BIO-373

Genetics & Genomics

Extension of Mendelian Genetics

Sebastian M. Waszak

School of Life Sciences

Laboratory of Computational Neuro-Oncology

Why do we need to go beyond Mendelian genetics?

Why do we need to go beyond Mendelian genetics?

Many phenotypes cannot be explained by Mendel's laws

➔ Co-dominance, incomplete dominance, epistasis, multiple alleles, lethal alleles, genomic imprinting…

Contents

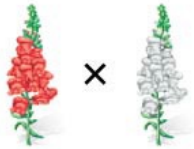
1. Incomplete (or partial) dominance

Incomplete (or partial) dominance

- Neither allele is dominant → intermediate phenotype
- **Each genotype has its own phenotype**

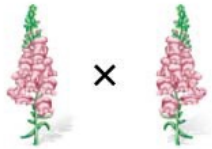
- Botanical example: snapdragon
- Cross between red and white flowers
  - F_1 offspring: pink flowers
  - F_2 generation: 1/4 red, 1/2 pink, 1/4 white
  - **Phenotypic and genotypic ratios are the same**

$R^1 R^1$ red × $R^2 R^2$ white — P_1



$R^1 R^2$ pink — F_1

$R^1 R^2 \times R^1 R^2$ — $F_1 \times F_1$



1/4 $R^1 R^1$ red
1/2 $R^1 R^2$ pink
1/4 $R^2 R^2$ white — F_2

2. Codominance

Codominance

- No dominance or recessiveness
- No incomplete or blending
- Joint expression of both alleles in a heterozygote
- Possible when 2 alleles have distinct phenotypic expression

Example of codominance in humans

- **MN Blood Group**
- M and N are two distinct forms of a glycoprotein that can be expressed on red blood cells
- Alleles L^M and L^N

Genotype	Phenotype
$L^M L^M$	M
$L^M L^N$	MN
$L^N L^N$	N

3. Multiple alleles of a gene

Multiple alleles

- Mutations can modify a gene in various ways → 3 or more alleles of the same gene might exist
- The resulting mode of inheritance is unique
- This can only be studied in populations and not in single individuals (who always carry two alleles per genetic locus)

ABO blood groups

- ABO blood group is controlled by a single gene (*ABO* on chromosome 9)
- *ABO* is an enzyme that modifies antigens on the surface of red blood cells (RBCs)
- *ABO* blood group is important for blood transfusion and organ transplantation
- Three possible alleles of a single ABO gene (*I* for isoagglutinogen, another term for antigen)
  - I^A → produces an enzyme that results in **A antigen** on RBCs
  - I^B → produces an enzyme that results in **B antigen** on RBCs
  - ***i*** → produces an inactive enzyme and results in the **O blood group**

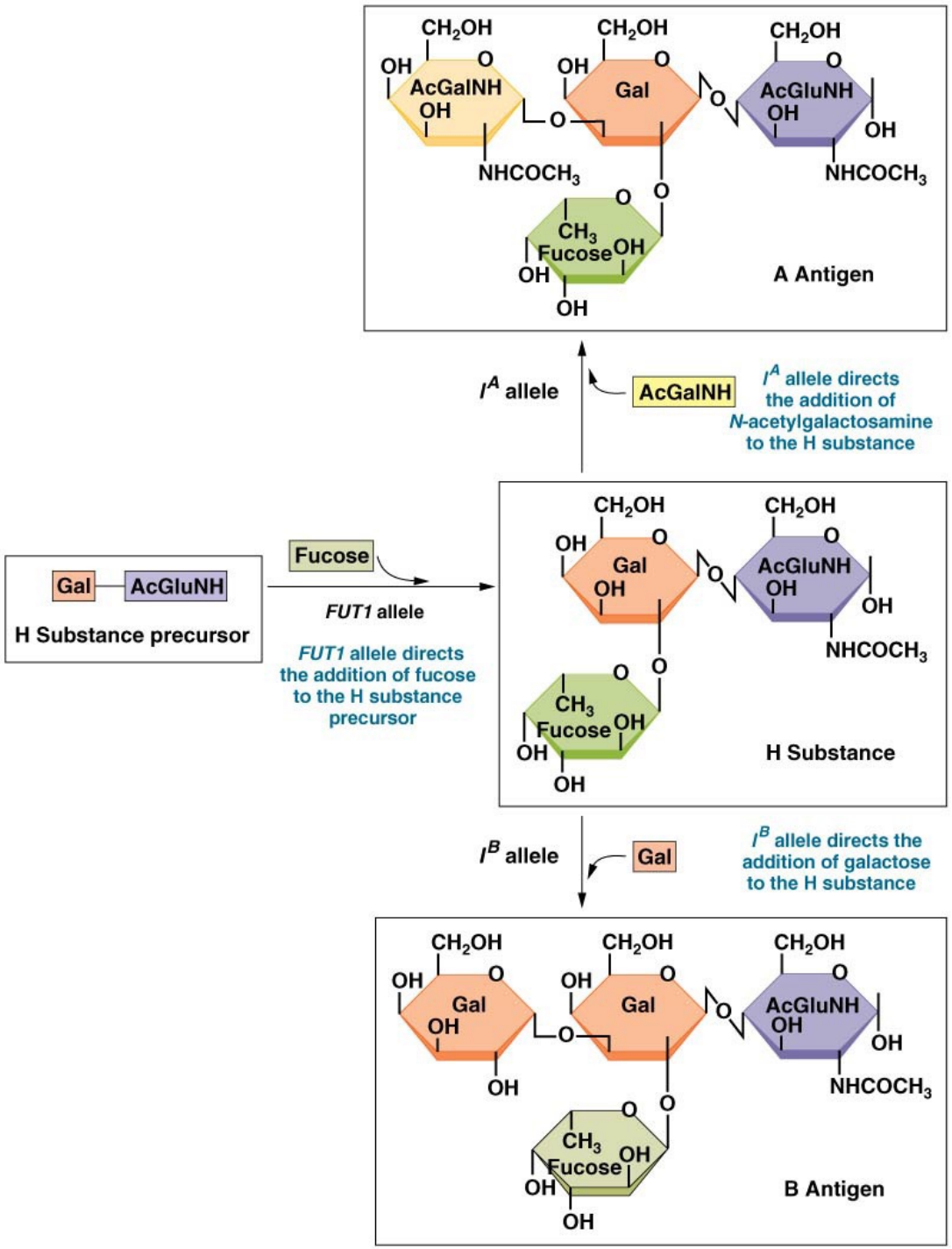
Genotype	Antigen	Phenotype
$I^A I^A$	A	A
$I^A i$	A	
$I^B I^B$	B	B
$I^B i$	B	
$I^A I^B$	A, B	AB
$i i$	Neither	O

