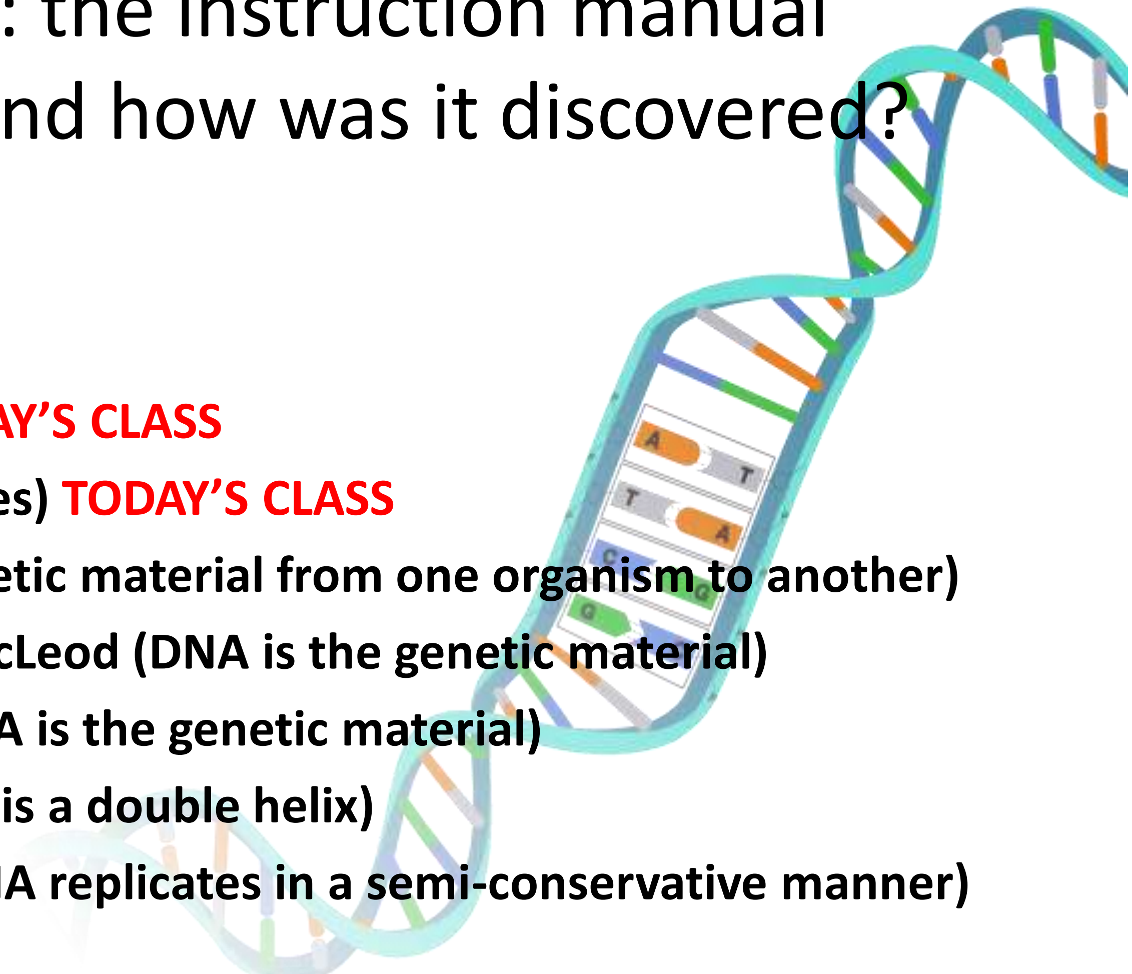
Lecture 3
The instruction manual of life

How was it discovered?

Mendel and heredity

Engineering a living machine

Step one: the instruction manual
What is it and how was it discovered?



Classical experiments:

- **Mendel (heredity) TODAY'S CLASS**
- **Flemming (chromosomes) TODAY'S CLASS**
- **Griffith (transfer of genetic material from one organism to another)**
- **Avery, McCarty and MacLeod (DNA is the genetic material)**
- **Hershey and Chase (DNA is the genetic material)**
- **Watson and Crick (DNA is a double helix)**
- **Meselson and Stahl (DNA replicates in a semi-conservative manner)**

Engineering biological systems: why and how?

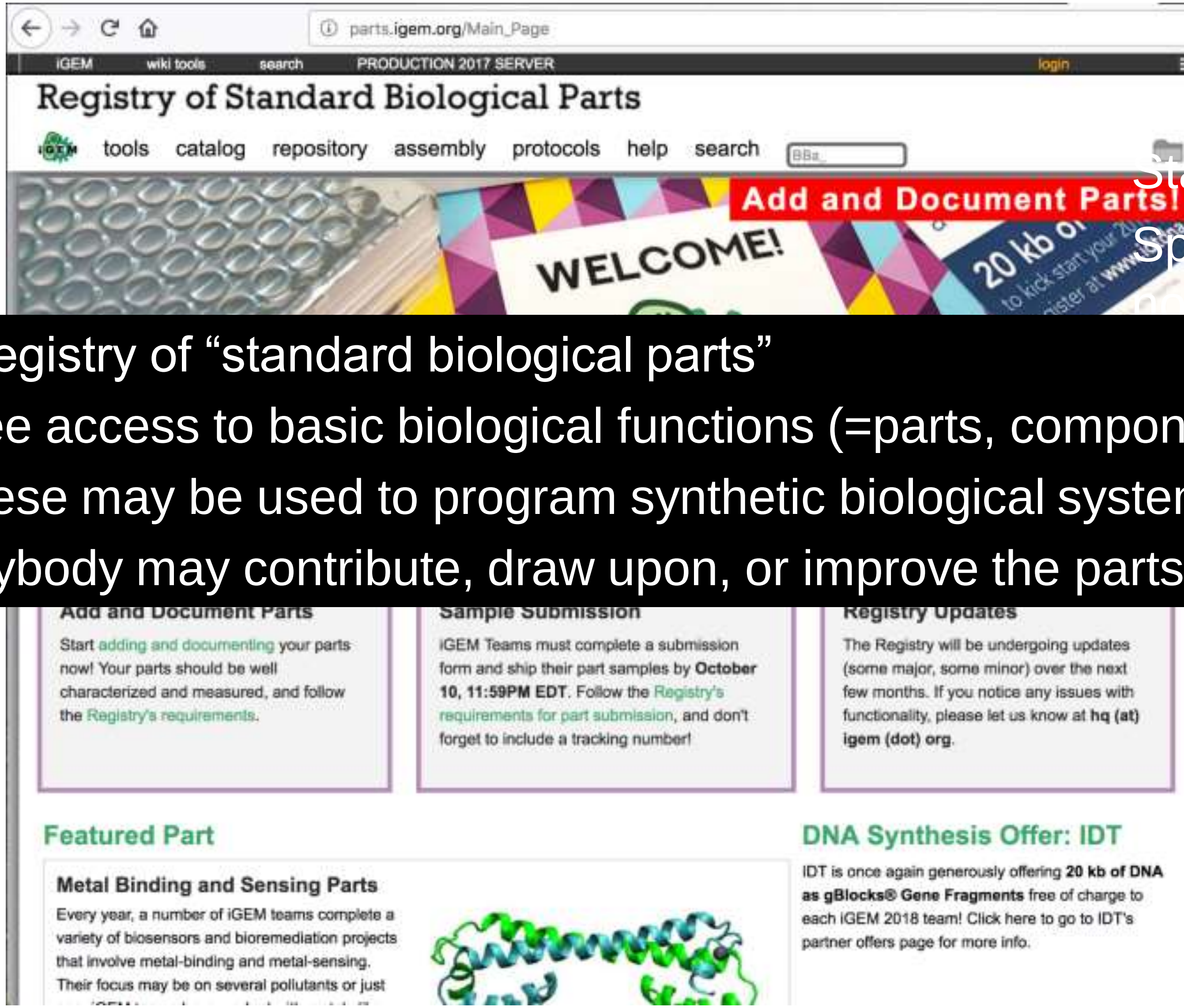
We engineer biological systems to

- Make vaccines (Covid-19)
- Construct materials
- Process chemicals
- Produce energy
- Provide food
- Help maintain and enhance human health and our environment

