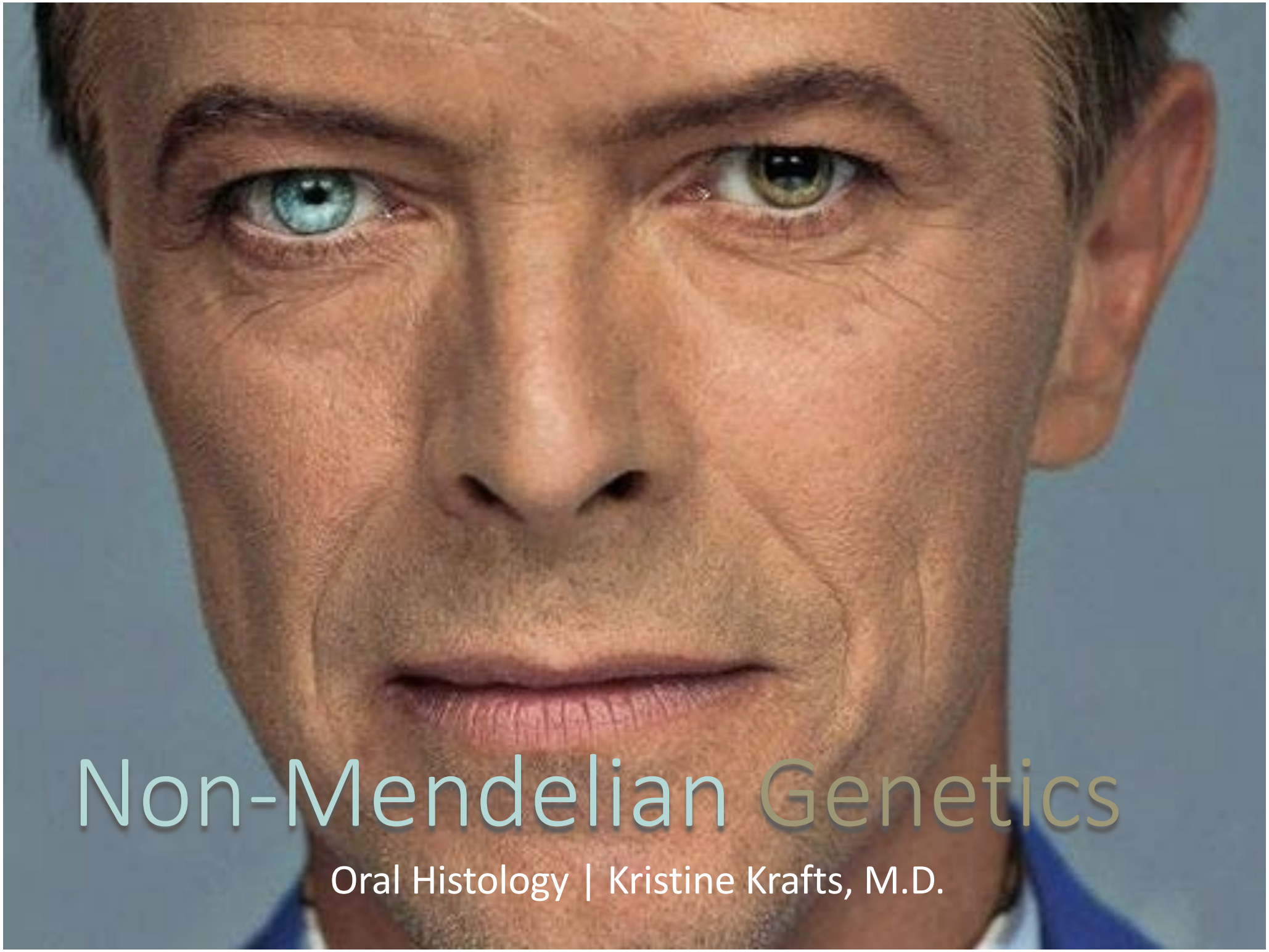


Non-Mendelian Genetics

Oral Histology | Kristine Krafts, M.D.

Objectives

- Describe some violations of Mendel's laws.
- Define mutation and polymorphism, and explain their similarities and differences.
- Explain how codominance and incomplete dominance are different than Mendelian dominance.
- Compare and contrast pleiotropy and polygenic inheritance.
- Compare and contrast penetrance and expressivity.
- Define "linked" genes, and explain why genes that are located very close together on a chromosome are likely to be linked.

Non-Mendelian Genetics

Introduction

Single-gene stuff

More complex stuff

Non-Mendelian Genetics

Introduction

What do you mean, non-Mendelian?

Mendel was spot-on! But the traits (and genes) he happened to choose were very simple:

- Each gene had only two alleles.
- One allele was always dominant.
- Each trait had two opposing features.
- The phenotypes were always predictable.

What do you mean, non-Mendelian?

But many genes are not so straightforward:

- Genes often have more than two alleles.
- Alleles aren't always completely dominant or completely recessive.
- Genes don't always act alone.
- The gene:trait relationship isn't always 1:1.

Non-Mendelian Genetics

Introduction

Single-gene stuff

- Multiple alleles
- Codominance
- Incomplete dominance
- Pleiotropy
- Penetrance
- Expressivity

Non-Mendelian Genetics

Introduction

Single-gene stuff

- Multiple alleles

Multiple Alleles

C c C^{ch} C^{h}

Genes often have several common alleles. Alleles that are present in >1% of the population are called “polymorphisms.”

New alleles arise by mutation.

Example: a gene for wing shape in flies

The normal ("wild-type") allele gives the fly straight wings

A mutated (or "variant") allele might cause the wings to be curly

“Mutation” and “polymorphism” are not interchangeable!

Mutation:

Any variation in the normal DNA sequence of a gene.

May be bad (disease-causing), silent, or good (protective).

Polymorphism:

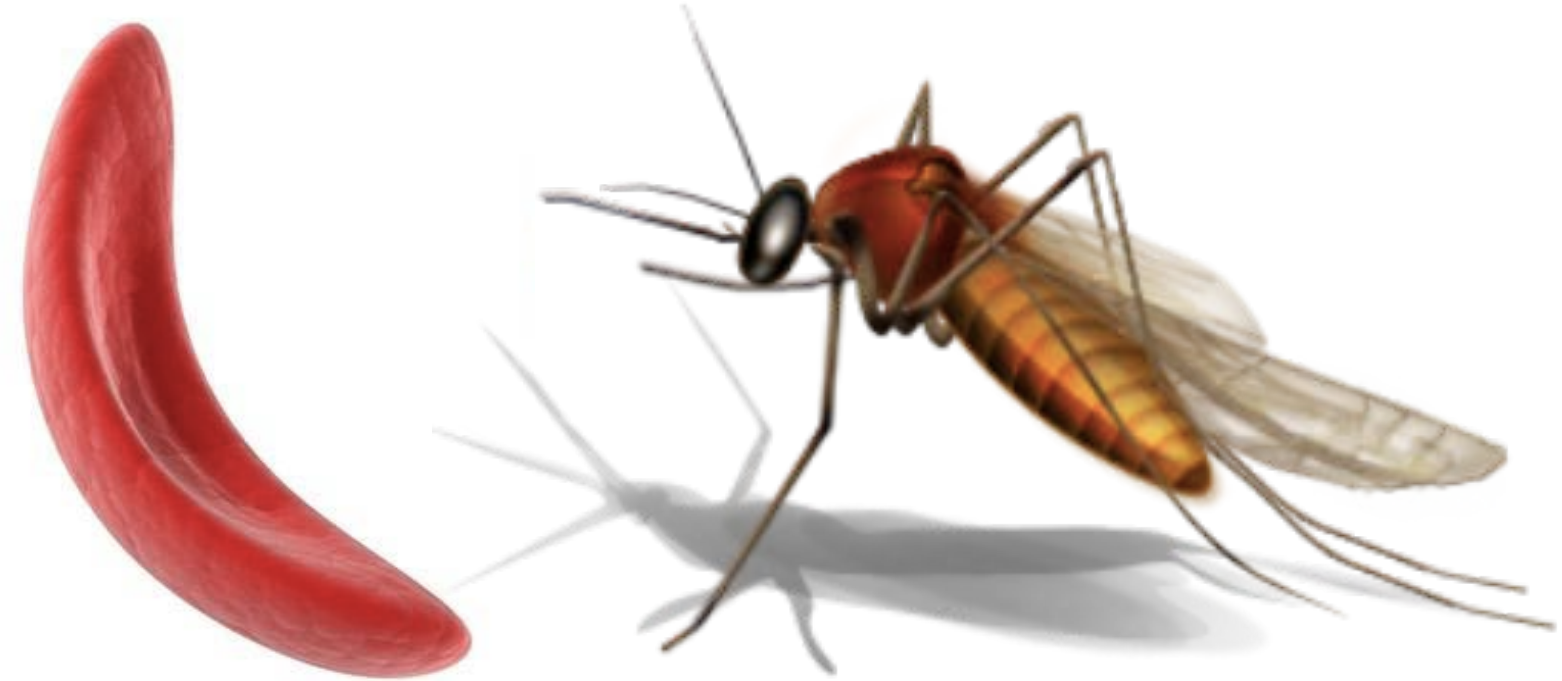
A common, normal variation in the DNA sequence of a gene.

“Common” = present in at least 1% of the population.

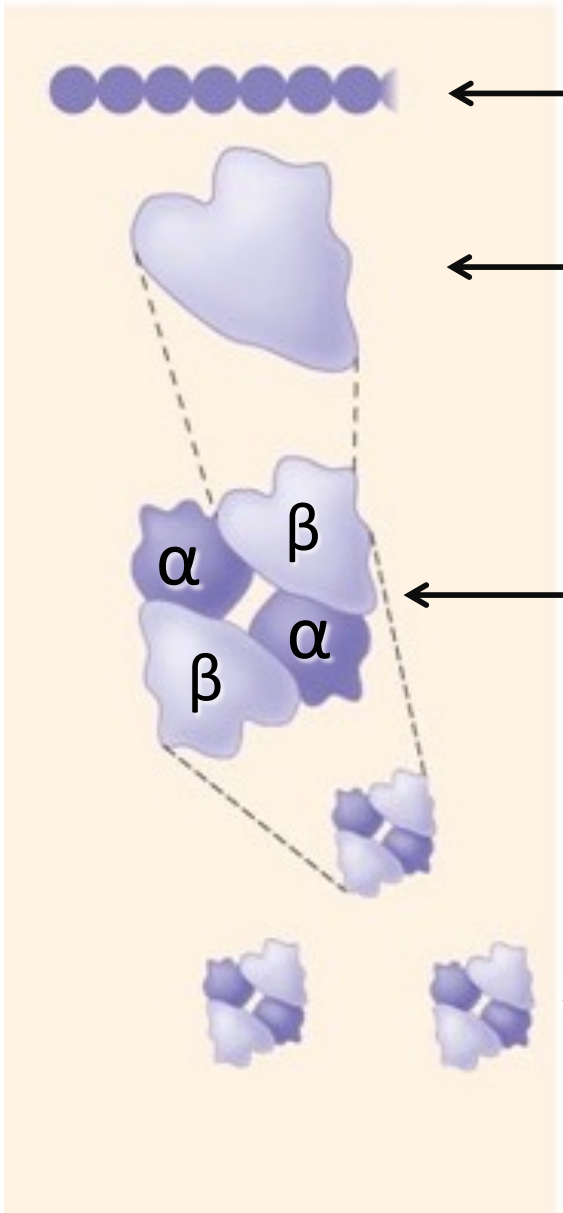
“Normal” = harmless.