I^A and I^B are dominant to *i*

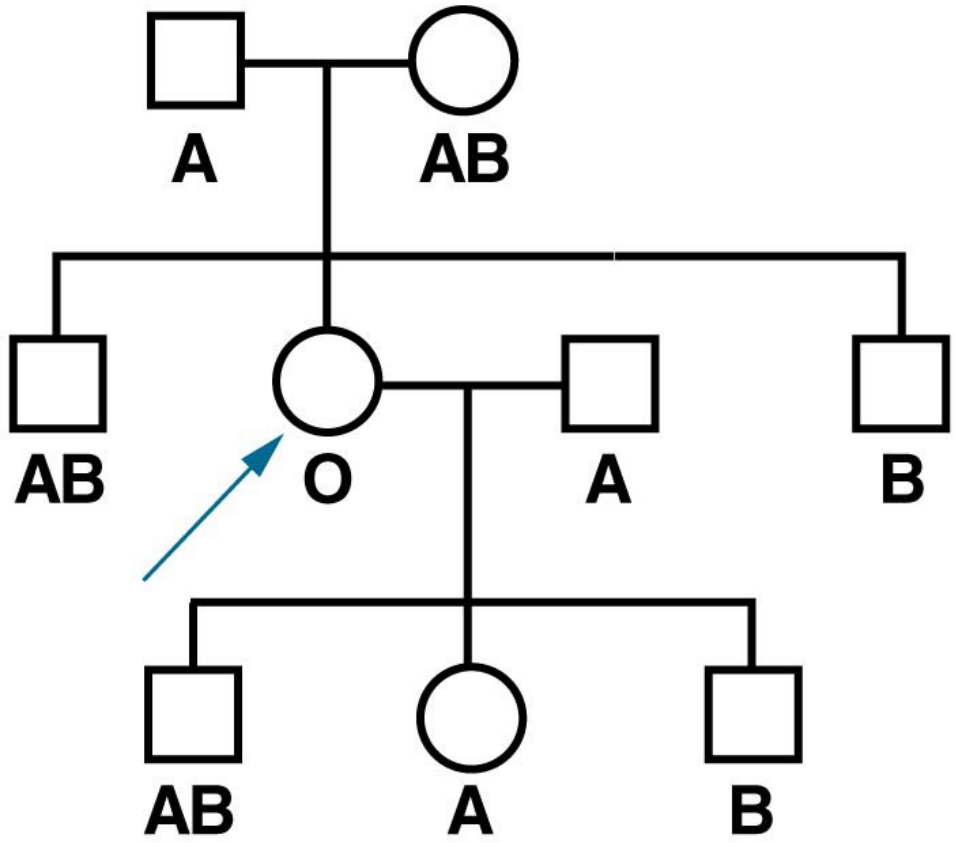
I^A and I^B are codominant to each other

ABO blood groups

- **A and B antigens**
  - Carbohydrate groups (N-Acetylgalactosamine for A antigen or galactose for B antigen) bound to H substance on red blood cells
- **H antigen (or also termed H substance)**
  - H antigen is the precursor to ABO antigens
  - Basic sugar layer at the surface of red blood cells
  - O blood types (*ii*) only have the H antigen (O stands for “Ohne” in German)


A Antigen
I^A allele
AcGalNH
I^A allele directs the addition of N-acetylgalactosamine to the H substance
Gal
AcGluNH
H Substance precursor
Fucose
FUT1 allele
FUT1 allele directs the addition of fucose to the H substance precursor
H Substance
I^B allele
Gal
I^B allele directs the addition of galactose to the H substance
B Antigen

A more complex case



Bombay phenotype

- Type O female, yet…
  - Mother has the AB antigen
  - Mother gave I^B allele to two other children
- Female found to be homozygous for a **FUT1** (fucosyl transferase) mutation
  - Prevents her from producing H antigen
  - No base substrate to make A or B antigens
  - Results functionally in type O