We try to understand biological systems so that we can engineer them

Nature (2005) Vol. 438, p449

International Genetically Engineered Machines (iGEM)



A registry of “standard biological parts”

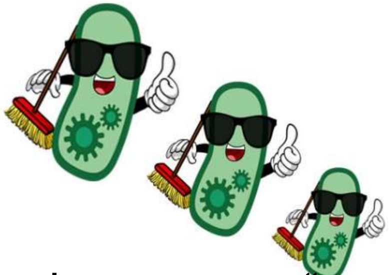
Free access to basic biological functions (=parts, components)

These may be used to program synthetic biological systems

Anybody may contribute, draw upon, or improve the parts

iGEM teams

Team from Ruia College, Mumbai: won several medals at various stages



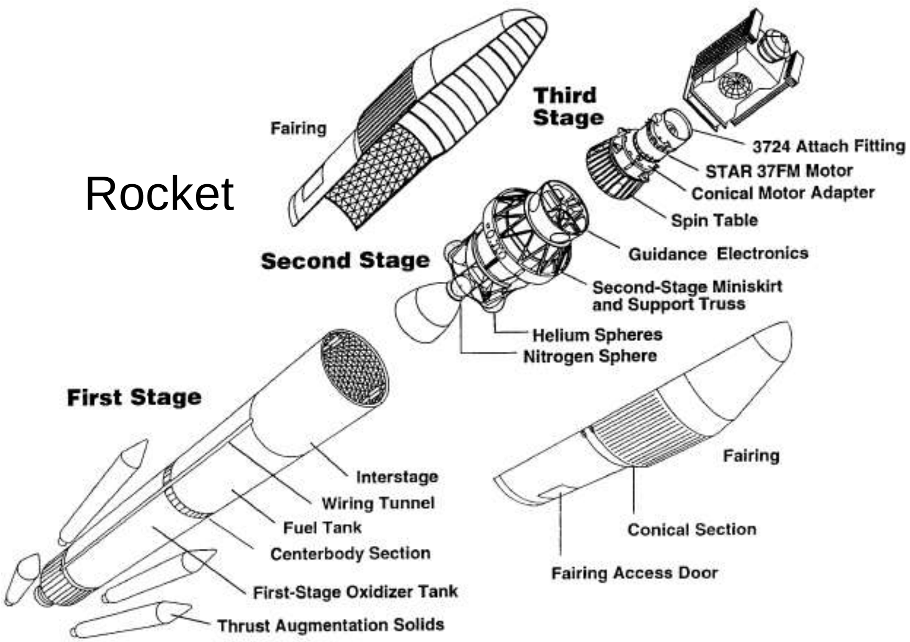
Bacteria that remove "paan" stains

When an iGEM team asks for a ‘part’ for their engineered biological system, what do they get?

Bottom-up approach: all parts known

Top-down approach: inner working unknown

Rocket



Bacteria

Order the part and attach it

Order a part of the manual and give it to the bacteria

Who actually makes the part? The organism!

What is the instruction manual for an organism?

- An organism: you, your friend, the causative agent of your sore throat, your dog, your favorite rosebush, etc.

- The instruction manual is the genetic material that not only controls the functioning of the organism, but actually drives the development of the organism: a self-driven program!

"The software makes its own hardware." J. Craig Venter

DNA is the genetic material of many organisms on planet Earth (exceptions are viruses)

How did we arrive at this conclusion?

First insights: Mendel and the idea of inheritance

1822-1884

Drawing from the Deck of Genes

Imagine the future……..

It is the year 2050. You have set IIT as your goal for your undergraduate degree. You enroll in one of the numerous coaching classes that have an excellent success rate for cracking the JEE.

The first day you show up to the coaching class, you are asked to give a sample of your blood, which is given to a genetic testing lab to test your intelligence and ability to be an engineer. After 2 days, the results of your genetic test shows that you have a 90% probability of being an outstanding engineer. You are admitted into IIT Bombay immediately!

You know that the genetic material is DNA, but how did we get to this knowledge?

Genotype & Phenotype

Genotype: An organism's full hereditary information (today, we know this to be the genome, consisting of DNA)

Phenotype: Actual observed properties

Flow of heritable traits

Before we knew about DNA, the most obvious visible manifestation was the presence of heritable traits

Phenotypic characters that are passed on from parent to offspring e.g. eye and hair color

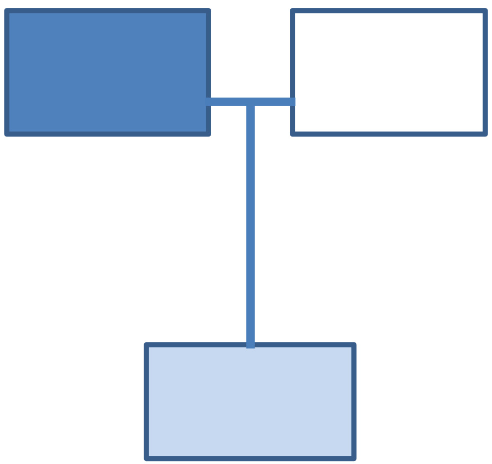
Some phenotypes: probability of getting breast cancer, Alzheimers disease, etc.

Today, Uzbekistan is using genetic testing to find future Olympians (phenotypes are based on the sport).

Early hypotheses about heredity

Blending hypothesis - similar to the color palette

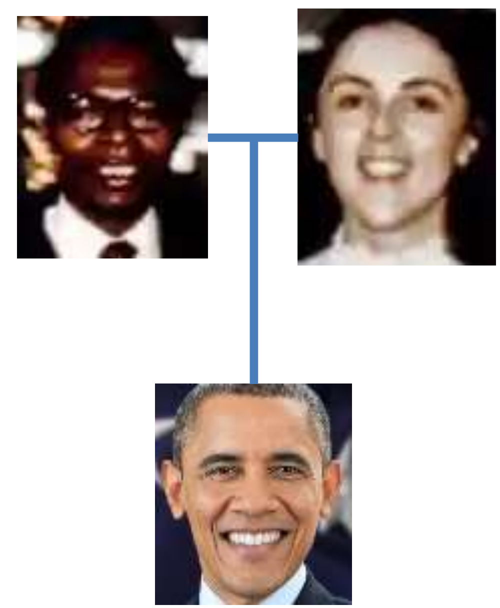
Color mixing



Parents

↓

Son/daughter



Gregor Mendel : elucidation of the principle of heredity

- Mendel's choice of experimental system -- pea plants

Why pea plants?