BUT...the distinction is not always clear-cut.

A mutation in one population may be
a polymorphism in another population.



Normal Hemoglobin



Normal Hemoglobin

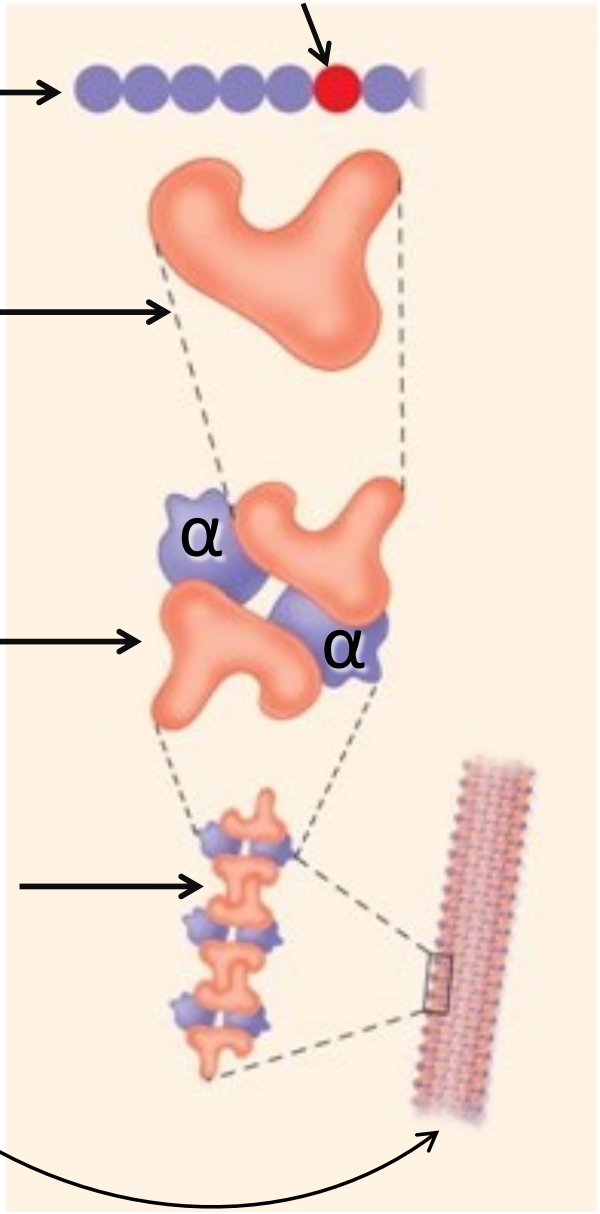
Sickle Hemoglobin

abnormal protein sequence

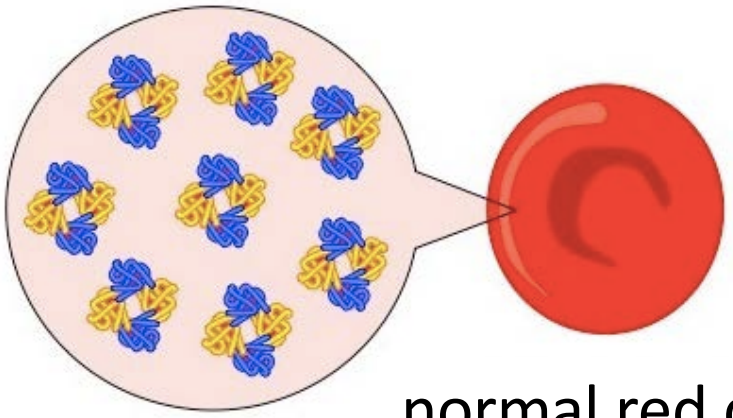
misfolded β globin subunit

"sticky" hemoglobin molecule

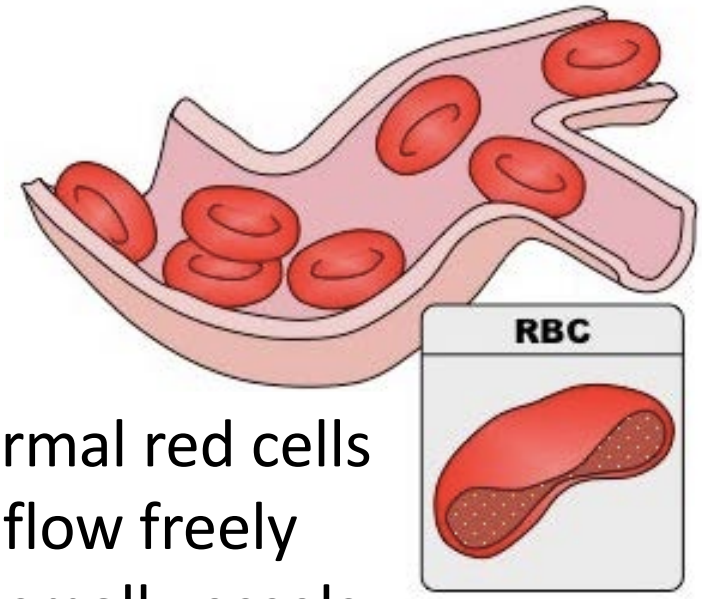
hemoglobin molecules polymerize, forming long crystals



normal
hemoglobin molecules

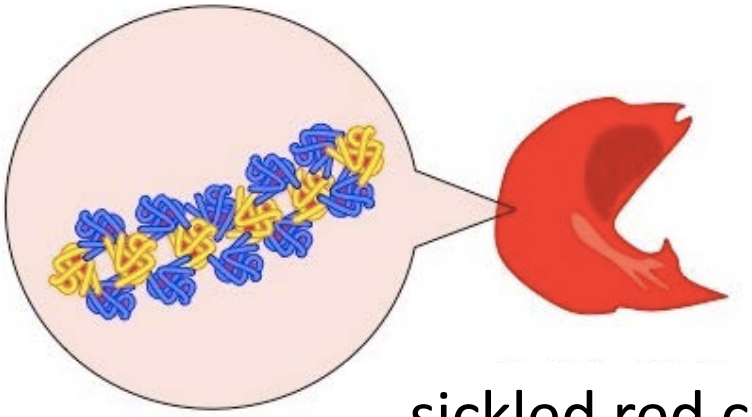


normal red cell

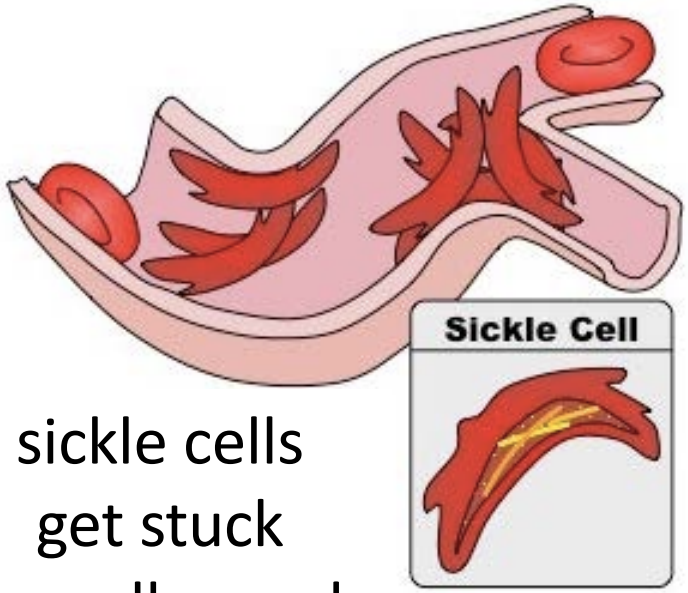


normal red cells
flow freely
in small vessels

abnormal, polymerized
hemoglobin molecules

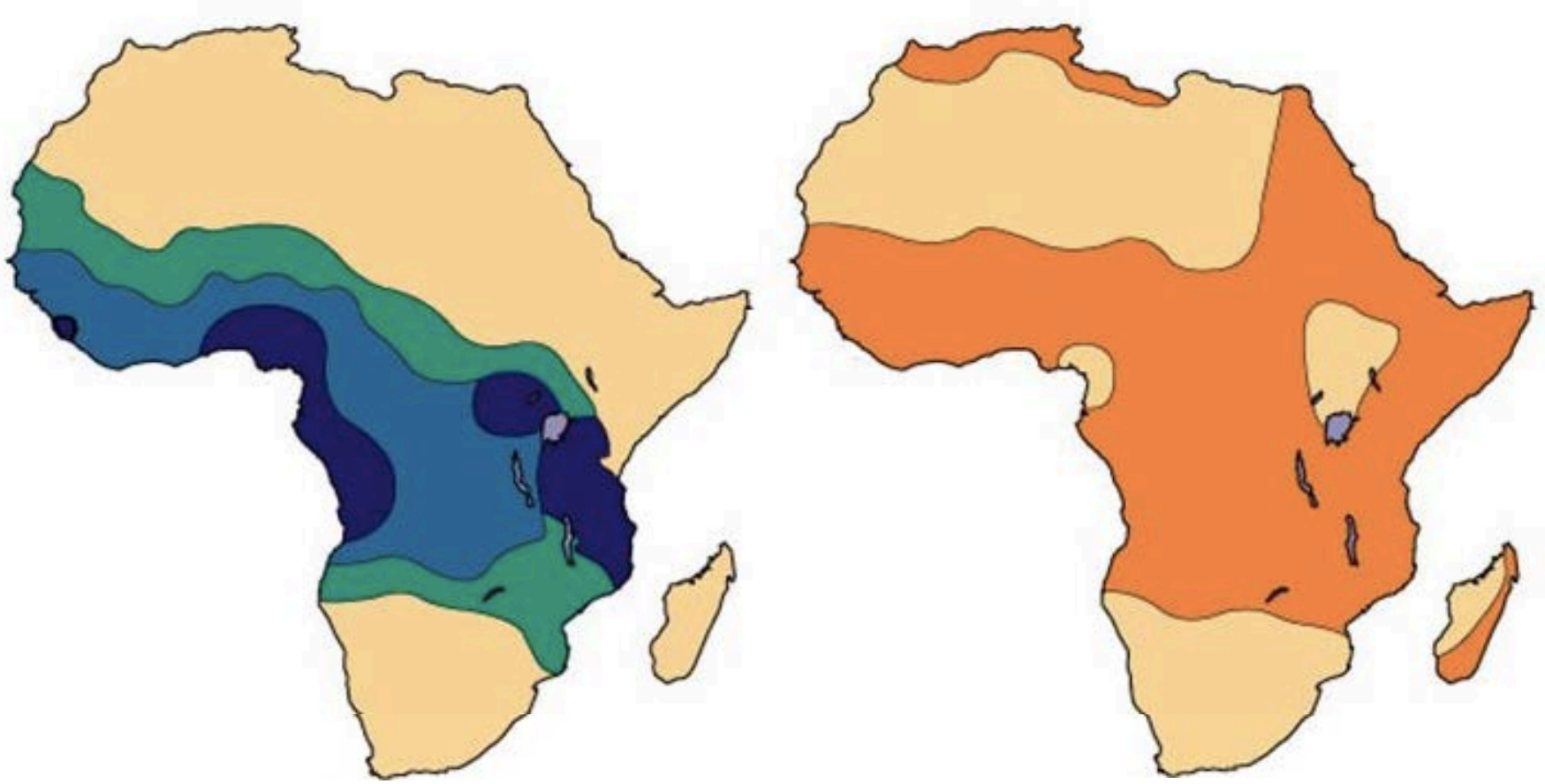


sickled red cell



sickle cells
get stuck
in small vessels

BUT: patients with the sickle cell mutation have a greater resistance against malaria infection!