Bombay phenotype

- One gene (*FUT1*) is masking the phenotypic effect of another one (*ABO*)
- Very rare allele
  - 1:10’000 in India
  - 1:100’000 in Europe
- Individuals with Bombay phenotype can only receive blood transfusion from Bombay donors

4. Lethal alleles and essential genes

Essential genes and lethal alleles

- Absolutely required for survival
- May contain lethal alleles

- **Dominant lethal allele**: the presence of a single copy is incompatible with life
- **Recessive lethal allele**: tolerated in heterozygous state

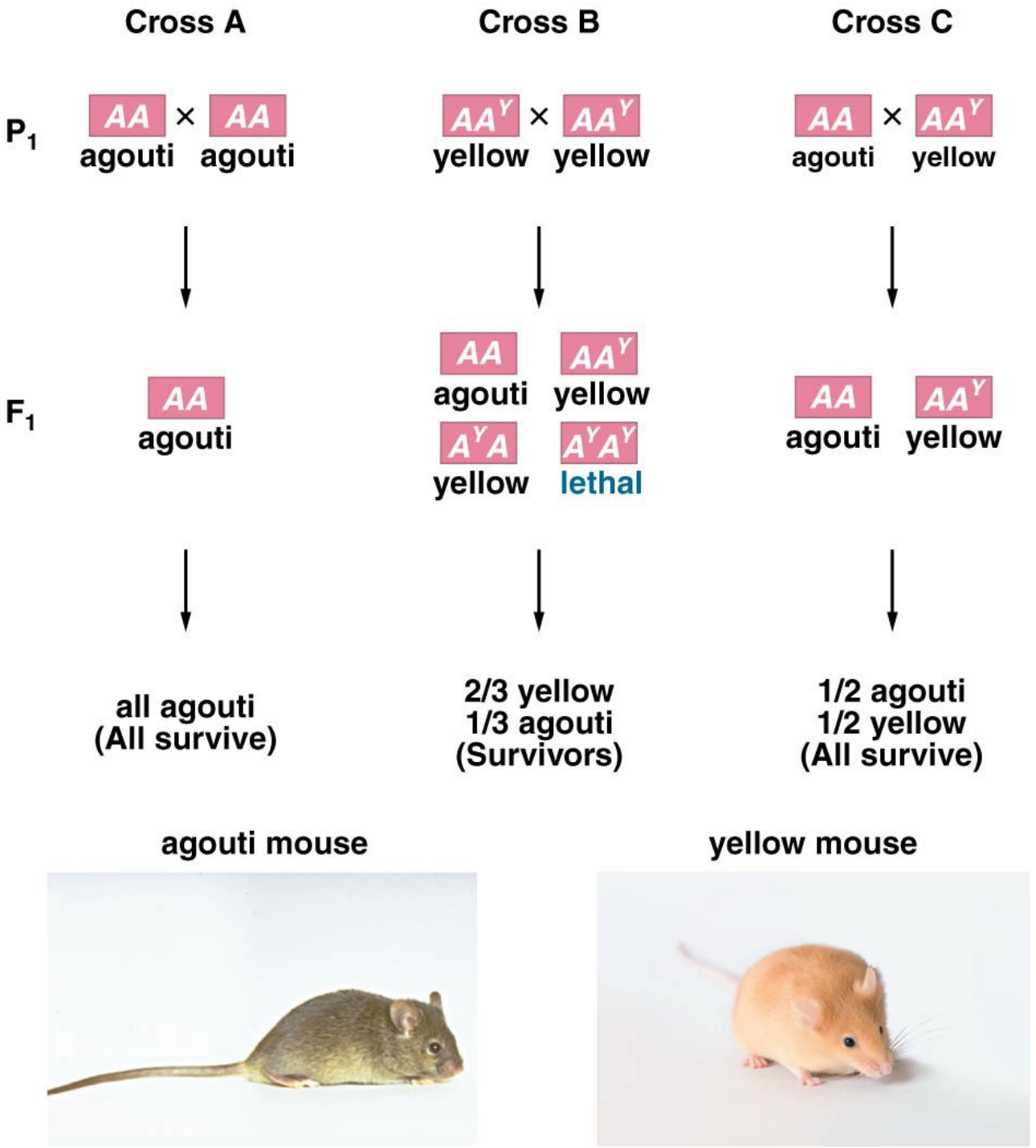
Dominant lethal allele in humans

- Huntington disease
  - Characterized by progressive degeneration of nervous system, dementia, and death
  - Due to allele *H* (abnormal number of CAG trinucleotide repeat in *HTT* gene)
  - Autosomal dominant = Hh genotype

Recessive lethal allele in mice

- **Agouti *(Asip)* gene:** responsible for coat color
  - Paracrine antagonist of MC1R on melanocytes
  - Agouti allele *A (eumelanin, black)*
  - Mutant *yellow* allele A^Y (phenomelanin, yellow)

Crosses				
(A) agouti	×	agouti	⟶	all agouti
(B) yellow	×	yellow	⟶	2/3 yellow: 1/3 agouti
(C) agouti	×	yellow	⟶	1/2 yellow: 1/2 agouti


