Noise, Cryptic Variation, Robustness, Quantitative Genetics, the Genotype-Phenotype Map

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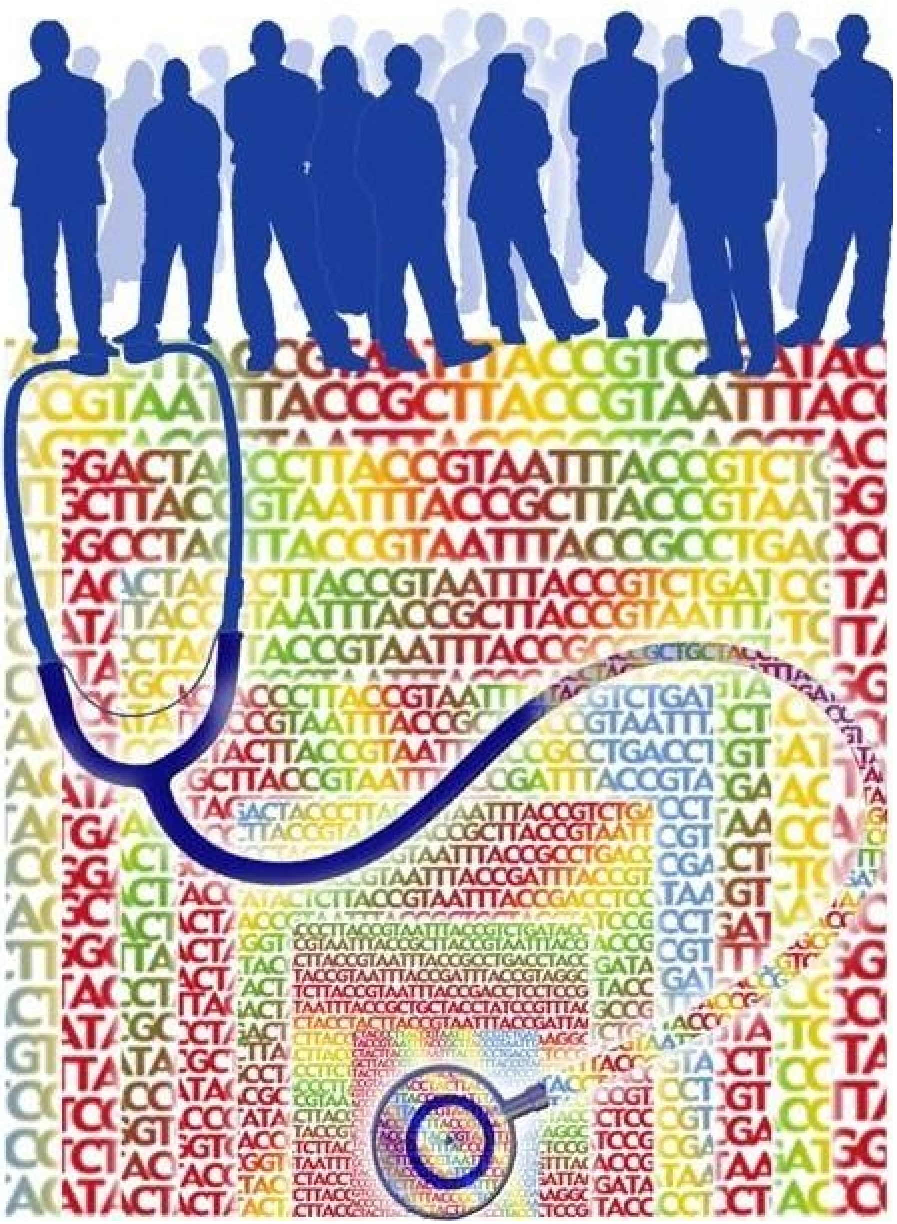
Human genetic diversity



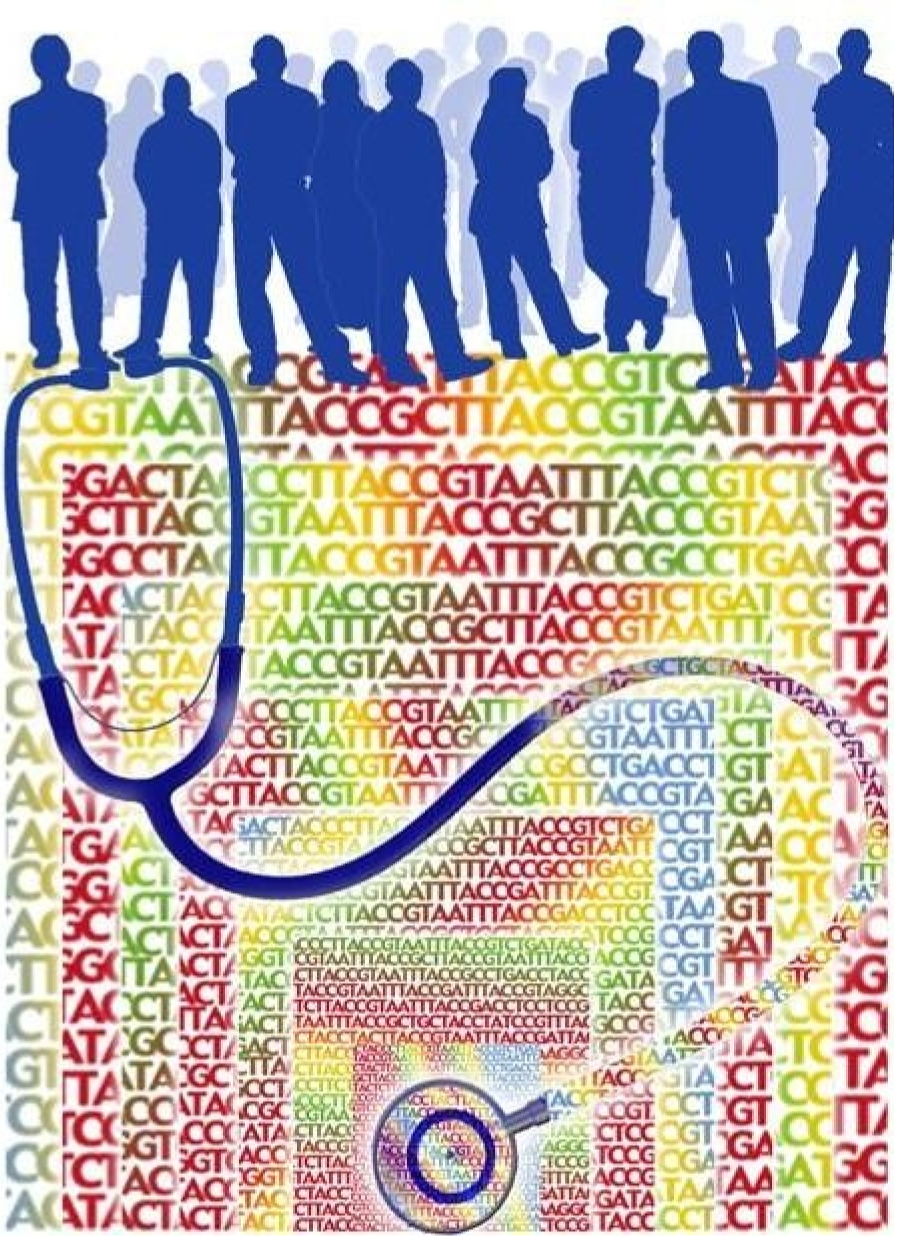
Genome size: 2.9 Gb
Gene number: 25 000
(1% of coding sequences)

In one individual:
~70 new mutations compared to his parents
~20 lethal mutations (heterozygous)

Genetic difference between two humans?

Genetic differences between humans and chimps?

Human genetic diversity



Genome size: 2.9 Gb
Gene number: 25 000
(1% of coding sequences)

In one individual:
~70 new mutations compared to his parents
~20 lethal mutations (heterozygous)

Genetic difference between two humans?

~0.1%

Genetic differences between humans and chimps?

~4% (<1% for coding sequences)


99.4% human?
Banners by www.zephyr-tvc.com

From laboratory to “real-life” data

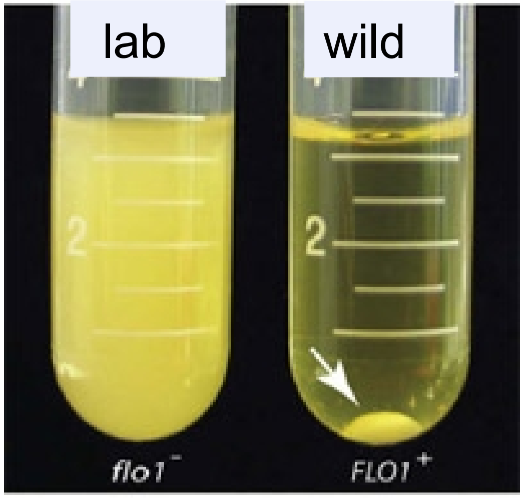
Knock out

Natural variation

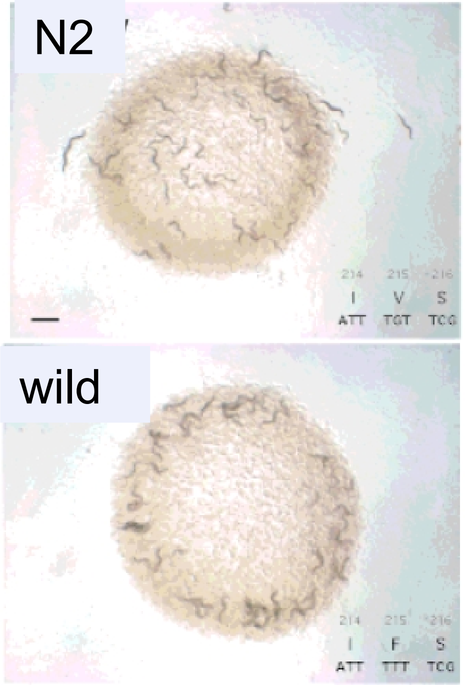
Domestication of laboratory strains

Arabidopsis thaliana

Saccharomyces cerevisiae



Caenorhabditis elegans



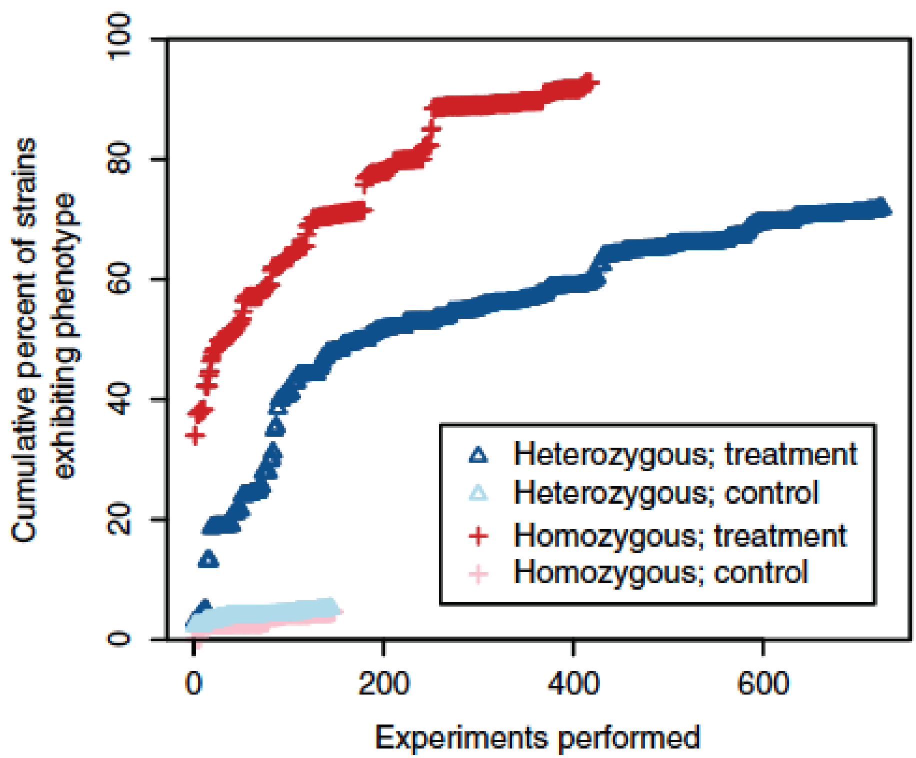
Domestication of laboratory strains
results in extreme phenotypic values
for many traits:
artificial selection and pleiotropy

Choice of laboratory environment

ca. 10-20 years ago: surprise at not finding phenotypes in gene knockouts

The Chemical Genomic Portrait of Yeast: Uncovering a Phenotype for All Genes
Maureen E. Hillenmeyer, *et al.*
Science **320**, 362 (2008);

1144 growth environments
for *S. cerevisiae*



Laboratory mutations

- Not in nature
- Extreme effects
- Would likely be lost under selection
- Must be induced

- Interrogates (nearly) all regions
- Readily cloned
- Strong effects

QTL

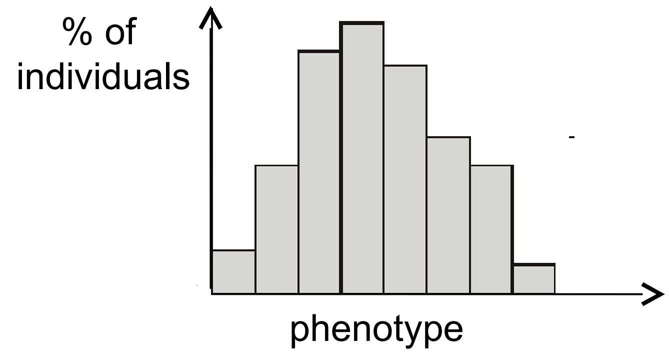
- Representative of nature
- Variants with small effects
- Sustained under selection
- Readily available

- Interrogates only variable regions
- Difficult to map
- Small effects

Quantitative genetics

Quantitative genetics

- If to each genotype corresponds a distribution of phenotypes
  = variable expressivity
  the character itself is quantitative

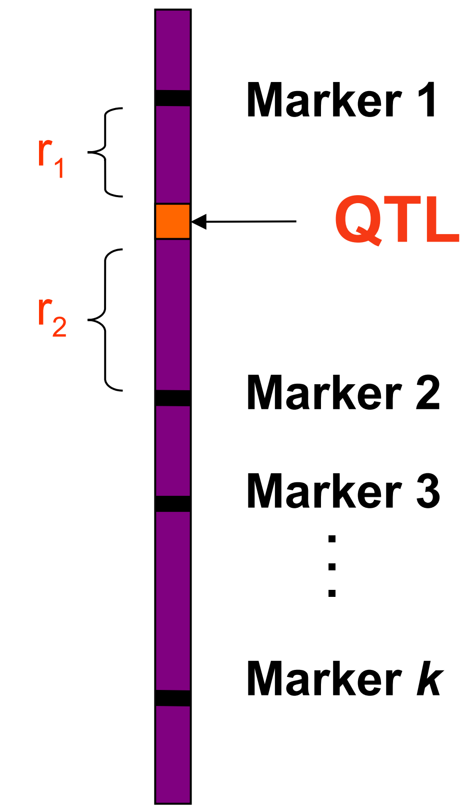


  and/or

- If the variation of many genes is involved in the phenotypic difference between two strains/individuals
  the segregation of the character is quantitative

Quantitative Trait Loci (QTL) mapping

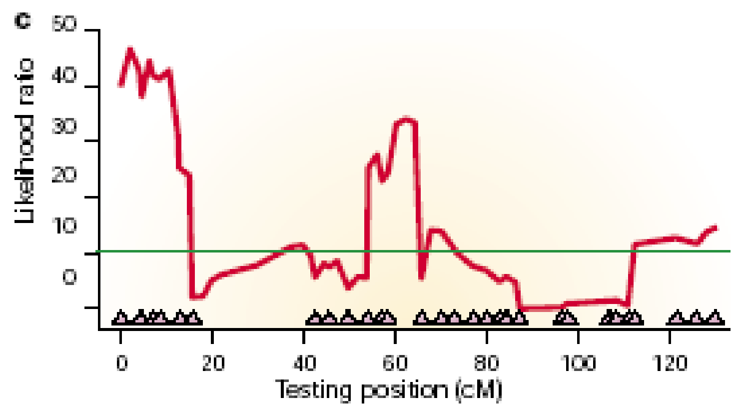
- QTL are specific genetic loci that affect quantitative traits.
- QTL can be detected by markers that are linked with it.