0. He was an avid gardener (& mathematician)

1. Availability in many variations
2. Short generation time
3. Large number of offspring from each mating
4. Cross pollination is easy due to well separated pollen producing and egg bearing organs

Distinct heritable variation: characters

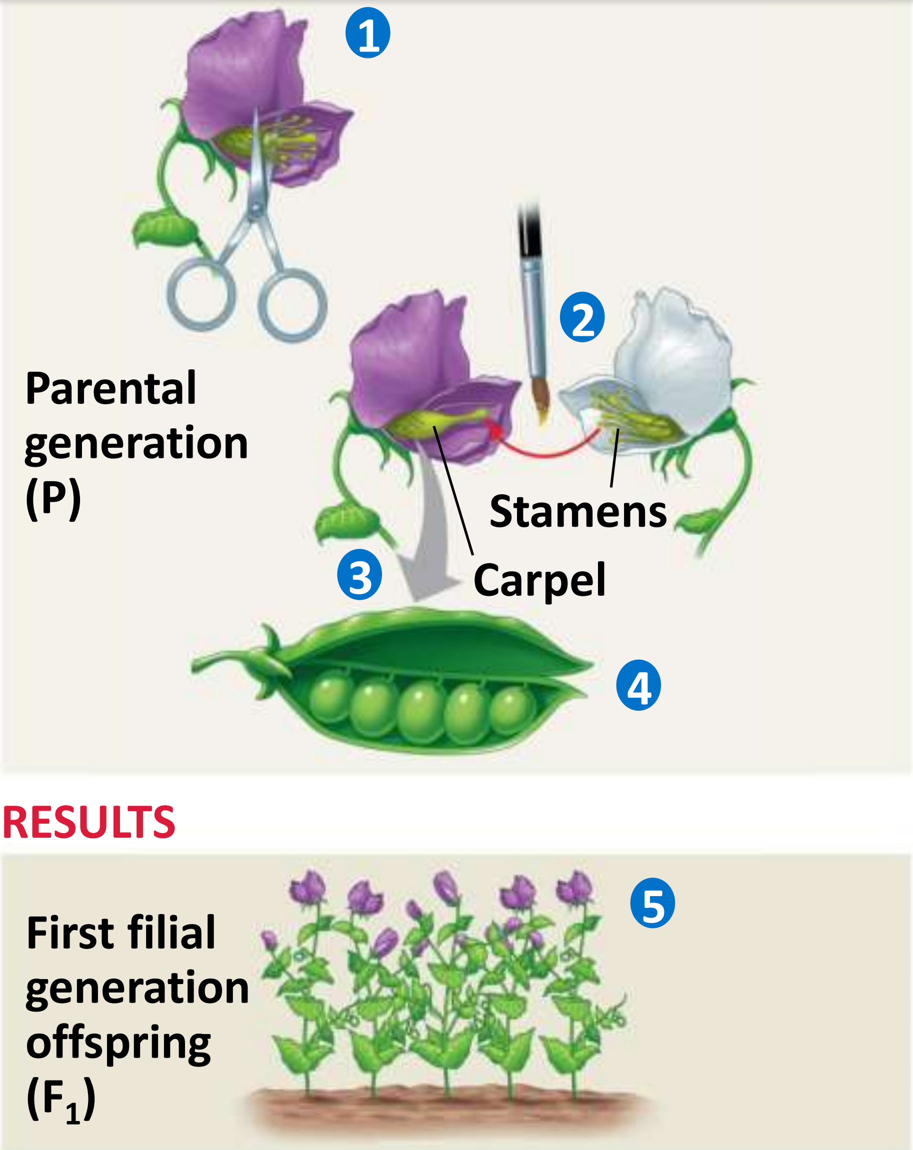
Mendel chose characters that showed distinct alternative forms

Character	Trait		
Flower color	Purple 	×	White 
Flower position	Axial 	×	Terminal 
Seed color	Yellow 	×	Green 
Seed shape	Round 	×	Wrinkled 

Character	Trait		
Pod shape	Inflated 	×	Constricted 
Pod color	Green 	×	Yellow 
Stem length	Tall 	×	Dwarf 

Character variants are called traits

What is cross-pollination?



A **carpel** is the ovule and seed producing reproductive organ in flowering plants (like female).
A **stamen** is the pollen-producing reproductive organ of a flower (like male).

Pea flowers have both!

1: Remove the stamens of purple flowers so they cannot pollinate

2 & 3: Pollinate a purple flower carpel with the stamens of a white flower

4: The fertilized purple flower will give rise to seeds which can be planted

5: Observe the offspring for the trait (based on blending, expect to see pink flowers)