Cross A
Cross B
Cross C
P1
AA × AA
agouti agouti
AAY × AAY
yellow yellow
AA × AAY
agouti yellow
F1
AA
agouti
AA AAY
agouti yellow
AYA AYAY
yellow lethal
AA AAY
agouti yellow
all agouti
(All survive)
2/3 yellow
1/3 agouti
(Survivors)
1/2 agouti
1/2 yellow
(All survive)
agouti mouse
yellow mouse

Recessive lethal allele in mice

- **Mutant allele** (A^Y)
  - Behaves dominantly to normal allele to control coat color
  - Behaves as homozygous recessive lethal allele
- Genotype $A^Y A^Y$ does not survive
- Why is the A^Y allele lethal*?*

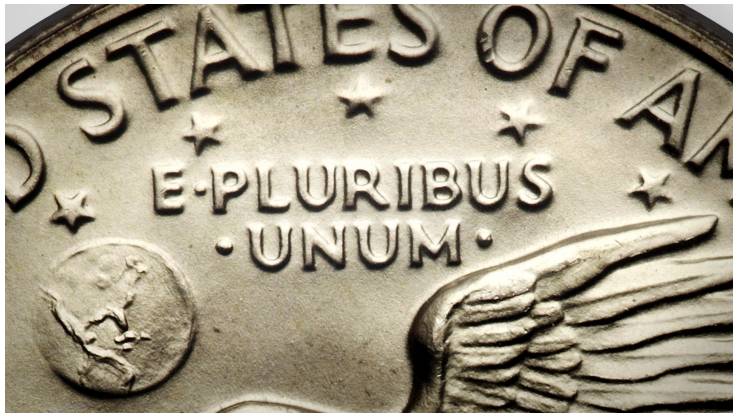
Recessive lethal allele in mice

- **Mutant allele** (A^Y)
  - Behaves dominantly to normal allele to control coat color
  - Behaves as homozygous recessive lethal allele
- Genotype $A^Y A^Y$ does not survive
- Why is the A^Y allele lethal*?*
  - The A^Y mutation is a large deletion that removes the *Raly* gene yet retains the *Raly* promoter
  - The *Raly* promoter drives expression of Asip (yellow coat color and other effects like obesity)
  - $A^Y A^Y$ is lethal due to complete loss of the *Raly* gene (essential for embryonic development)

5. Impact of multiple genes on a phenotype

E pluribus unum (“out of many, one”)

- Most phenotype result from the influence of multiple genes
- **Genic interaction**: several genes influence a trait; doesn’t imply direct interaction
- **Epistatic interaction**: direct interaction between alleles of different genes

