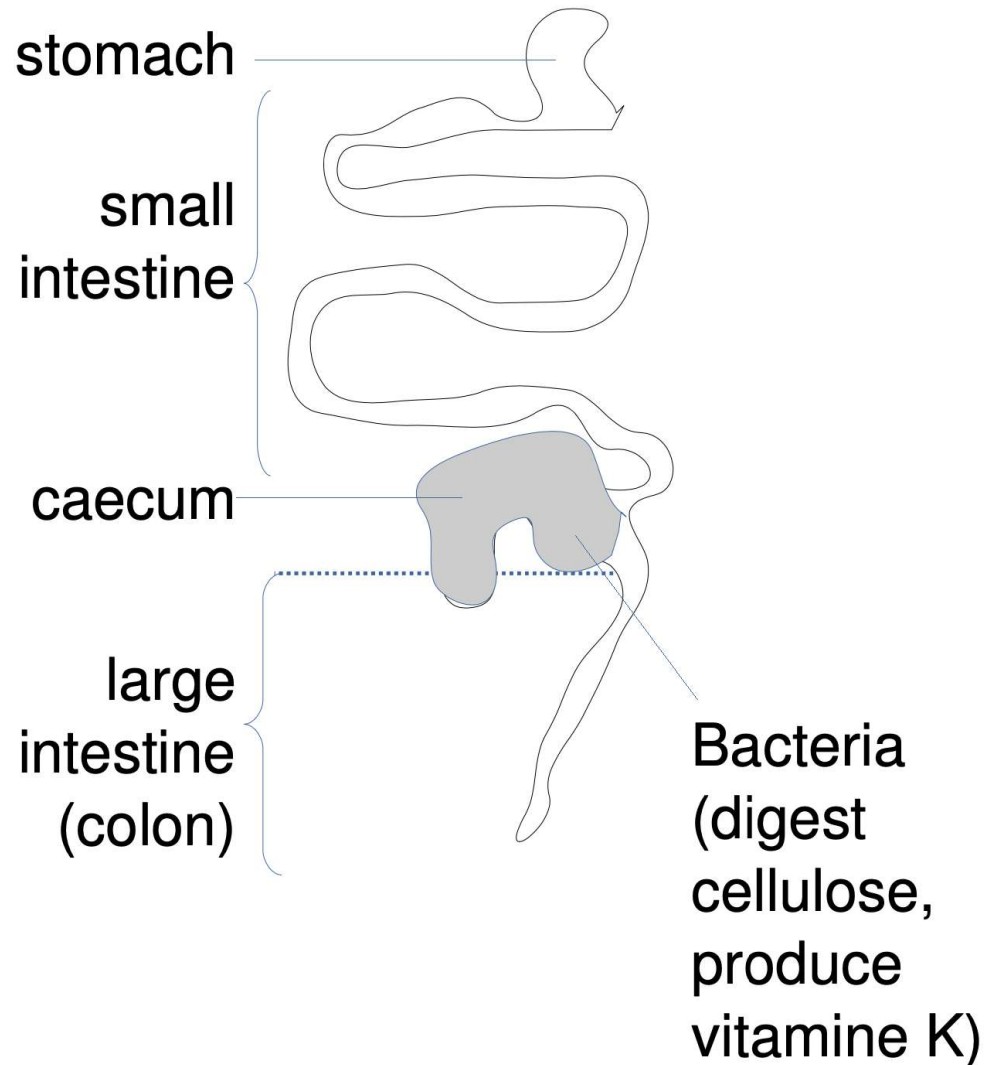


B gephe perspective



Mouse caecum development

An other example of GxE



germfree

normal

Causes of phenotypic differences?