The sickle cell mutation is most common in parts of the world where malaria is endemic.

Non-Mendelian Genetics

Introduction

Single-gene stuff

- Multiple alleles
- Codominance

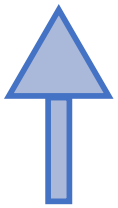
Mendelian Dominance

- One allele is always dominant; the is other always recessive.
- Heterozygotes express the phenotype of the dominant allele.

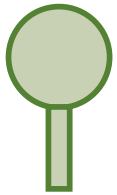
Codominance

- Both alleles are always expressed.
- Heterozygotes express the phenotypes of BOTH alleles.

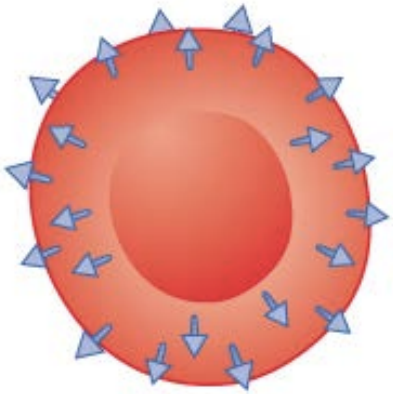
Example: The ABO Blood Group System



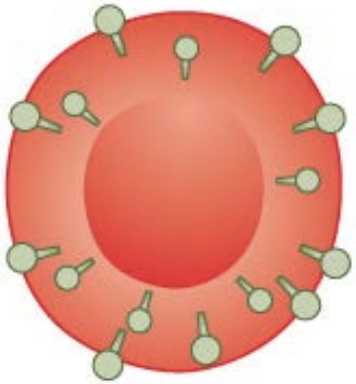
A antigen



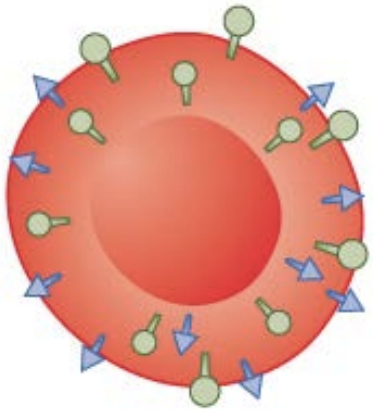
B antigen



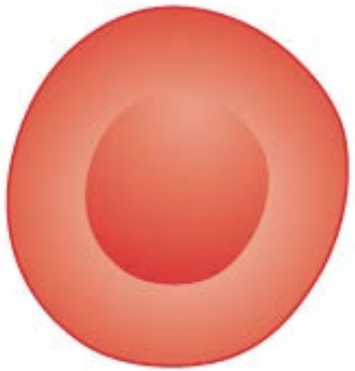
Type A



Type B



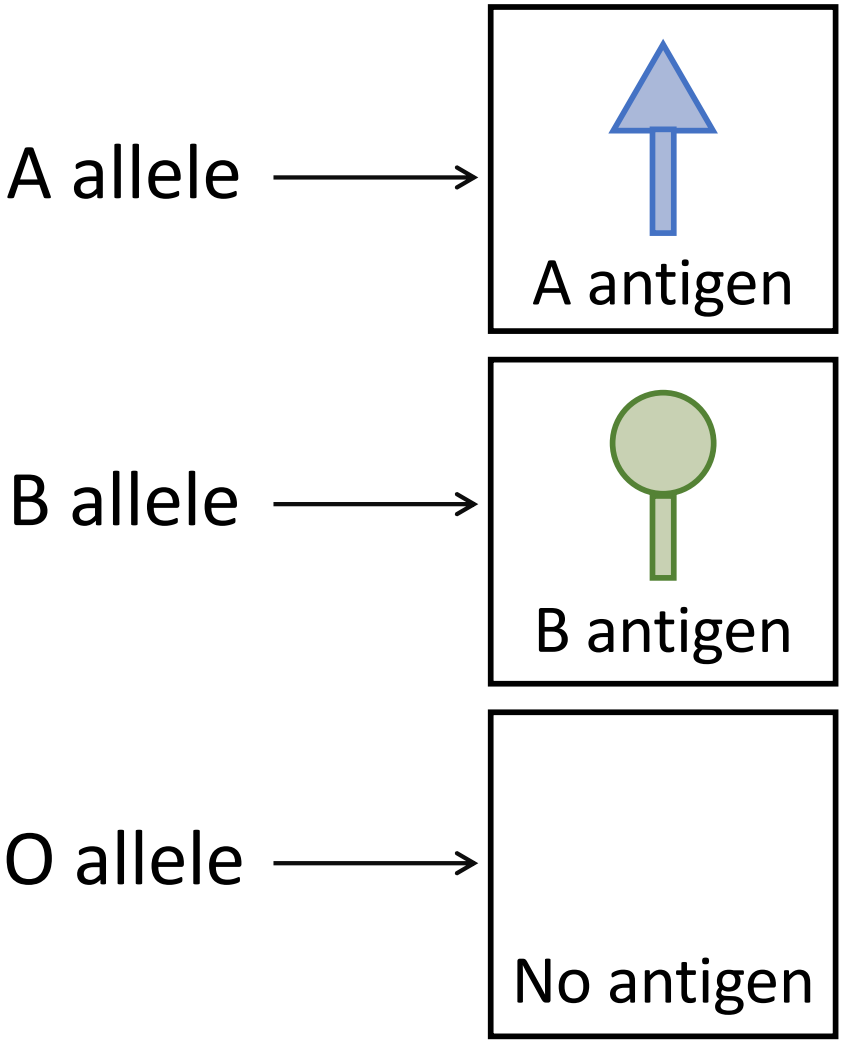
Type AB



Type O

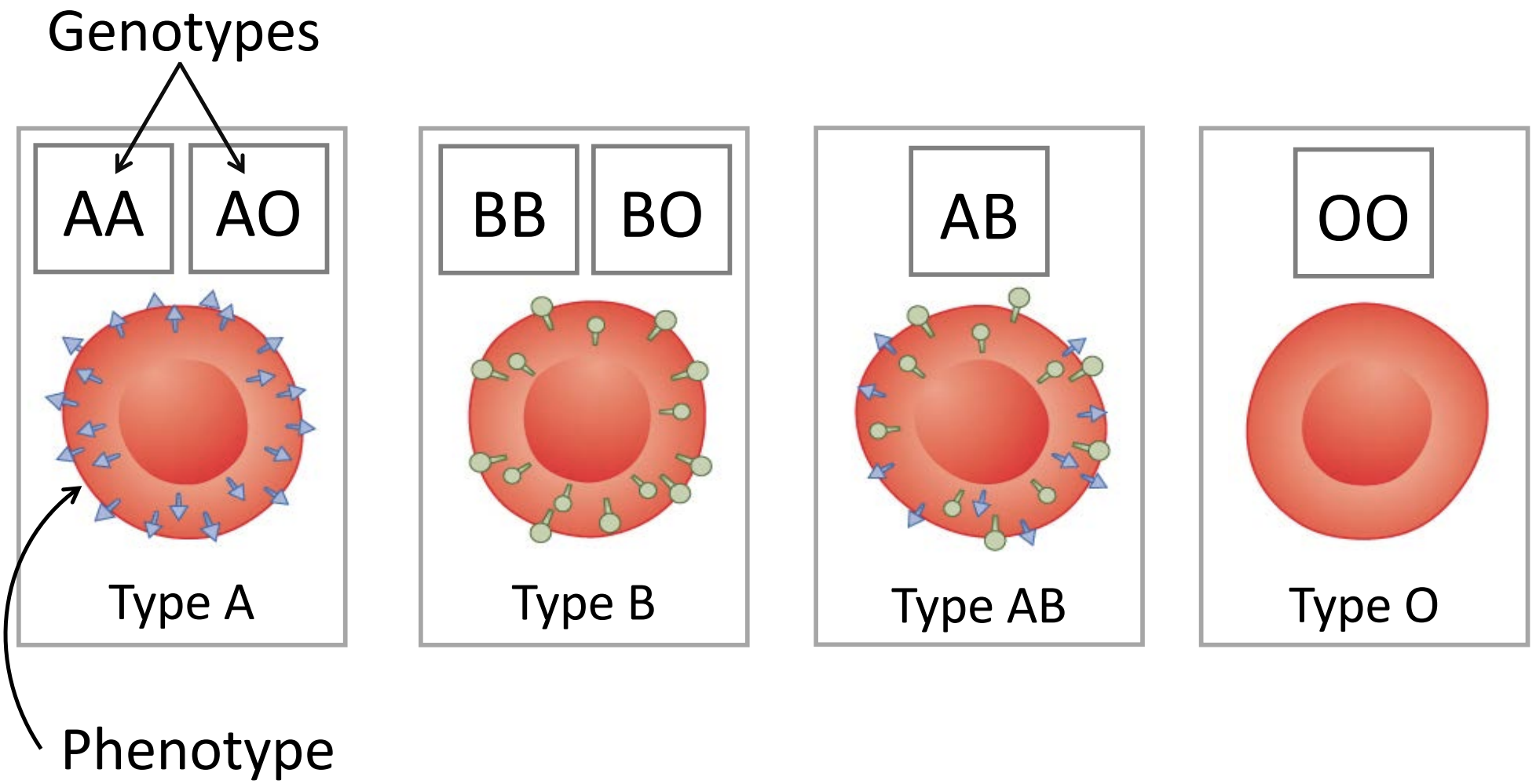
Three alleles:
A, B, and O