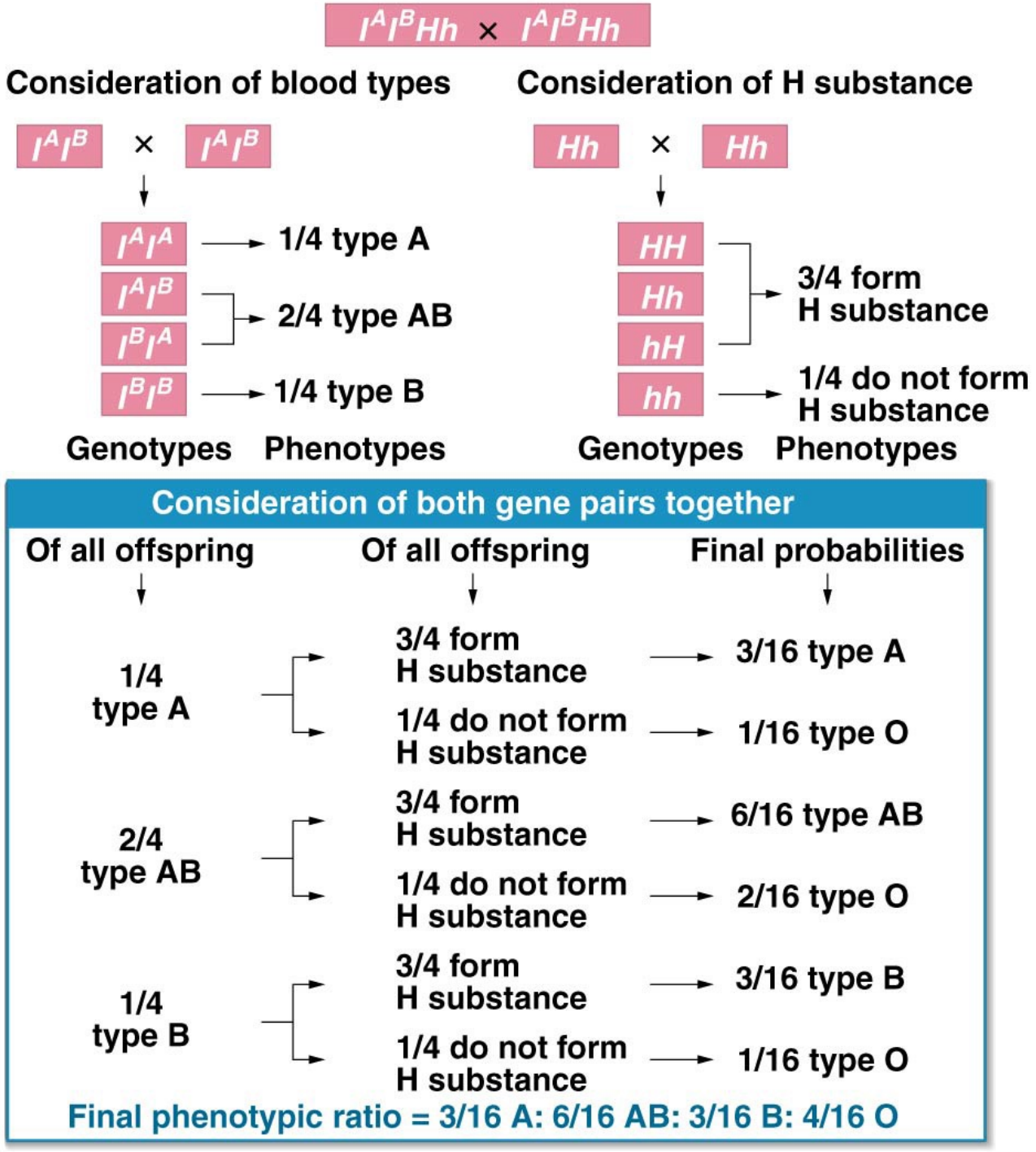


Example of genic interaction

- **Hereditary deafness**
  - Many genes are involved in ear formation
  - These genes interact to produce a common phenotype
  - Many mutations can interrupt development and lead to hereditary deafness

Example of epistasic interaction

- **Back to Bombay…**
  - First locus masks expression of second locus
  - Homozygous mutation in *FUT1* gene masks expression of I^A and I^B alleles
  - A and B antigen forms only when individual has at least one wild-type allele

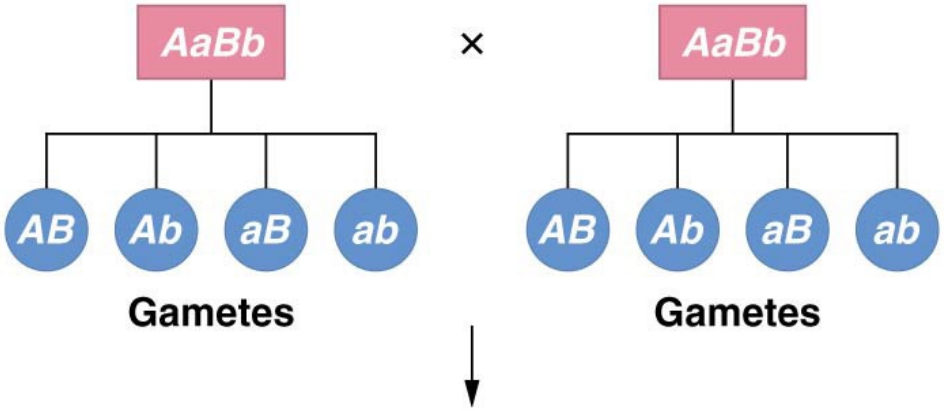

$I^AI^BHh \times I^AI^BHh$
Consideration of blood types
$I^AI^B \times I^AI^B$
I^AI^A → 1/4 type A
I^AI^B
I^BI^A → 2/4 type AB
I^BI^B → 1/4 type B
Genotypes
Phenotypes
Consideration of H substance
$Hh \times Hh$
HH
Hh
hH → 3/4 form H substance
hh → 1/4 do not form H substance
Genotypes
Phenotypes
Consideration of both gene pairs together
Of all offspring
Of all offspring
Final probabilities
1/4 type A
3/4 form H substance → 3/16 type A
1/4 do not form H substance → 1/16 type O
2/4 type AB
3/4 form H substance → 6/16 type AB
1/4 do not form H substance → 2/16 type O
1/4 type B
3/4 form H substance → 3/16 type B
1/4 do not form H substance → 1/16 type O
Final phenotypic ratio = 3/16 A: 6/16 AB: 3/16 B: 4/16 O

Impact of epistasis on phenotypic ratio

- Epistatic interactions modify the phenotypic ratios expected under Mendel's transmission laws.
- Dihybrid cross: 9:3:3:1
- Effect possible on one or more of four phenotypic categories

Digenic epistatic ratios:
gene interactions that modify mendelian ratios

- **No interaction (simple dominance):** 9:3:3:1
- **Dominant epistasis:** 12:3:1
  A dominant allele (A-) at one locus masks the other locus.
- **Recessive epistasis:** 9:3:4
  Homozygous recessive (aa) at one locus masks the other locus.
- **Duplicate recessive epistasis:** 9:7
  Need at least one dominant allele at both loci (A-B-) for the main phenotype.
- **Duplicate interaction:** 9:6:1
  Both dominants together give one phenotype, either single dominant gives a second; double recessive gives a third.
- **Duplicate dominant epistasis:** 15:1
  A dominant allele at either loci gives the same phenotype.



