Introduction on genetics
and
the genotype-phenotype map

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The distinction between genotype and phenotype is the basis of genetics

“The view of natural inheritance as realized by an act of transmission, viz., the transmission of the parent's (or ancestor's) personal qualities to the progeny, is the most naive and oldest conception of heredity.”

“All "types" of organisms, distinguishable by direct inspection or only by finer methods of measuring or description, may be characterized as "**phenotypes**.”

“ A "**genotype**" is the sum of all the "genes" in a gamete or in a zygote.”

Johansen 1911

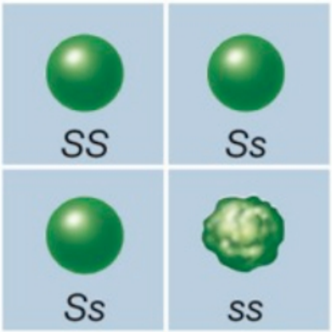
Phenotype = observable attributes of an individual

Genotype = inheritable genetic material
= DNA or RNA

How do genotypes map onto phenotypes ?

A very brief history of genetics

Transmission + *Phenotypic expression*



- **Mendel 1860s**
Controlled breeding, use of probabilities
Dominant/recessive/intermediate expression of traits
Random transmission of "factors"

- **Cytology from 1880-90s** Flemming, Boveri, Sutton
chromosomes as support of heredity, meiosis

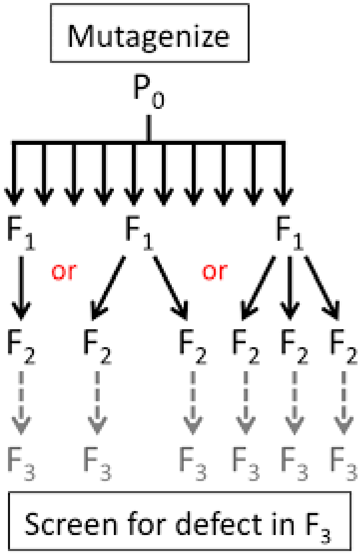
- **Classical genetics 1900-1950**
distinction genotype-phenotype
segregation of characters & genes
genetic map, sex chromosomes
penetrance - expressivity

"Rediscovery" of Mendel's law
Extension to animals

- **Foundation of molecular biology 1940-1970**

  in part using bacteria and phage genetics

  DNA as the material support of heredity



- Deciphering the role of the genes: 1970-

Cellular, developmental, behavioral genetics: Screens

"High-throughput" versions   2000-   (e.g. deletion libraries)

Reverse genetics

- Association mapping on natural populations: 2000-

Genetics of natural variation

- Evolutionary genetics 1900-

Biometricians versus Mendelians: continuous versus discrete hereditary variation

- Neo-darwinian synthesis 1930

mostly population genetics on allele frequencies, not phenotypes

- Human genetics

Now:
Bridging of "laboratory" and evolutionary genetics
Use of genomic data in model and "non-model" organisms

Divergences and syntheses

Mendelian genetics
"Mendelians"

Statistical genetics
"Biometricians"

1900

agriculture

"Néodarwininian
synthesis"

1930

<u>Laboratory</u>
genetics

Population genetics
<u>evolution</u>
genotype

Quantitative
genetics
phenotype

1950 Molecular
biology

Molecular genetics
cell biology,
development
physiology, etc.

1975

Molecular evolution

Molecular
markers

2000

Functional
genomics

<u>Evo</u>-
Devo

Evolutionary
genomics

Quantitative
genetics
molecular basis

Present syntheses

Basic principles of genetics

Genetic nomenclature

- Genetic nomenclature is different for each species

examples: *lacZ* in *Escherichia coli*
CDC28 in *Saccharomyces cerevisiae*,
cdc2 in *Schizosaccharomyces pombe*
cdk-1 in *Caenorhabditis elegans*
yellow (*y*) in *Drosophila melanogaster*
FUNNYNAME5 (*FNN5*) in *Arapidopsis thaliana*

Allele nomenclature...

- Wild-type allele "+*"* compared to mutation "*m"*

= for laboratory mutations
no reference wild-type allele in natural populations

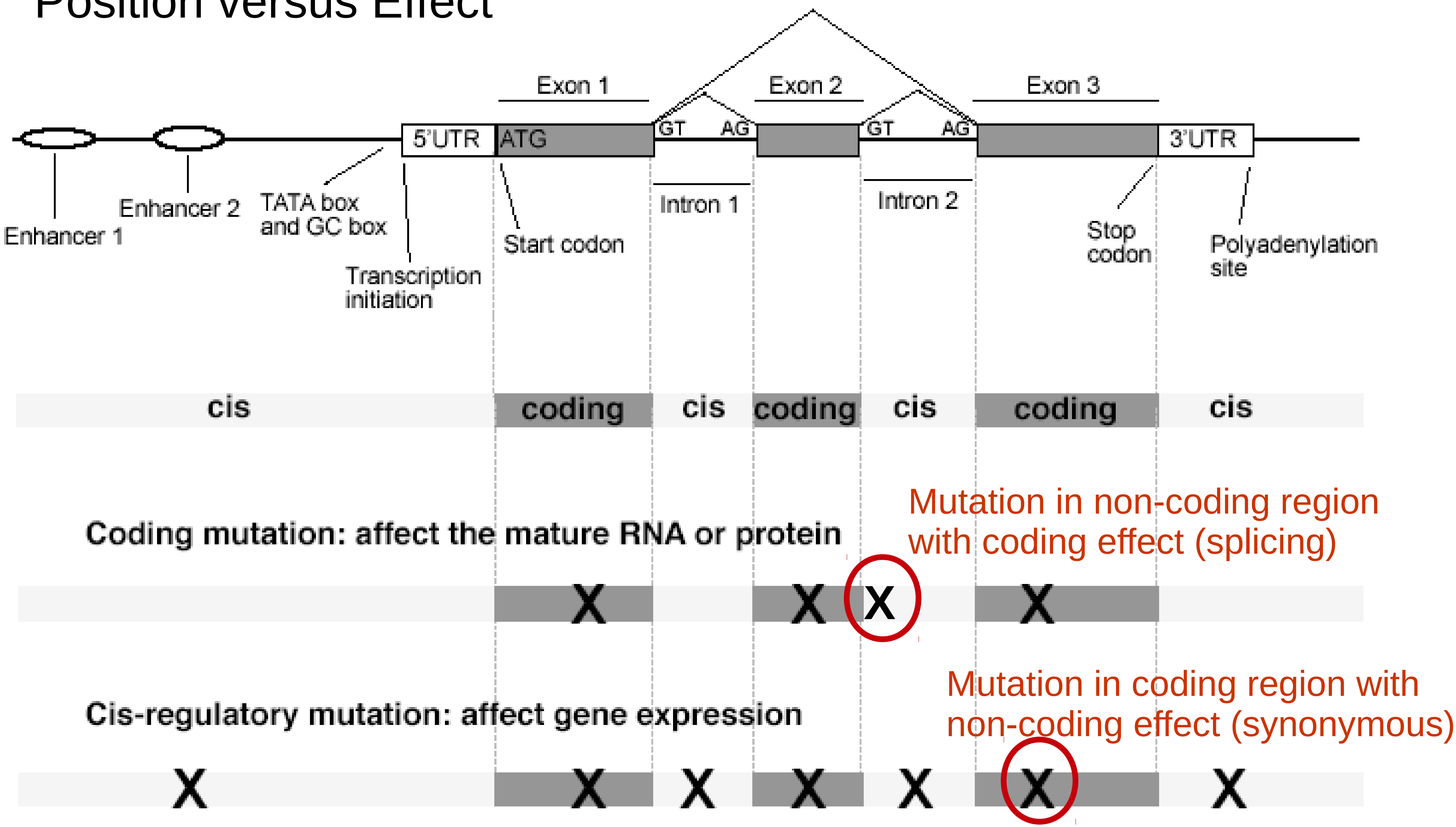
Aberration Types

SNP
Insertion
Deletion
Indel
Inversion
Translocation
Complex change
(Epigenetic change)

Estimation of mutation rates
Mutation accumulation lines, sequencing family trio, across a phylogeny

Coding versus cis-regulatory

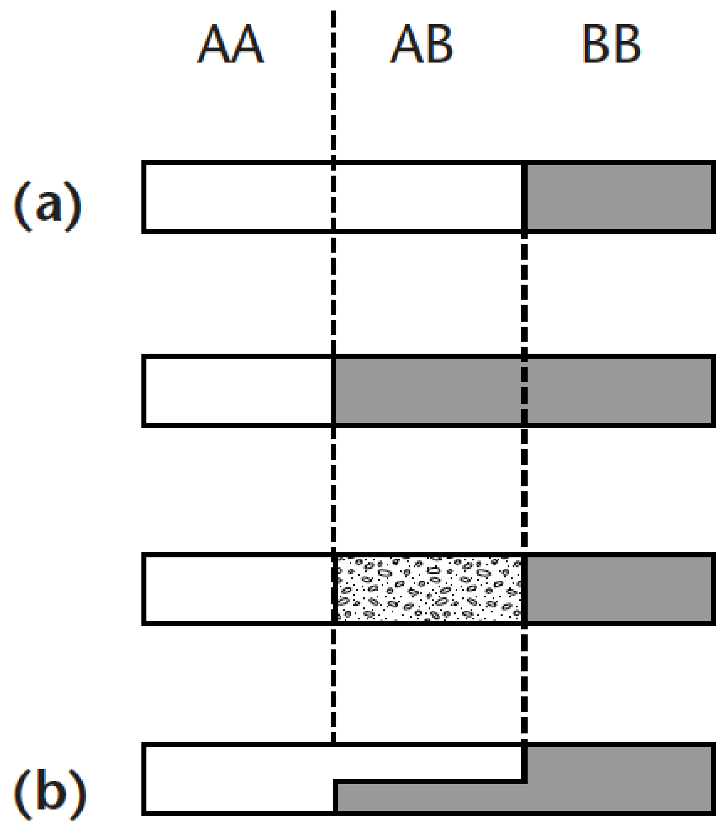
Position versus Effect



Coding versus cis-regulatory

Coding
Cis-regulatory
Gene loss
Gene amplification
(Gene rearrangement)

Levels of dominance



A is dominant to B

A is recessive to B

A and B are semidominant

Ex: pink flowers

A and B are codominant

Ex: AB blood groups, red and white flowers

Can be quantified as deviation from midpoint between parents

Levels of activity of the various alleles

- **Null**: no activity, equivalent to gene deletion
- **Hypomorph ou loss-of-function**: reduced activity
- **Silent**: no influence on the phenotype
- **Hypermorph or gain-of-function**: increased activity
- **Neomorph**: new activity, can be ectopic expression

Relationship with dominance

- Dominant (or semi-dominant) null allele:
  haplo-insufficiency – dose effect
- Dominant-negative via a poison effect
- Dominant gain-of-function/neomorph: common when gain-of-function,
  also with neomorph

Dominance is not an intrinsic to an allele

- It is <u>relative to another allele</u>, not to *all* other alleles

- It is a property of their effect <u>on a given phenotypic trait</u>

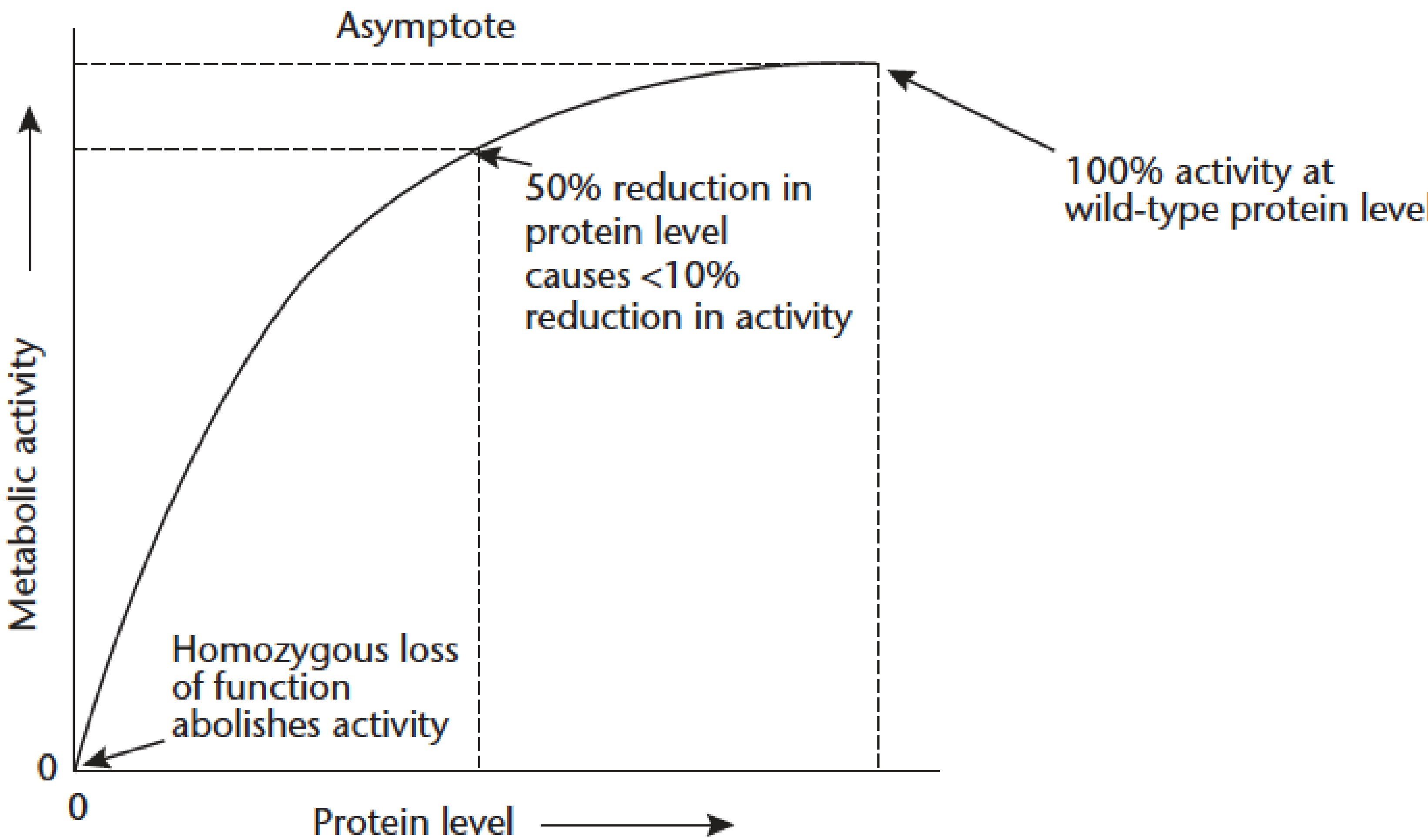
as in "dominance of *a1* over *a2* for a particular trait"