Two goals:

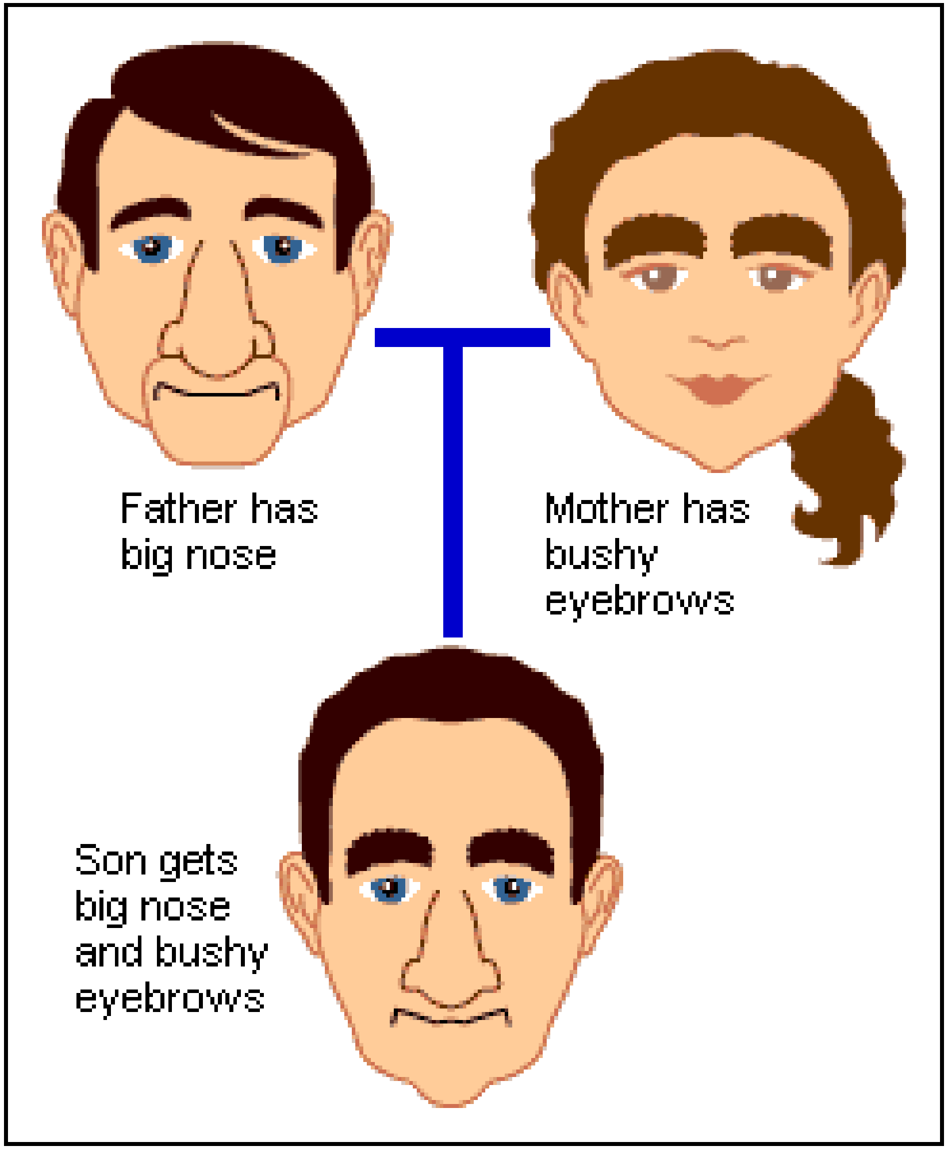
Identify the location of the QTL

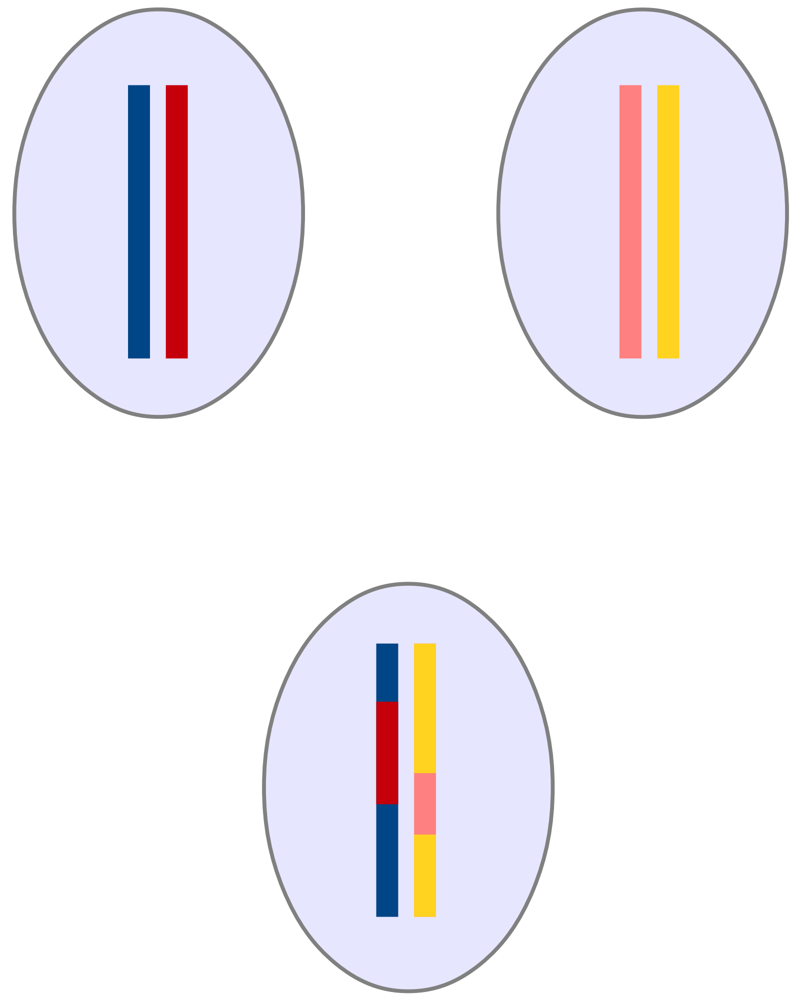
Estimate the genetic effects of the QTL



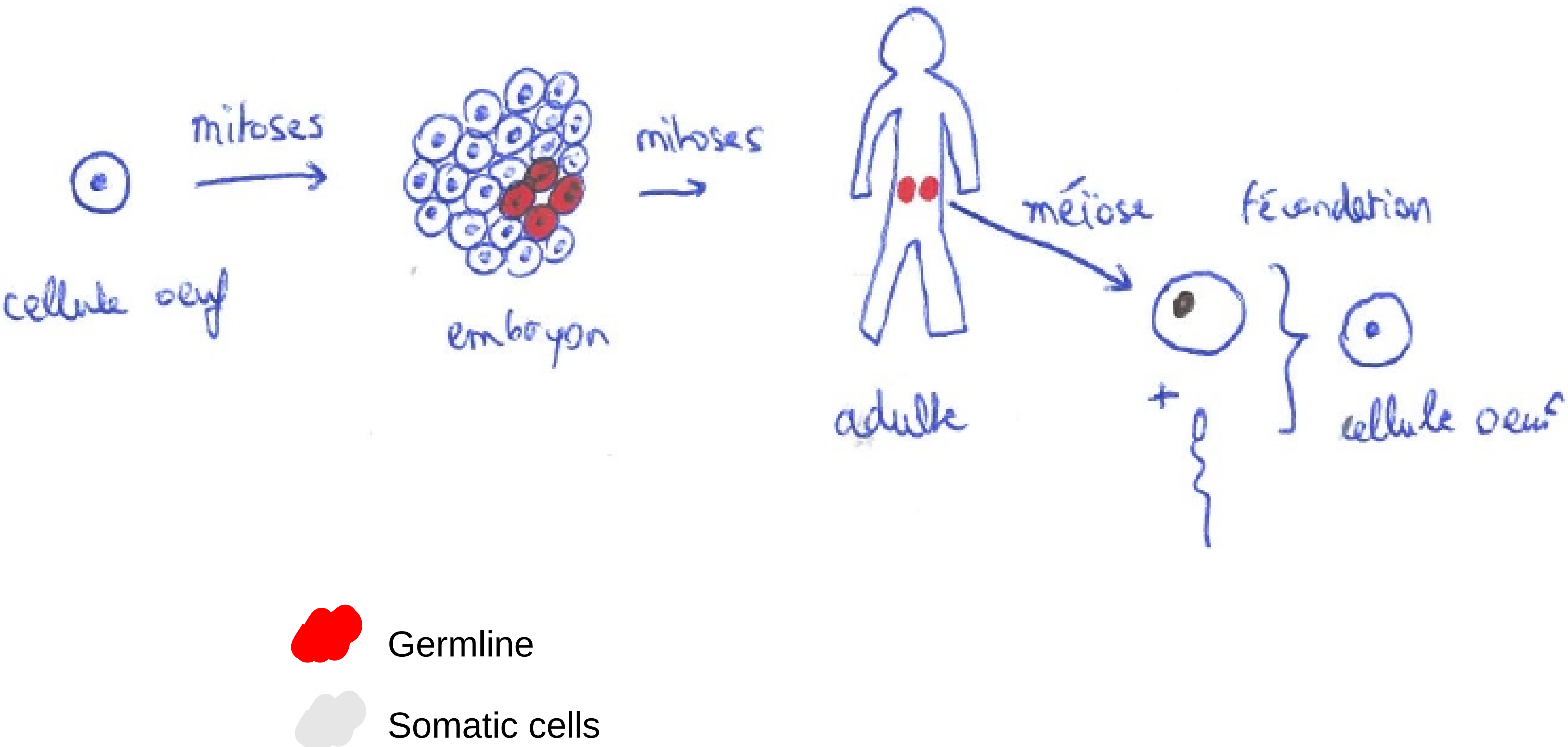
Noise

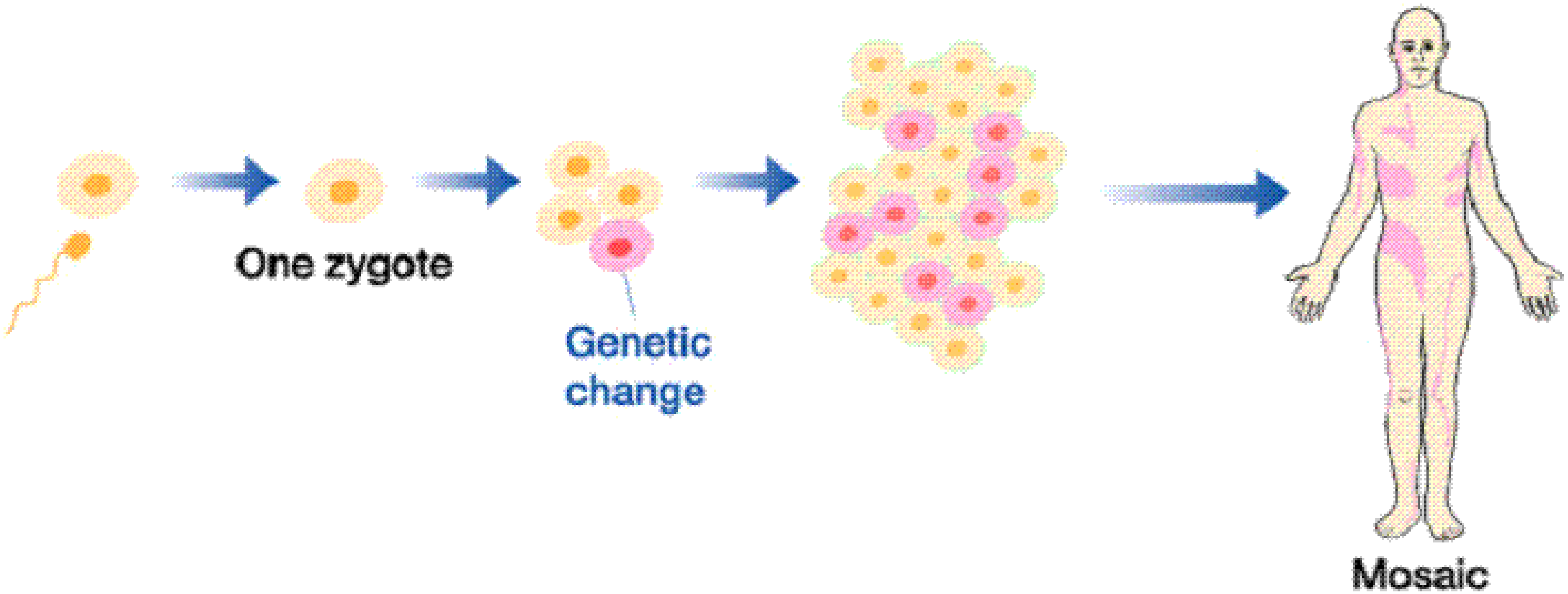
Assortment of chromosomes from father and mother