Heritable

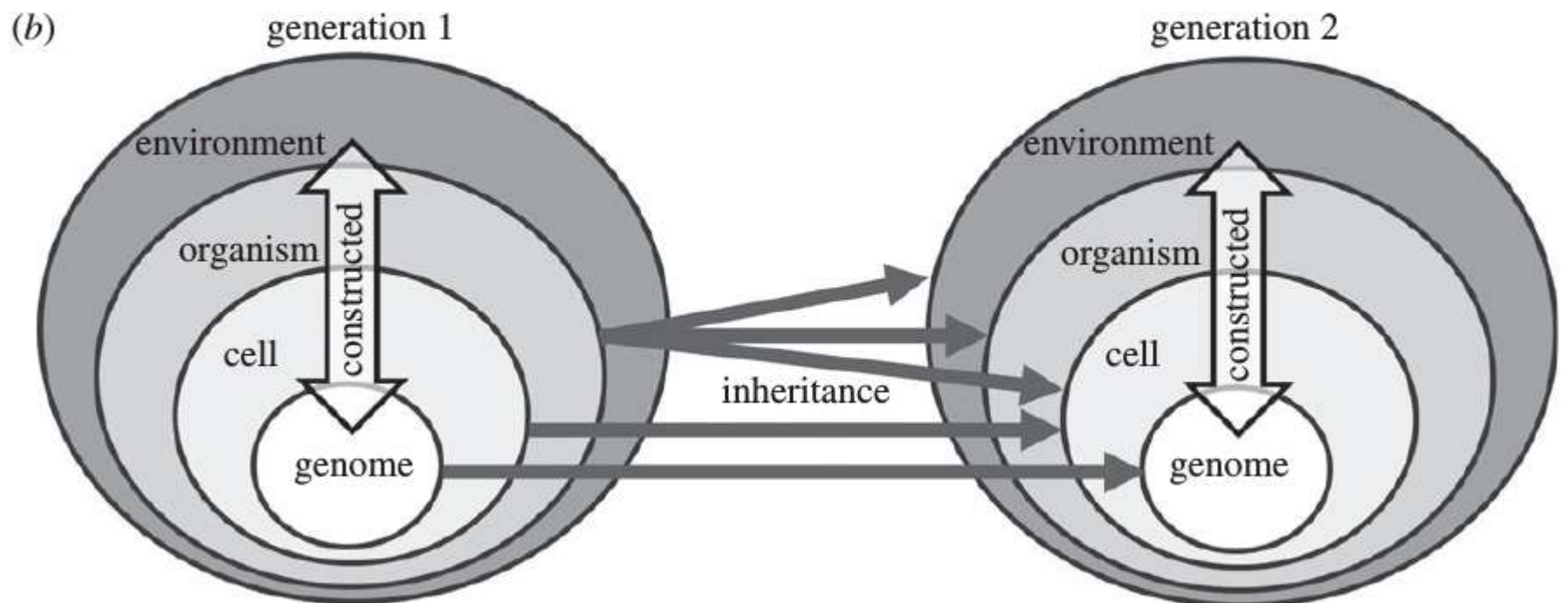
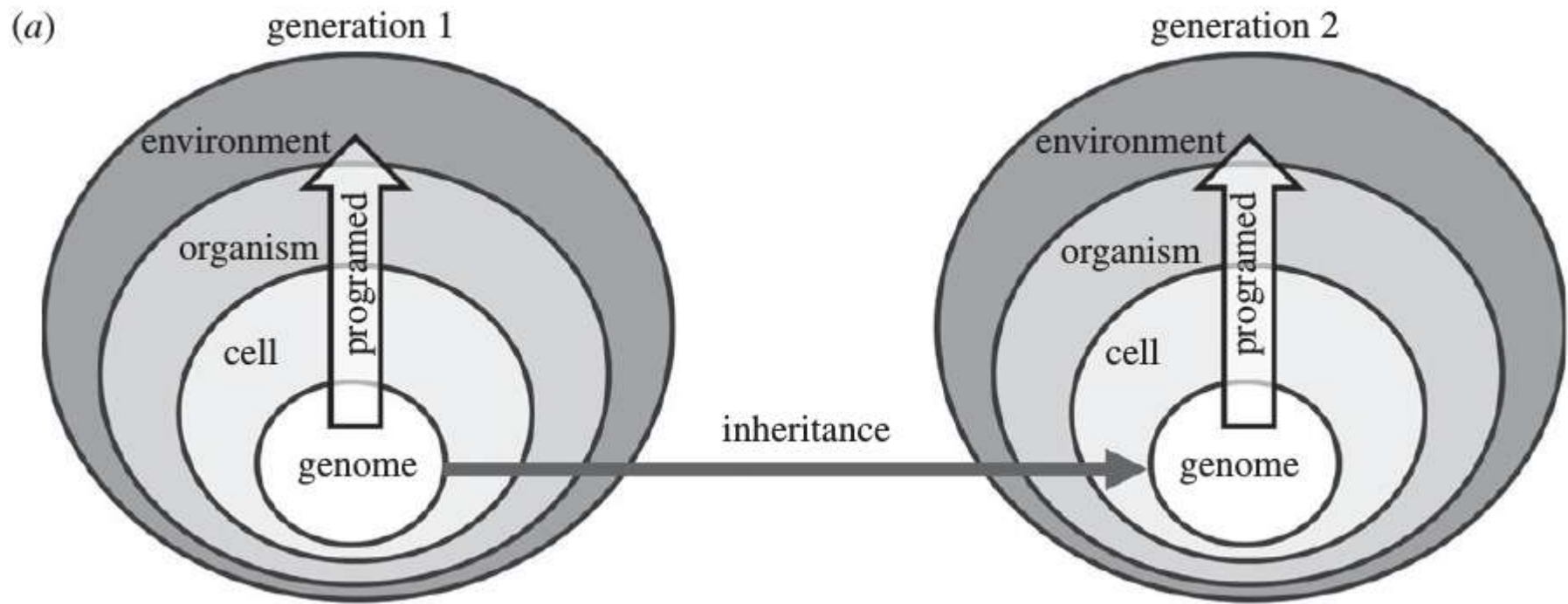


Non heritable



$$\text{Phenotype} = H + NH + H \times NH$$

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



Complexifications of the G-P map

Genetic Linkage

Epistasis

Supergene

Pleiotropy

GxE (introduction)