Example of the *agouti* locus in mouse

yellow allele is **dominant** over the + allele <u>for coat color</u>
yellow allele is **recessive** over the + allele <u>for lethality</u>

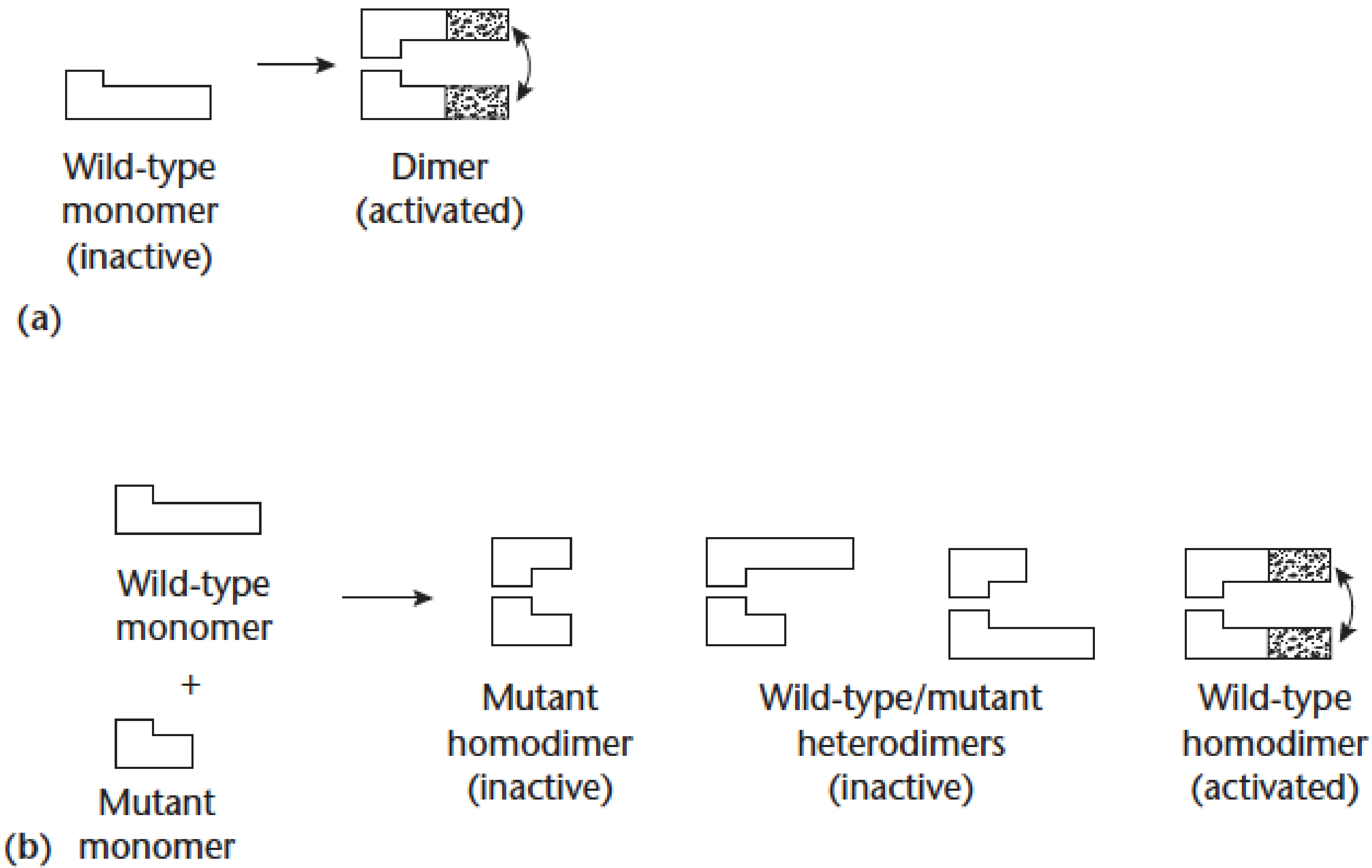
Why are most wild alleles dominant?

Robustness to half-dose:



Wilkie 2005

One type of dominant-negative mutation sequestration of wild-type in dimer



Wilkie 2005

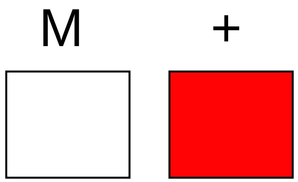
Mechanisms of dominance

Category of mutation	Mechanism	Affected gene/protein
Loss-of-function		
Haploinsufficiency	Metabolic rate determining step	LDL receptor
	Developmental regulator	Transcription factors
Dominant-negative		
Substrate sequestration	Binding by inactive monomer	Ligands, transcription factors
Dimer sequestration	Formation of inactive dimers	Receptors
Disruption of structure	Missense substitution	Collagens
Dominant-positive		
Increased gene dosage	Duplication	*PMP22*
	Amplification	Oncogene products
Altered mRNA expression	Increased gene expression	γ Hemoglobin
	Alternative splicing	*WT1*
	Toxic RNA inclusions	*DMPK*
Altered protein activity	Constitutive activity	Ion channels, receptors
	Increased binding affinity	Hemoglobin
	Formation of toxic proteins	Diverse
Novel protein activity	Altered substrate specificity	α1 Antitrypsin
	Chimeric protein (translocation)	Transcription factors

Wilkie 2005

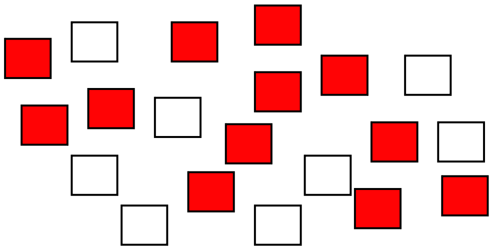
Penetrance

Discrete binary phenotype



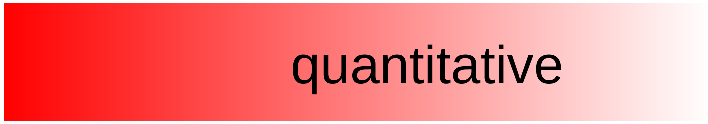
% of individuals showing the phenotype

ex: 40% of individuals have a white color
Partial penetrance

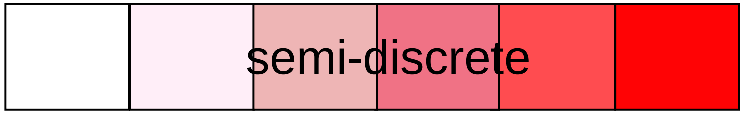


Expressivity

Phenotype with different degrees of severity



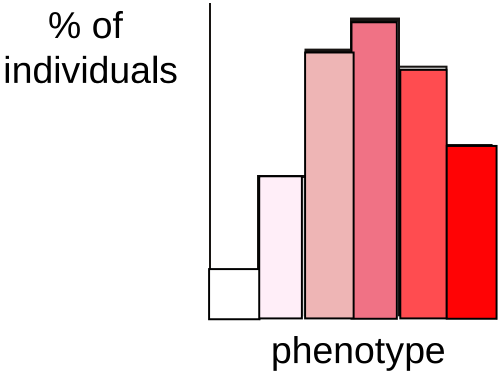
or



Degree of severity of the phenotype

ex: - number of affected ommatidia
- light pink color

often shown as a distribution of
phenotypic values of individuals:



Maternal (or paternal) effect

**The genotype of the parent matters,
not that of the individual itself.**

Frequent for mutations affecting early embryonic development

m/m ♀ x *+/+* ♂

phenotype ? phenotype ?

F1 $\boxed{m/+}$ x *+/+* or *m/m* or *m/+* ♂

phenotype **M**

F2 *m/+* or *m/m or +/+*

$\boxed{\text{phenotype } \mathbf{+}}$

+/+ ♀ x *m/m* ♂

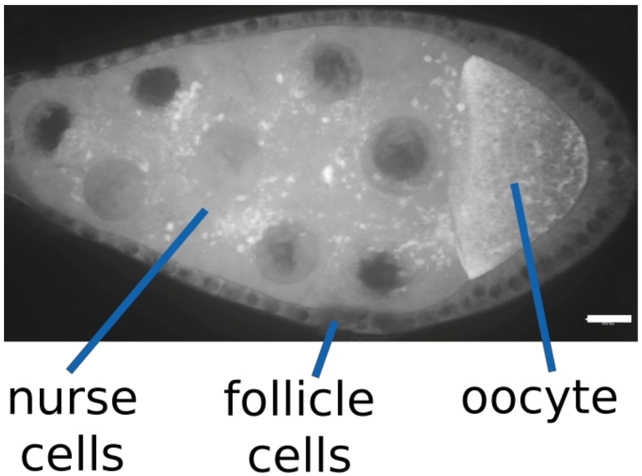
phenotype ? phenotype ?

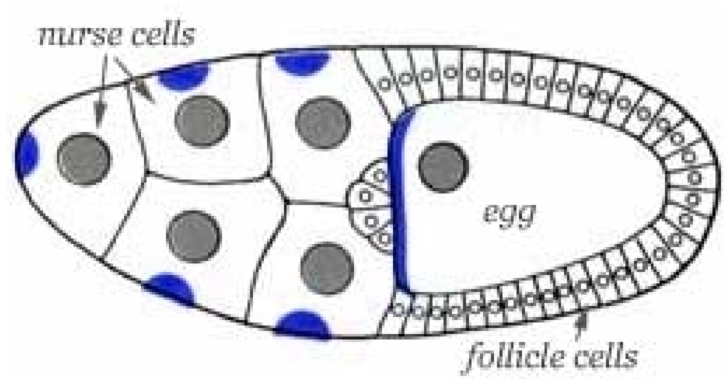
F1 *m/+*

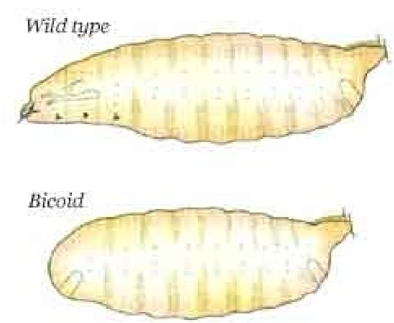
phenotype **+**

An example of maternal effect

deposition of mRNA or protein by maternal accessory cells into oocyte







Maternal (or paternal) effect of *m*

m/m ♀ x +/+ ♂

phenotype ? phenotype ?

F1 *m*/+ x ♂

phenotype **M**

F2 *m/m* or *m*/+ or +/+

phenotype **+**

Maternal (or paternal) rescue by the + allele

Less restrictive and more common than the maternal effect in the strict sense for phenotypes late in life

***m*/+** ♀ x *m*/+ ♂

<u>phenotype +</u> <u>phenotype +</u>

F1 *m/m* *m*/+ +/+

phenotype **+**

In contrast to maternal effect:

m/+ ♀ x *m*/+ ♂

phenotype ? phenotype ?

F1 *m*/+

phenotype **+**

Heredity with sex-linked transmission

Example: mutation on the X chromosome
in a species reproducing with XX ♀ x XY ♂

m/m ♀ x *+/Y* ♂

phenotype M phenotype +

↓

F1 *m/+* ♀ + *m/Y* ♂

females of phenotype + males of phenotype M

Heredity with sex-linked expression

Example: mutation that affects the phenotype only in females

Alleles

***m1* and *m2* are allelic if they are in the same gene**

in practice
- if the two mutations do not complement (at the phenotype level)
- or defined using sequence variations

Complementation test

if *m1/m1* and *m2/m2* show the phenotype M
and act recessively

m1/m1 x *m2/m2*

↓

F1

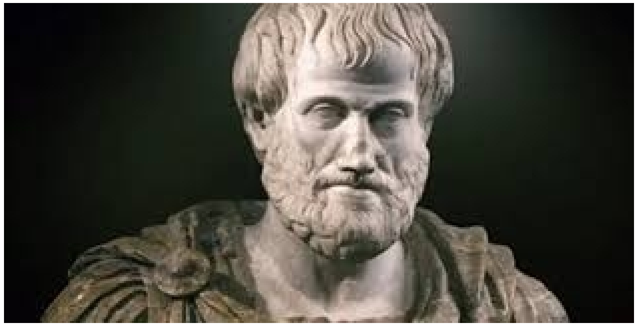
		Interpretation	
• if Phenotype M	**non-complementation**	*m1/m2*	same gene (alleles)
• if Phenotype +	**complementation**	*m1/+; +/m2*	two genes (non allelic)

The genotype-phenotype map

Different kinds of phenotypes

Morphology

Color
Size and shape
Presence/absence
Position



Aristote, Historia animalium, book I, 2, 300BC

Physiology

Behavior

Genotype & Phenotype

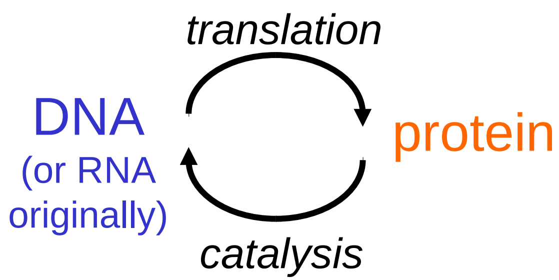
= what engenders = what is apparent

DNA/RNA

- **Regulation of gene expression**
- **Biochemical reactions**
- **Subcellular architecture**
- **Assembly of cells**
- **Organism morphology and behavior**

etc.

distinction appeared at the origin of life:



Francis Crick Central Dogma
A reductionist view of the GP relationship

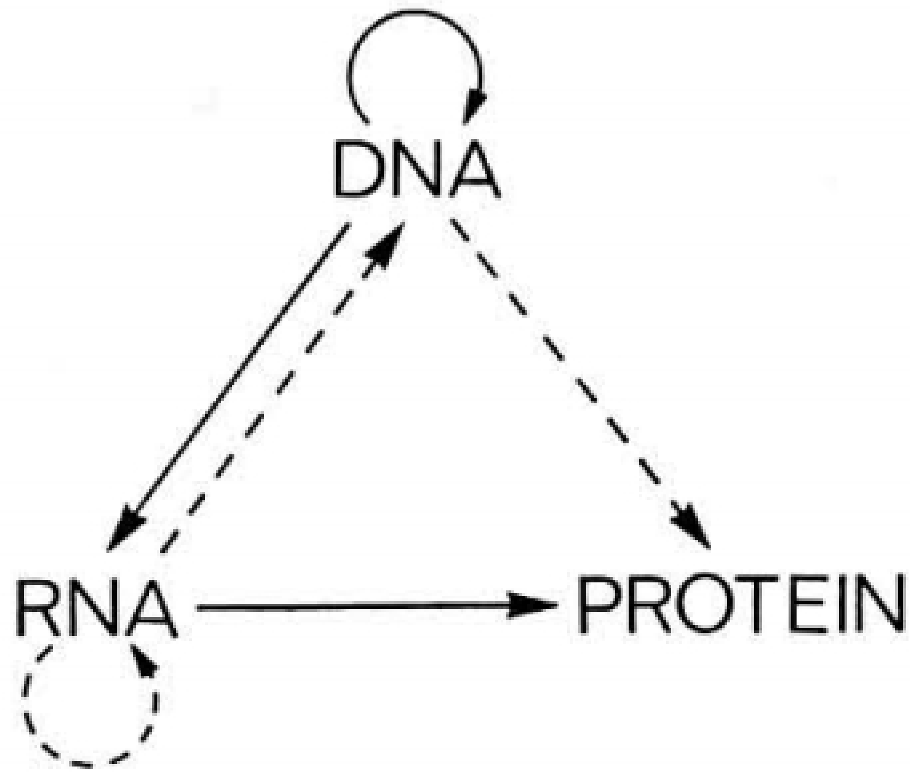
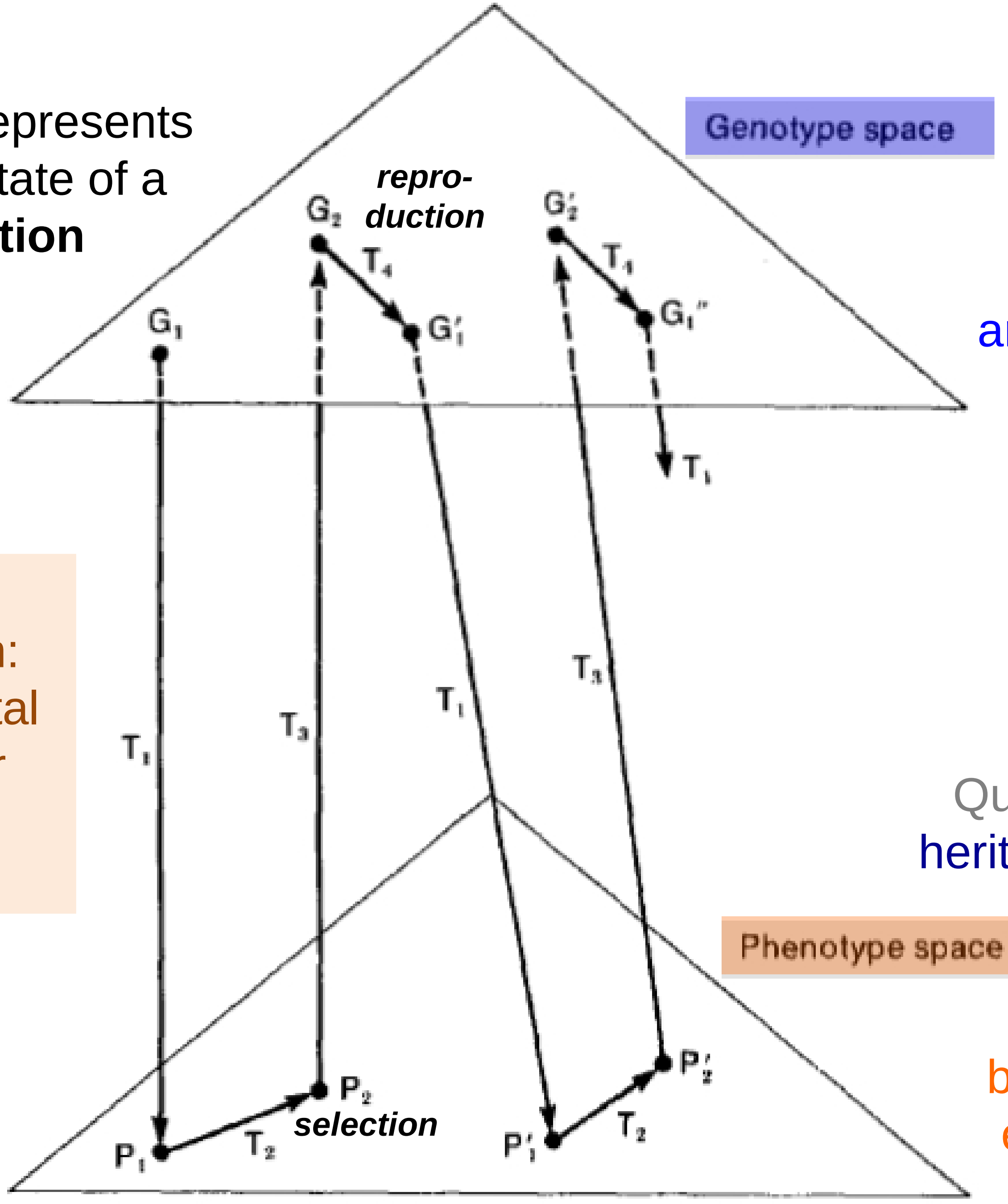


Fig. 3. A tentative classification for the present day. Solid arrows show general transfers; dotted arrows show special transfers. Again, the absent arrows are the undetected transfers specified by the central dogma.

Crick 1958
Crick 1970

The first genotype-phenotype map

Here a dot represents the mean state of a **population**



Population genetics: stochastic processes and selection coefficient

Phenotype construction: developmental and cellular biology physiology

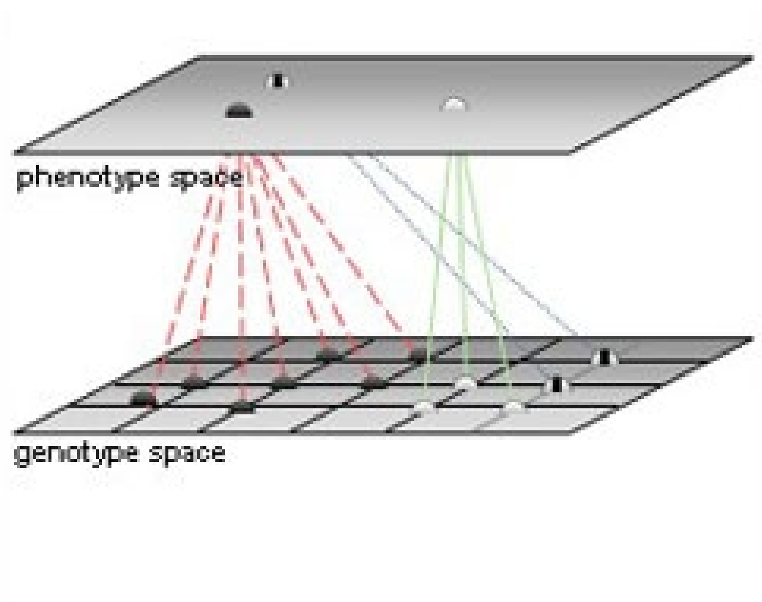
Quantitative genetics: heritability of phenotypes

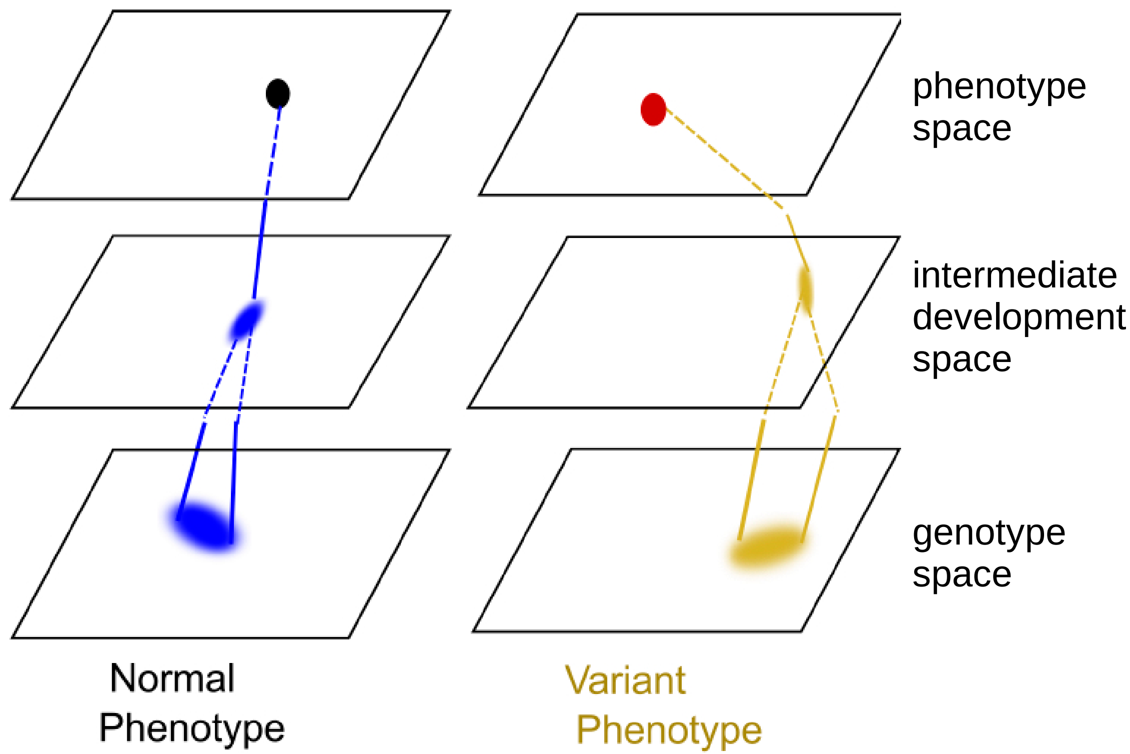
Evolutionary biology of phenotypes, evolutionary ecology