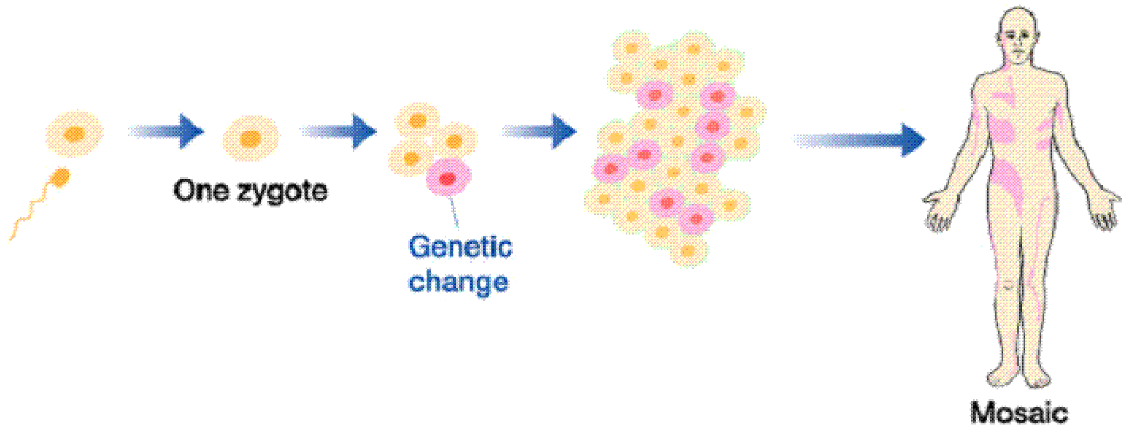


http://evolution.berkeley.edu


mitoses
cellule oeuf
embryon
mitoses
adulte
méiose
fécondation
+
cellule oeuf
Germline
Somatic cells

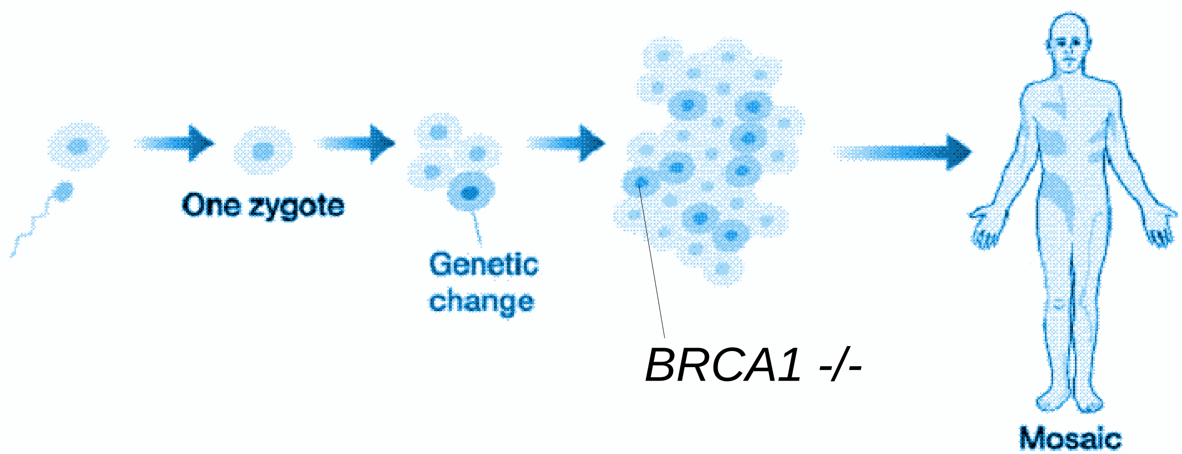

One zygote
Genetic
change
Mosaic

woman
BRCA1 +/+



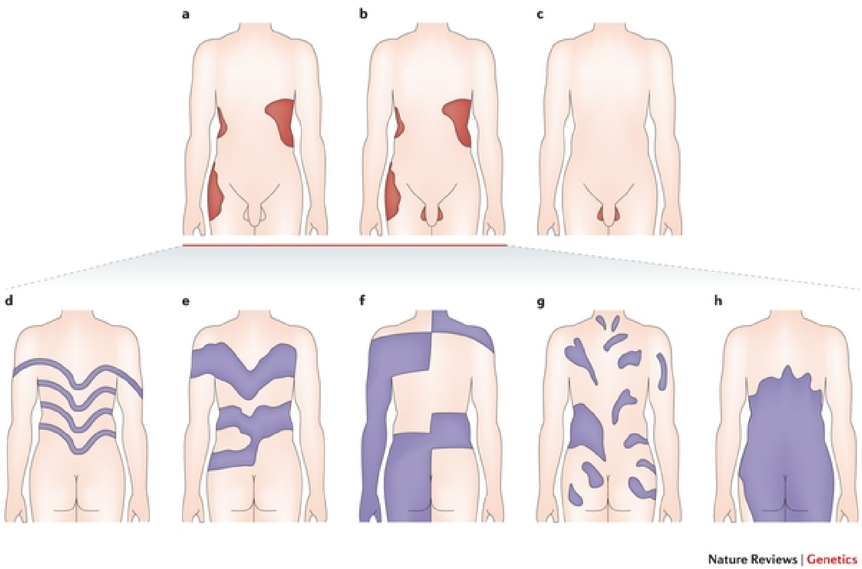
10% chance to develop breast cancer

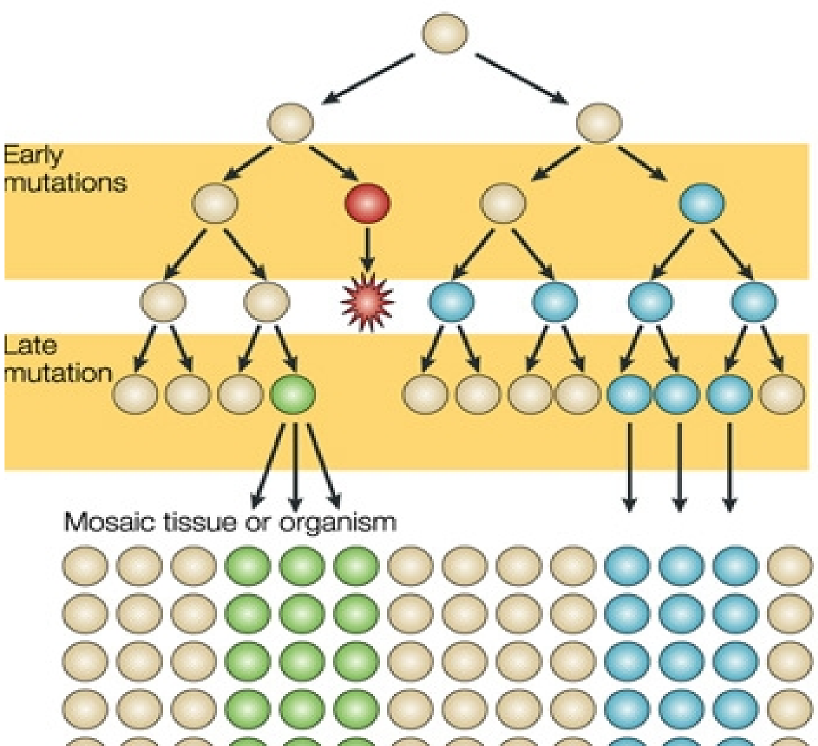
woman
BRCA1 +/-



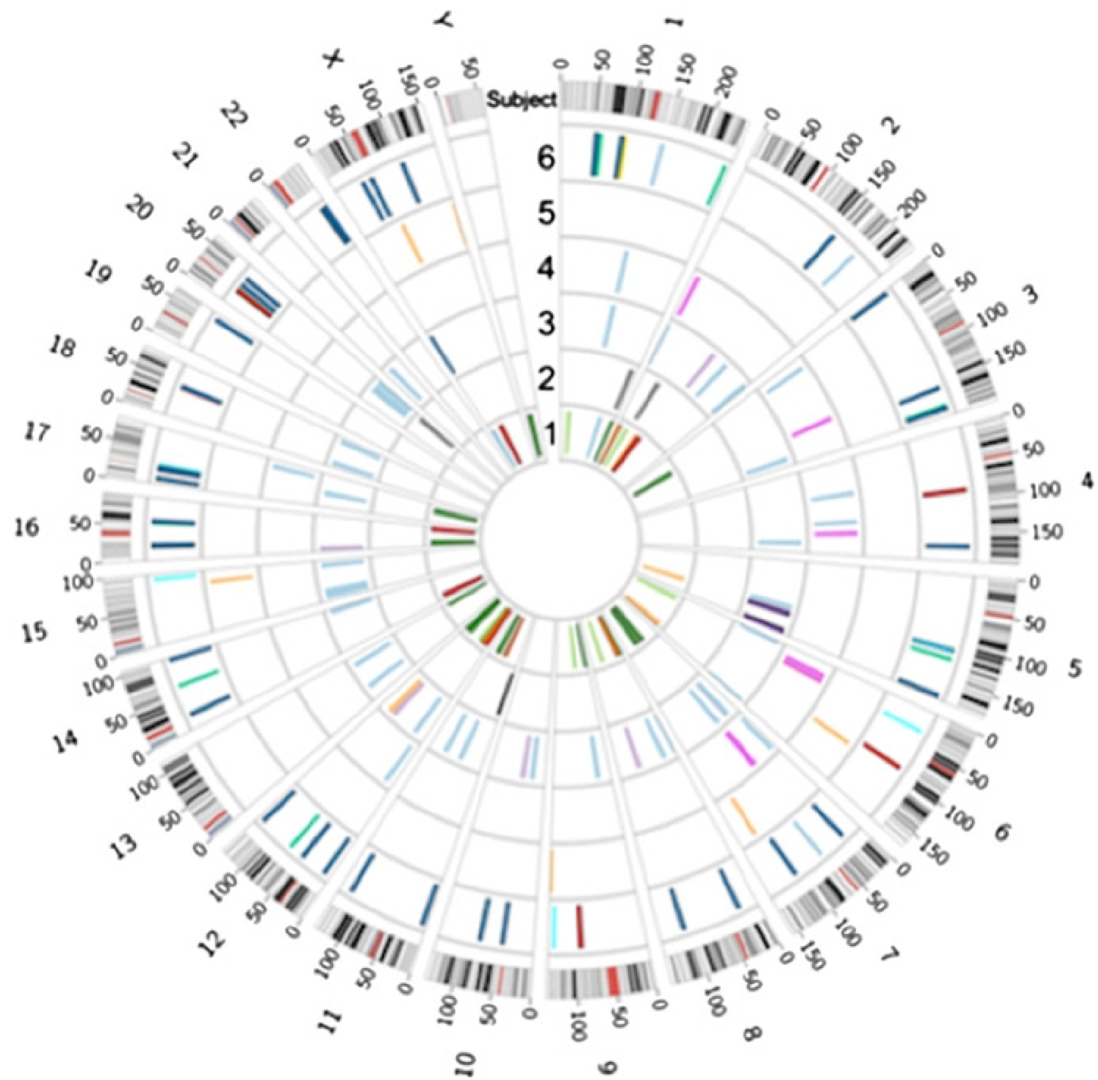
45% chance to develop breast cancer before 70 years old
Cancer cells will be *BRCA1 -/-*