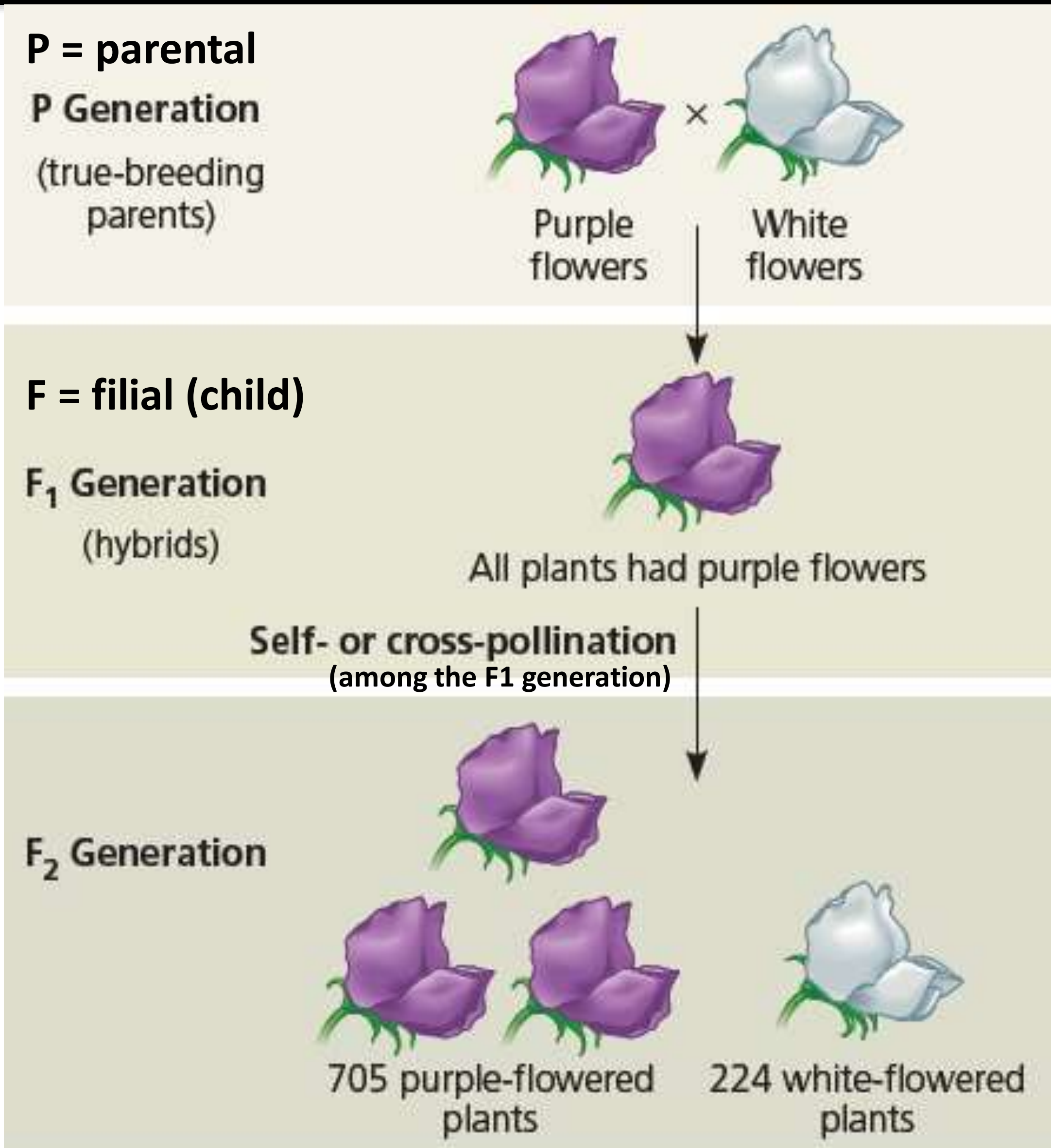
Before starting the real experiment…

Mendel made sure to choose only **true breeding** varieties

Purple-flowered plant X Purple-flowered plant

Always purple-flowered plant

Results of mating (crossing) of two contrasting traits



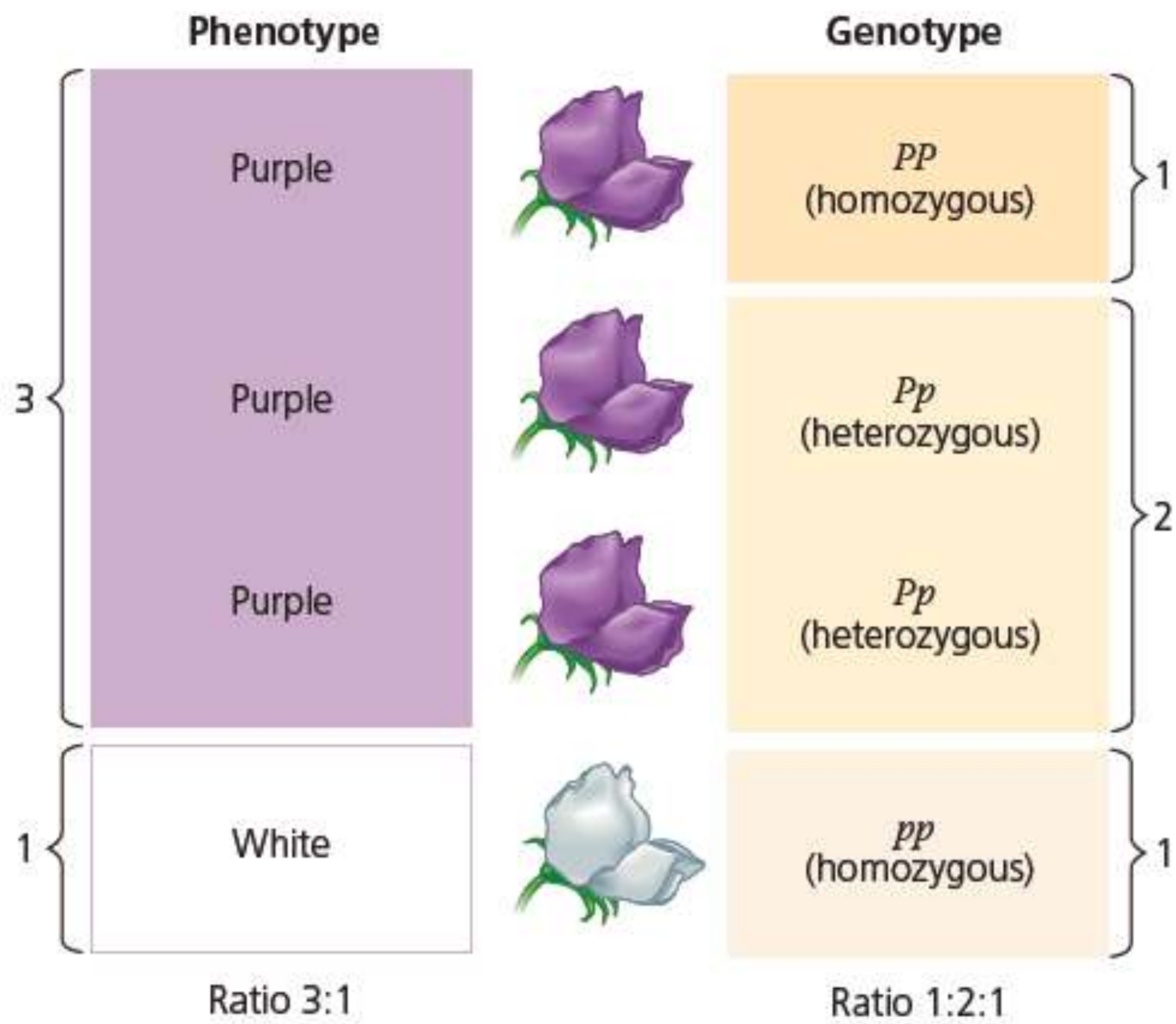
Surprises!

1) Most importantly, no blending!
2) F1 were all purple; where did the white go?
3) F2 showed the presence of the missing white
4) 3:1 ratio of purple to white in the F2 generation; why this ratio and what does it mean?