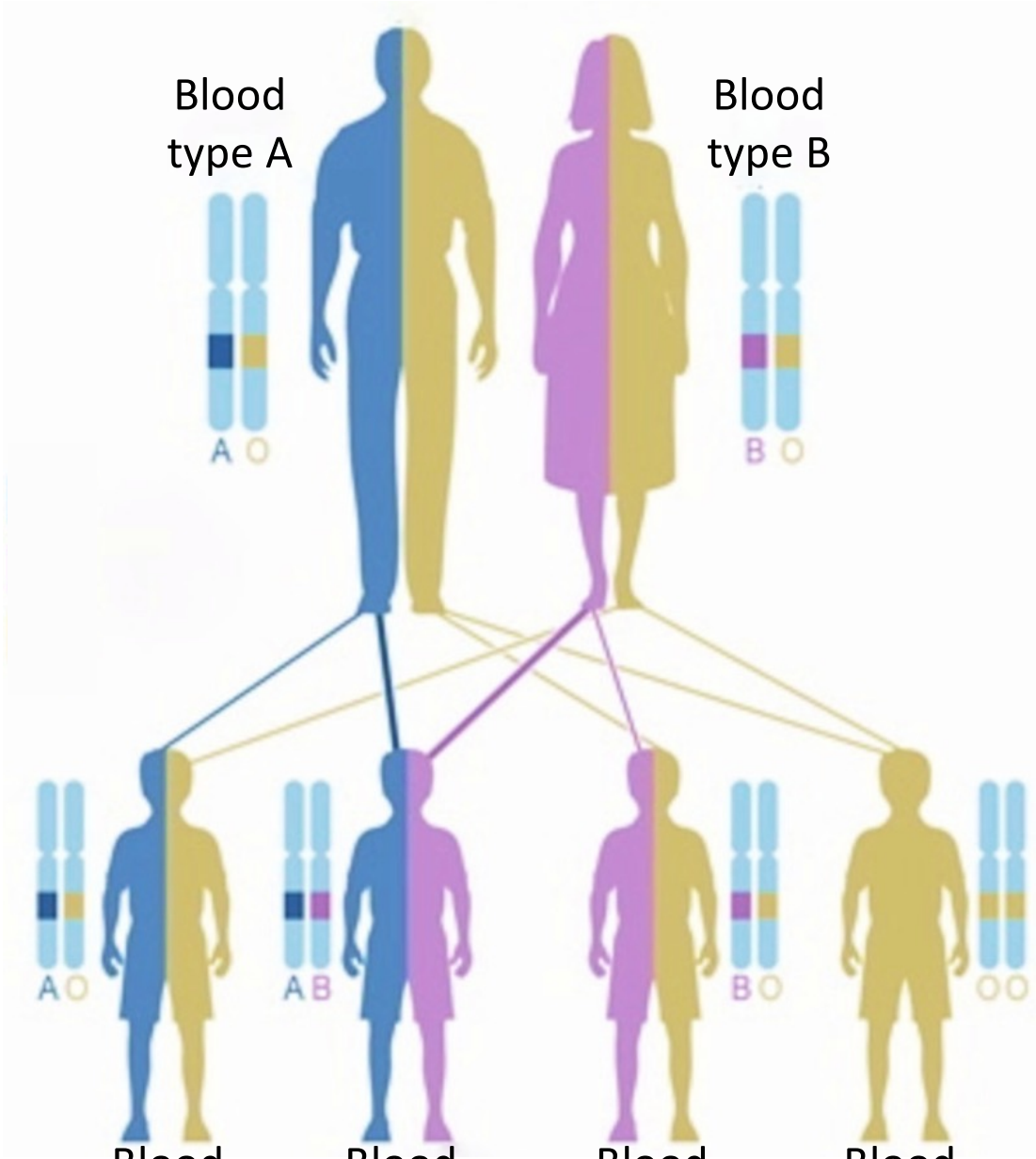
Six possible genotypes



A A	A O
B B	B O
A B	O O

Every genotype always expresses BOTH alleles!
So the ABO alleles are codominant.




Blood type A
Blood type B
A O
B O
A O
A B
B O
O O
Blood type A
Blood type AB
Blood type B
Blood type O

Non-Mendelian Genetics

Introduction

Single-gene stuff

- Multiple alleles
- Codominance
- Incomplete dominance

Mendelian Dominance

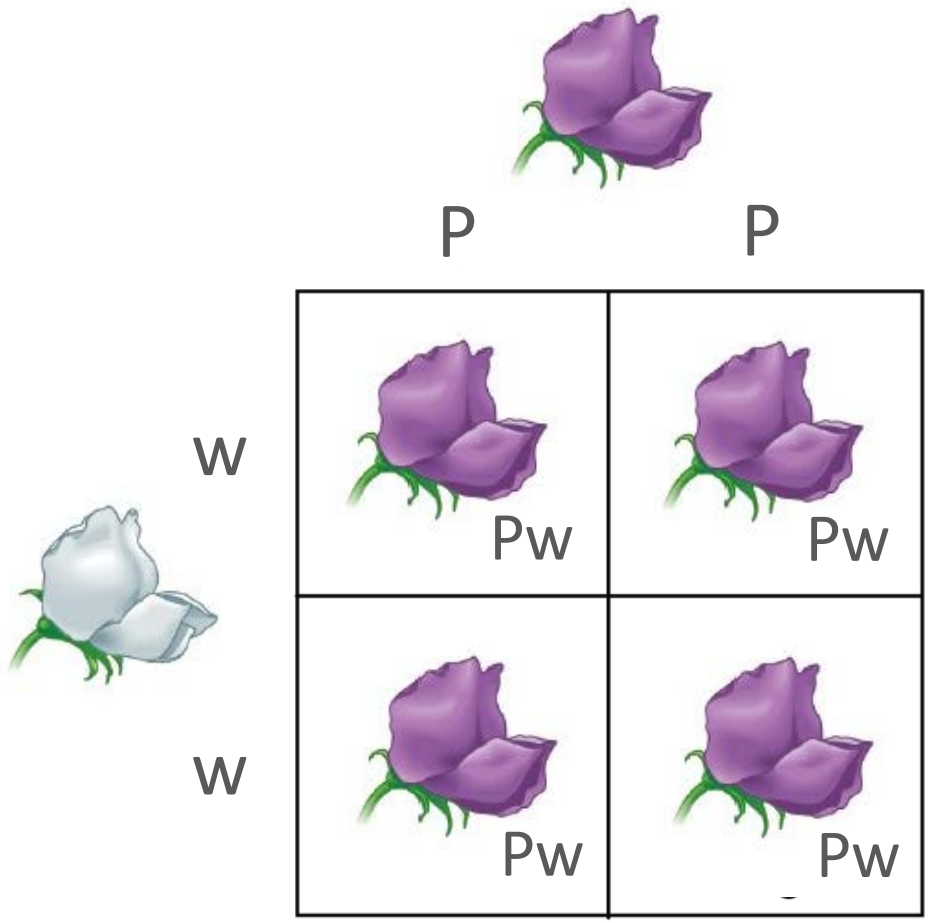
- For a given pair of alleles, there are only two possible phenotypes.
- Heterozygotes express the phenotype of the dominant allele.

Incomplete Dominance

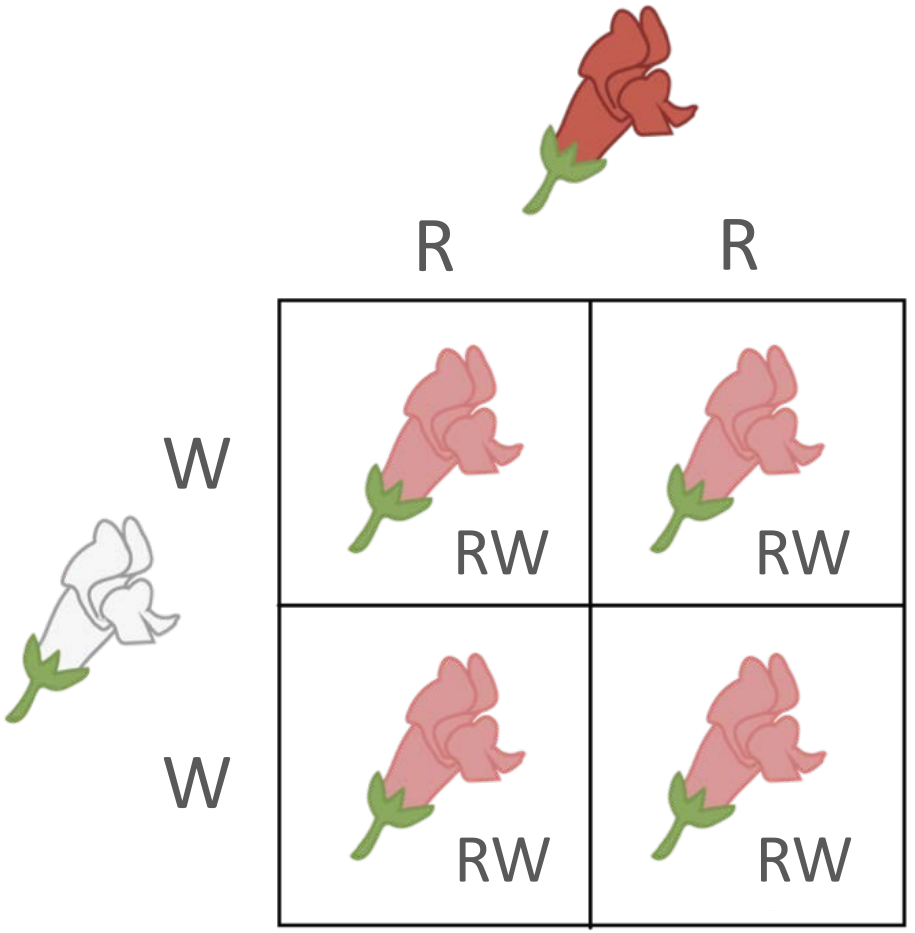
- For a given pair of alleles, there are three possible phenotypes!
- Heterozygotes express a phenotype that is a “blend” of the two homozygous phenotypes.

Example: Flower Color in Snapdragons

Pea flower color alleles show Mendelian dominance.