Somatic mosaicism



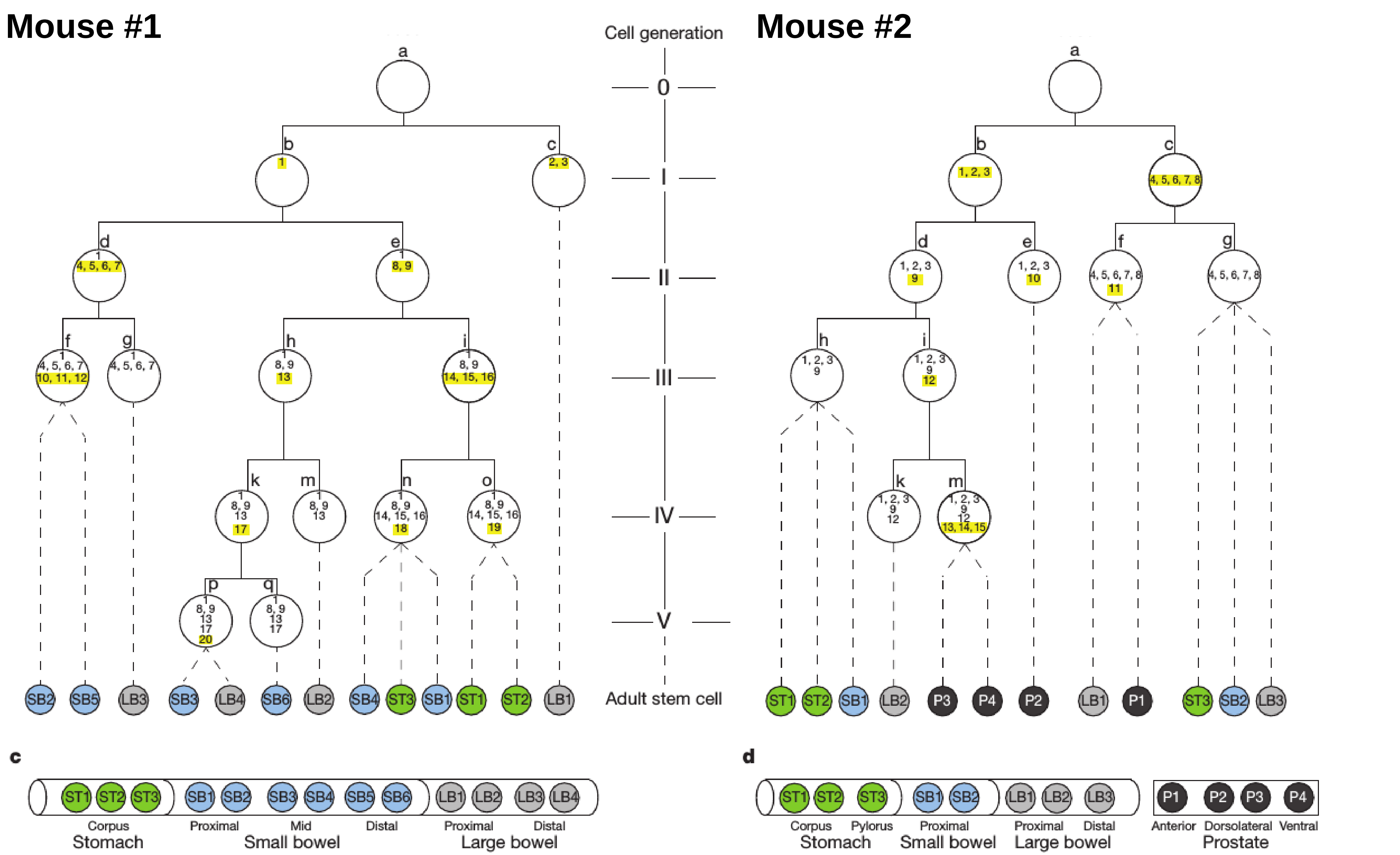


73 somatic CNVs in 11 tissues of six persons



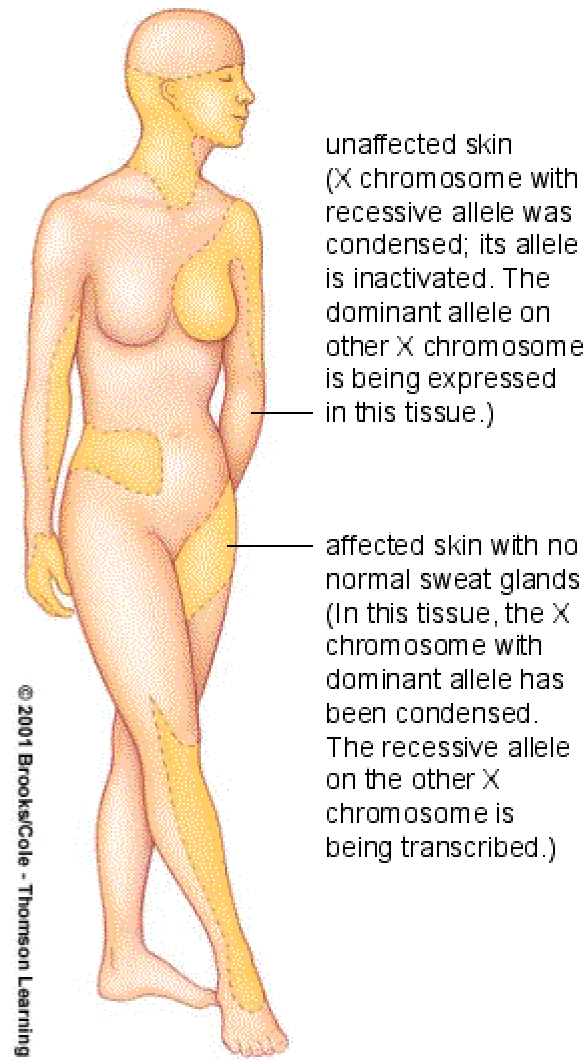
- O'Huallachain 2012 PNAS

Somatic mosaicism used to reconstruct cell lineages

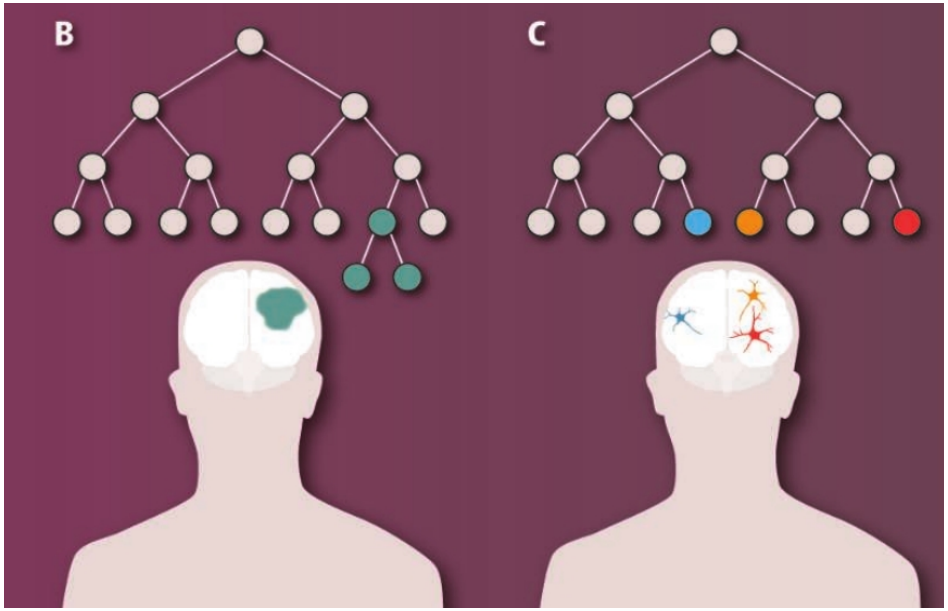


Behjati 2014 Nature

Female mosaicism
X inactivation pattern



Somatic transposition in human brain



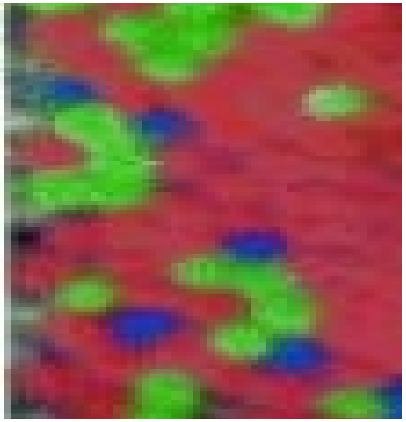
In three individuals:

in the hippocampus and caudate nucleus
7,743 somatic L1 insertions, 13,692 somatic Alu insertions and 1,350 SVA insertions

Baillie 2011 Nature

Developmental noise

Differences between left and right sides of the body

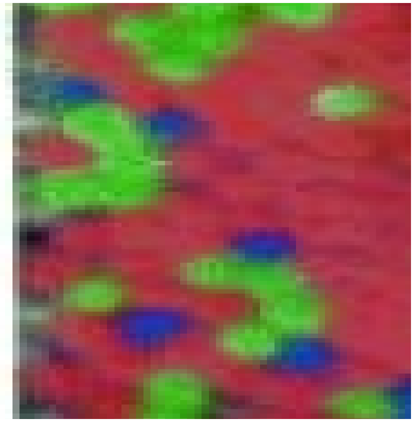
   

ear shape, neuron connectivity, olfactory receptor gene expression, X inactivation pattern, organ cell number and size...

Developmental noise

Differences between left and right sides of the body






ear shape, neuron connectivity, olfactory receptor gene expression, X inactivation pattern, organ cell number and size...

Differences between twins

immune system cells, gait, arms crossing, voice, heart beat, brain waves...

Some can be attributed to variation in the number of determinant molecules

During terminal differentiation of mouse 3T3-L1 pre-adipocytes, individual TF abundance differs dramatically (from ~250 to >300,000 copies per nucleus) and the dynamic range can vary up to fivefold during differentiation.

Simicevic 2013 Nature

Causes of phenotypic differences ?

Genetic

Epigenetic

Environment

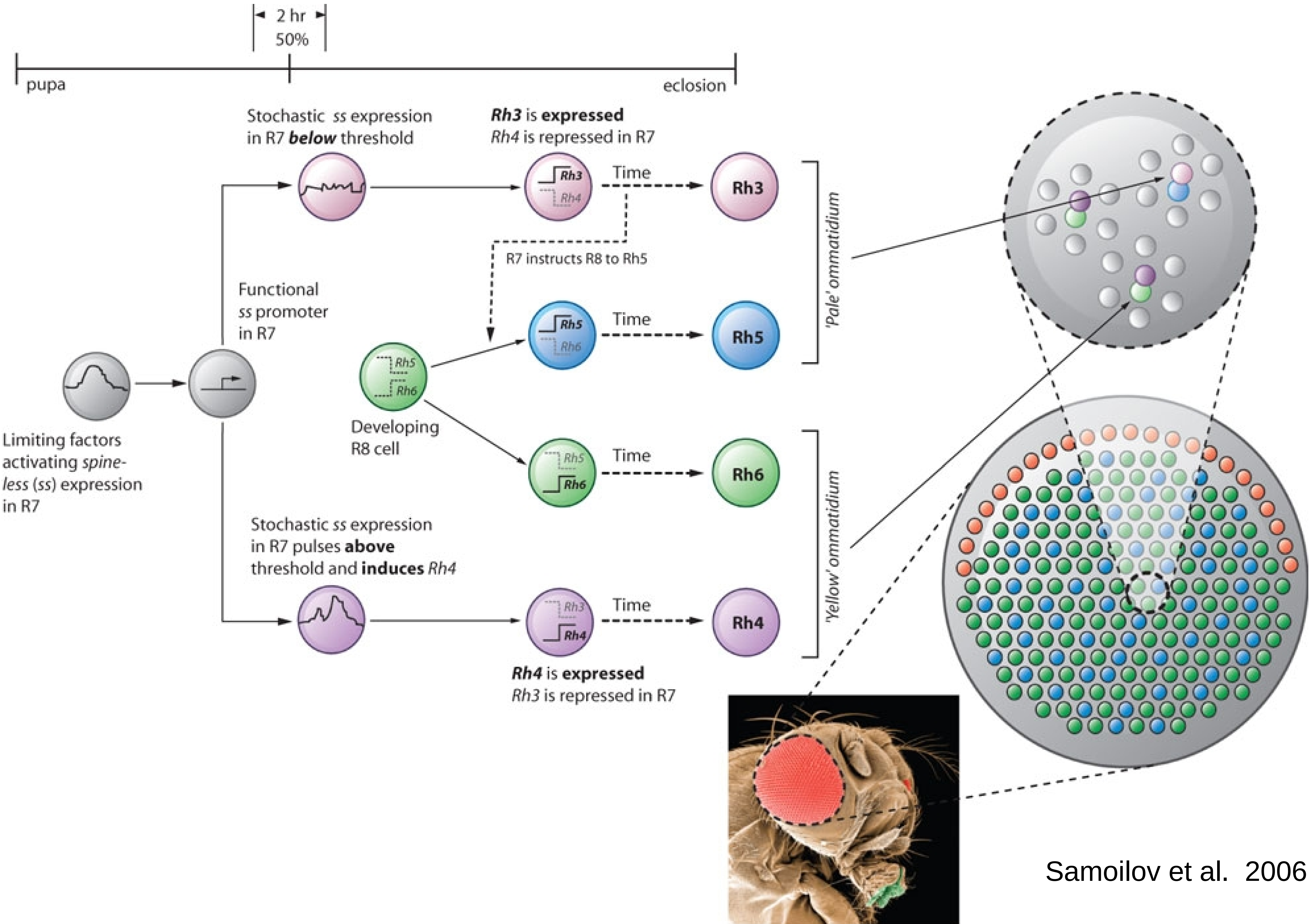
Stochasticity

Transmitted

Determistic

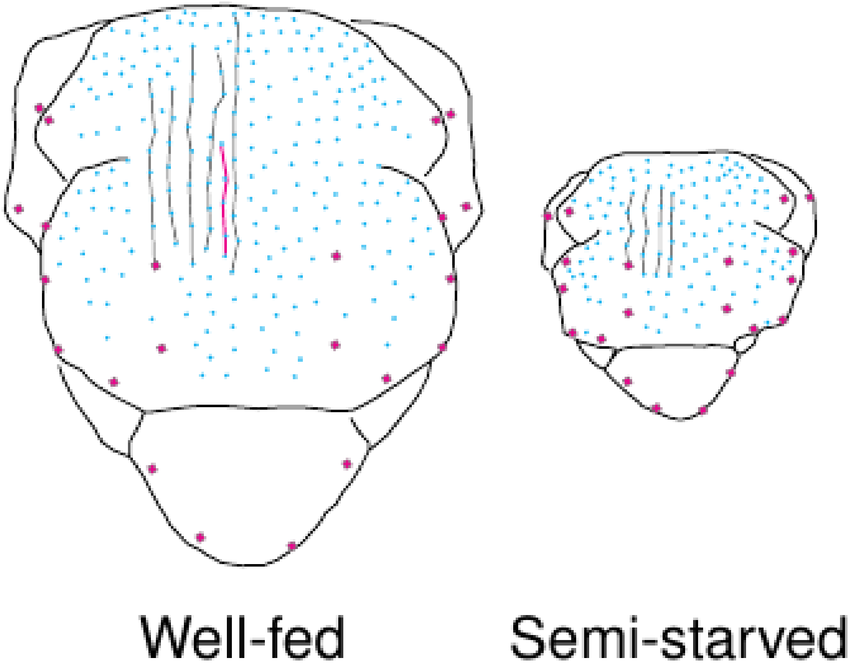
Interactions

Developmental noise can be "good"



Samoilov et al. 2006

Robustness



Robustness

Absence or low variation of a phenotype when faced with an incoming variation

1) Of what?

2) To what?