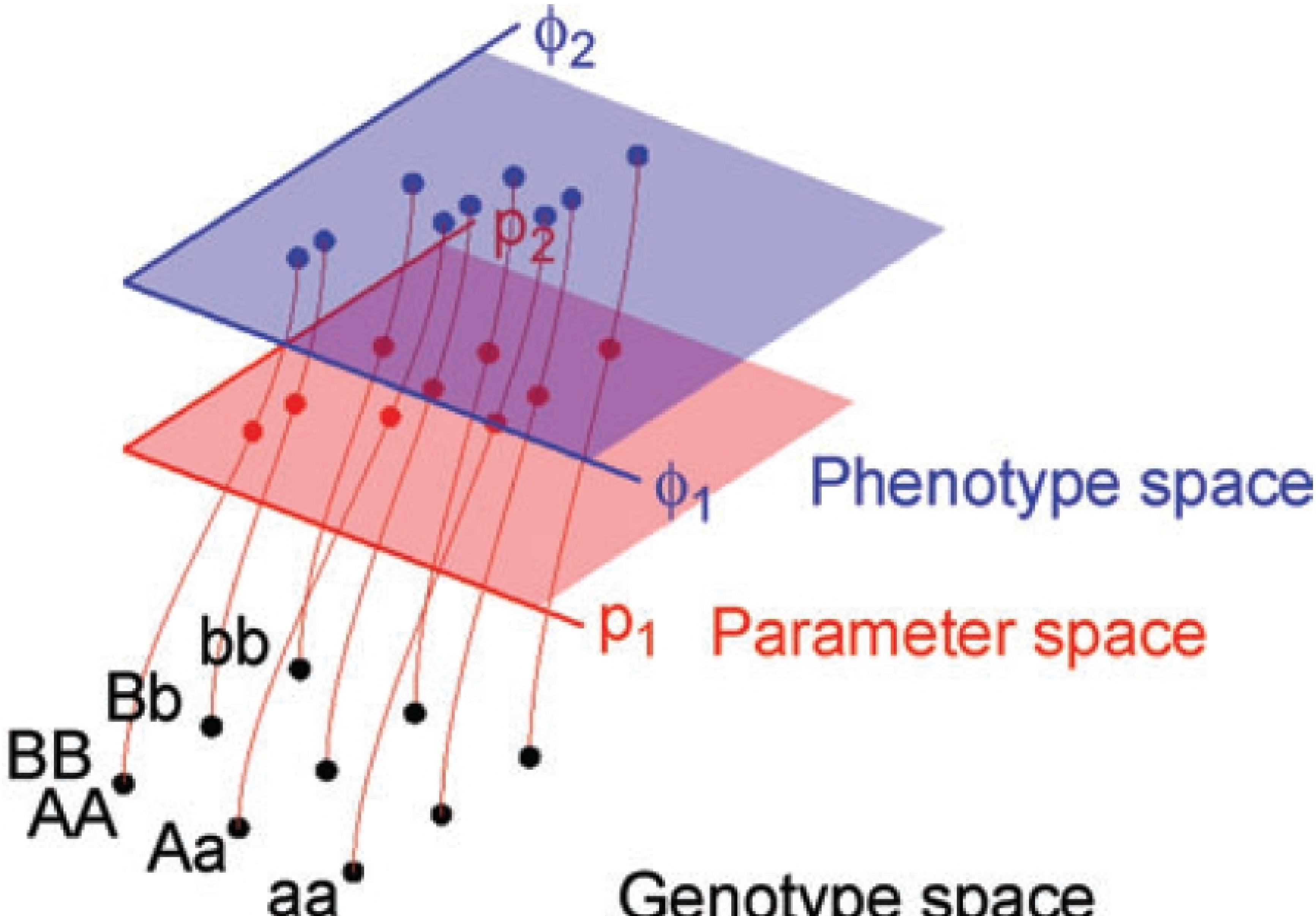
Lewontin 1974

Intermediate steps in the genotype-phenotype map

Here a dot represents one **individual**



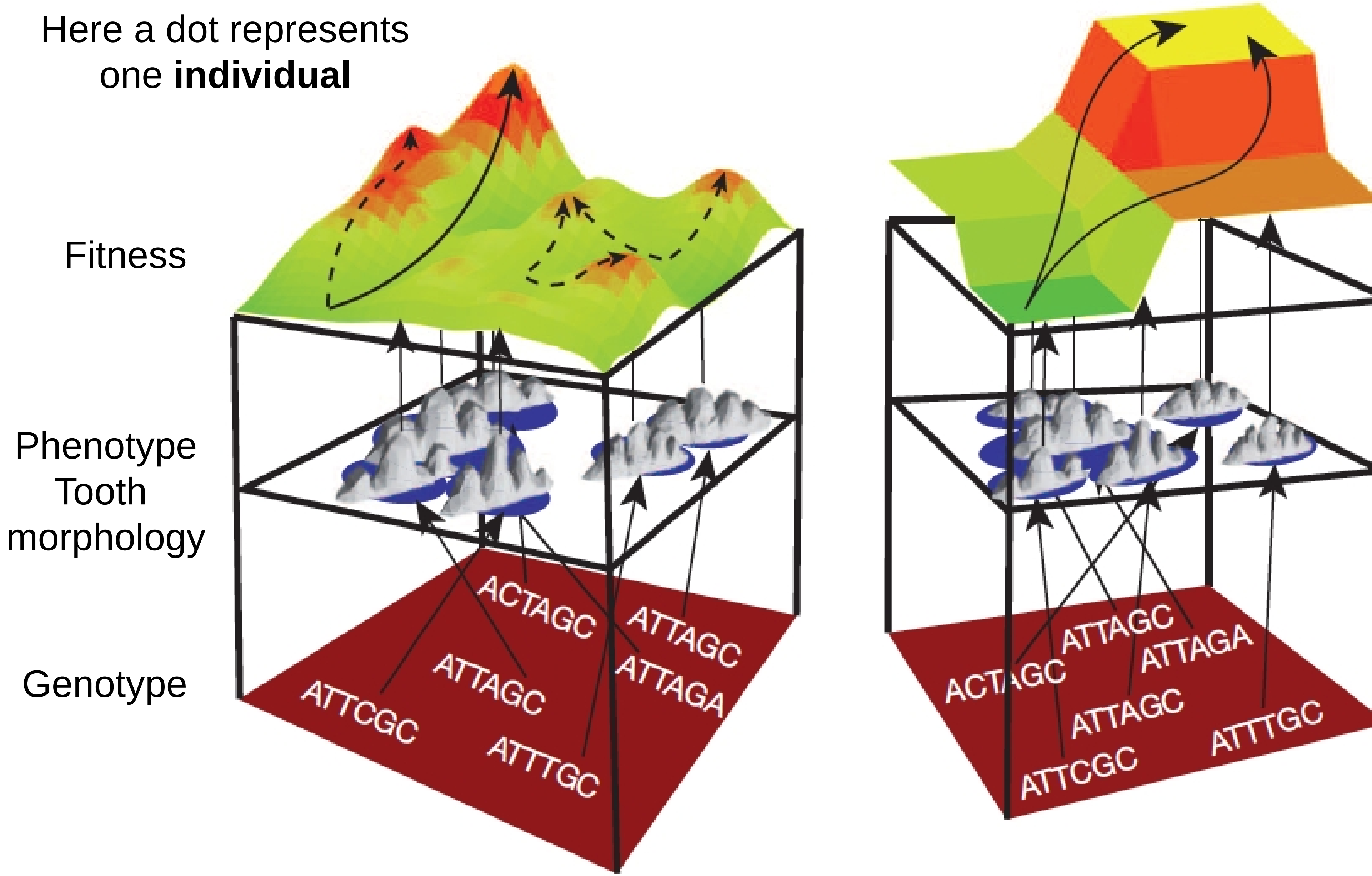




Gjuvsland et al. 2013

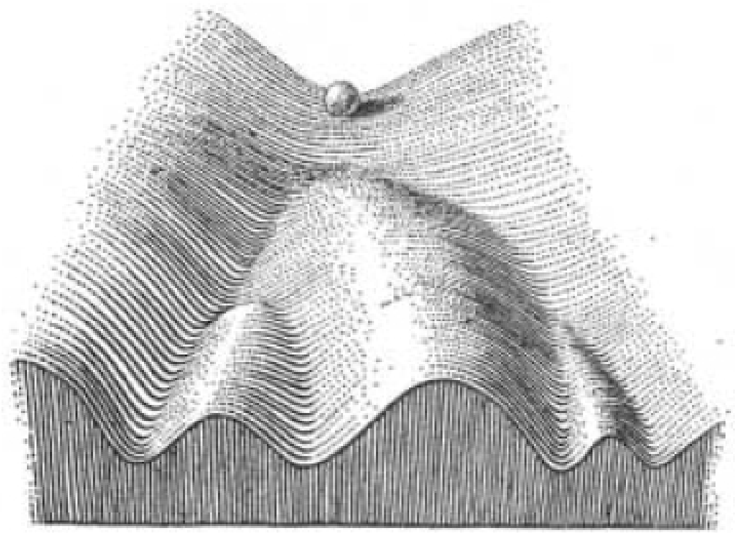
The genotype-phenotype-fitness map

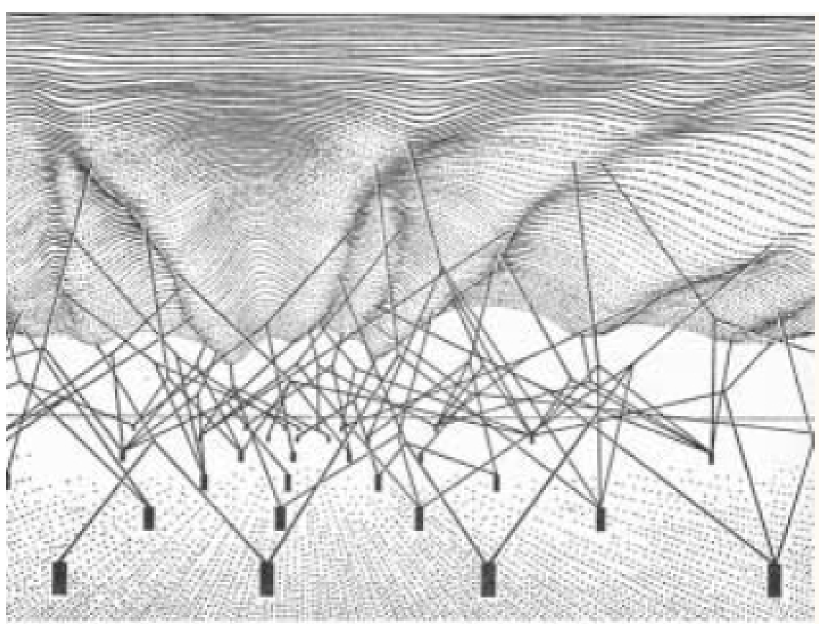
Here a dot represents
one **individual**