1/16 *AABB*
2/16 *AABb*
2/16 *AaBB*
4/16 *AaBb*
→ 1/16 + 2/16 + 2/16 + 4/16

1/16 *AAbb*
2/16 *Aabb*
→ 1/16 + 2/16

1/16 *aaBB*
2/16 *aaBb*
→ 1/16 + 2/16

1/16 *aabb*
→ 1/16

Dihybrid ratio	Modified ratios				
9/16 *A–B–*	9/16	12/16	9/16	9/16	15/16
3/16 *A–bb*	3/16		7/16	6/16	
3/16 *aaB–*	4/16	3/16			
1/16 *aabb*		1/16		1/16	1/16

9:3:3:1

Dominant epistasis

- Dominant allele at one locus masks an allele at second locus

- Summer squash fruit colour
  - Determined by 2 loci, A and B
  - Dominant allele *A* = **white** fruit
    - Regardless of second loci allele
  - Absence of *A* allele (*aa*)
    - Genotypes *BB*, *Bb* = **yellow** fruit
    - Genotype *bb* = **green** fruit

Dominant epistasis

$$F_1: AaBb \times AaBb$$
$$\downarrow$$

F_2 Ratio	Genotype	Phenotype	Final Phenotypic Ratio
9/16	*A–B–*	white	12/16 white
3/16	*A–bb*	white	
3/16	*aaB–*	yellow	3/16 yellow
1/16	*aabb*	green	1/16 green

Recessive epistasis

- Homozygous recessive allele at one locus masks an allele at second locus
- Mouse coat color (again…):
  - *A* allele (dominant): agouti phenotype
  - *B* allele: black pigment
  - *bb* genotype: no black pigment, even if *A* or *a* alleles present ➔ mouse is albino
- bb genotype masks the expression of the *A* allele: **recessive epistasis**

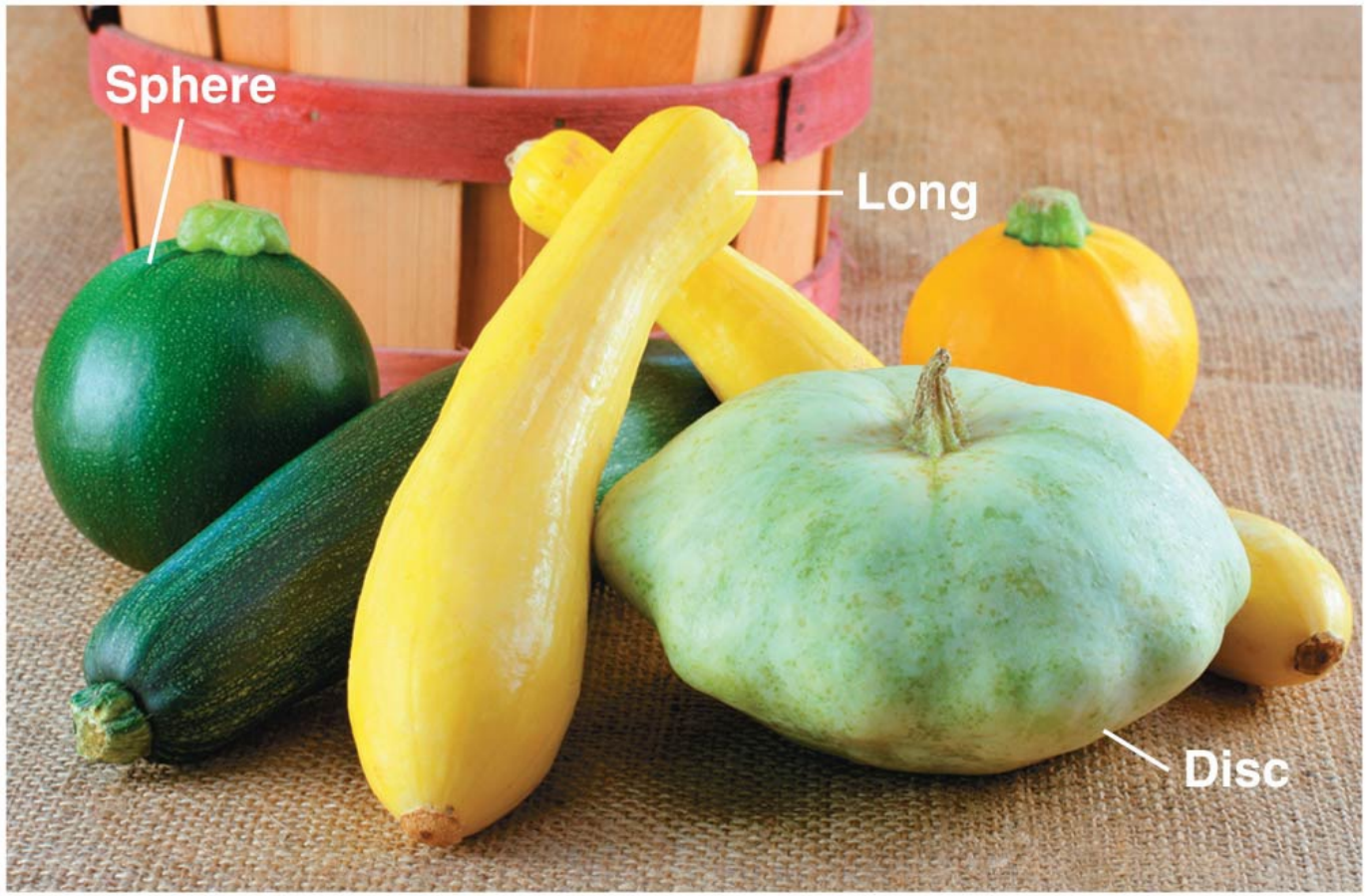
Recessive epistasis

$$F_1: AaBb \times AaBb$$

$$\downarrow$$

F_2 Ratio	Genotype	Phenotype	Final Phenotypic Ratio
9/16	*A–B–*	agouti	9/16 agouti
3/16	*A–bb*	albino	3/16 black
3/16	*aaB–*	black	4/16 albino
1/16	*aabb*	albino	