To either:
- stochastic variation
- environmental variation: specify
- genetic variation: specify

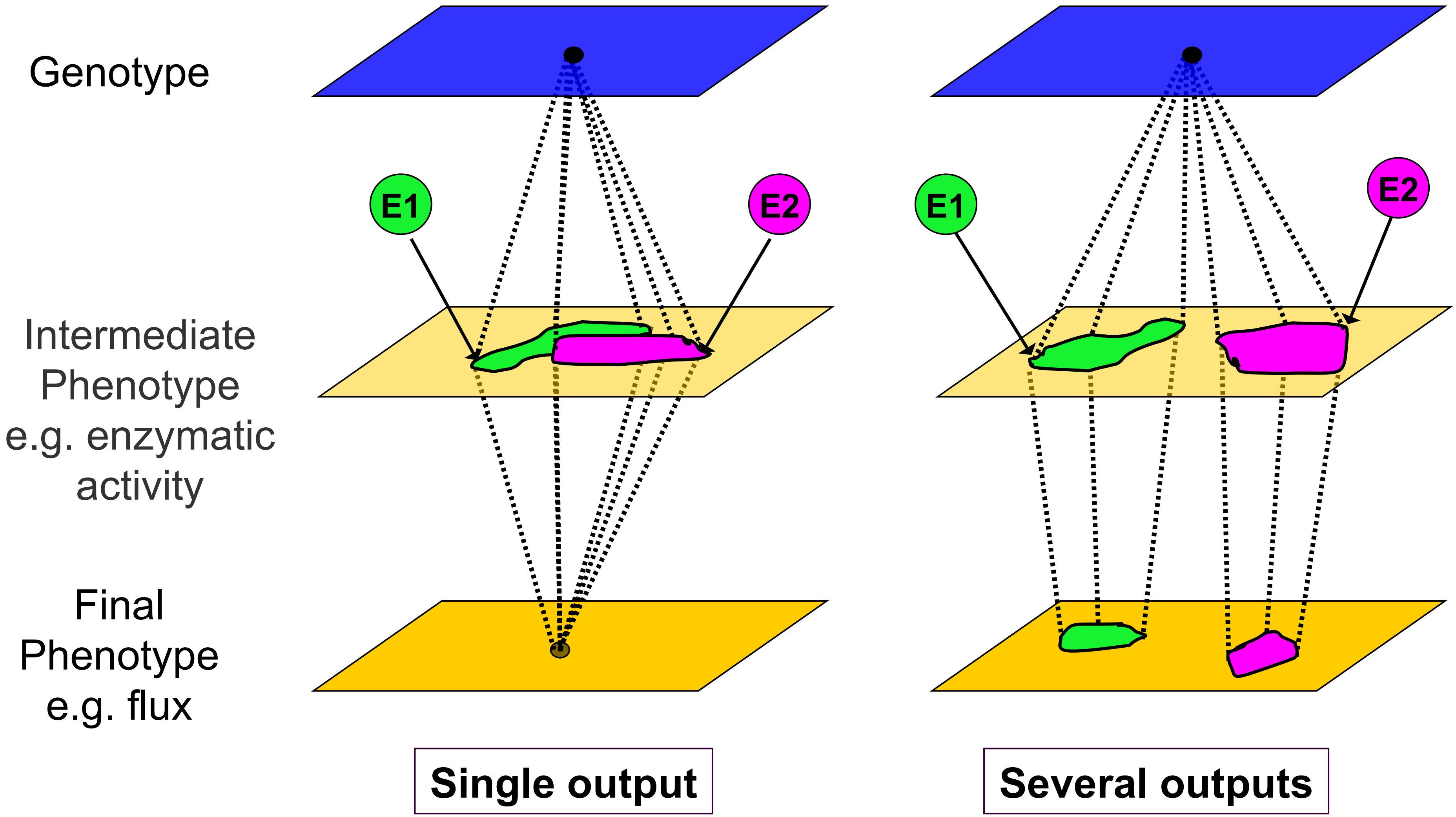
3) How much?

Different phenotypic metrics
Coefficient of variation: standard deviation/mean

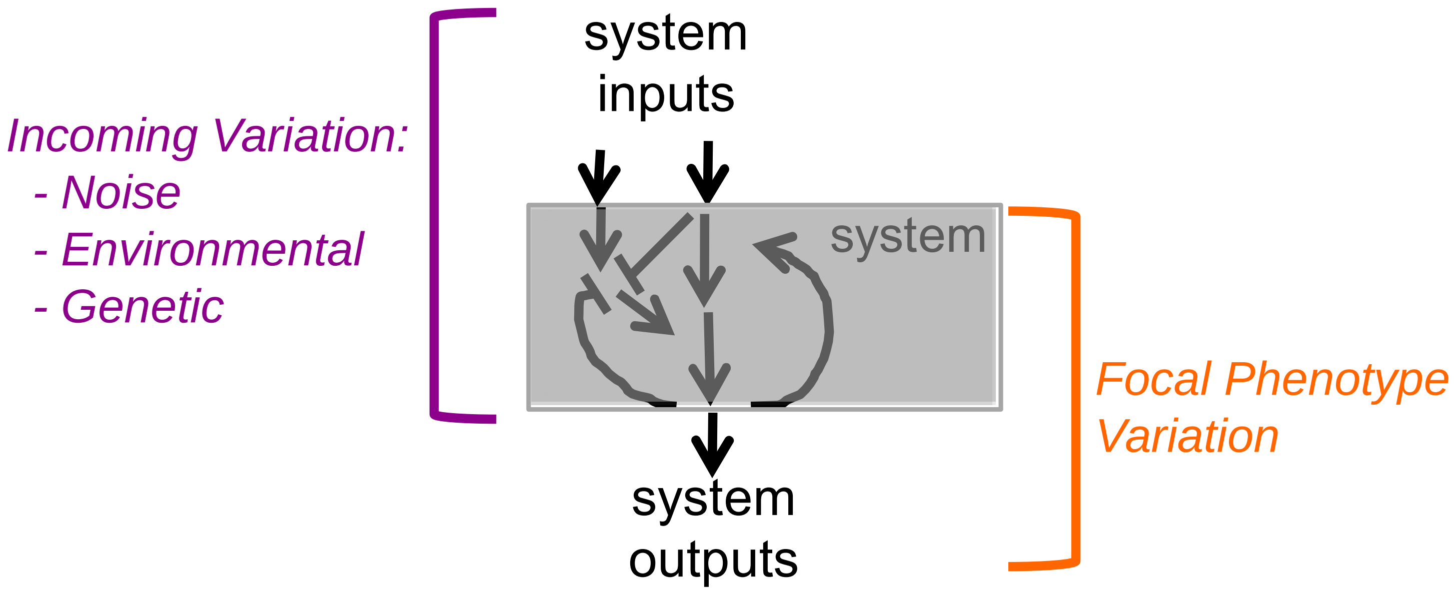
Historically:
quantitative genetics (low variance, canalization)
physics/chemistry/engineering (robustness, buffering)

Canalization: mechanisms that make the system follow a certain trajectory

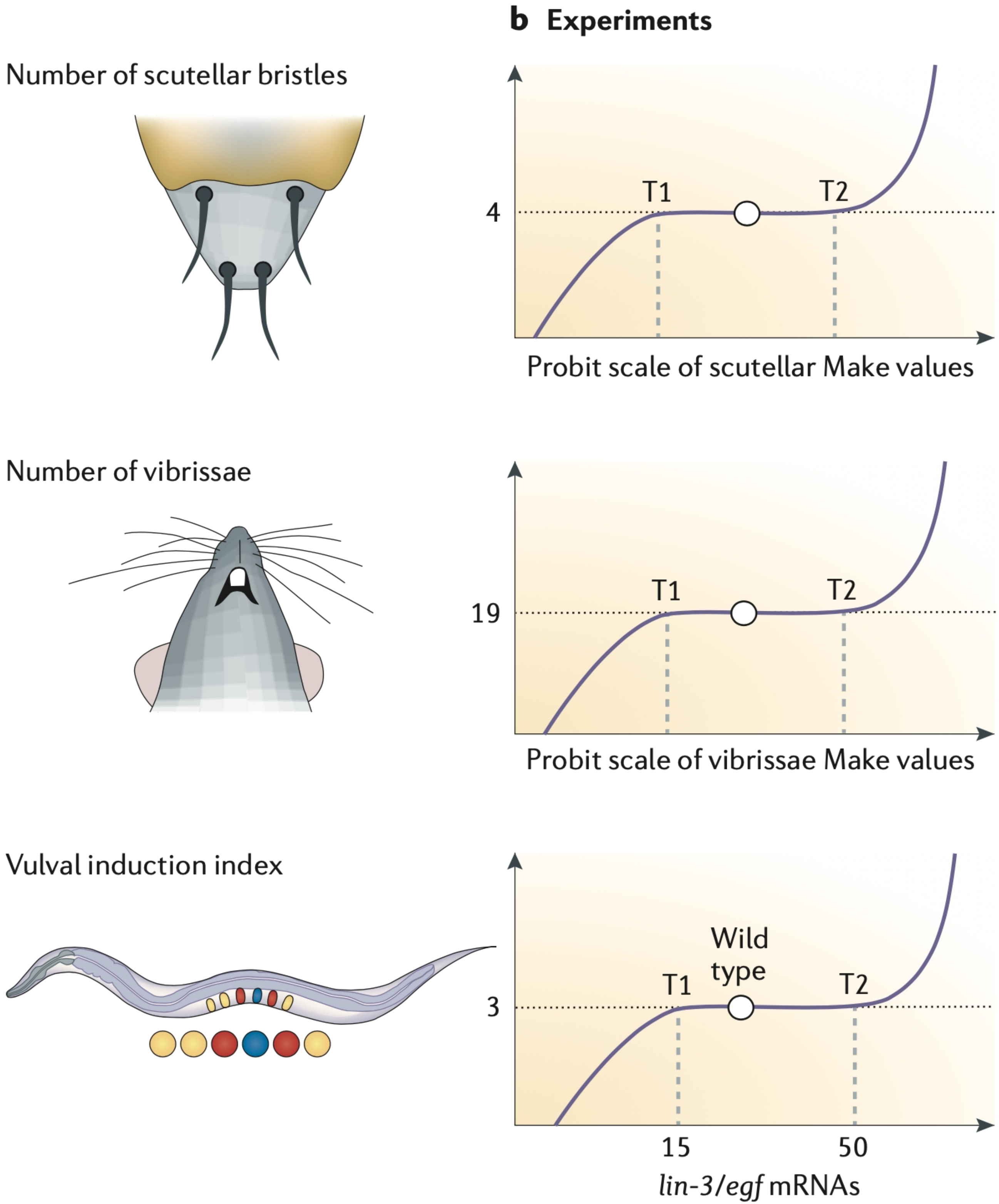
Trait plasticity versus invariance (robustness) at different levels of the genotype-phenotype map



Propagation of variation



Felix & Barkoulas 2015



Felix & Barkoulas 2015

Causes of robustness

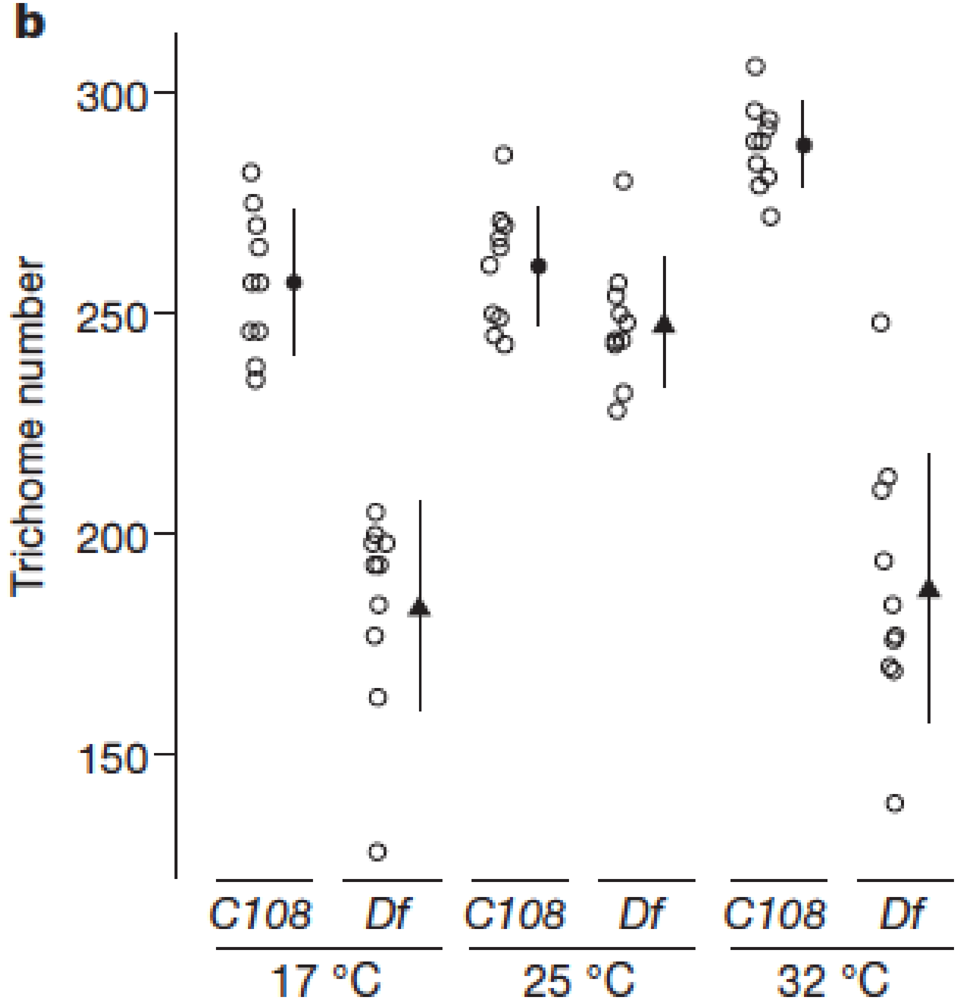
Non-linearity

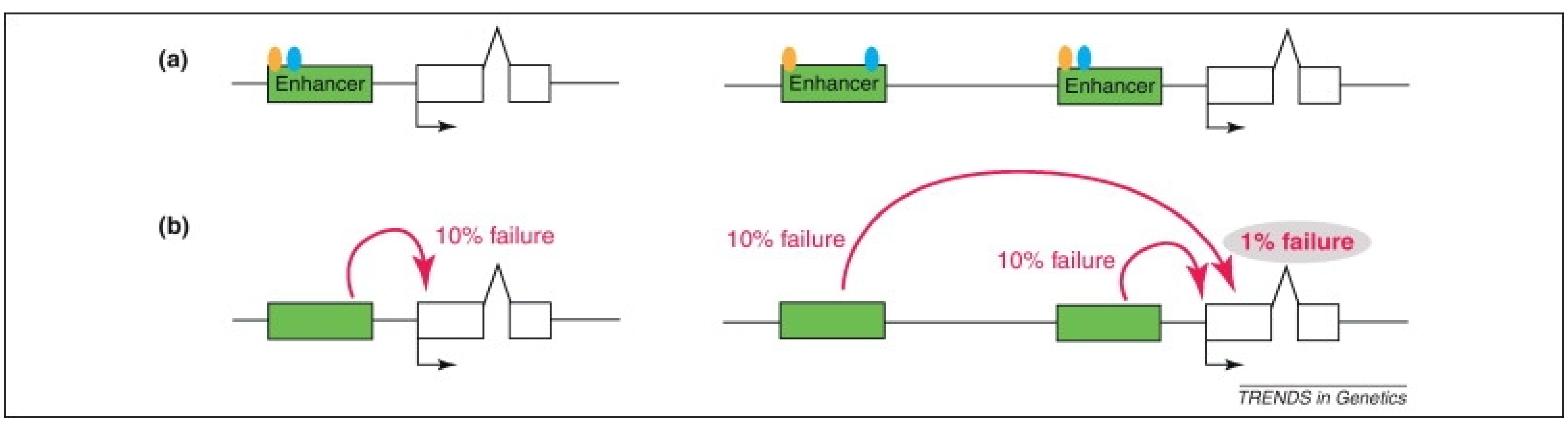
Redundancy

nature Vol 466|22 July 2010|doi:10.1038/nature09158

LETTERS

Phenotypic robustness conferred by apparently redundant transcriptional enhancers