Salazar-Cuidad & Martin-Riera 2013

The Epigenetic Landscape
A metaphor for the G-P relationship



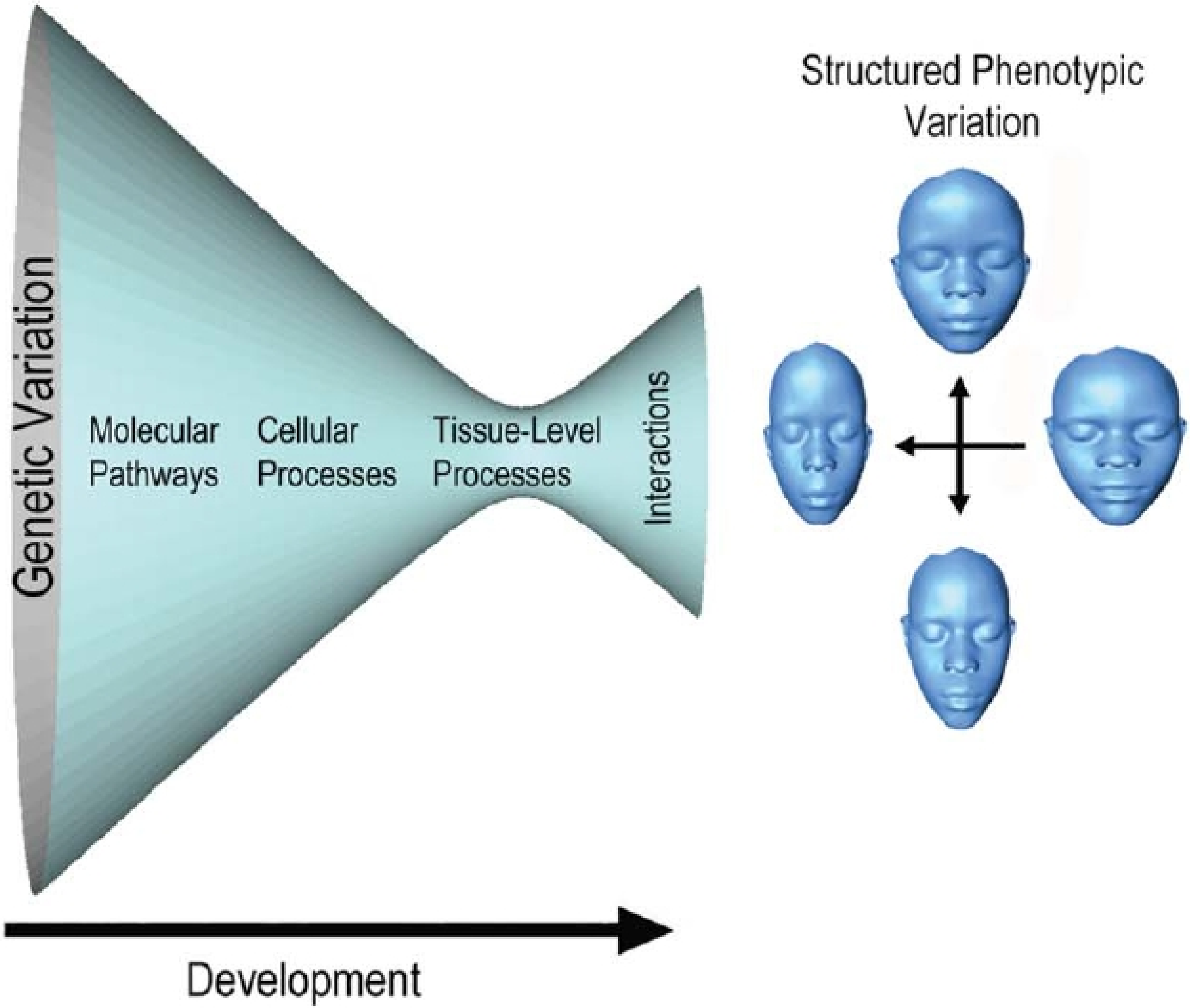


Development

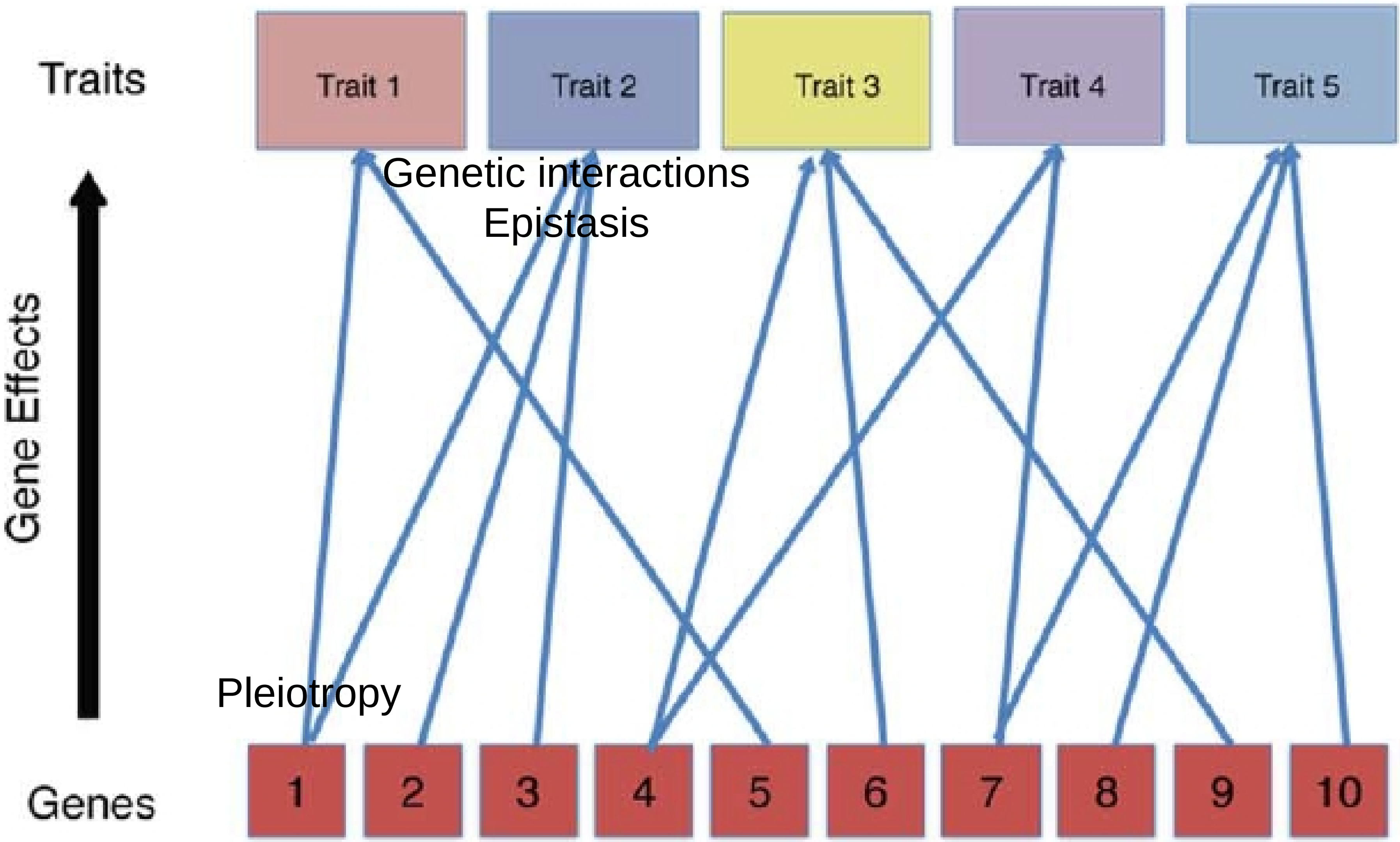
Canalization

Genes underlying
the landscape

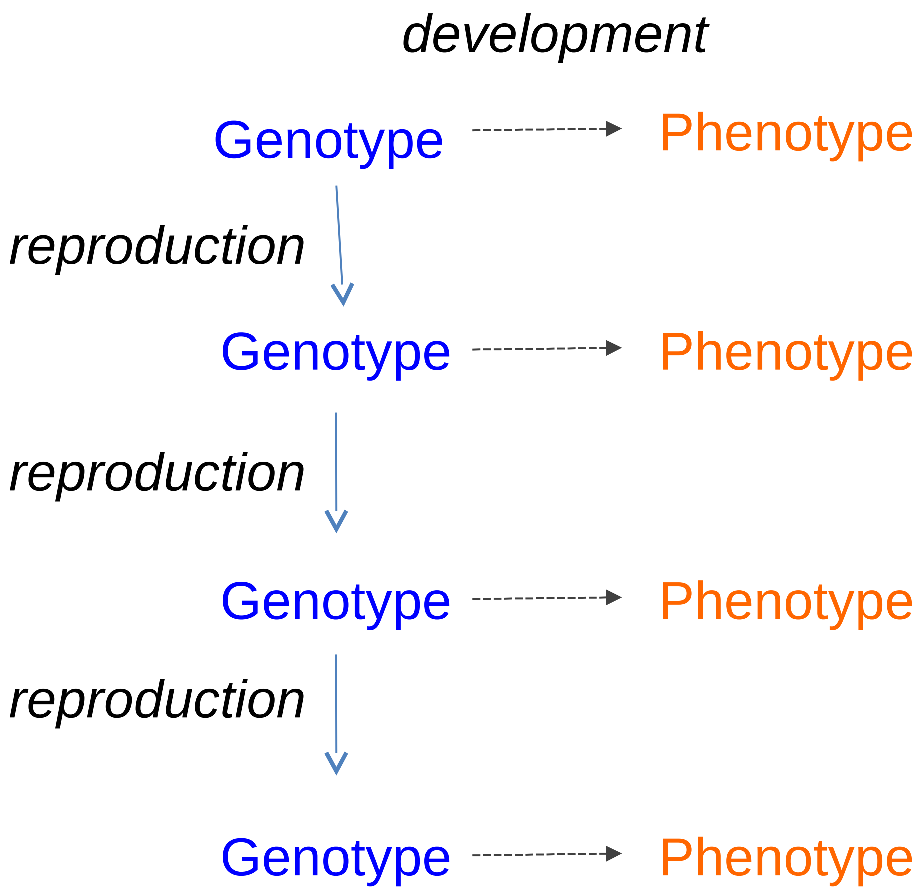
Waddington 1957



Hallgrimsson et al. 2014



Hallgrimsson et al. 2014


development
Genotype
Phenotype
reproduction
Genotype
Phenotype
reproduction
Genotype
Phenotype
reproduction
Genotype
Phenotype

A simplistic view

development

Genotype → Phenotype

reproduction ↓

Genotype → Phenotype

reproduction ↓

Genotype → Phenotype

reproduction ↓

Genotype → Phenotype

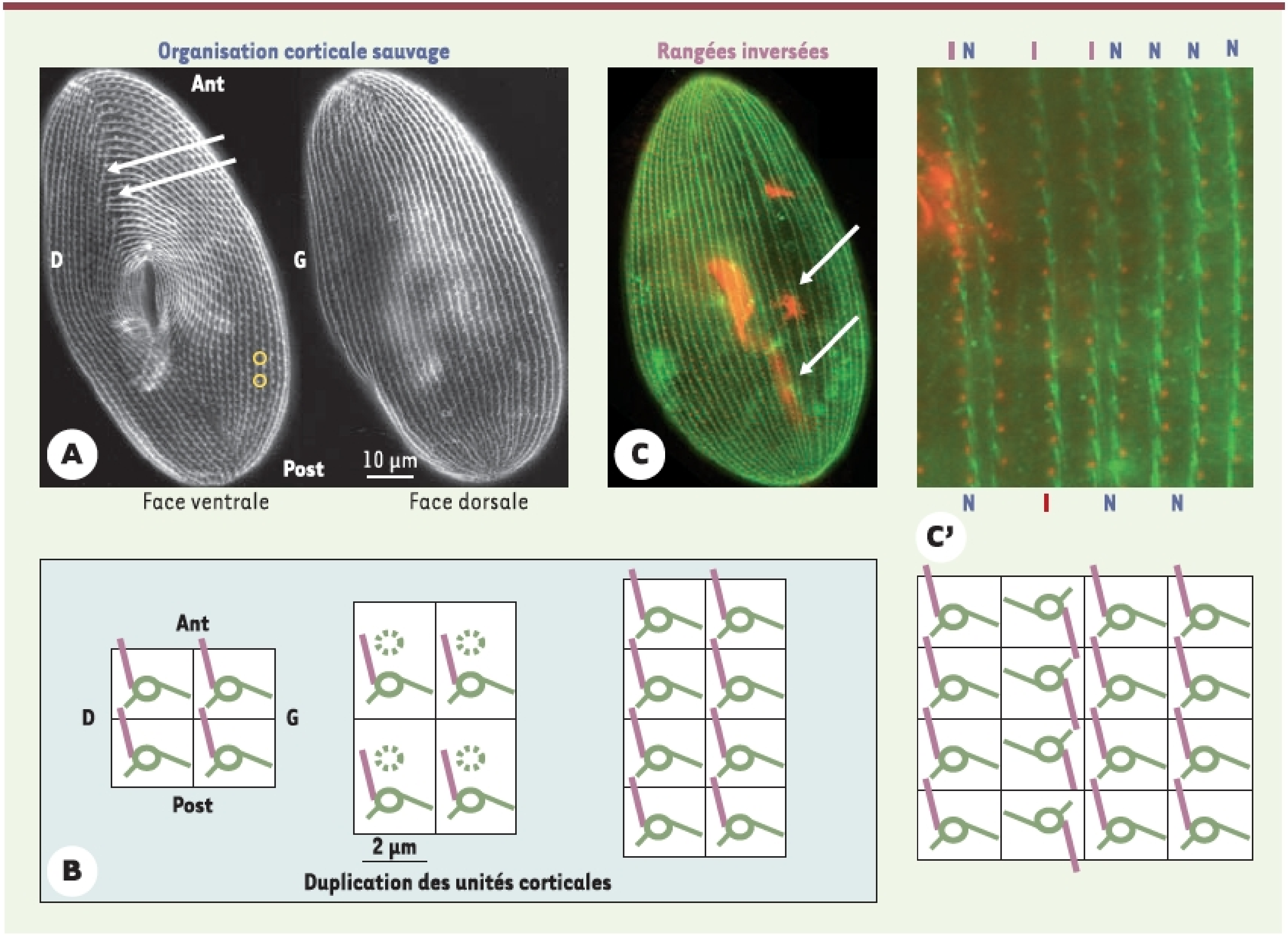
Heritable traits are
not always
due to genes

The genotype does
not determine entirely
the phenotype

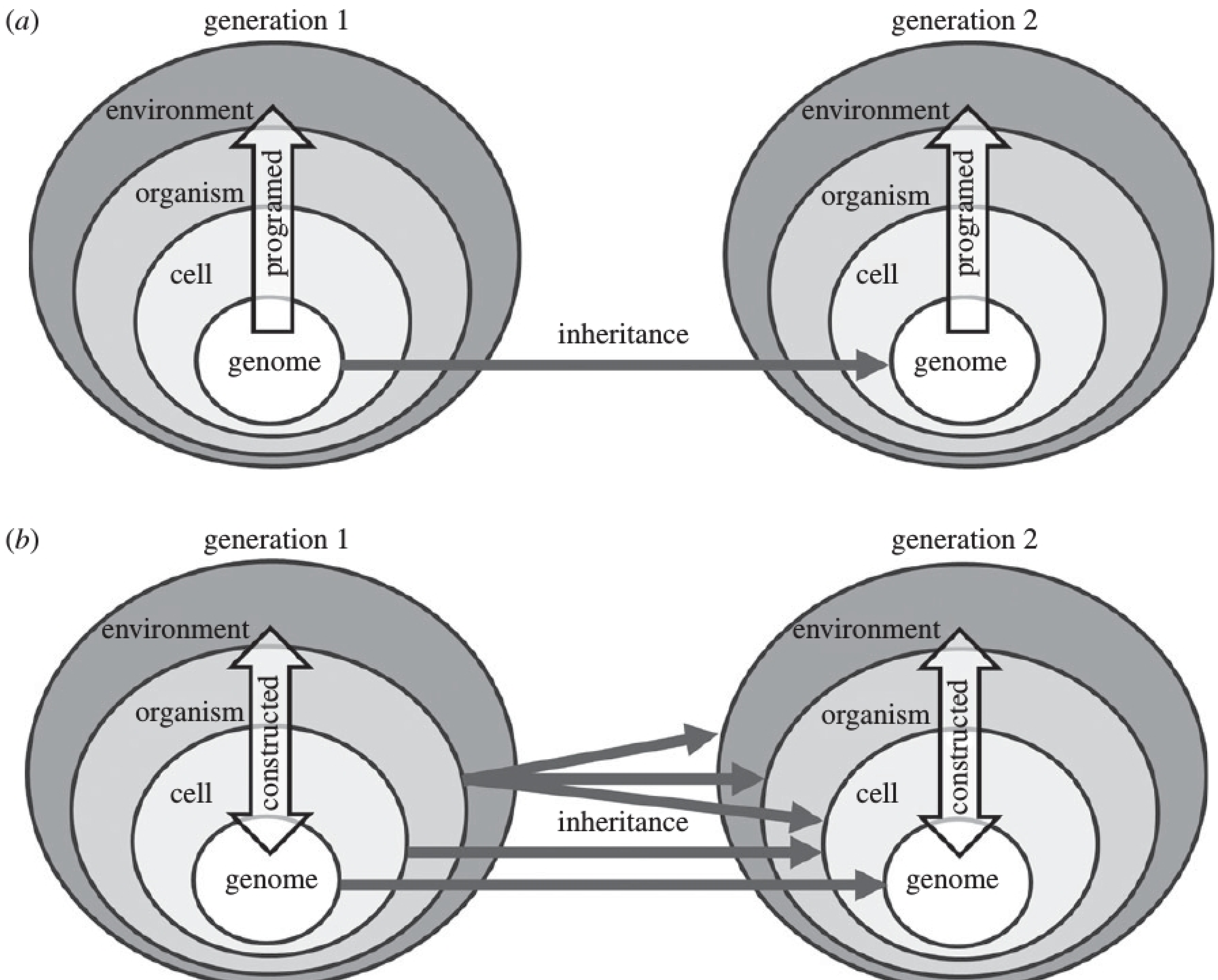
The genotype
cannot
replicate
by itself

Genotype and phenotype
imply variation

Cortical heredity in *Paramecium*



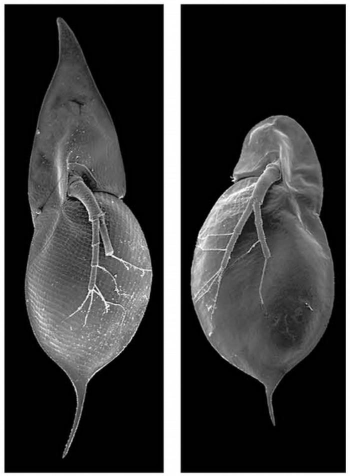
Meyer & Beisson M/S 2005


(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

Plasticity: one genotype → several phenotypes

Daphnia



with helmet — without helmet

Nemoria arizonaria caterillars

spring: caterpillars feed on catkins

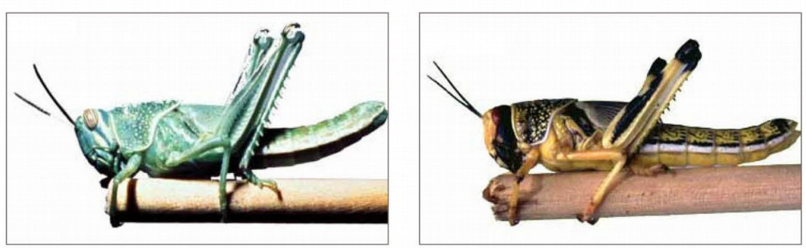
summer: caterpillars feed on leaves

Water crowfoot plant

leaves growing above water

leaves growing below water

Desert locusts



solitary

gregarious

Commodore butterfly

winter

summer

Commodore butterly: Michael Wild, CC-BY-SA-3.0 (winter), Svdmolen, CC-BY-SA-3.0 (summer)

Daphnia: Agrawal *et al* (1999)

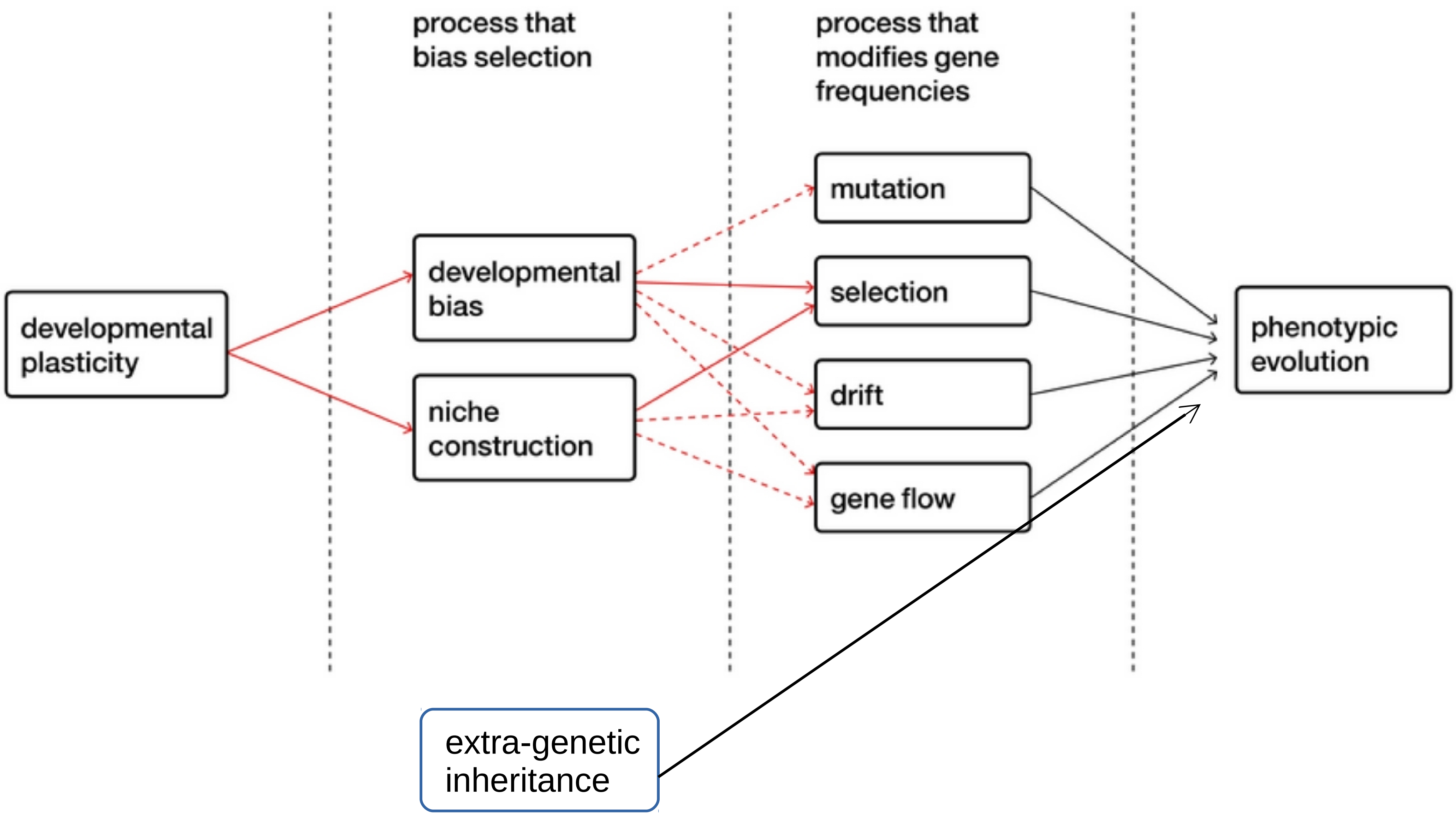
Nemoria arizonaria caterillars: Sadava *et al* (2014)