Duplicate interaction: epistasis resulting in a novel phenotype



Duplicate interaction: epistasis resulting in a novel phenotype

- Two loci contribute to the same trait and dominant alleles have an additive effect
- Shape of summer squash: **disc-shaped** fruit (*AABB*) crossed with **long** fruit (*aabb*)
- F_1: all **disc-shaped** fruit
- F_2: includes the two parental phenotypes and a new **spherical** variant
  - Dominant alleles at 2 loci → disc-shaped
  - Dominant allele at 1 locus → spherical
  - Only recessive alleles → long

Duplicate interaction: epistasis resulting in a novel phenotypes

$$F_1: AaBb \times AaBb$$
$$\text{disc} \quad \text{disc}$$
$$\downarrow$$

F_2 Ratio	Genotype	Phenotype	Final Phenotypic Ratio
9/16	*A–B–*	disc	9/16 disc
3/16	*A–bb*	sphere	6/16 sphere
3/16	*aaB–*	sphere	1/16 long
1/16	*aabb*	long	

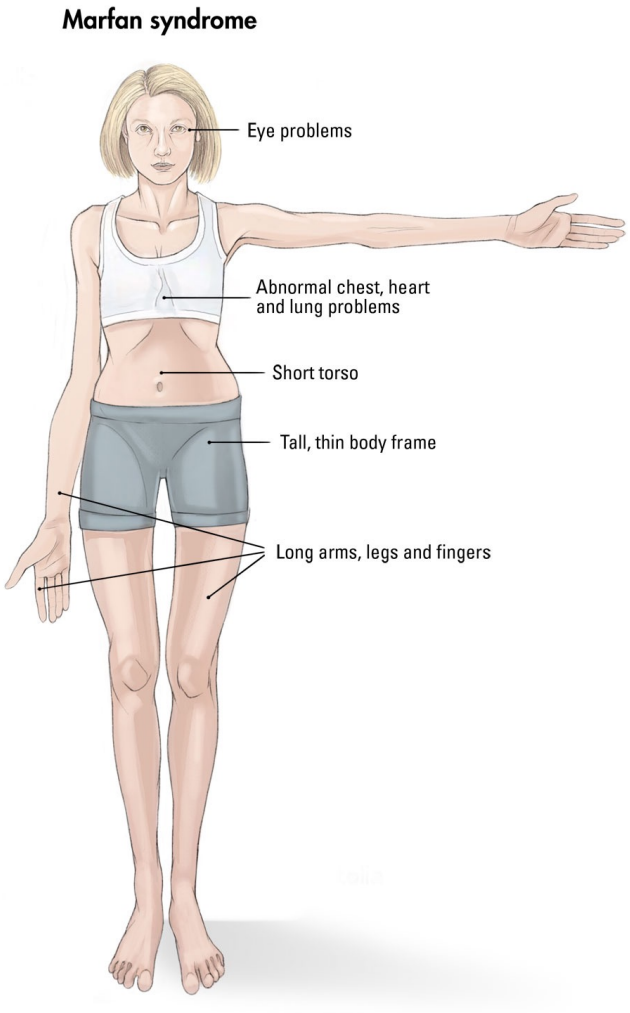
6. Pleiotropy

Pleiotropy

- We just saw that several genes can influence a single phenotype
- The opposite situation, where a single gene has multiple phenotypic effects, is called **pleiotropy**
- Extremely frequent

Example of pleiotropy in humans

- **Marfan syndrome**
  - Autosomal dominant allele in fibrillin gene, encoding a protein important for connective tissues
  - Multiple phenotypic consequences:
    - Lens dislocation
    - Aortic aneurism
    - Extension of long bones
    - …