Cryptic genetic variation

Cryptic genetic variation

First requires defining the *phenotype of interest*

Genetic variation that has no effect on phenotype of interest

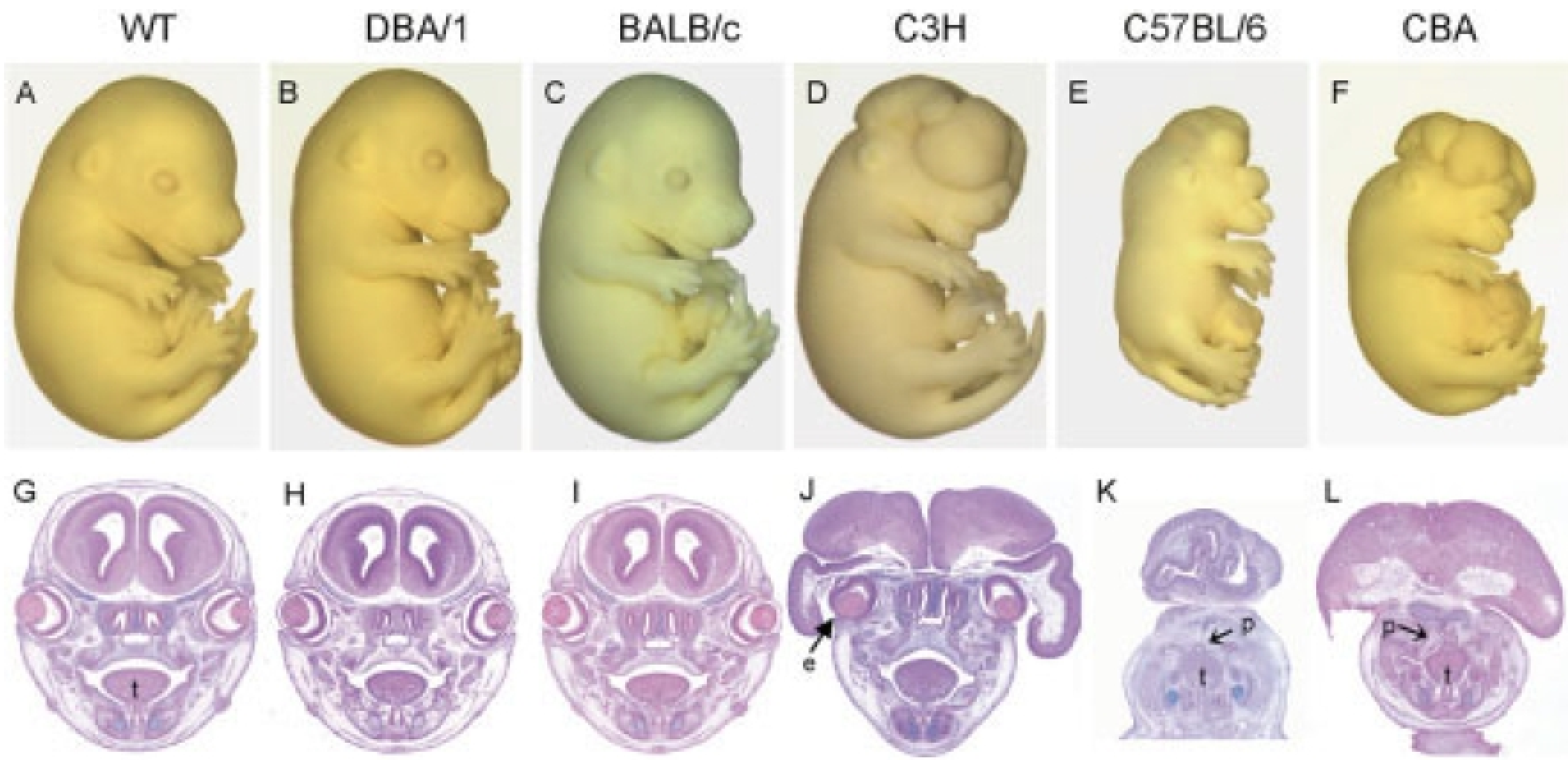
... but may be revealed *under some circumstances*
by its effect on this phenotype

Cryptic genetic variation (CGV) is defined as standing genetic variation that does not contribute to the normal range of phenotypes observed in a population, but that is available to modify a phenotype that arises after environmental change or the introduction of novel alleles.

Gibson & Dworkin *Nat Rev Gen* 2004

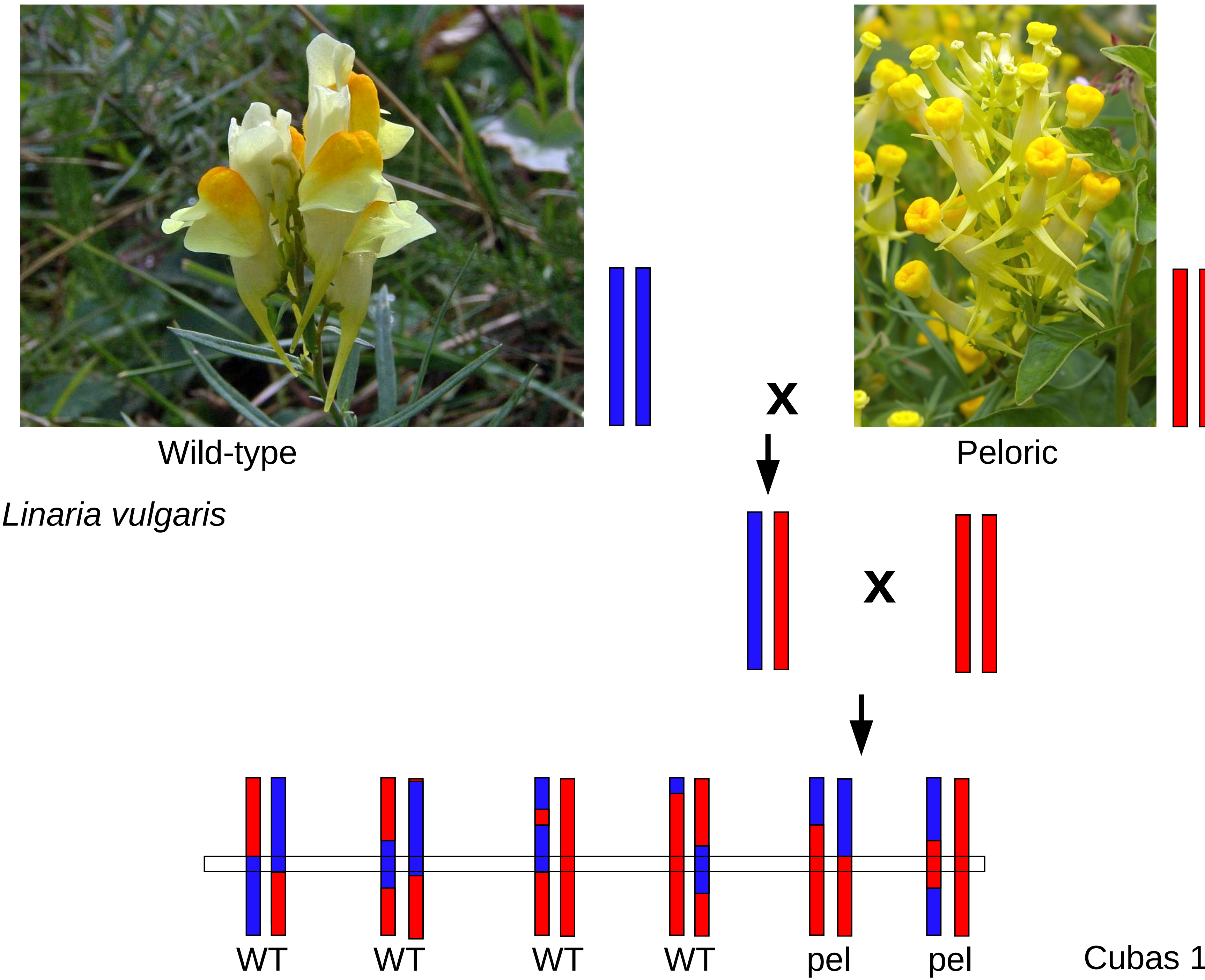
Expressivity of one mutation varies with wild genetic gackground

Tcof1/- heterozygote mice



Dixon & Dixon *Dev Dyn* 2004

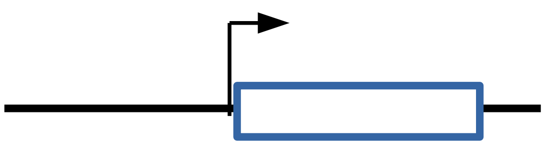
Epigenetics



Cubas 1999 Nature

An epimutation

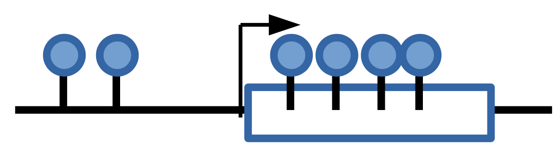
Wild-type



CYCLOIDEA

Presence of
CYCLOIDEA
proteins

Peloric



CYCLOIDEA

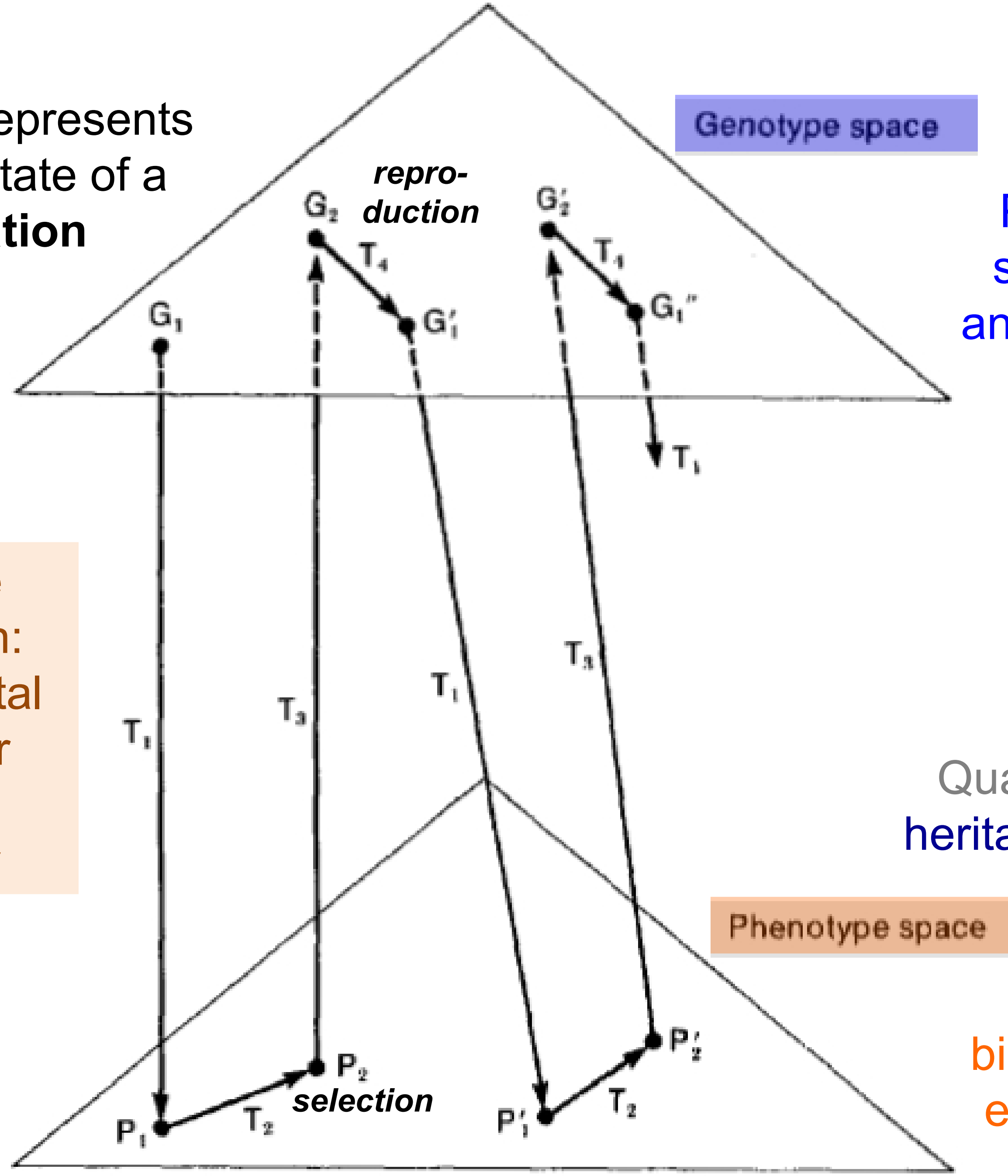
Methylated DNA

Absence of
CYCLOIDEA
proteins

The Genotype-Phenotype Map

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

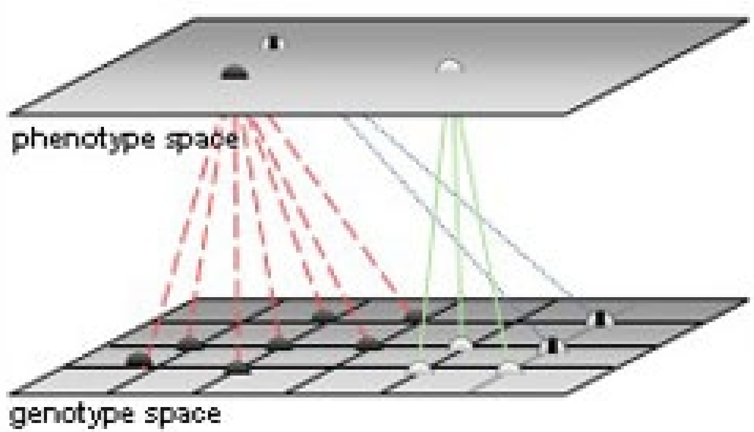
Quantitative genetics: heritability of phenotypes