Water crowfoot plant: J R Crellin, CC BY-NC-ND 3.0

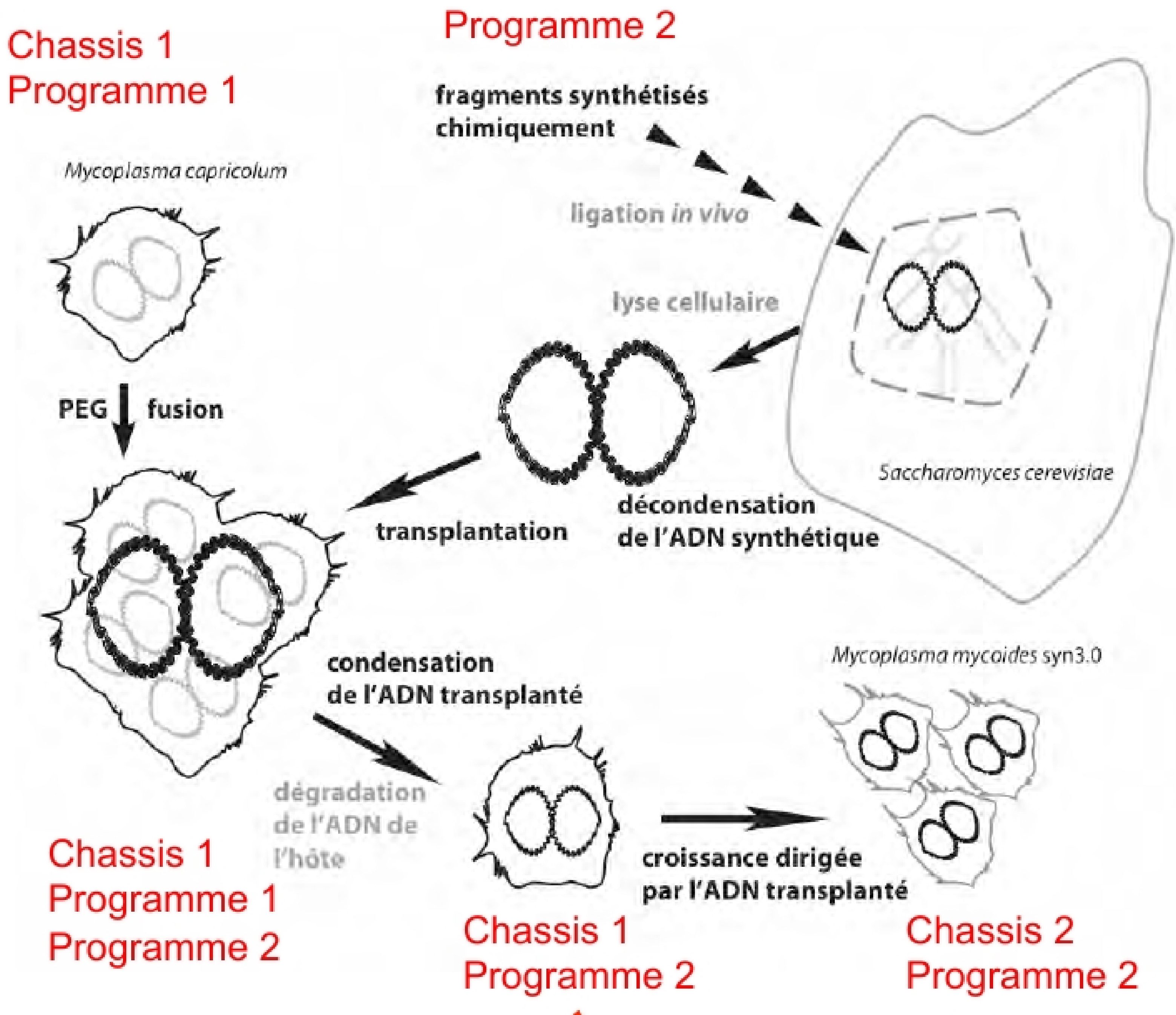
Extended evolutionary synthesis

Additions

Classical view



DNA is an inert molecule



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?

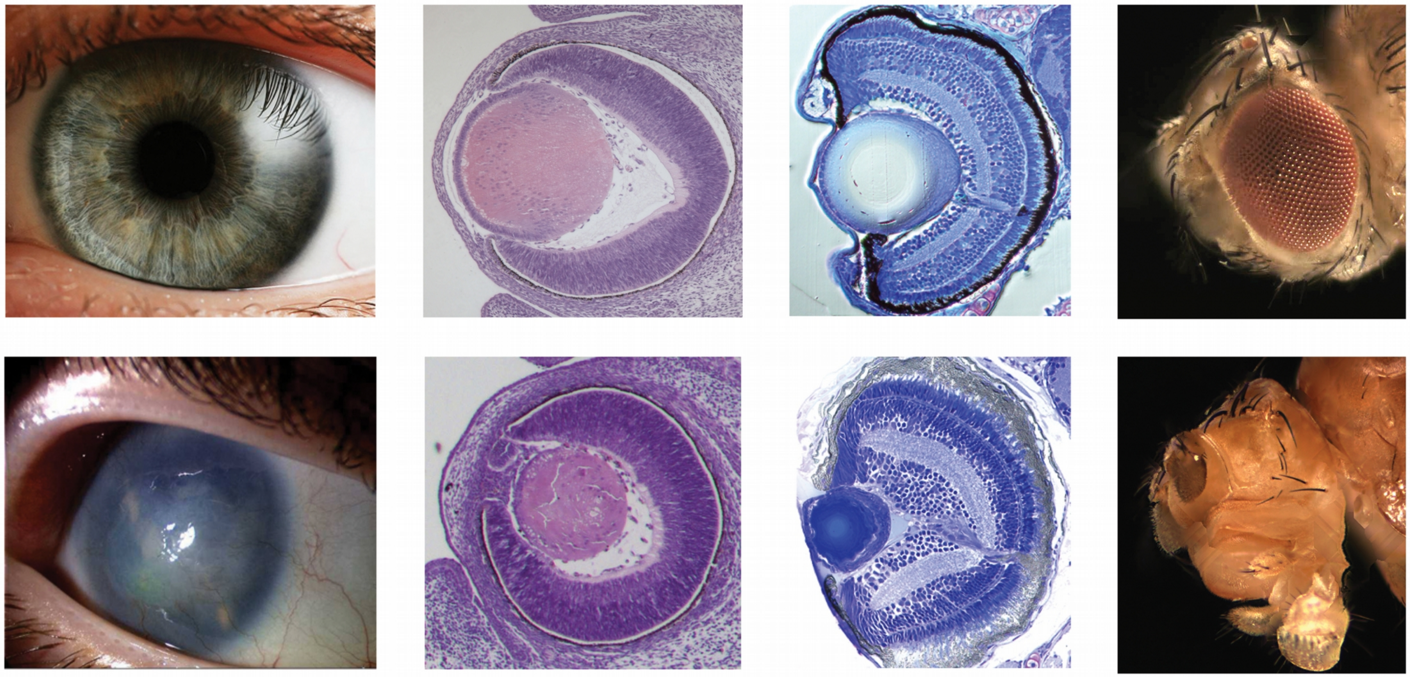
> *One of the central problems of biology is that of differentiation - how does an egg develop into a complex many-celled organism? That is, of course, the traditional major problem of embryology; but it also appears in genetics in the form of the question,* ***"How do genes produce their effects?***
>
> Sturtevant, 1932

How do genes produce observable traits?

Gene → Observable character

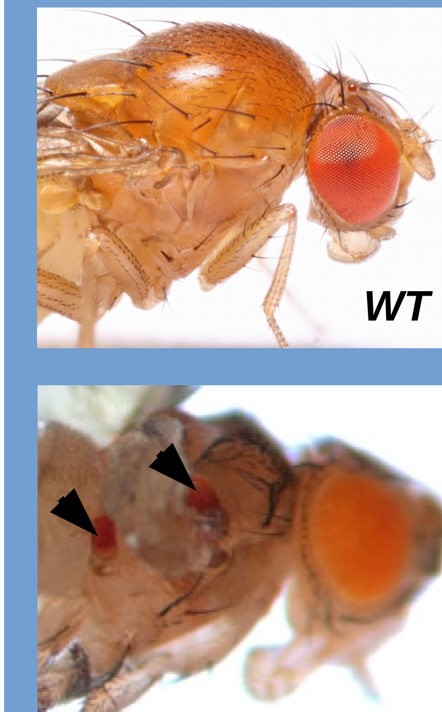
Pax6 : an eye gene ?