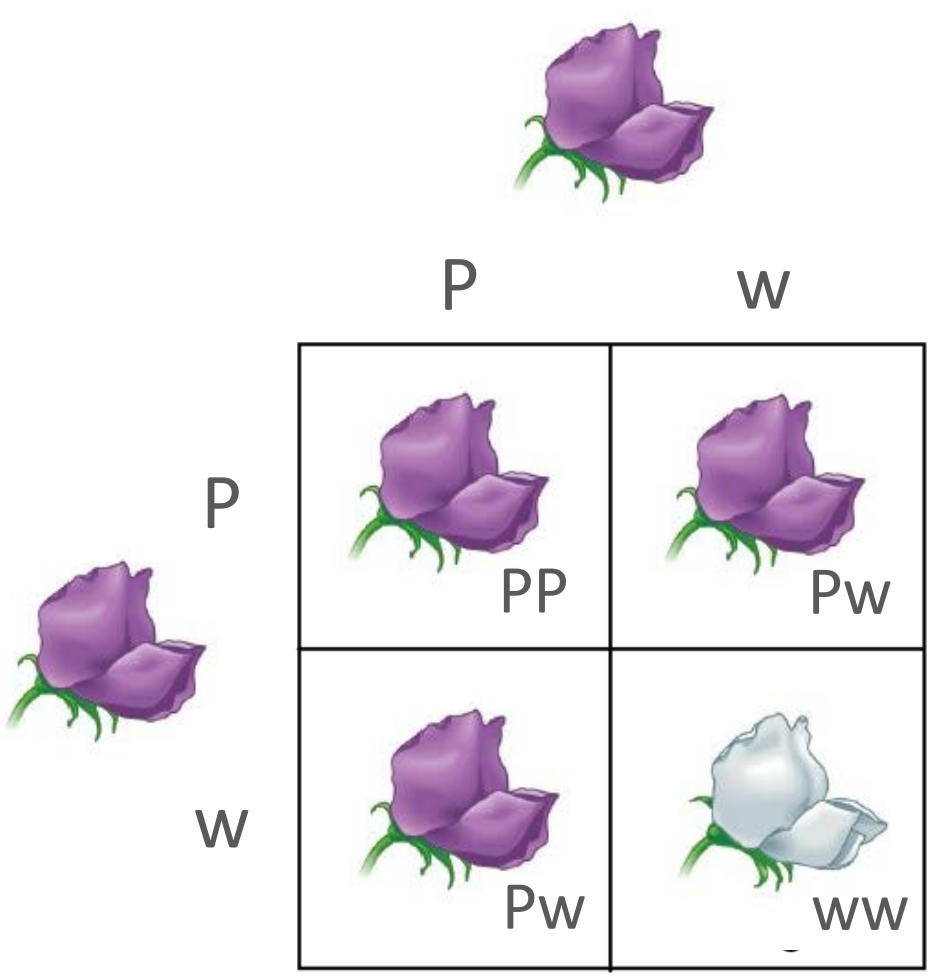


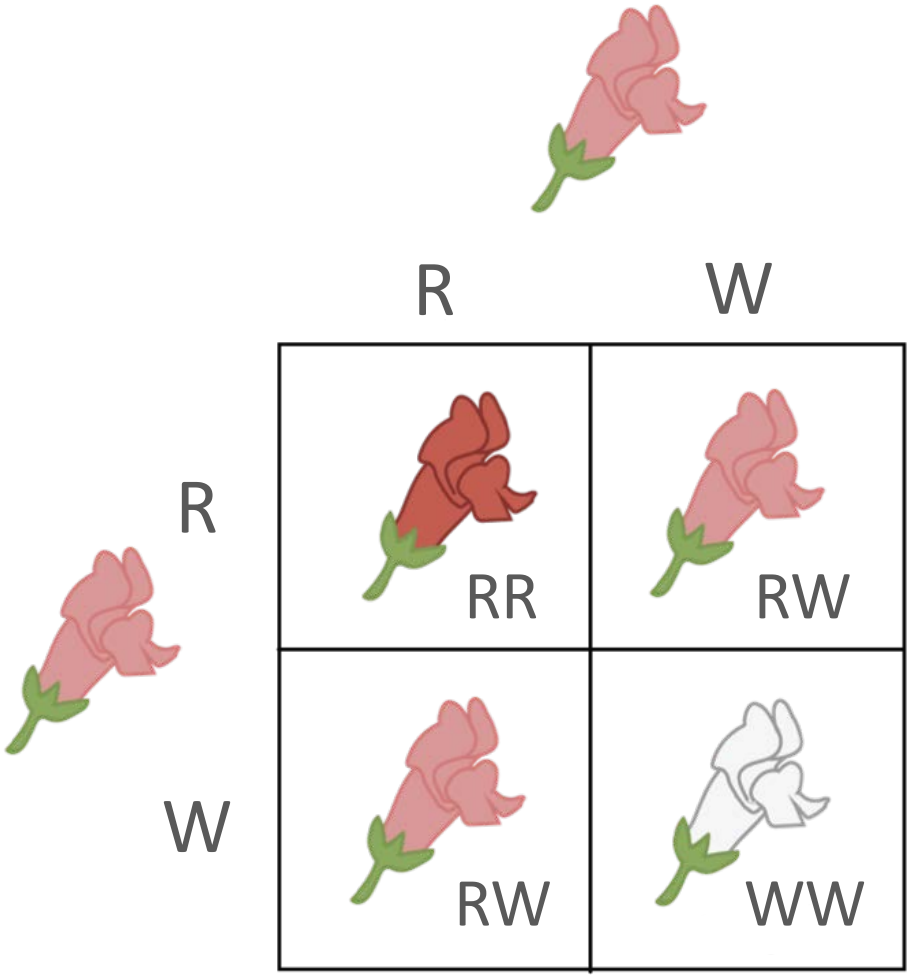
Snapdragon flower color alleles show incomplete dominance!



What about the F_2 generation?

Notice that alleles are always inherited according to Mendel's rules (even when they show incomplete dominance).





Non-Mendelian Genetics

Introduction

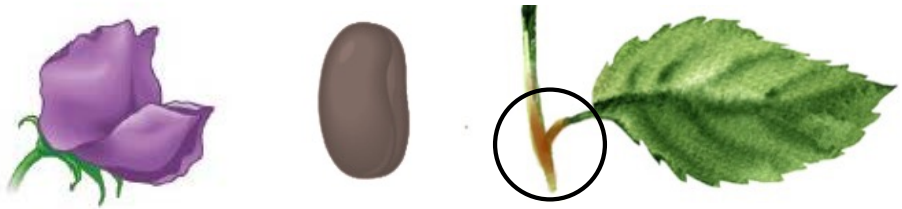
Single-gene stuff

- Multiple alleles
- Codominance
- Incomplete dominance
- Pleiotropy

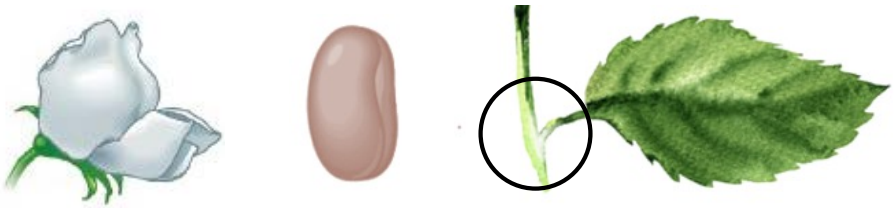
Pleiotropy

- Mendel's genes each controlled a single feature.
- Pleiotropic genes affect many features.
- Note that pleiotropic alleles are still inherited in the normal, Mendelian fashion.

Mendel noticed this, actually!



Plants with purple flowers always had brown seed coats and reddish axils.



Plants with white flowers always had clear seed coats and clear axils.

Turns out the gene for pea flower color is pleiotropic.

It encodes a pigment-producing protein that affects the color of the flower, seed coat, and axil.

Example: Marfan Syndrome

- Caused by a mutation in the *fibrillin* gene.
- Patients have many findings: tall height, heart valve abnormalities, aortic rupture, visual problems.
- ...so the mutated fibrillin allele is pleiotropic.
- Findings seem unrelated but actually, they make sense (fibrillin encodes a connective tissue protein).

Non-Mendelian Genetics

Introduction

Single-gene stuff

- Multiple alleles
- Codominance
- Incomplete dominance
- Pleiotropy
- Penetrance
- Expressivity

Penetrance and Expressivity

In Mendel's work, plants with a particular genotype ALWAYS had the same phenotype.

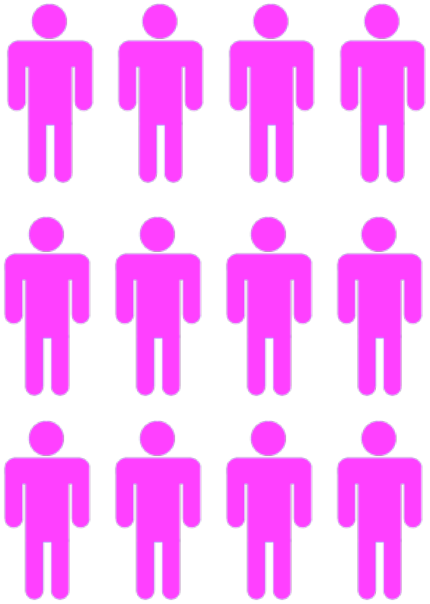
We now know that for some genes, this doesn't hold true.

- The same gene may produce different phenotypes in different people.
- The same gene may be expressed in some people but not in others.

Penetrance

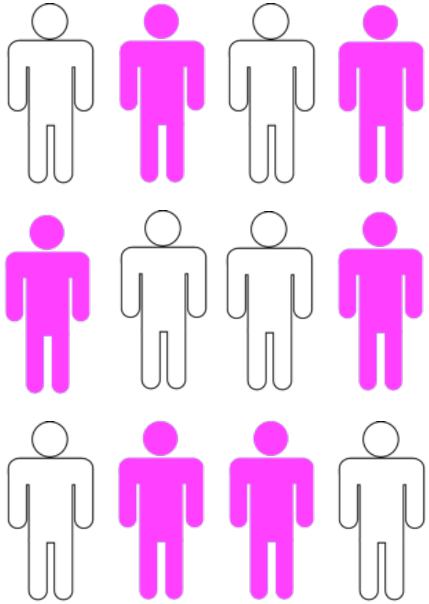
Sometimes, despite being dominant, a gene will simply not be expressed!

Complete Penetrance



Everyone with the allele expresses the trait.

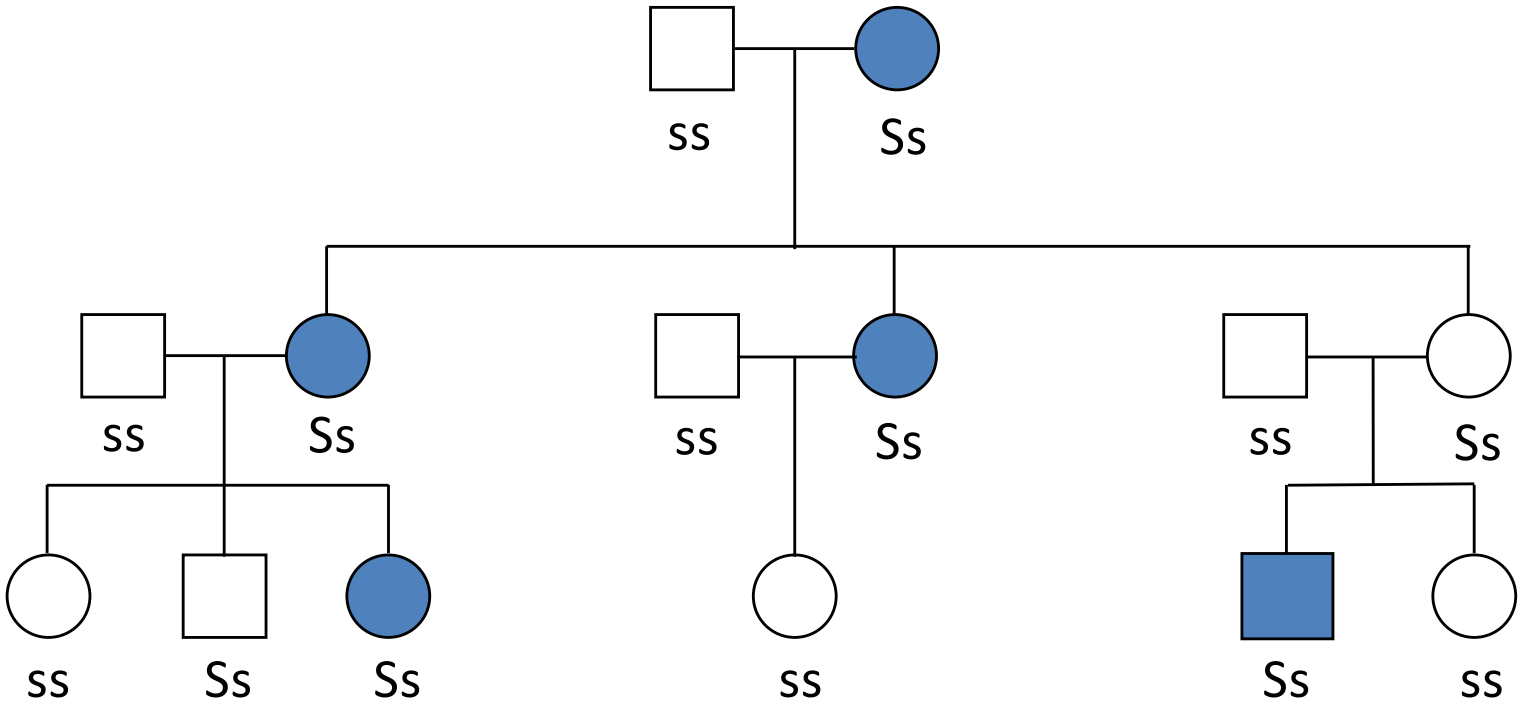
Reduced Penetrance



Some people with the allele express the trait; some don't.