7. Gene x environment interactions

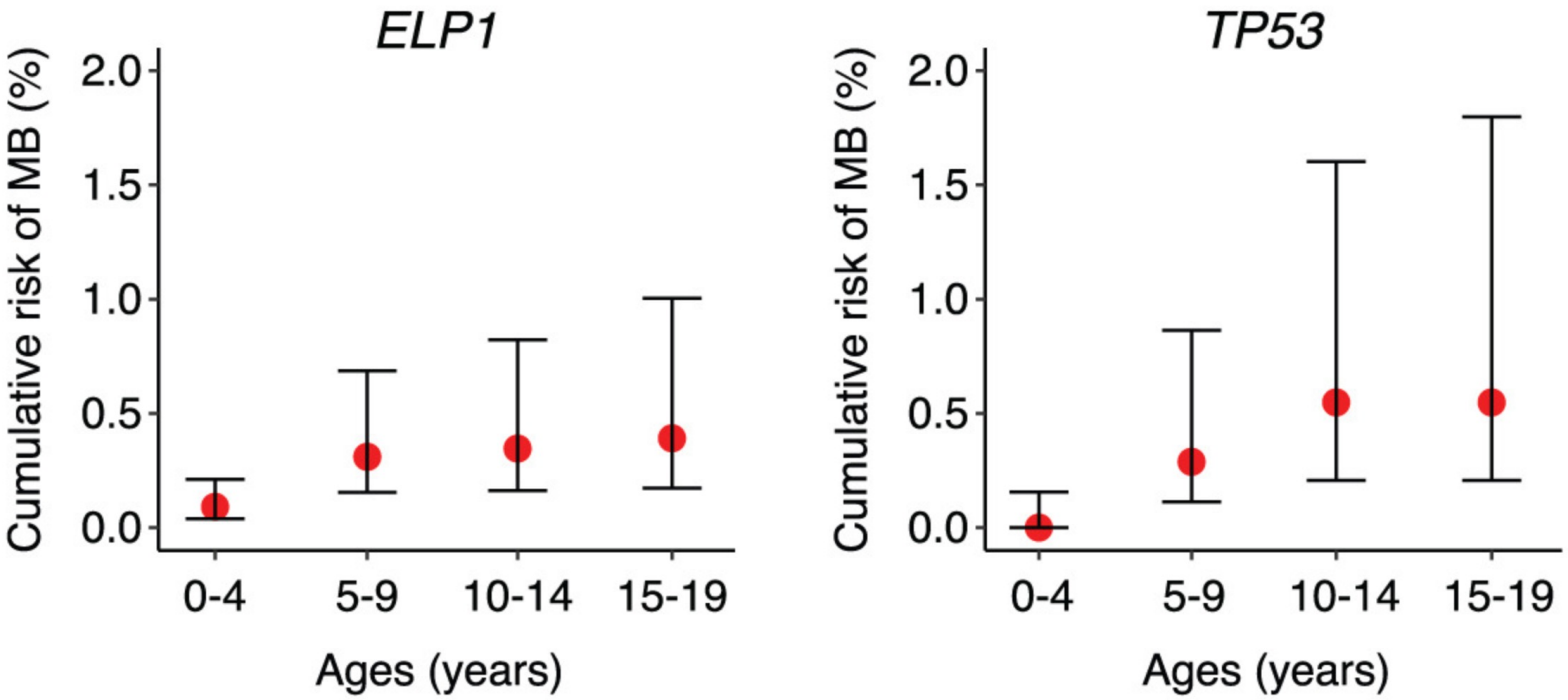
Phenotype = direct expression of genotype?

- **A phenotype usually results from multiple influences**
  - Core gene
  - Other genotypes (genic and epistatic influences)
  - Environment

- Often difficult to disentangle the respective influences of genes and environment ⇔ long-standing debate between “innate” and “acquired”

Penetrance and expressivity

- **Penetrance**
  - Percentage of expression of the mutant genotype in a population
  - Incomplete, age-dependent, and incomplete, age-dependent penetrance
  - Rare mutations in *ELP1* or *TP53* predispose to medulloblastoma, a rare childhood brain tumor: incomplete, age-dependent penentrance



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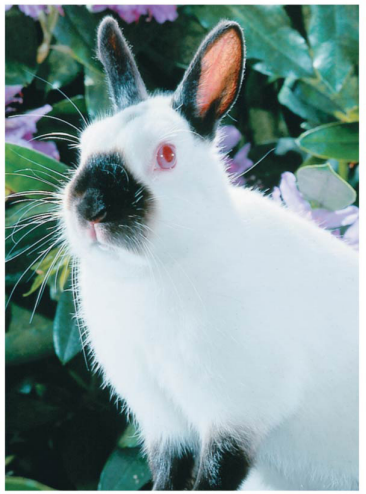
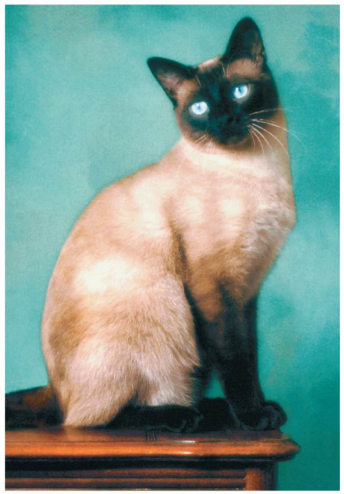
Penetrance and expressivity

- **Expressivity**
  - Range of expression (degree of severity) of mutant phenotype (eg, mild vs severe)
  - Result of genetic background differences and/or environmental effects

Causes of variable expressivity

- **Temperature effects**
  - Evening primrose
    - Red flowers at 23°C
    - White flowers at 18°C
  - Siamese cats and Himalayan rabbits
    - Darker fur on cooler areas of body (tail, feet, ears)
    - Enzymes responsible for pigment formation lose catalytic function at higher temperature





Causes of variable expressivity

- **Temperature-sensitive mutations**
  - Known in viruses, bacteria, fungi, and *Drosophila*
  - Mutant allele expresses mutant phenotype at one temperature, wild-type phenotype at another
  - Broadly used in viral genetics: temperature-sensitive mutations are easily induced and isolated in viruses

Causes of variable expressivity

- **Nutritional effects**
  - Some alleles prevent the synthesis of essential nutrients in microbes, they are called **auxotrophs**
  - Phenotype expression can be modulated by diet, which is very useful for *in vitro* studies
  - In humans, diseases are caused by alleles that stops the metabolization of some substances:
    - **Phenylketonuria**: loss of enzyme to metabolize amino acid phenylalanine, severe problems unless low-Phe diet
    - **Galactosemia, lactose intolerance, …**