	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

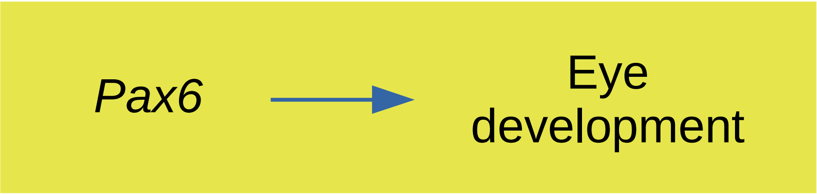
Drosophila



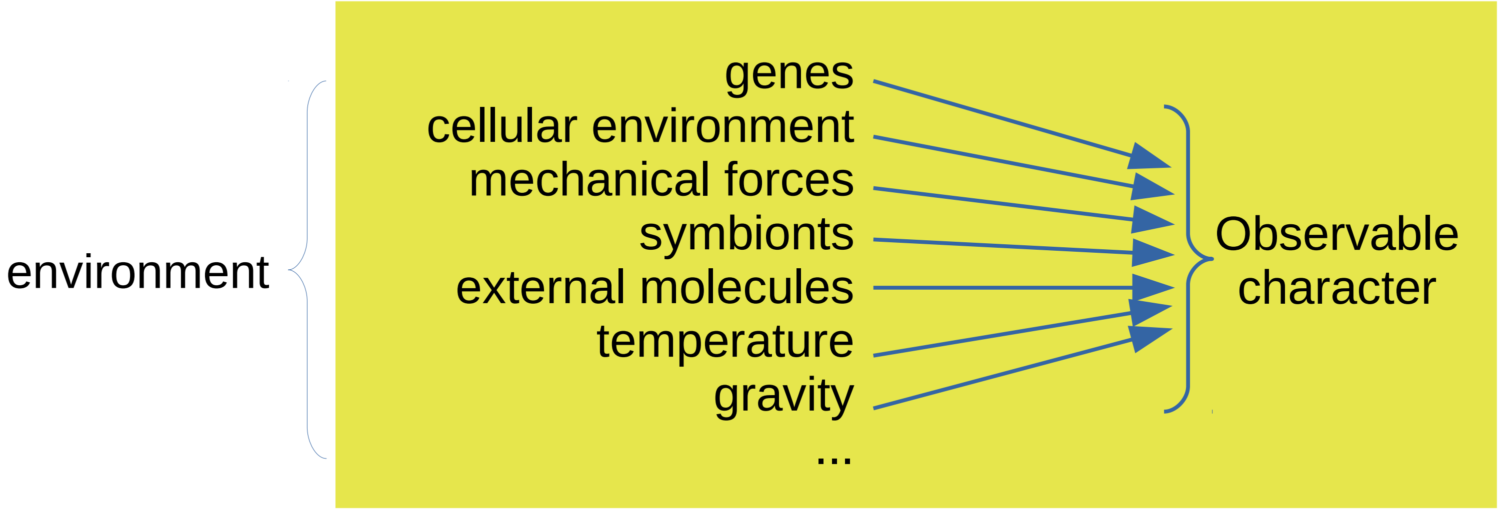
Ectopic expression of Pax6

Gene → Observable character

Pax6 → Eye development

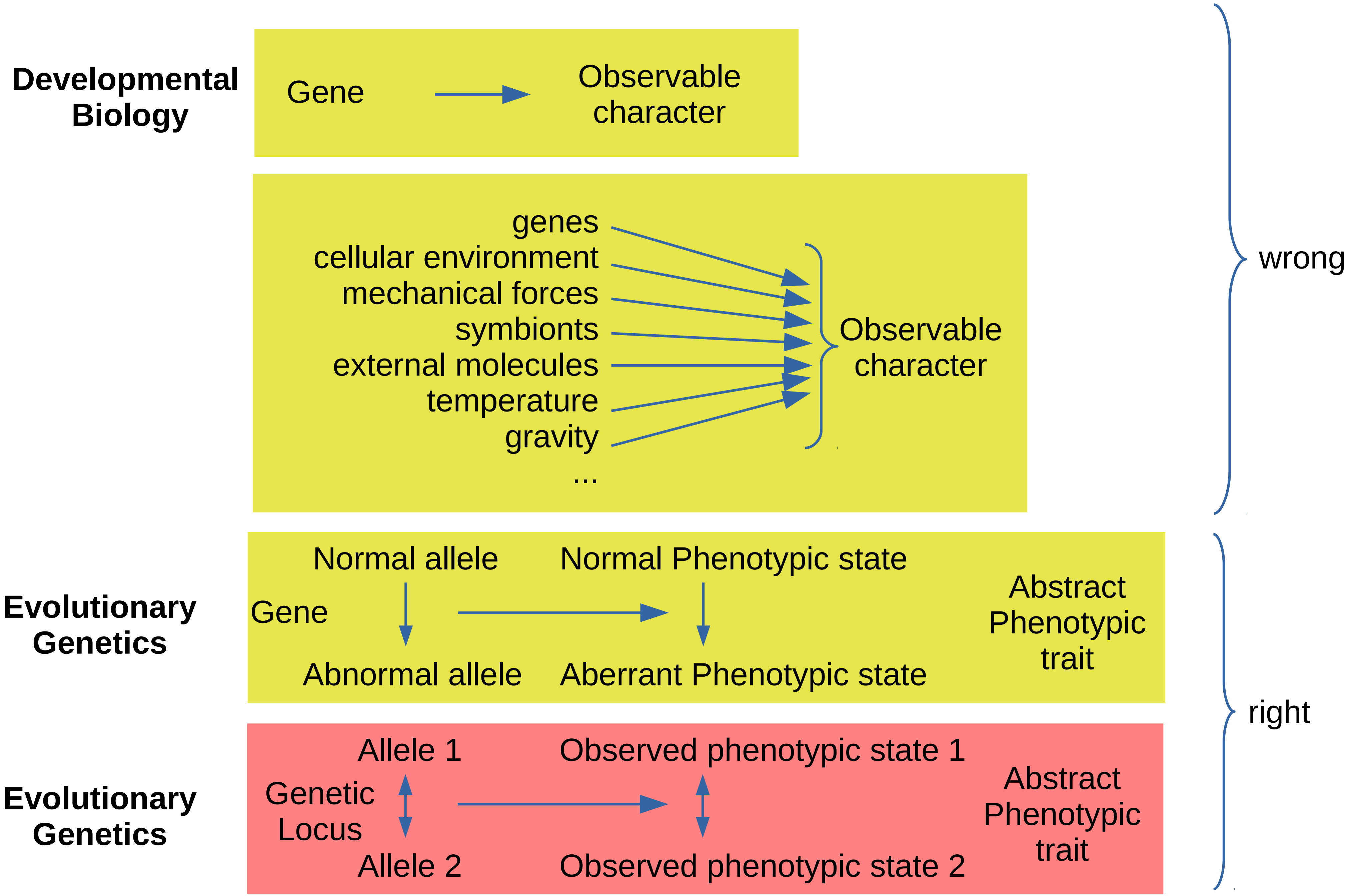


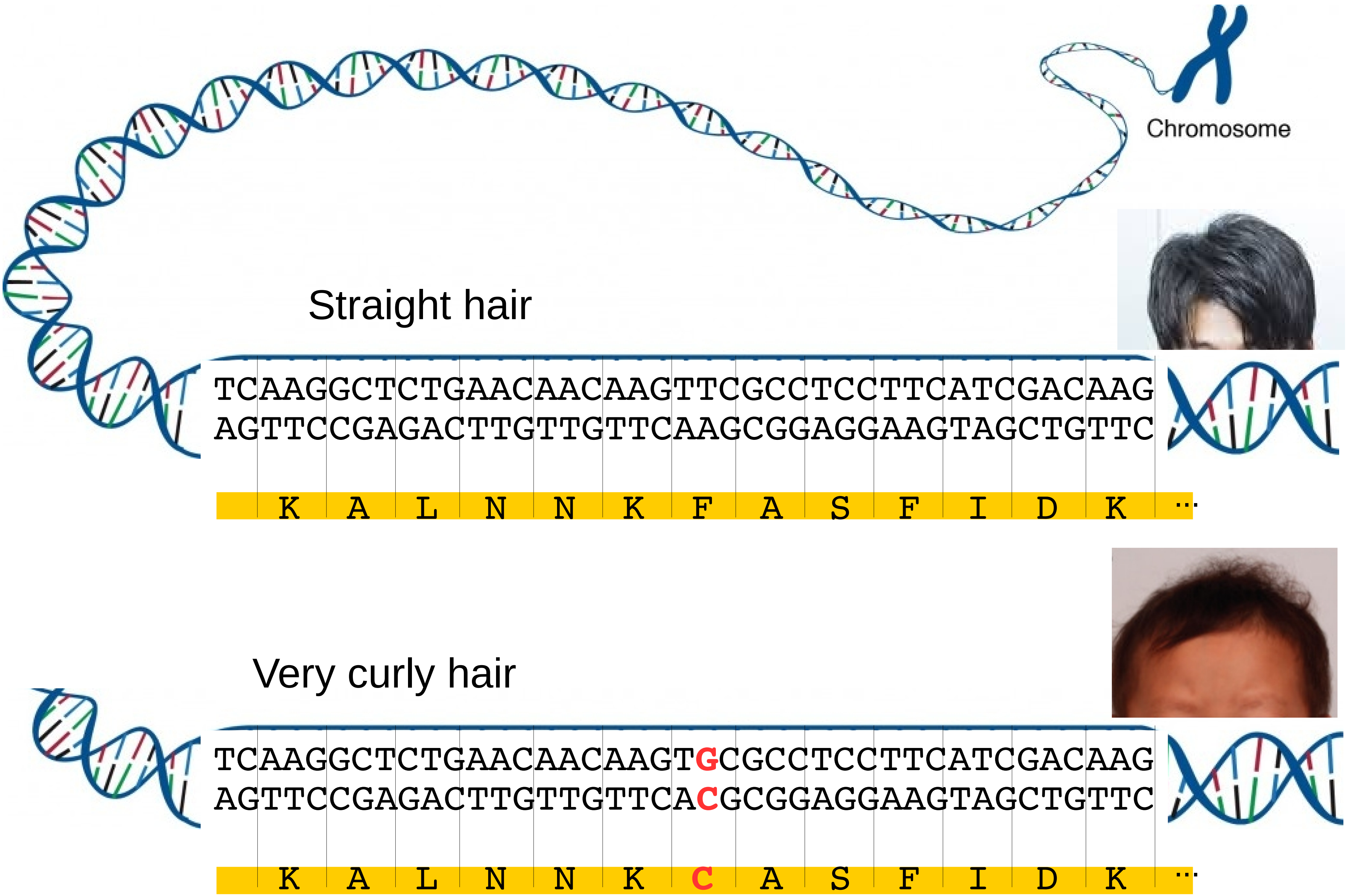
Too simplistic



Better, but difficult to disentangle the effects

The wrong and the right perspectives




Chromosome
Straight hair
TCAAGGCTCTGAACAACAAGTTCGCCTCCTTCATCGACAAG
AGTTCCGAGACTTGTTGTTCAAGCGGAGGAAGTAGCTGTTC
K A L N N K F A S F I D K ...
Very curly hair
TCAAGGCTCTGAACAACAAGTGCGCCTCCTTCATCGACAAG
AGTTCCGAGACTTGTTGTTCACGCGGAGGAAGTAGCTGTTC
K A L N N K C A S F I D K ...

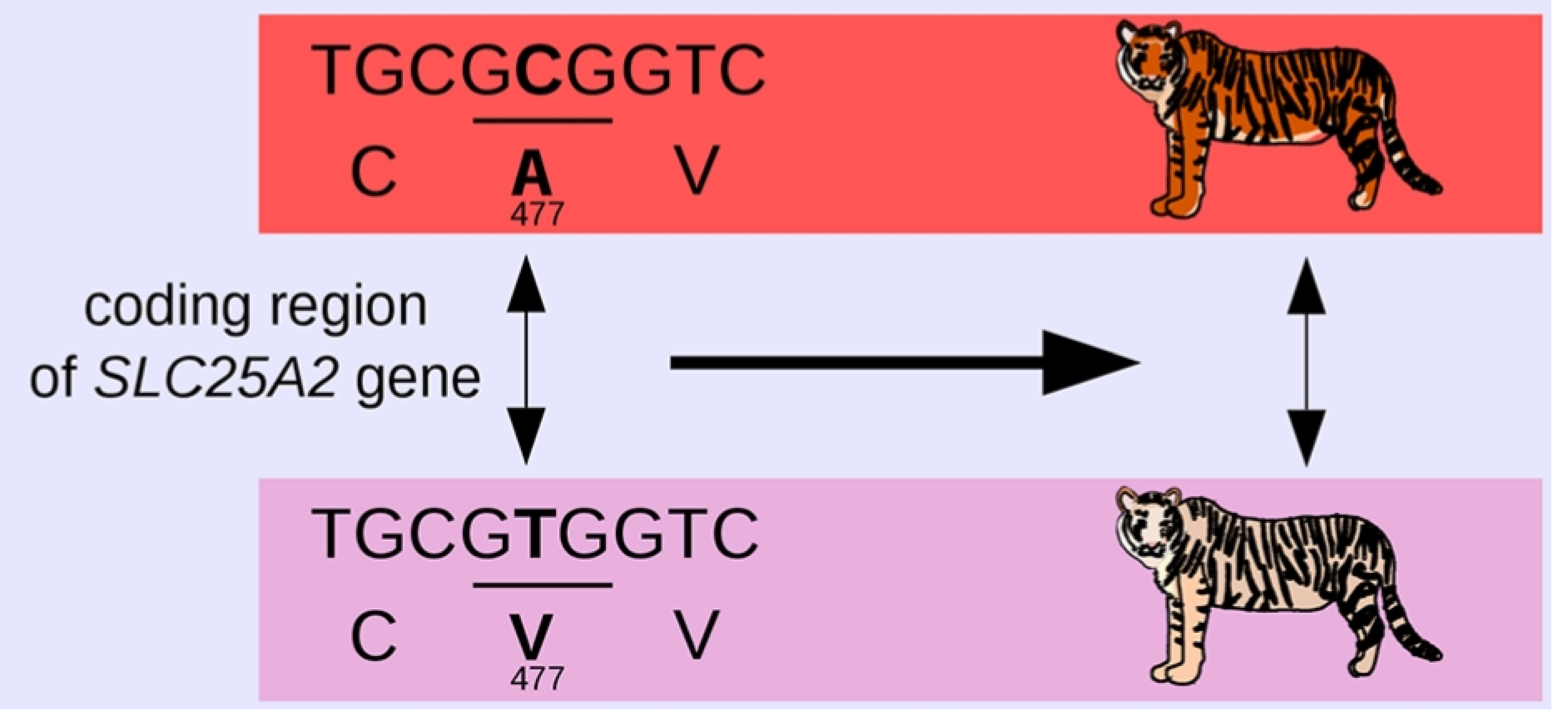
Genotype = “the genetic makeup of an organism that determines a specific phenotype (trait), from one generation to the next, and potentially throughout the population”.

Report of the National Academy of Sciences on gene drive, 2016

NO!

The genotype-phenotype connection is about differences

The genotype-phenotype connection



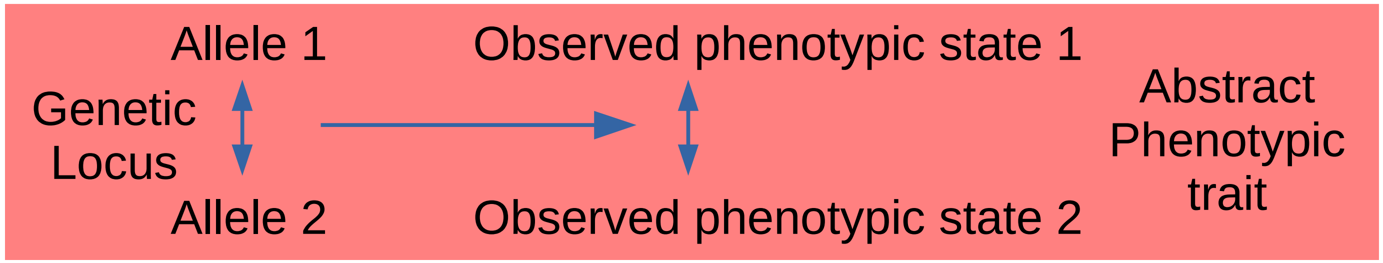
Xu et al 2013 Current Biology

Orgogozo et al 2015 Frontiers Genetics

Example: the causes of a difference in hair color

Genes coding for pigment synthesizing enzymes
Amount of received sun light
Hair dyeing
Age
...