Dominant trait

Recessive trait

To understand Mendel's data: Phenotype vs genotype



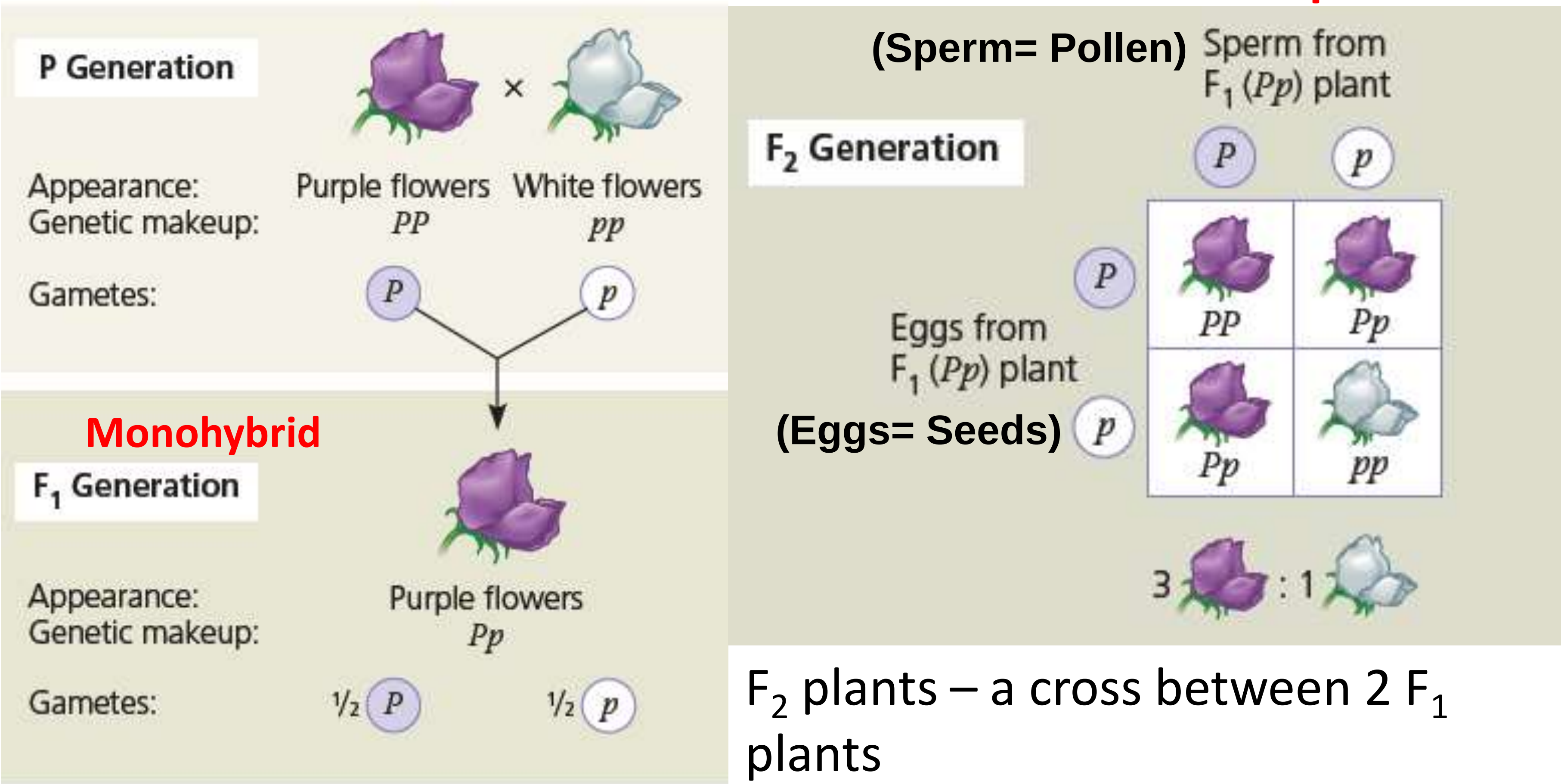
Identical alleles: Homozygous

Different alleles: Heterozygous

The 3:1 ratio can be explained by the concept of alleles

- Law of segregation -- Two units (called alleles today) for a heritable traits separate from each other during gamete formation and end up in different gametes

Punnett square

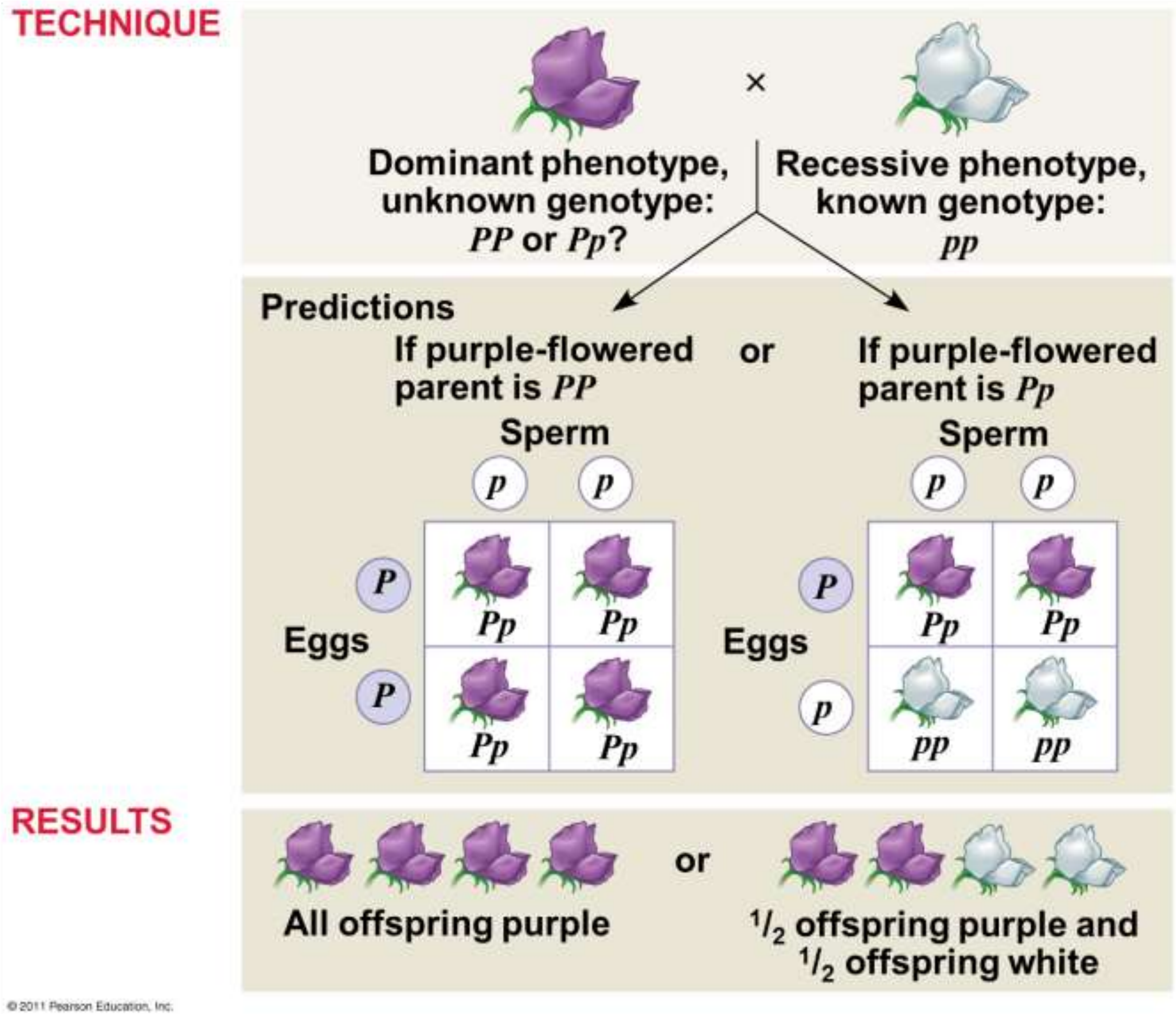


F_2 plants – a cross between 2 F_1 plants

Mendel got the 3:1 ratio in all his crosses

Character	Dominant Trait	×	Recessive Trait	F_2 Generation Dominant: Recessive	Ratio
Flower color	Purple 	×	White 	705:224	3.15:1
Flower position	Axial 	×	Terminal 	651:207	3.14:1

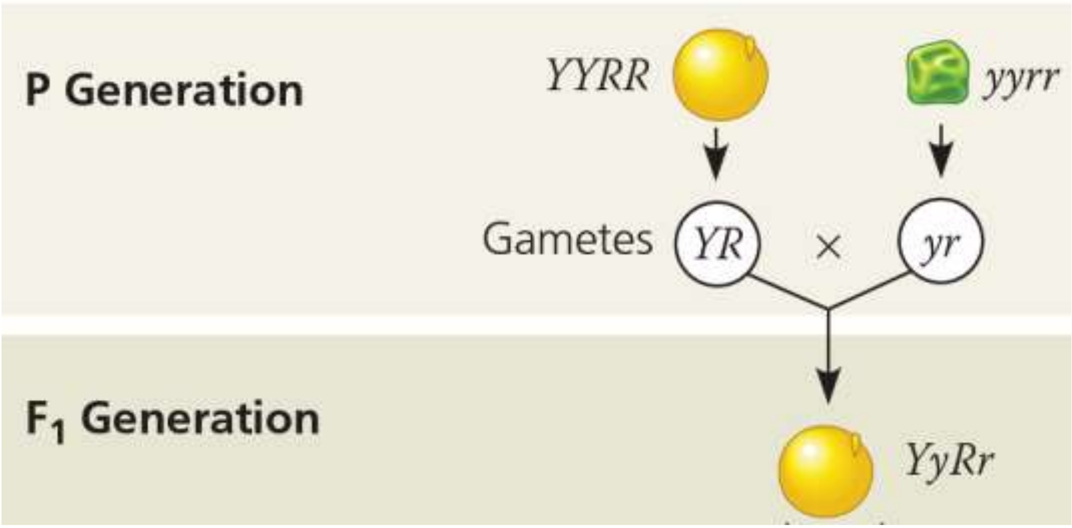
How can we tell the genotype of an individual with the dominant phenotype?