Split-hand deformity

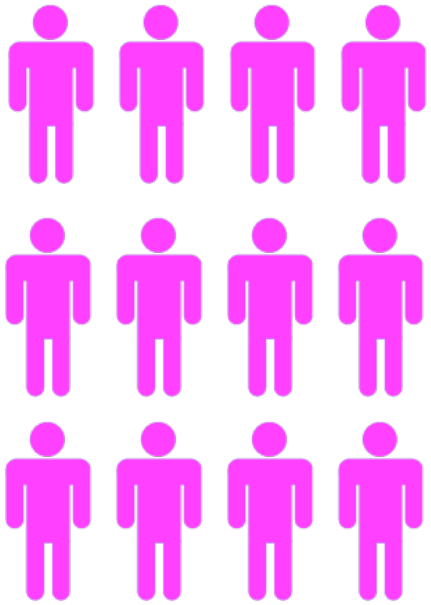
Reduced Penetrance in a Kindred with Split Hand Deformity



Expressivity

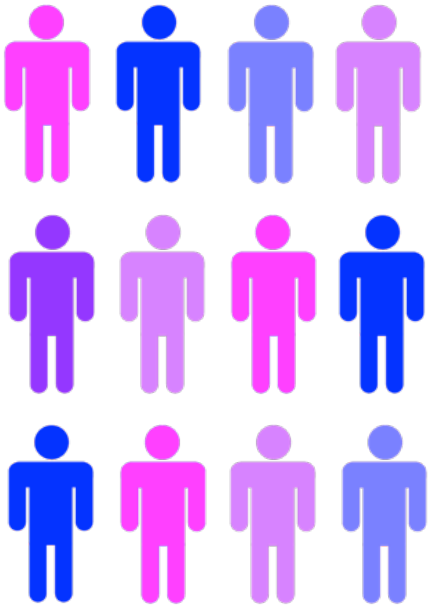
Sometimes, the same genotype produces different phenotypes in different people!

Narrow Expressivity



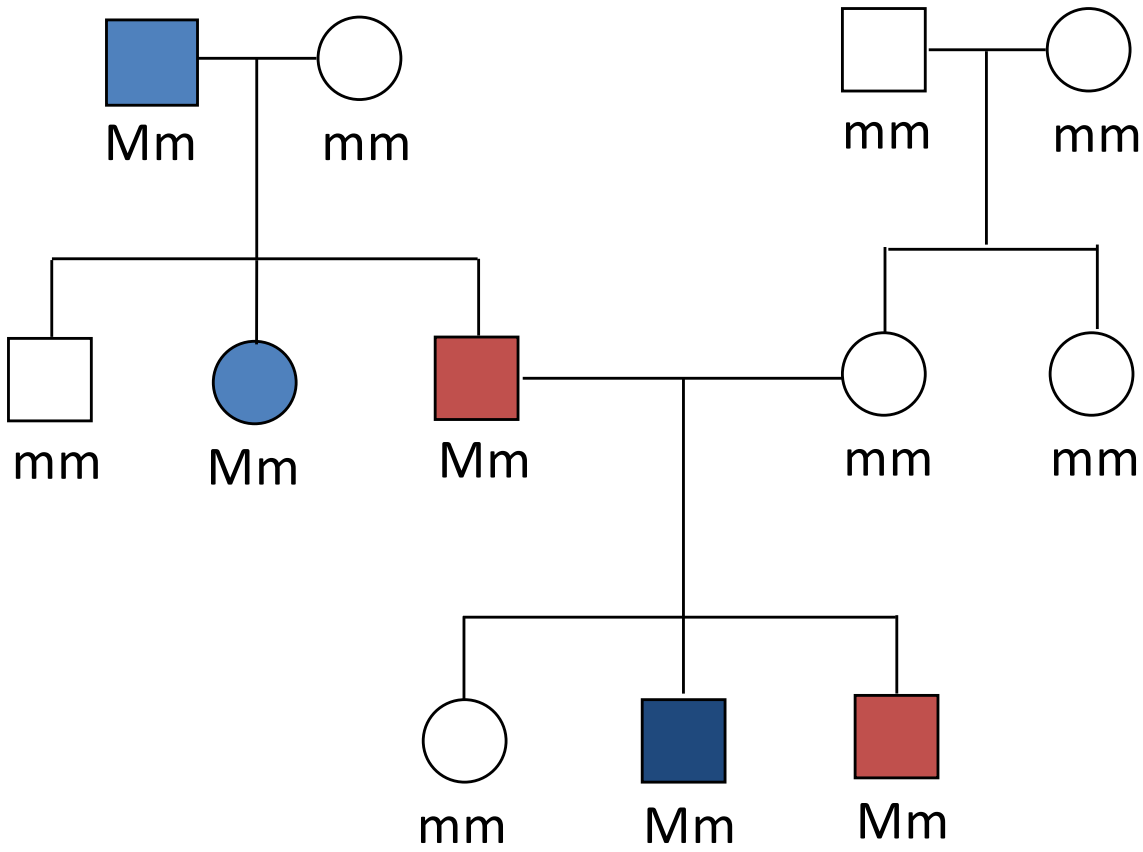
Same genotype,
same phenotype.

Variable Expressivity



Same genotype,
different phenotypes.

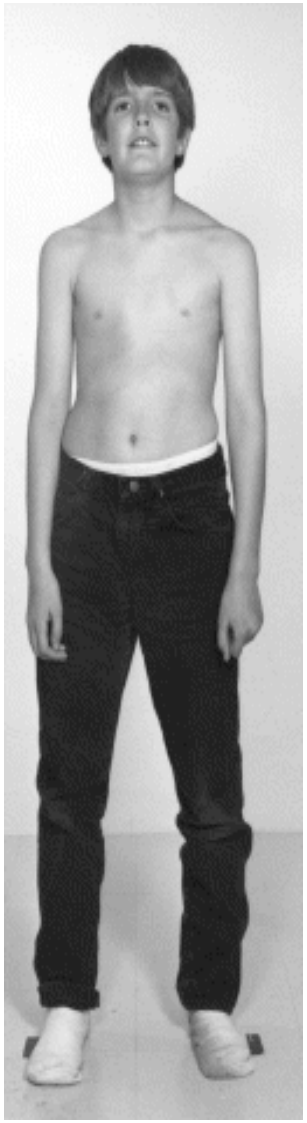
Variable Expressivity in a Kindred with Marfan Syndrome



Tall, dilated aorta

Dislocated lenses, dilated aorta

Tall, dislocated lenses, dilated aorta



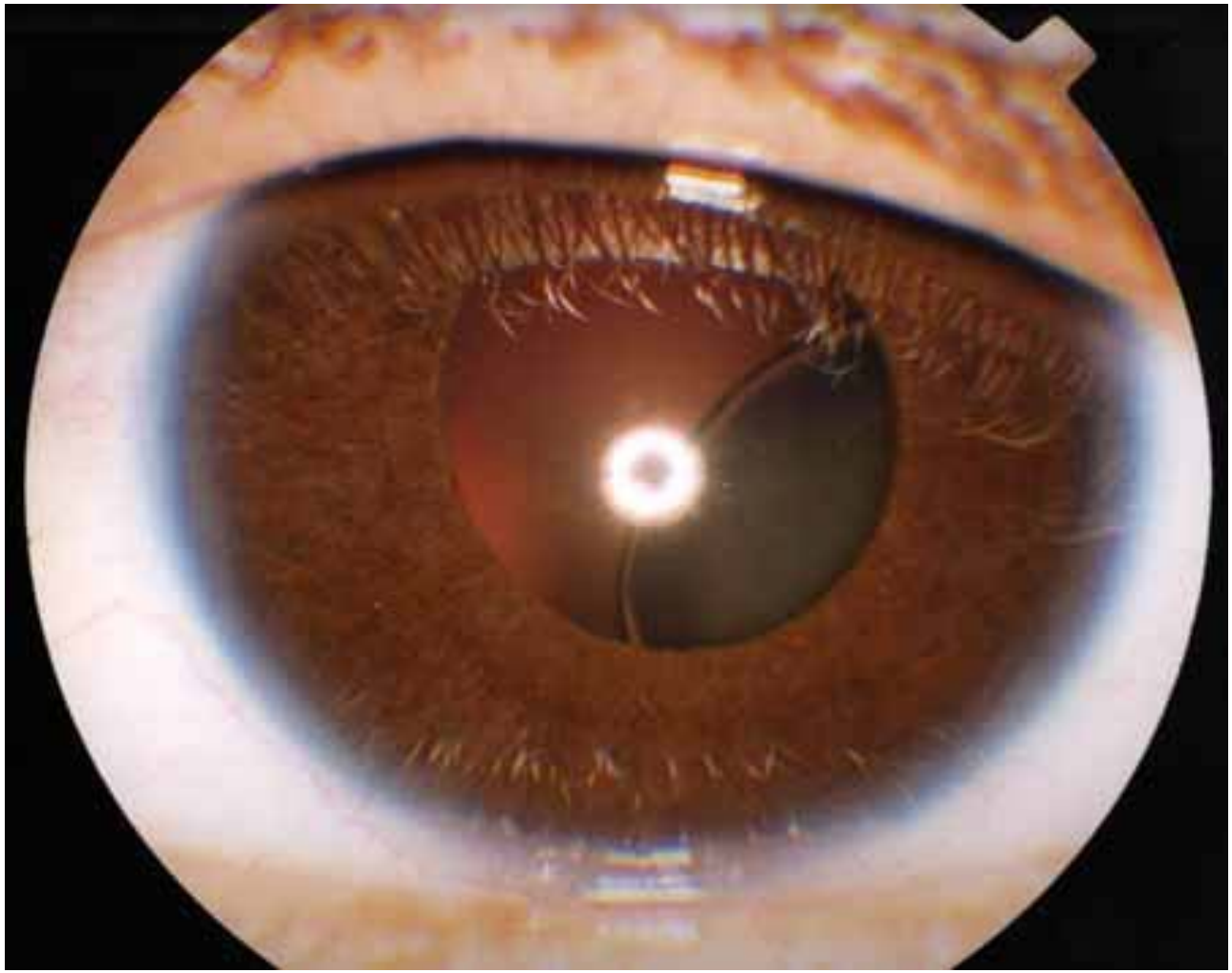
Marfan syndrome: tall, thin patient with long limbs