Gephe: a relationship between two levels of variation



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

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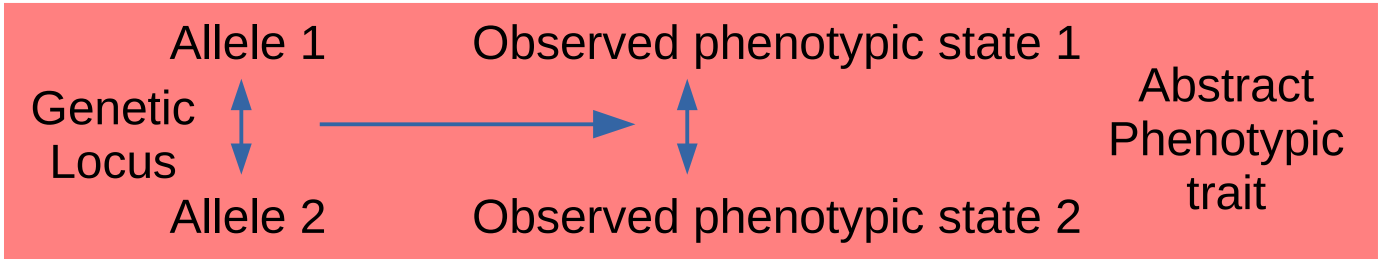
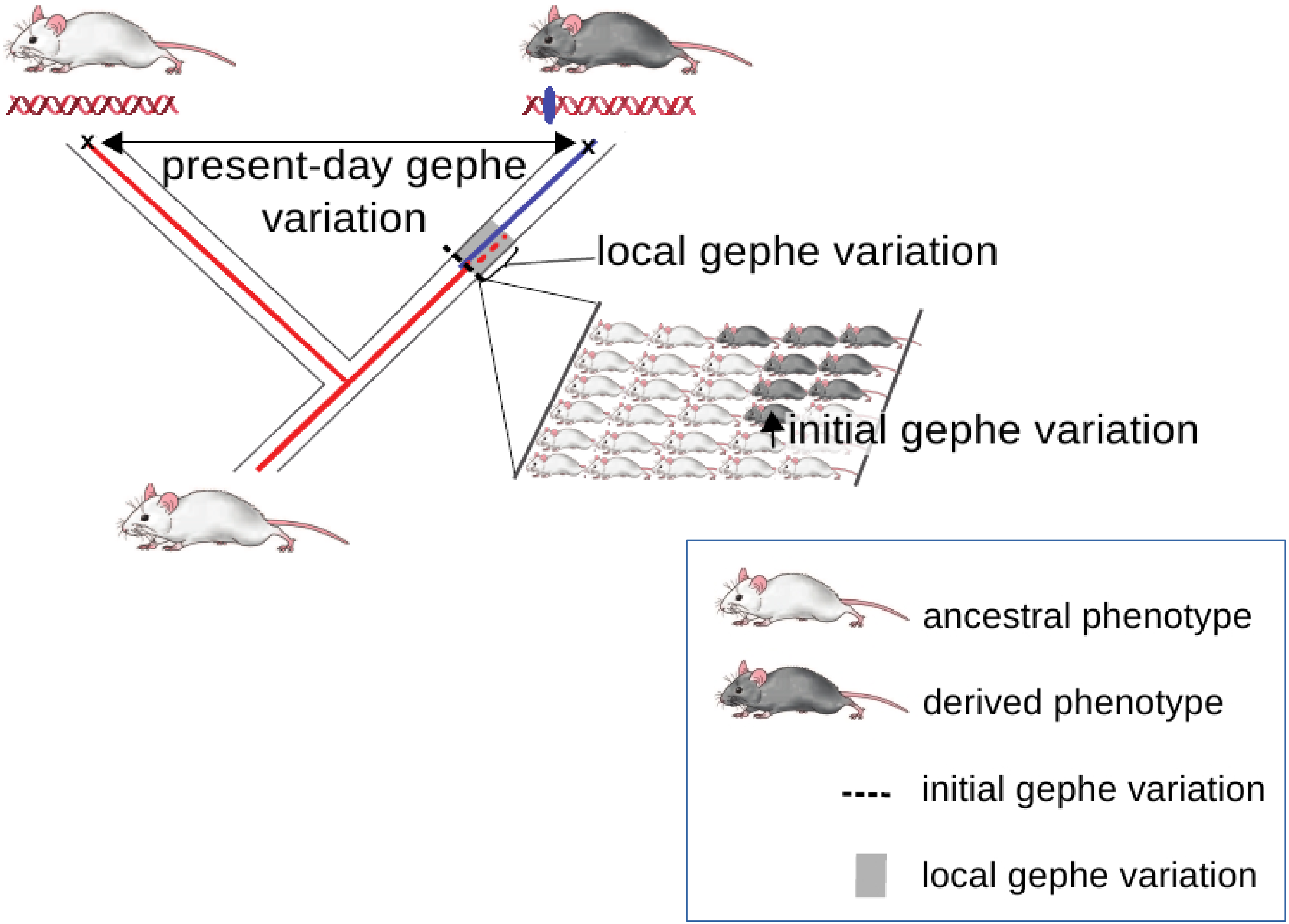


The genetic locus in the gephe concept is **not necessarily a gene.**
it can span a particular base-pair, a coding region, a cis-regulatory region, or extend to an entire gene or even a gene cluster (Table 1). This view rejoins previous reflections by Scott Gilbert (2000), David Stern (2000) and Lenny Moss (2003) on the distinct concepts of gene in developmental biology and in evolutionary biology.

Gephe: a difference at various levels



A simplistic view

development

Genotype → Phenotype

reproduction ↓

Genotype → Phenotype

reproduction ↓

Genotype → Phenotype

reproduction ↓

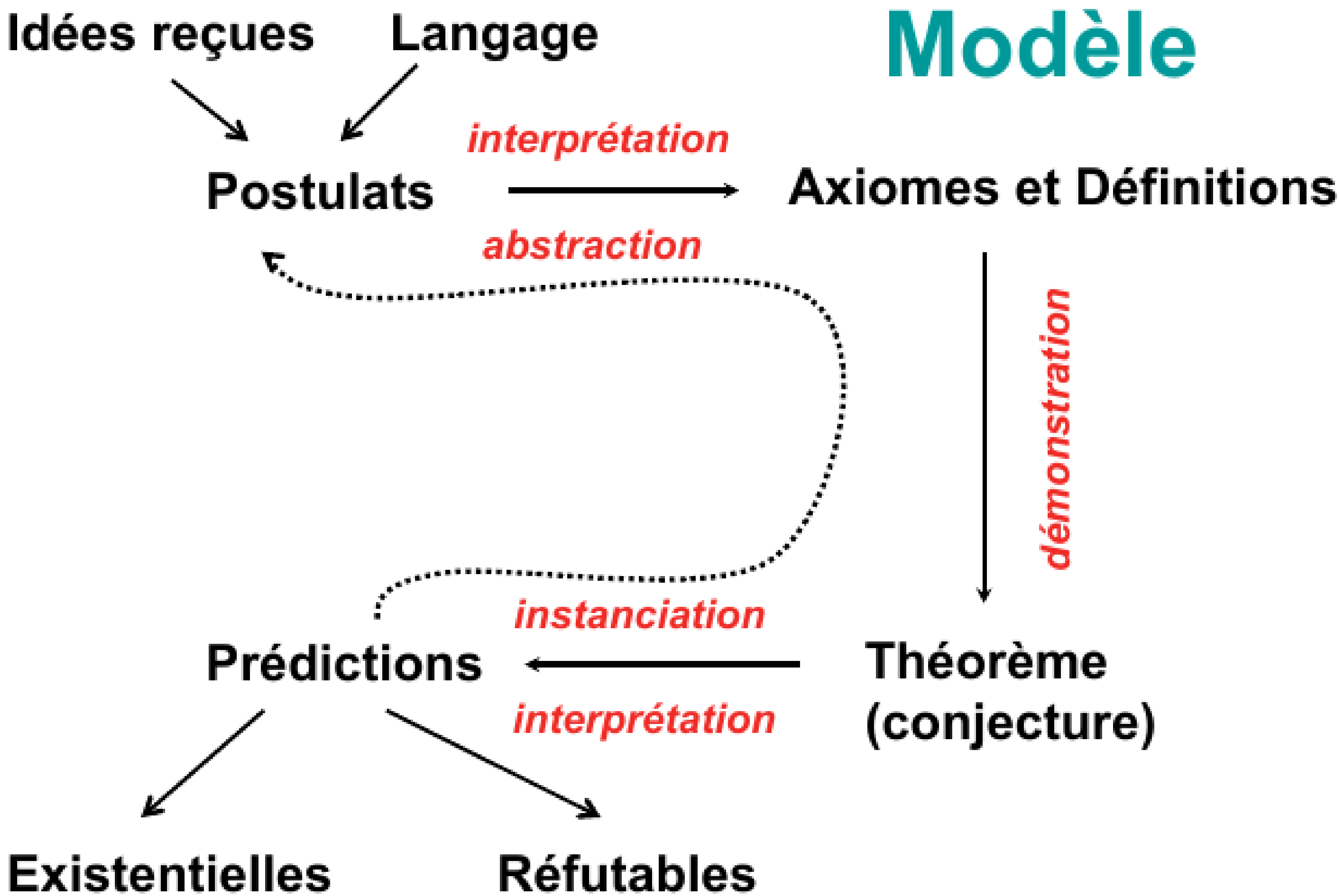
Genotype → Phenotype

Heritable traits are not always due to genes

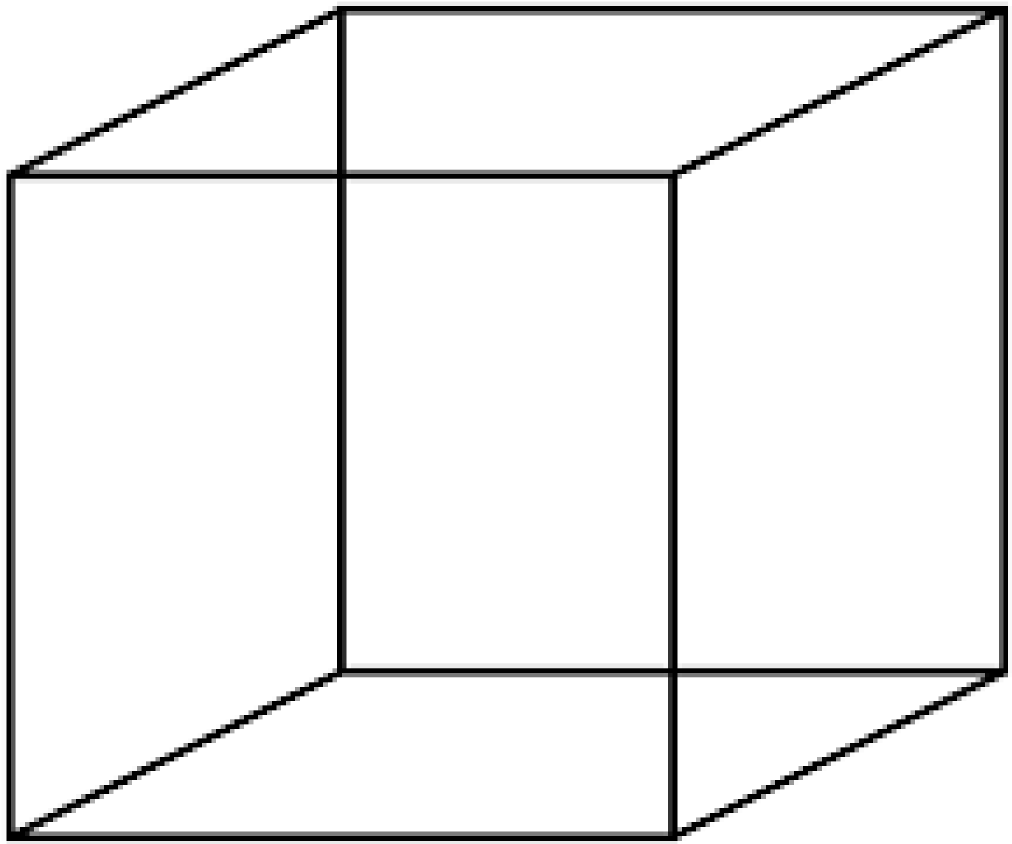
The genotype does not determine entirely the phenotype

The genotype cannot replicate by itself

Genotype and phenotype imply variation



We sometimes seem to have forgotten that the original question in genetics was not what makes a protein but rather 'what makes a dog a dog, a man a man'.
(D. Noble – The Music of Life)

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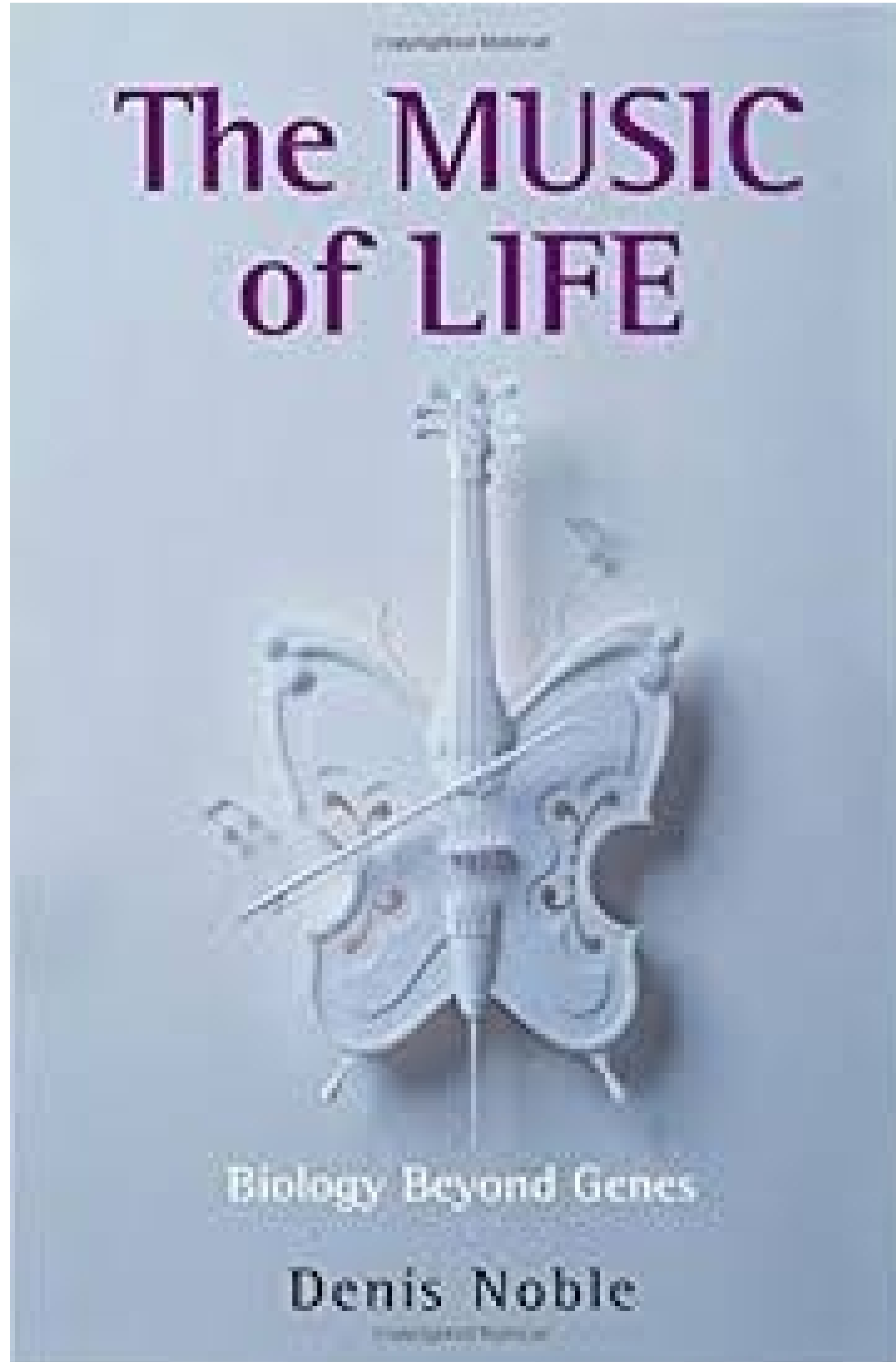
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Biology Beyond Genes
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