Law of independent assortment

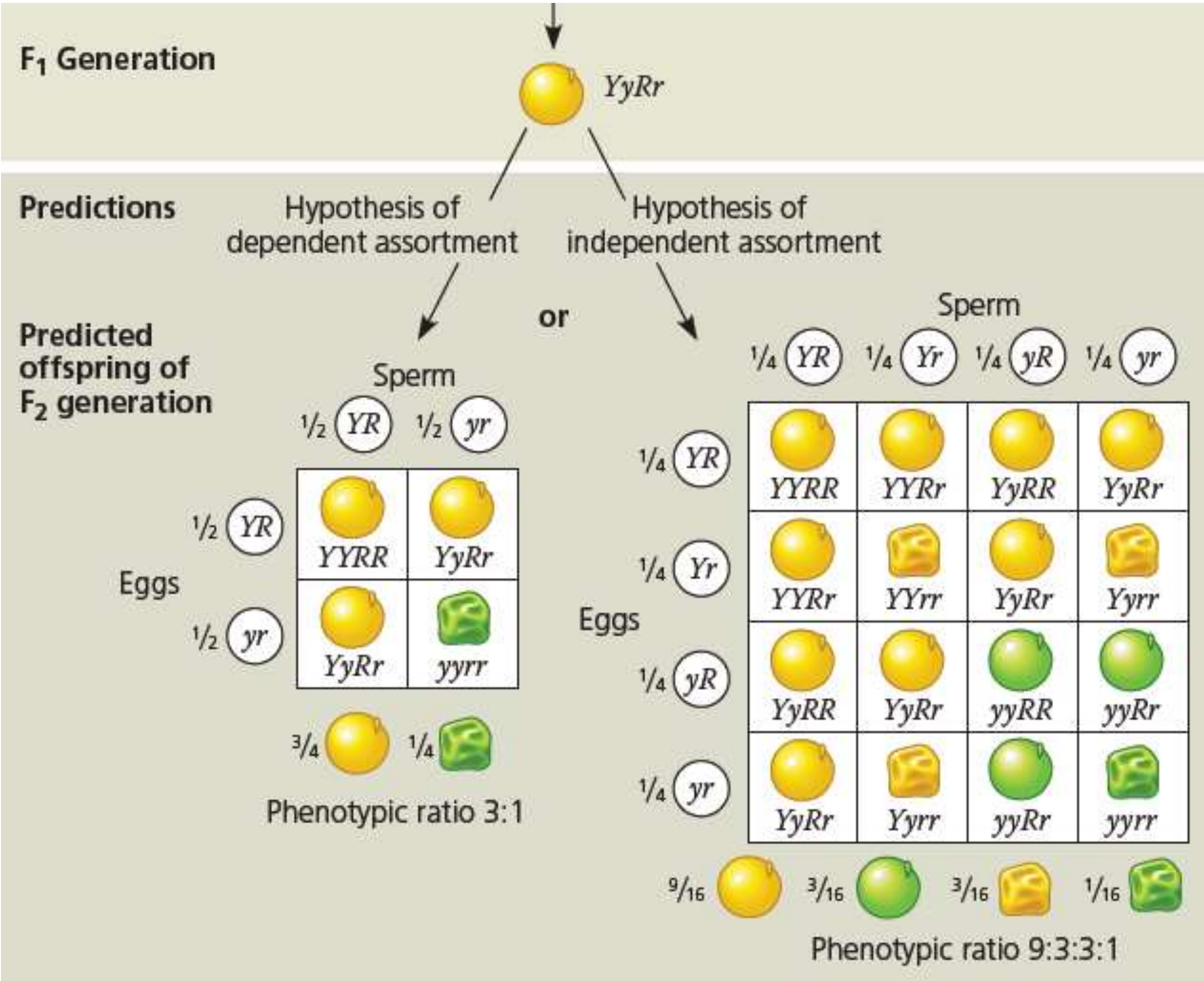
- 2 traits were simultaneous studied e.g.

Dominant (*YYRR*) Recessive (*yyrr*)



Dihybrid

Results of dihybrid cross



Law of independent assortment :

Each pair of alleles segregates independently of each other pair of alleles during gamete formation

Inferences made by Mendel (1865)

1. Inheritance of each trait is determined by "units" or "factors" that are passed on to descendants unchanged

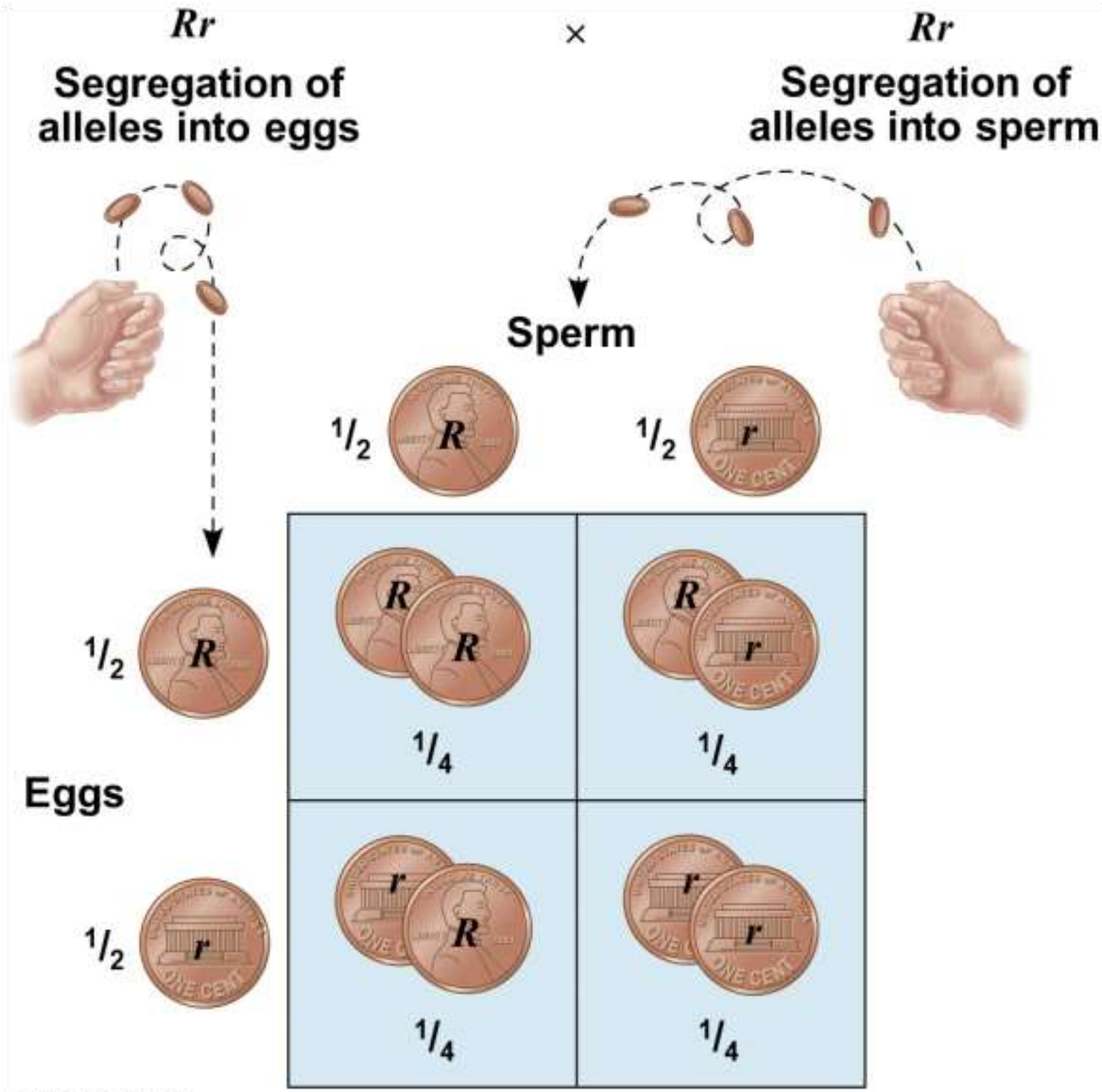
2. Individual inherits one such unit from each parent for each trait