Marfan syndrome: arachnodactyly

A couple physical exam signs present in Marfan syndrome

Thumb sticks out of fist

Thumb and middle finger overlap when encircling wrist



Marfan syndrome: dislocated lens

Non-Mendelian Genetics

Introduction

Single-gene stuff

More complex stuff

- Polygenic inheritance
- Linkage

Non-Mendelian Genetics

Introduction

Single-gene stuff

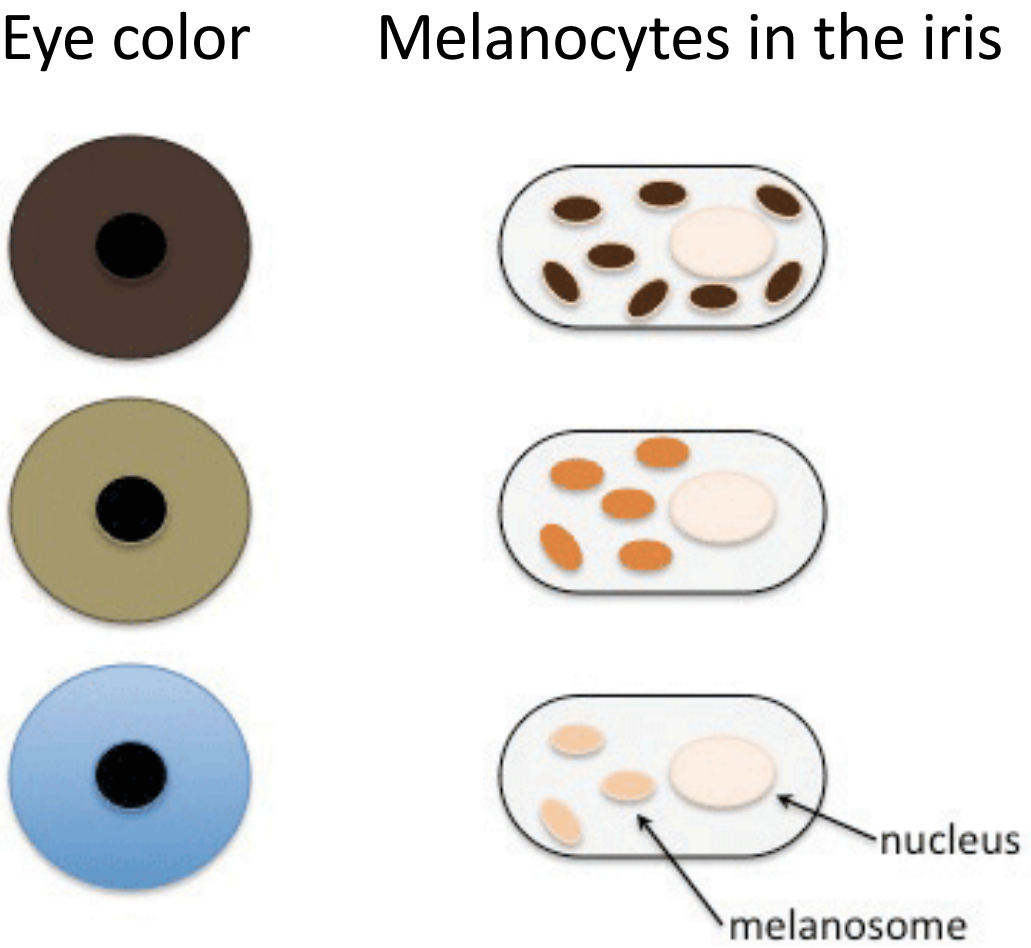
More complex stuff

- Polygenic inheritance

Polygenic Inheritance

- In Mendel's work, each feature (like flower color) was encoded by a single gene.
- In humans, it's not that straightforward.
- Human features like eye color, hair color, skin color, and height are controlled by many genes (poly = many, genic = genes).
- Disease risk sometimes involves multiple genes.
- This makes things complicated, but interesting.

Eye color is not a simple Mendelian trait!



It’s determined by 16 genes,
most of which are involved in melanin production.

Non-Mendelian Genetics

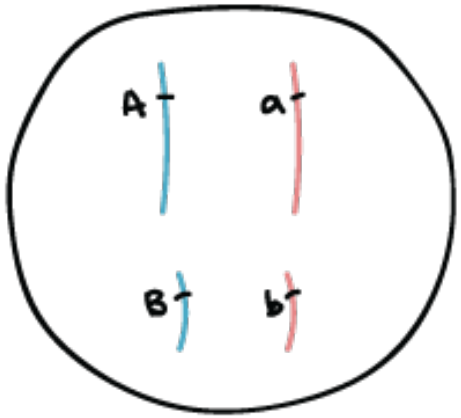
Introduction

Single-gene stuff

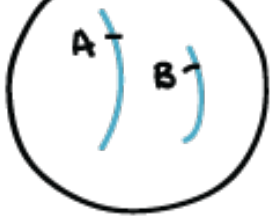
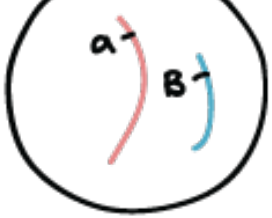
More complex stuff

- Polygenic inheritance
- Linkage

Genes on *separate chromosomes* assort independently, like Mendel said.

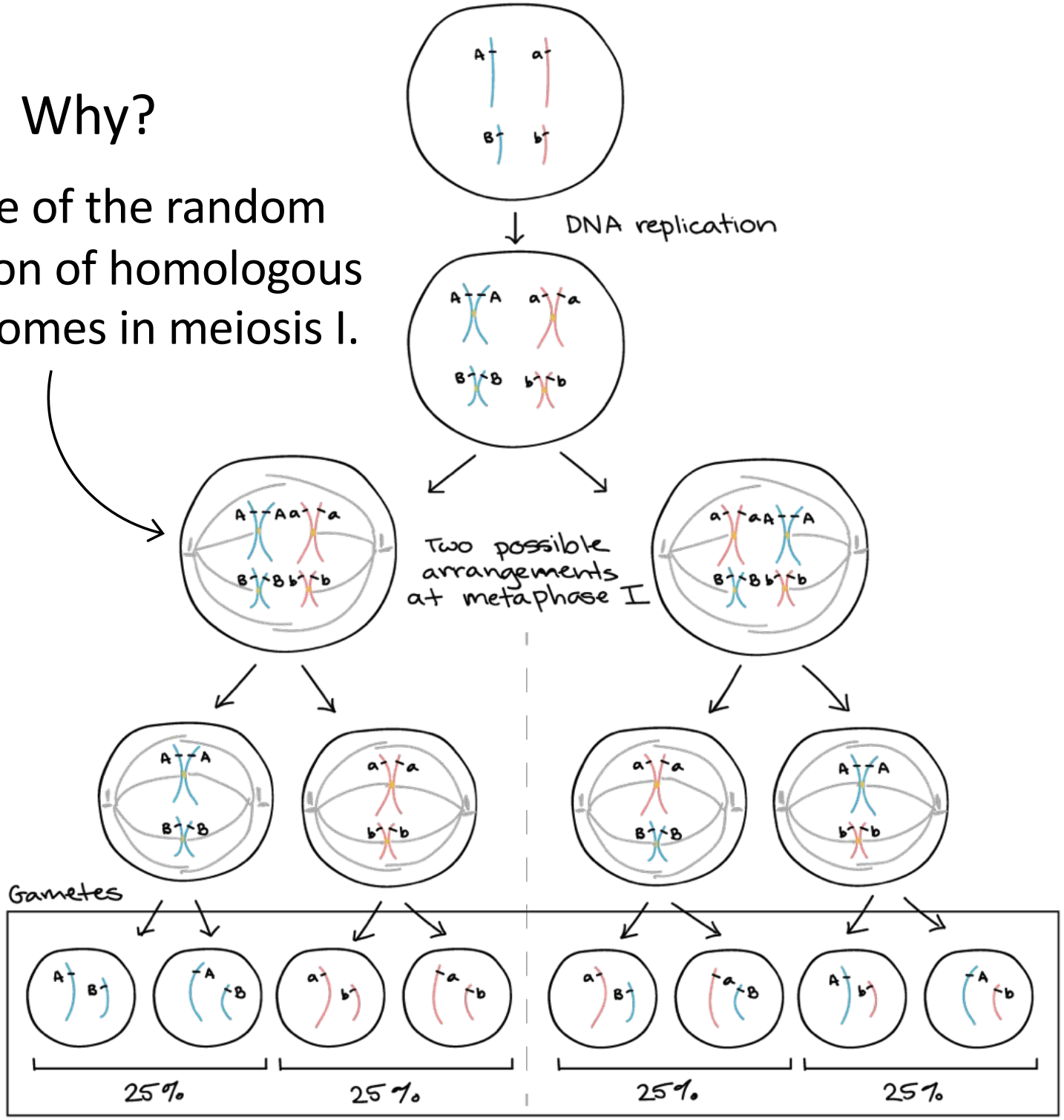


Gametes made:

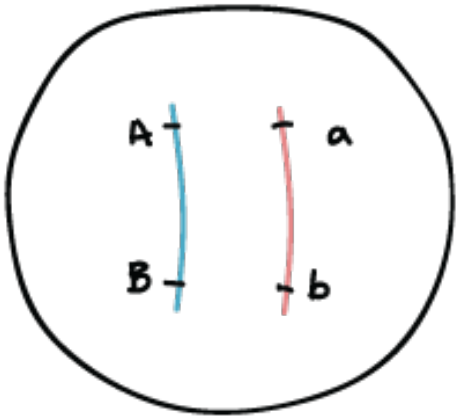
AB	ab	aB	Ab
			
25%	25%	25%	25%

Why?

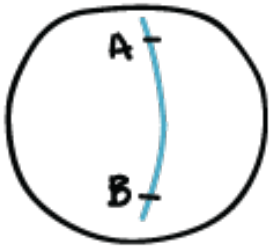
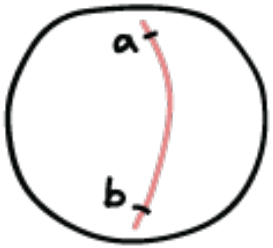
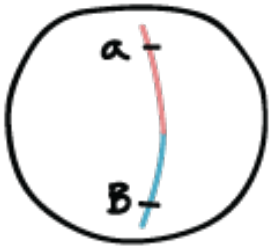
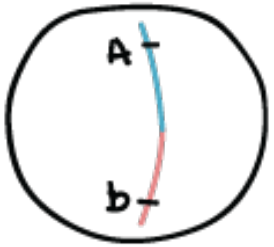
Because of the random orientation of homologous chromosomes in meiosis I.



Genes *far apart on the same chromosome* also assort independently.