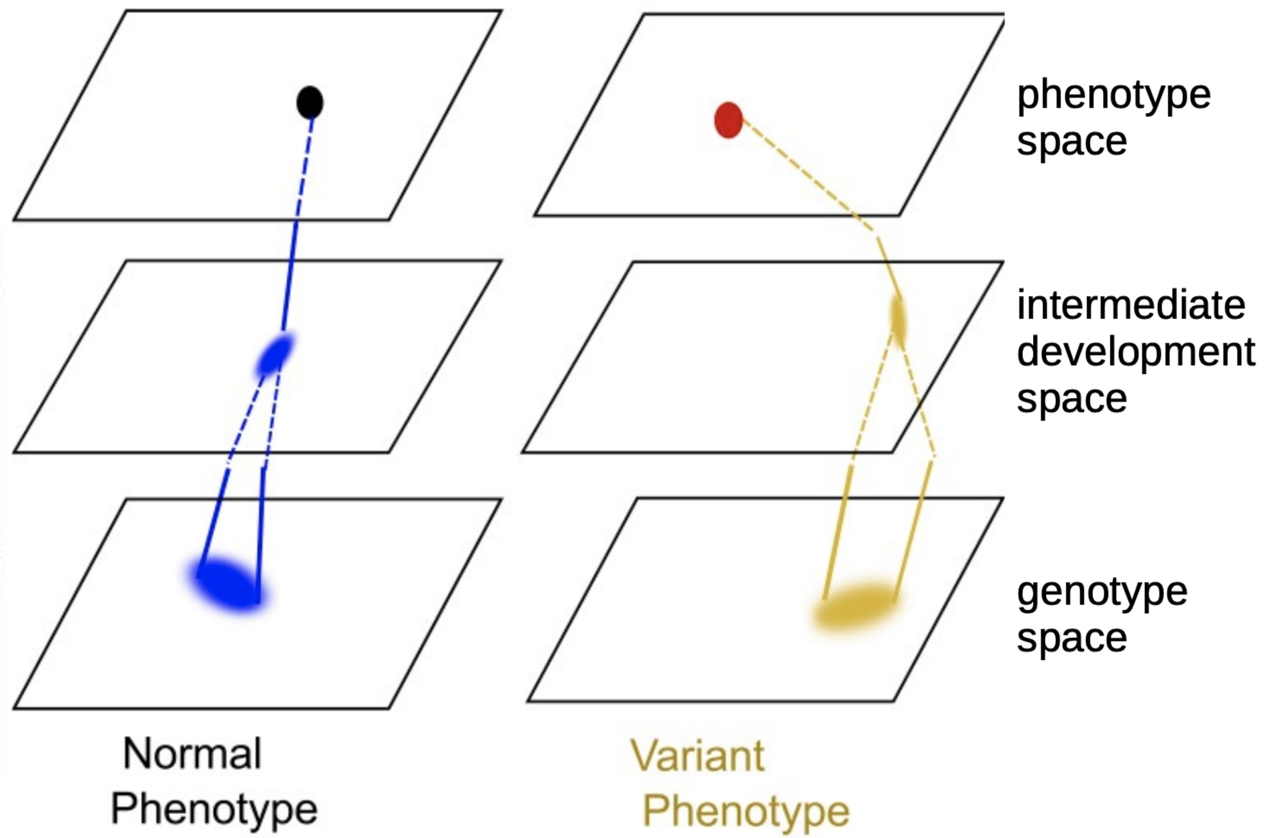
Evolutionary biology of phenotypes, evolutionary ecology