3. A trait may not show up in an individual but can still be passed on to the next generation

These were not consistent with the ‘blending’ hypothesis of heredity and led to a new ‘particulate’ hypothesis: genetic material must be in the form of discrete units

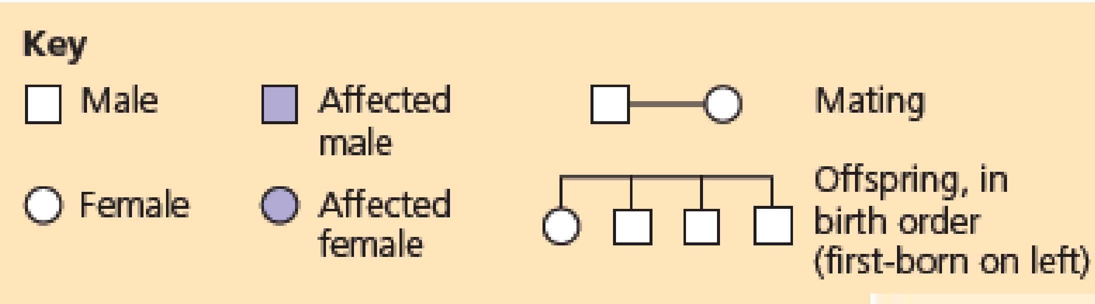
The laws of probability govern Mendelian inheritance

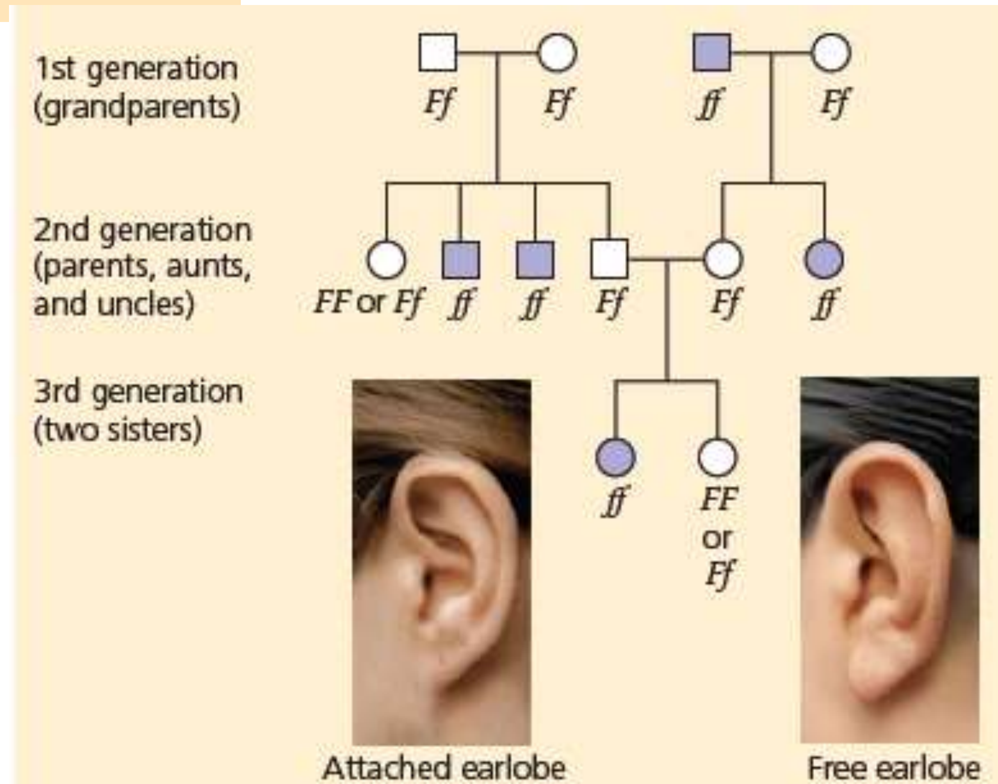
- Both laws reflect the rules of probability
- Monohybrid crosses also follow rules
- You are the result of a genetic lottery!



Human traits that follow Mendelian genetics

- Attached earlobe (recessive trait)





Human traits that follow Mendelian genetics

Single gene human diseases:

- Phenylketonuria
- Hemophilia
- Sickle cell disease
- Beta-thalassemia

Online Mendelian Inheritance in Man (OMIM) database identifies some 4000 Mendelian disorders.

Other traits:

- Resistance to HIV
- Ability to taste phenylthiocarbamide

Examples of deviation from Mendelian genetics

- Multiple alleles (when genes exist in more than 2 allelic forms)

(a) The three alleles for the ABO blood groups and their carbohydrates. Each allele codes for an enzyme that may add a specific carbohydrate (designated by the superscript on the allele and shown as a triangle or circle) to red blood cells.

Allele	I^A	I^B	i
Carbohydrate	A △	B ●	none

(b) Blood group genotypes and phenotypes. There are six possible genotypes, resulting in four different phenotypes.

Genotype	I^AI^A or I^Ai	I^BI^B or I^Bi	I^AI^B	ii
Red blood cell appearance				
Phenotype (blood group)	A	B	AB	O