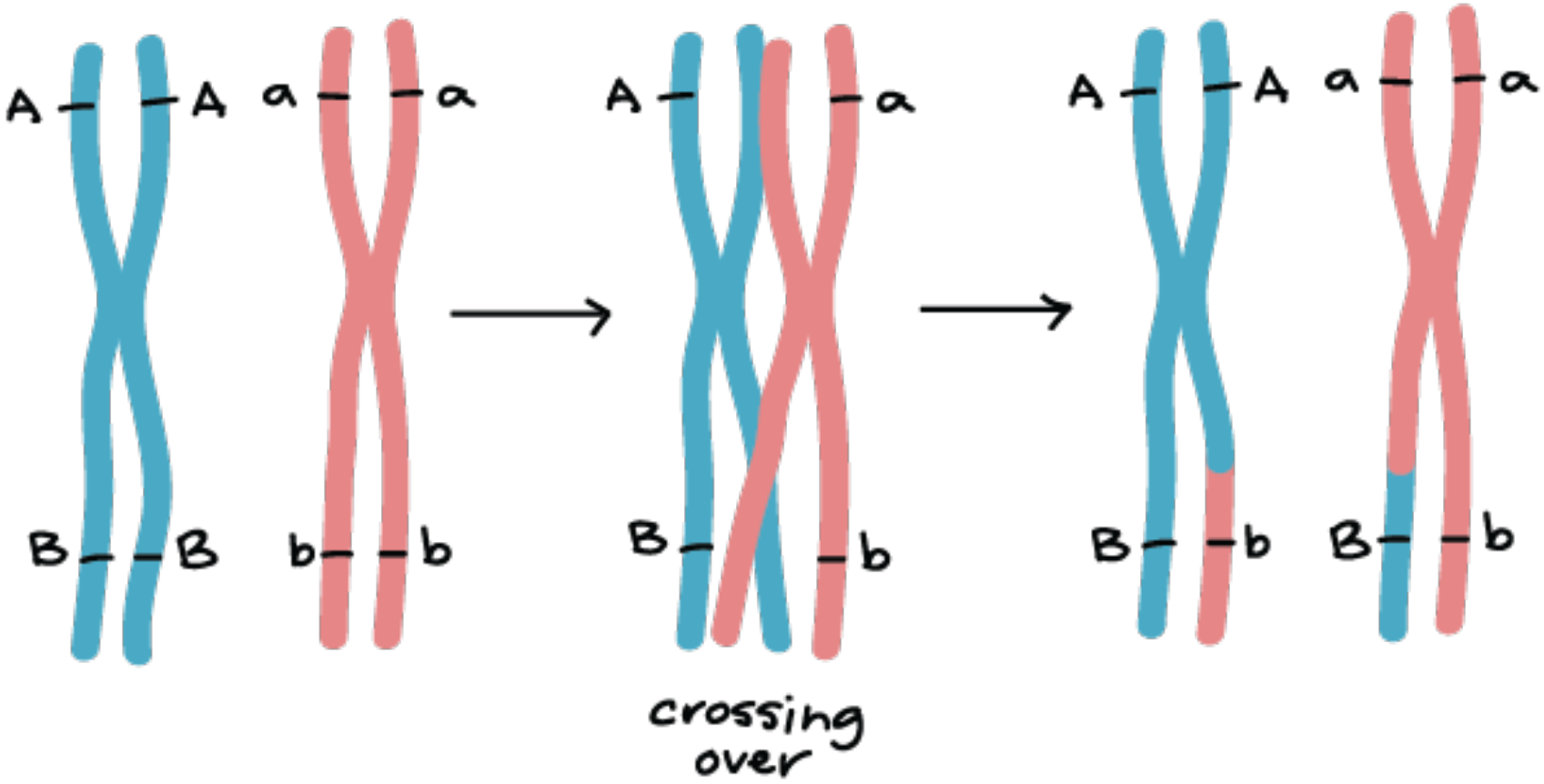


Gametes made:

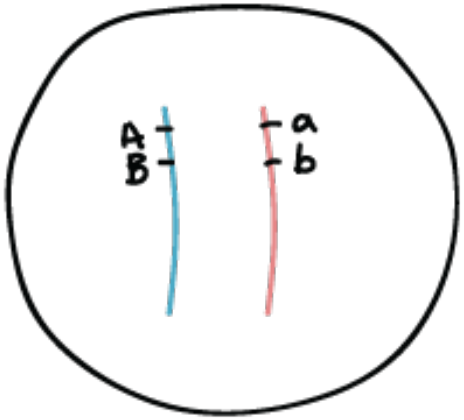
AB	ab	aB	Ab
			
25%	25%	25%	25%

Why?

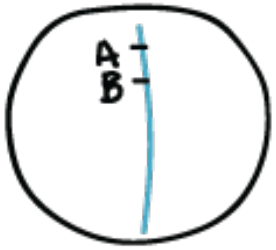
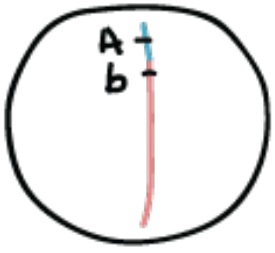
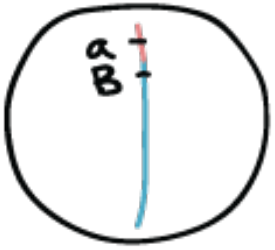
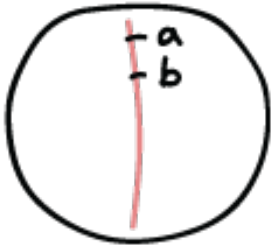
Because of crossing over (“homologous recombination”).



Genes *close together on the same chromosome* don't assort independently.

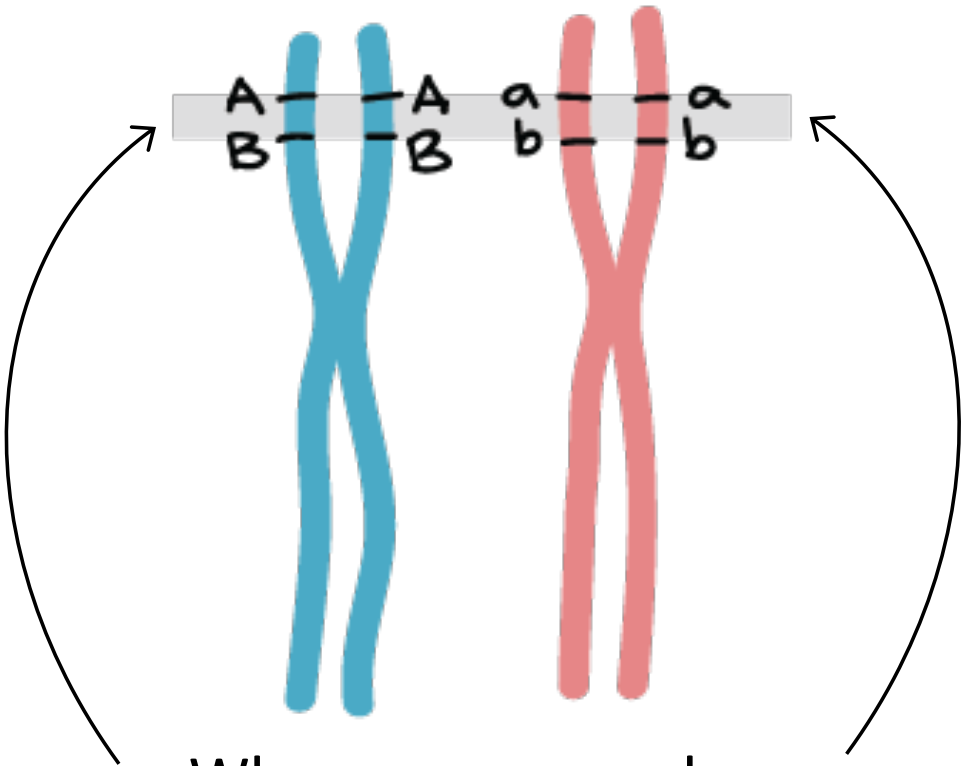


Gametes made:

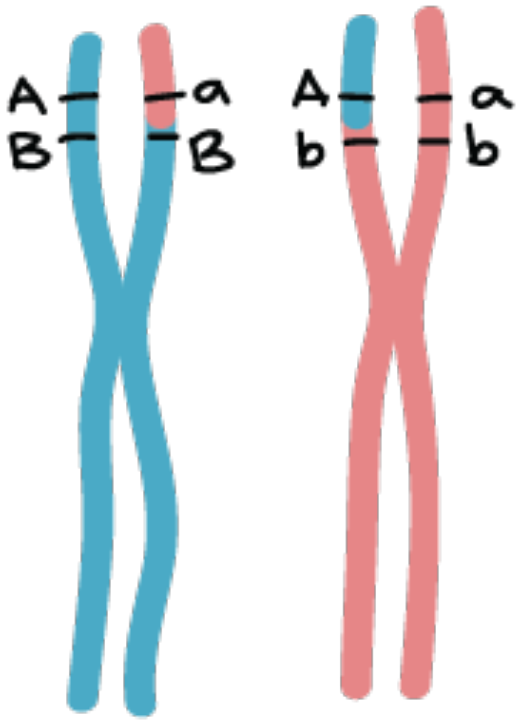
AB	Ab	aB	ab
			
48%	2%	2%	**48%**

Why?

Because crossovers between genes that are close together are uncommon.



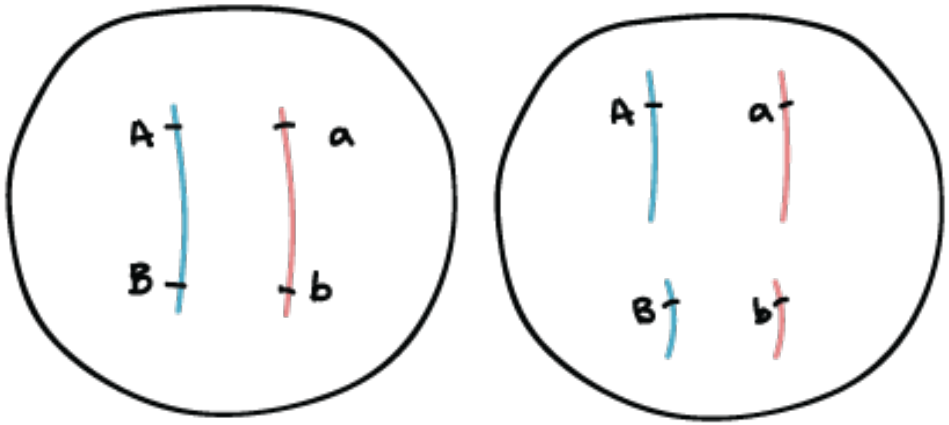
When genes are close together, there's not much room for crossover.



So although recombination can happen, it's not common.

Summary: Linkage

Unlinked genes

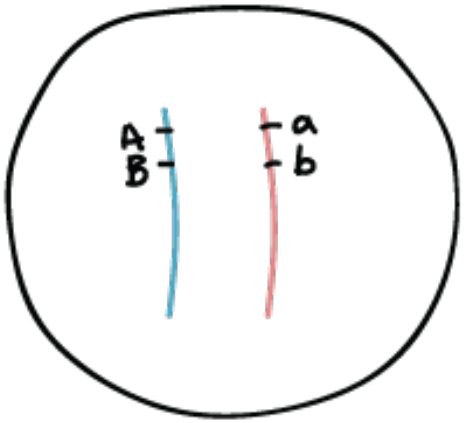


Located on different chromosomes, or far apart on the same chromosome.

Sorted into gametes independently of each other.

Follow Mendel's law of independent assortment.

Linked genes



Located close to each other on the same chromosome.

Usually sorted into gametes together as a unit.

Violate Mendel's law of independent assortment.