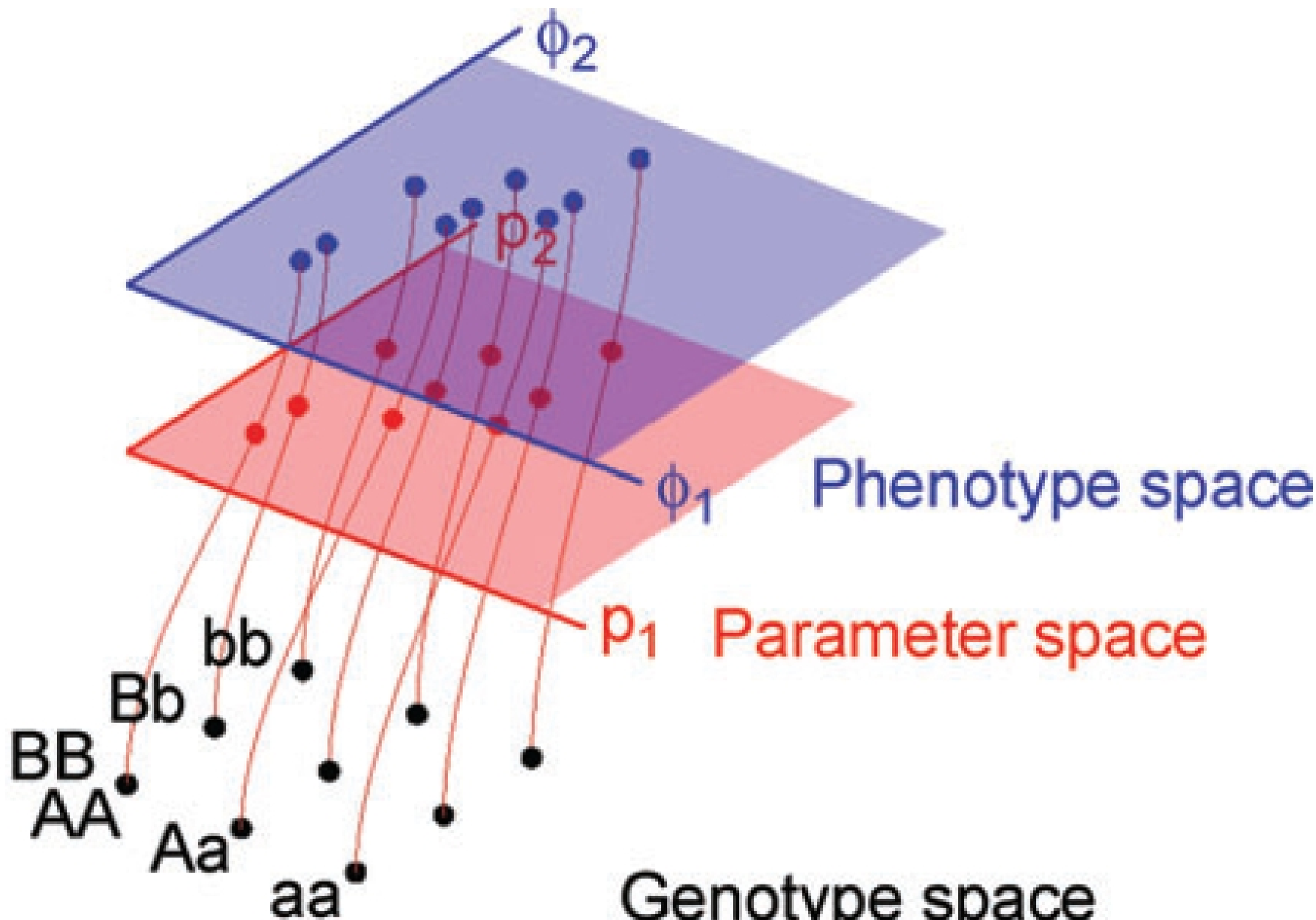
Lewontin 1974

Intermediate steps in the genotype-phenotype map

Here a dot represents one **individual**







Gjuvsland et al. 2013

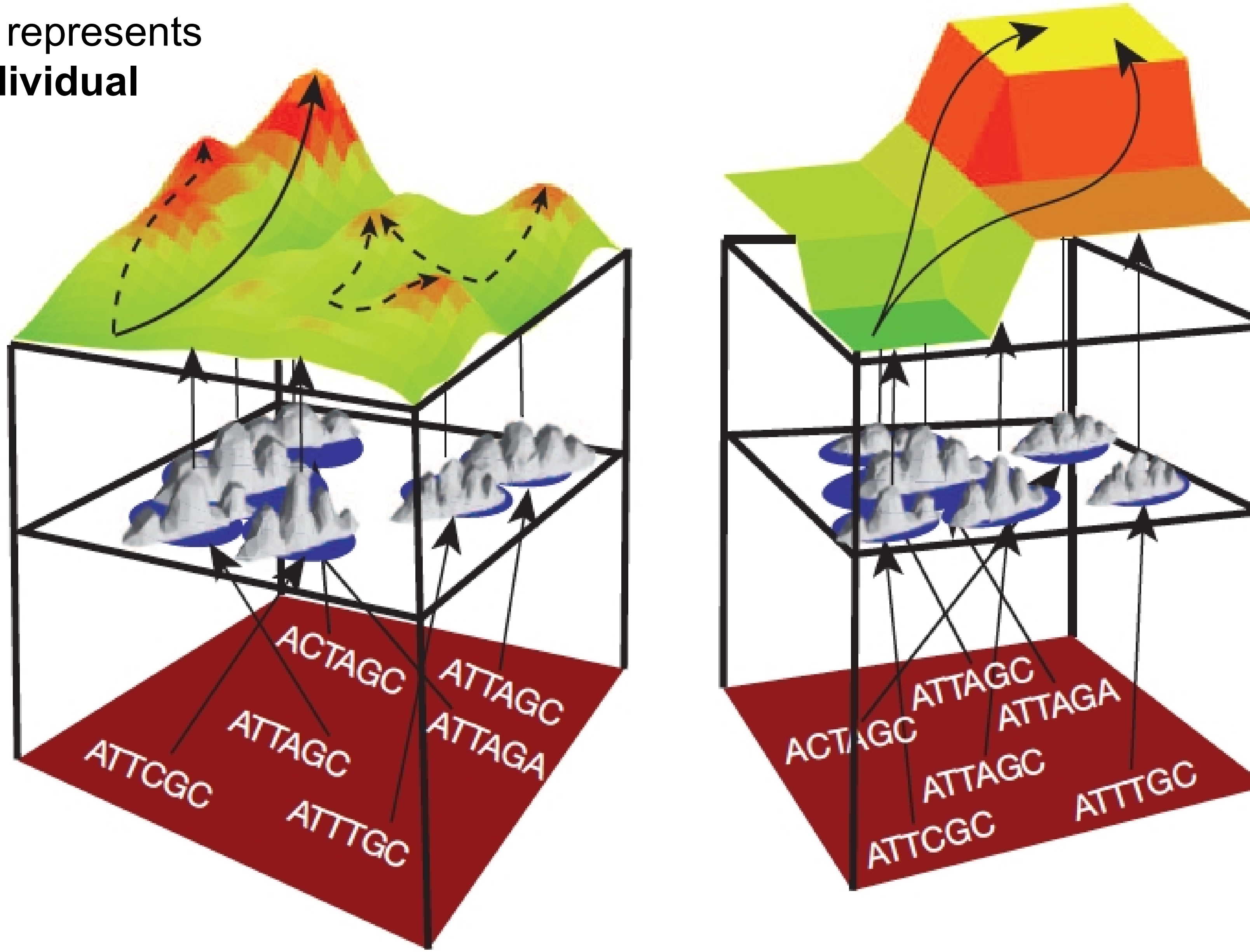
The genotype-phenotype-fitness map

Here a dot represents one **individual**

Fitness

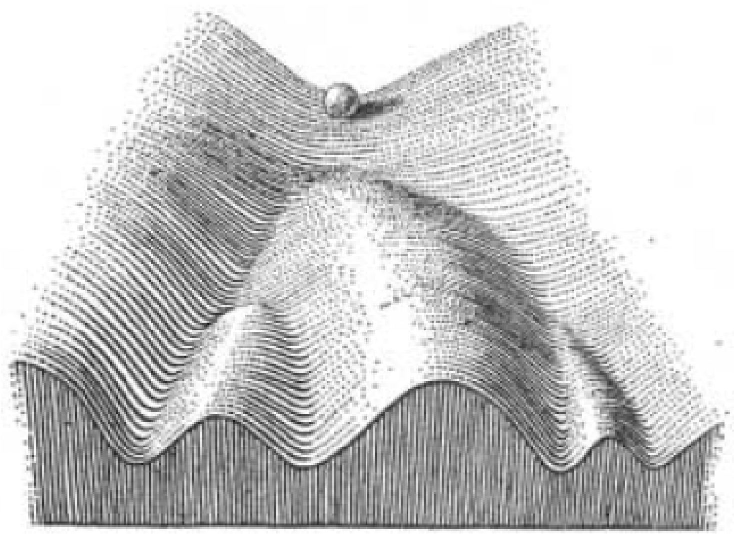
Phenotype
Tooth
morphology

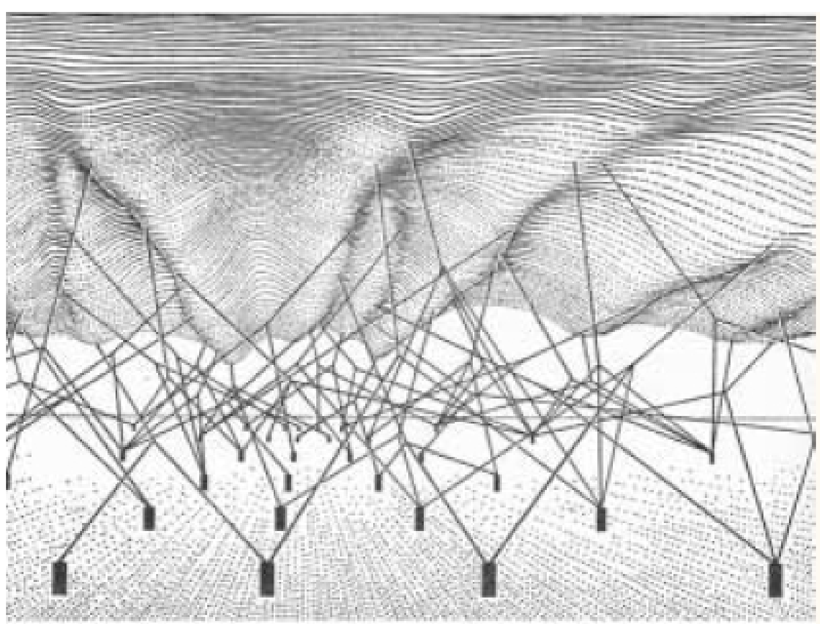
Genotype



Salazar-Cuidad & Martin-Riera 2013

The Epigenetic Landscape
A metaphor for the G-P relationship



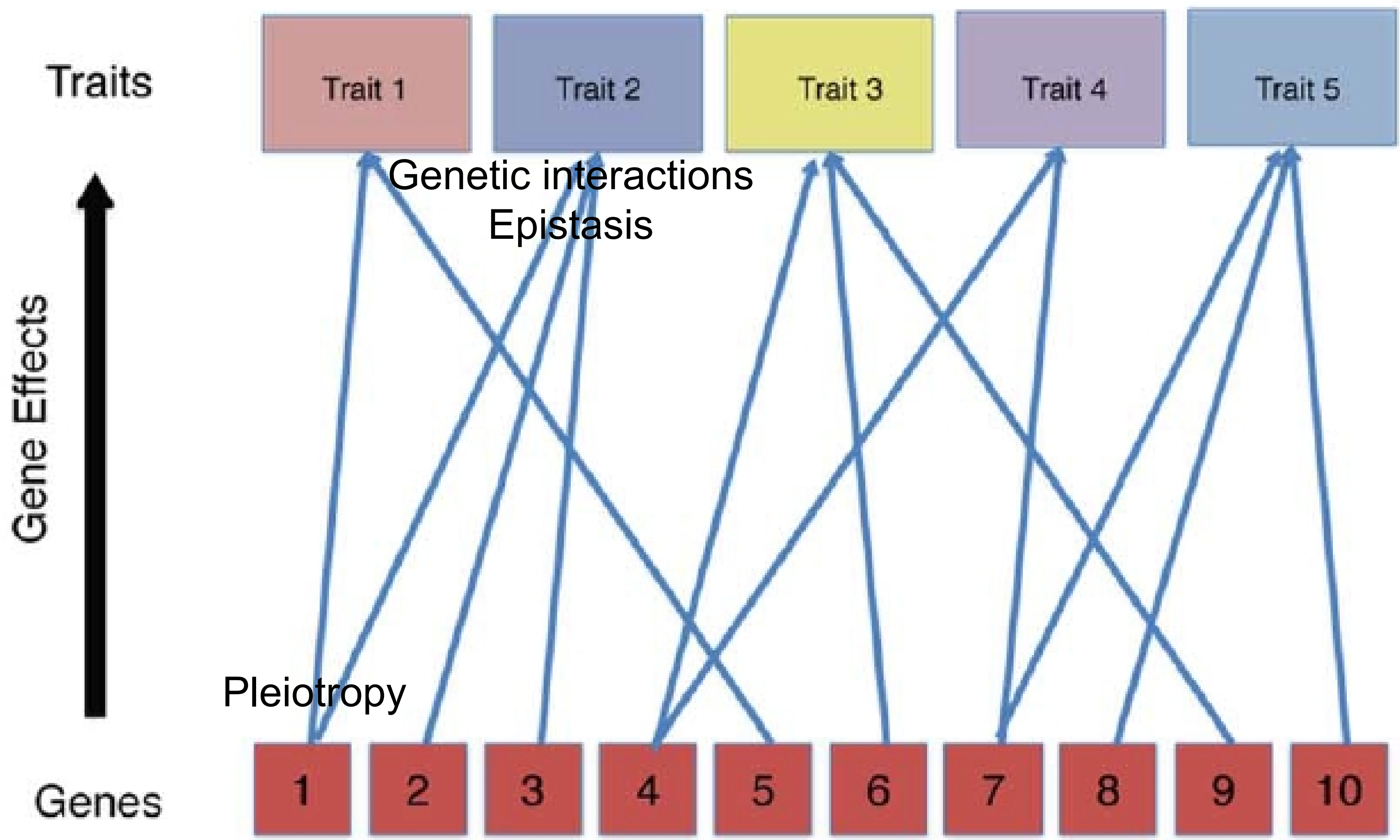


Development

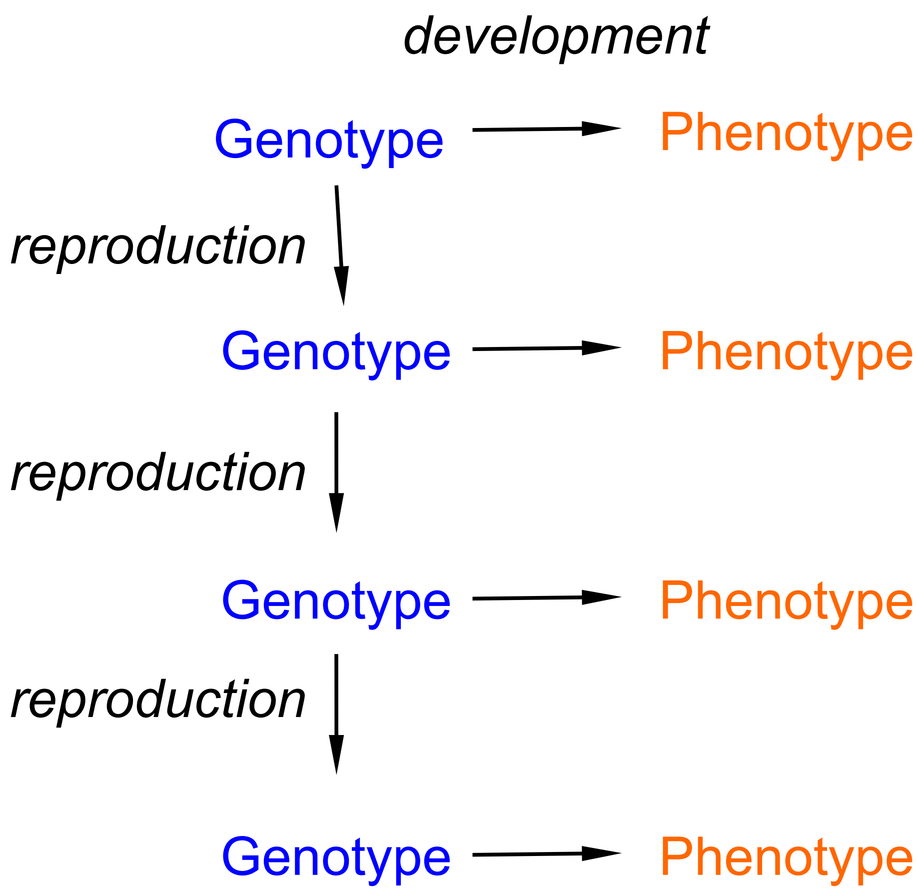
Canalization

Genes underlying
the landscape

Waddington 1957



Hallgrimsson et al. 2014


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

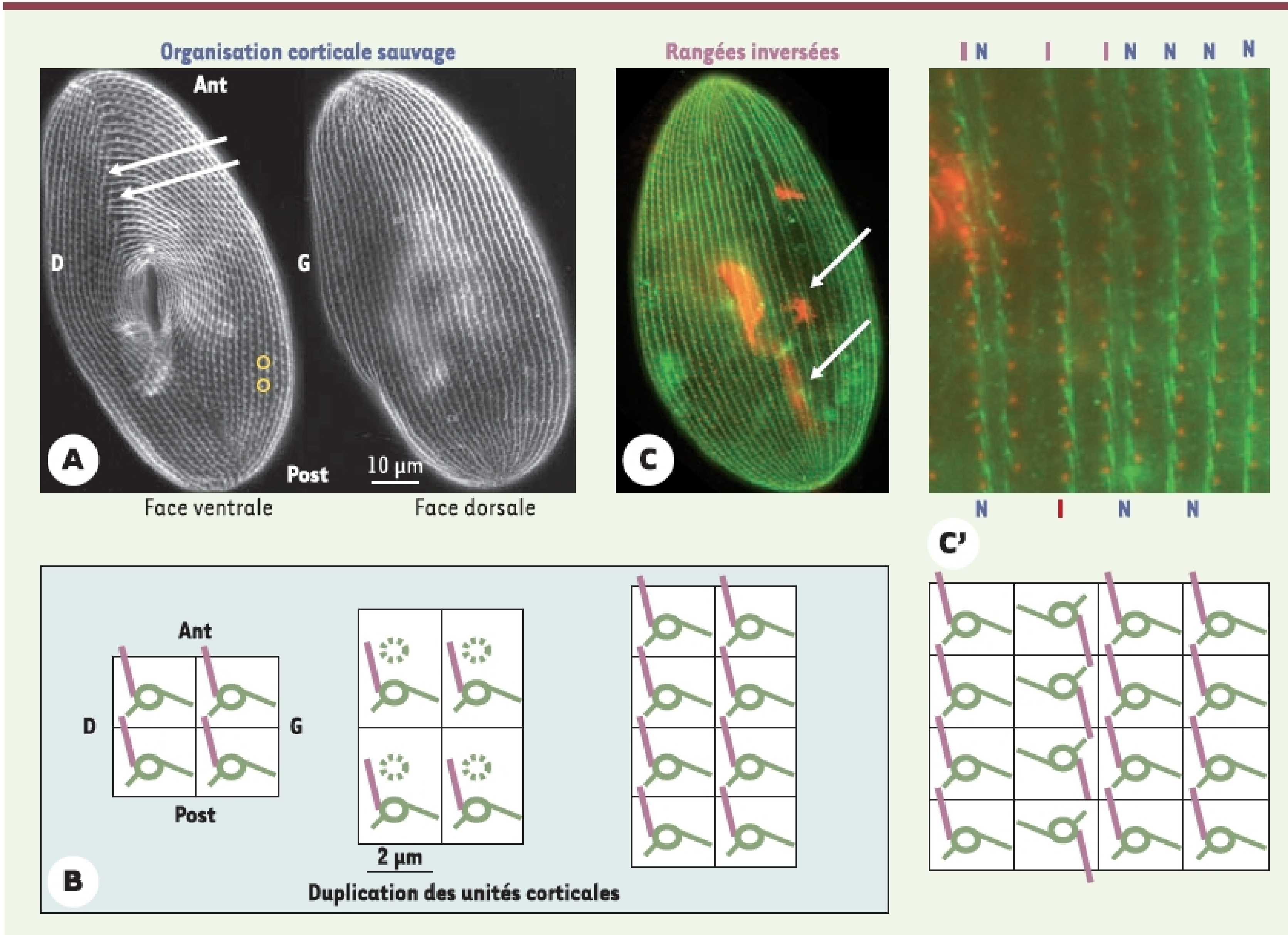
Heritable traits are not always due to genes

The genotype does not determine entirely the phenotype

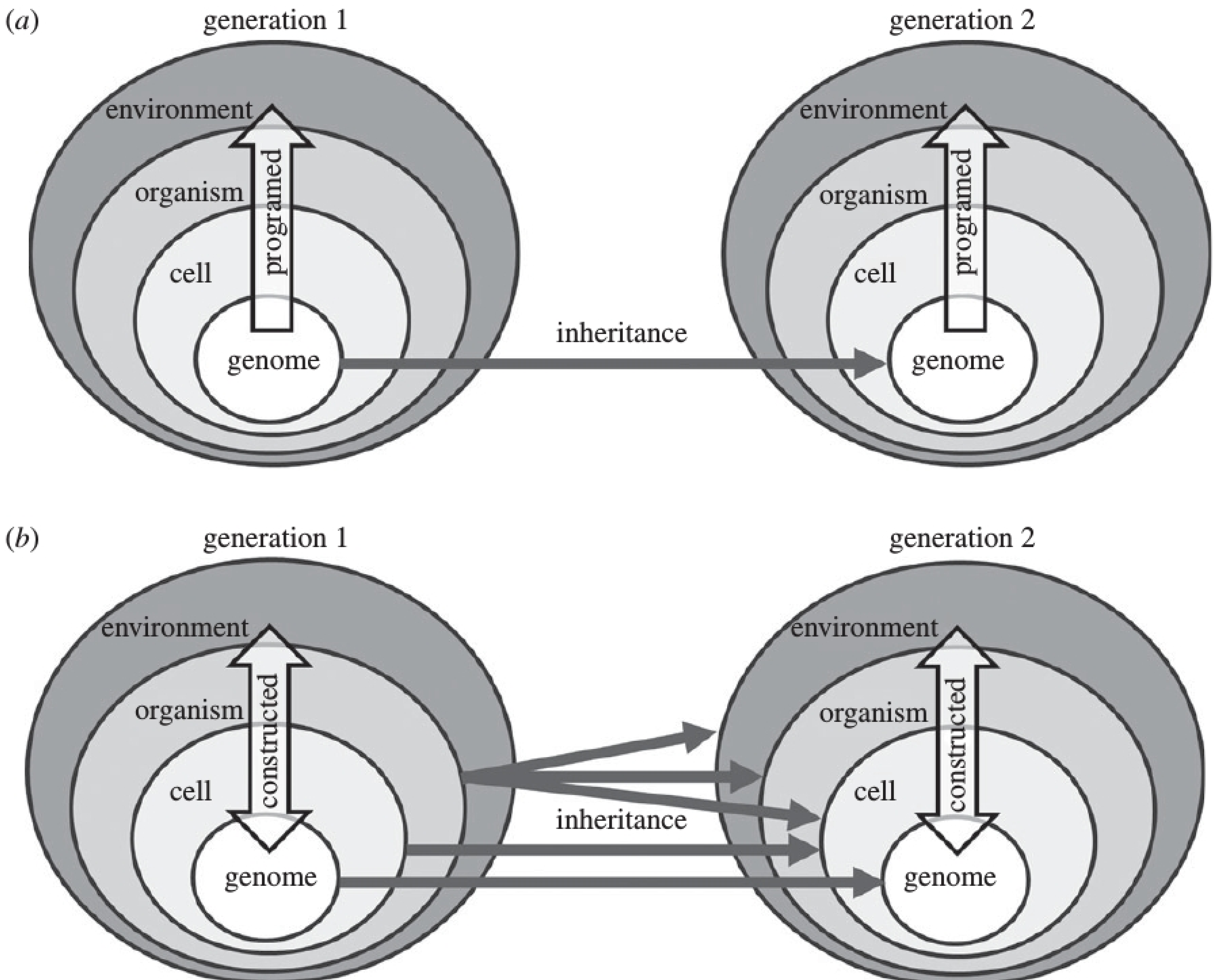
The genotype cannot replicate by itself

Genotype and phenotype imply variation

Cortical heredity in *Paramecium*



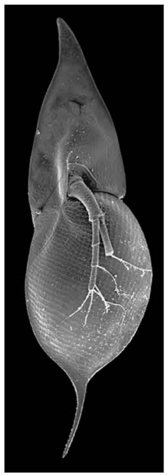
Meyer & Beisson M/S 2005

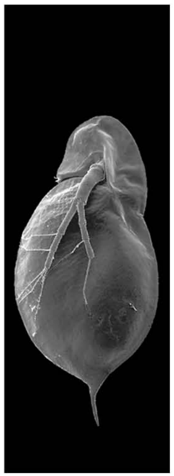

(a)
generation 1
generation 2
environment
organism
cell
programed
genome
inheritance
environment
organism
cell
programed
genome
(b)
generation 1
generation 2
environment
organism
cell
constructed
genome
inheritance
environment
organism
cell
constructed
genome

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

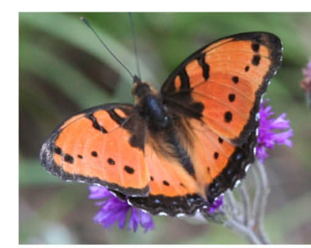
Desert locusts


solitary


gregarious

Commodore butterfly


winter


summer

Complexifications of the G-P map

Genetic Linkage

Epistasis

Supergene

Pleiotropy

GxE
Plasticity

Large number of alleles

Noise

Robustness

Cryptic genetic variation

Epigenetics