ABO gene- glycosyltransferase

I^A and I^B are dominant

i is recessive

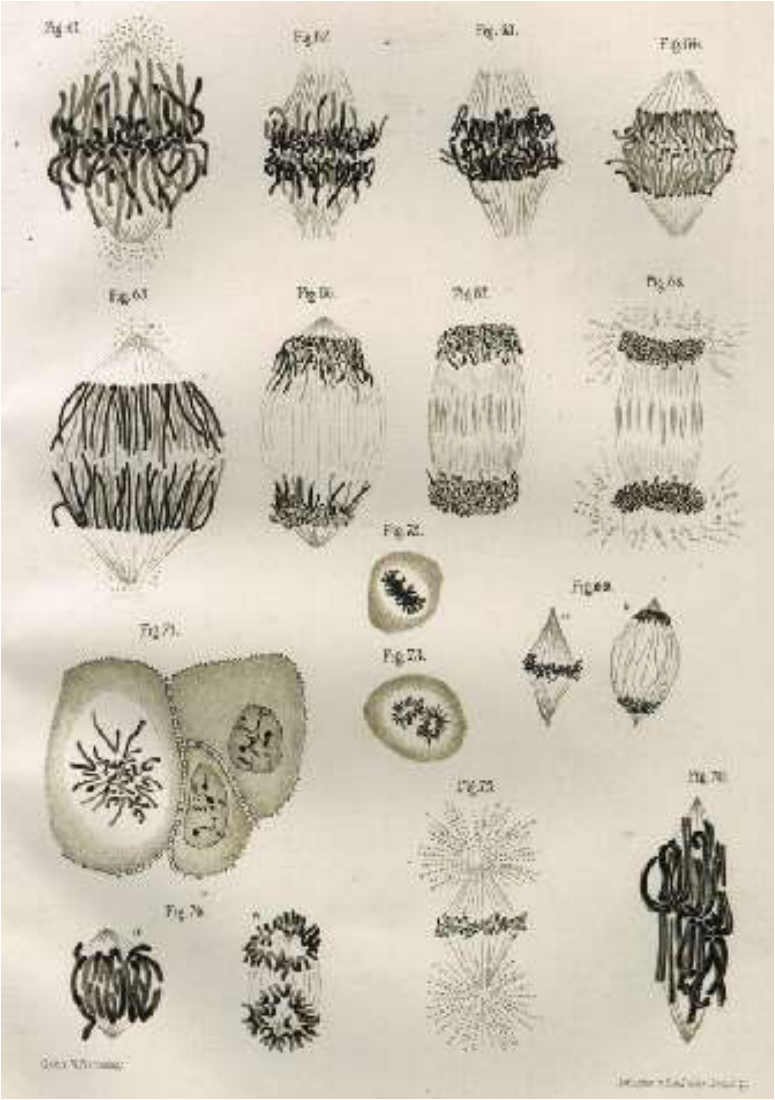
Pleiotropy multiple phenotypic effects

Mendel's results were explained when chromosomes were discovered

Around 20 years after Mendel's experiments, Walther Flemming used stains to visualize cells and found strands of material that could be stained (called "chromatin").

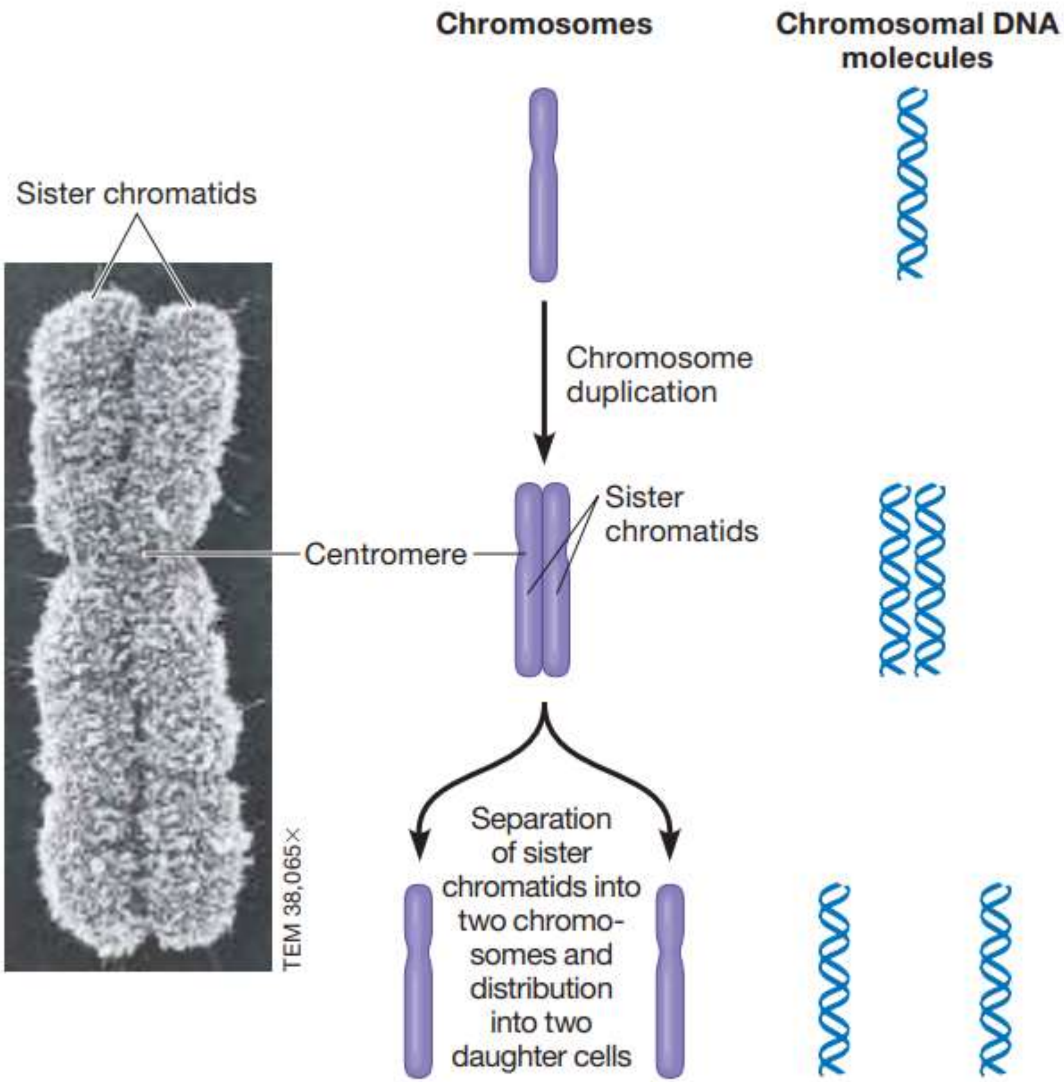
These turned out to be chromosomes and they were the 'units' that Mendel had predicted. Pea plants have 2 copies of each chromosome.

Yes, he drew gorgeous pictures of his microscopy studies.



Drawing of mitosis by Walther Flemming.
Flemming, W. Zellsubstanz, Kern und Zelltheilung (F. C. W. Vogel, Leipzig, 1882).

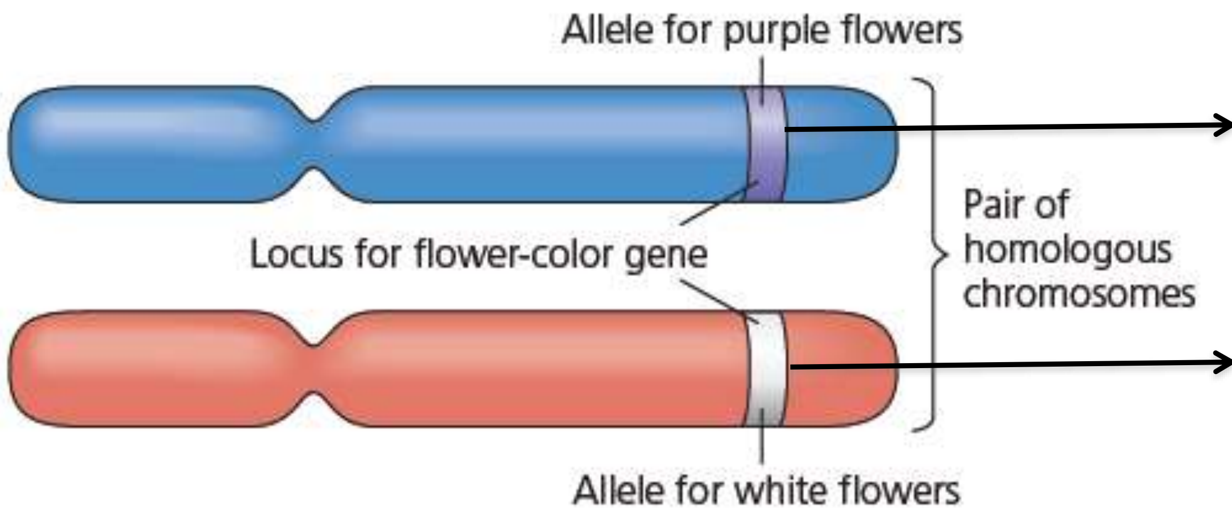
Mendel's results were explained when chromosomes were discovered



▲ **Figure 8.3B** **Chromosome duplication and distribution**

Mendel's results were explained when DNA was discovered

- Alternative variations of genes (alleles) account for variation

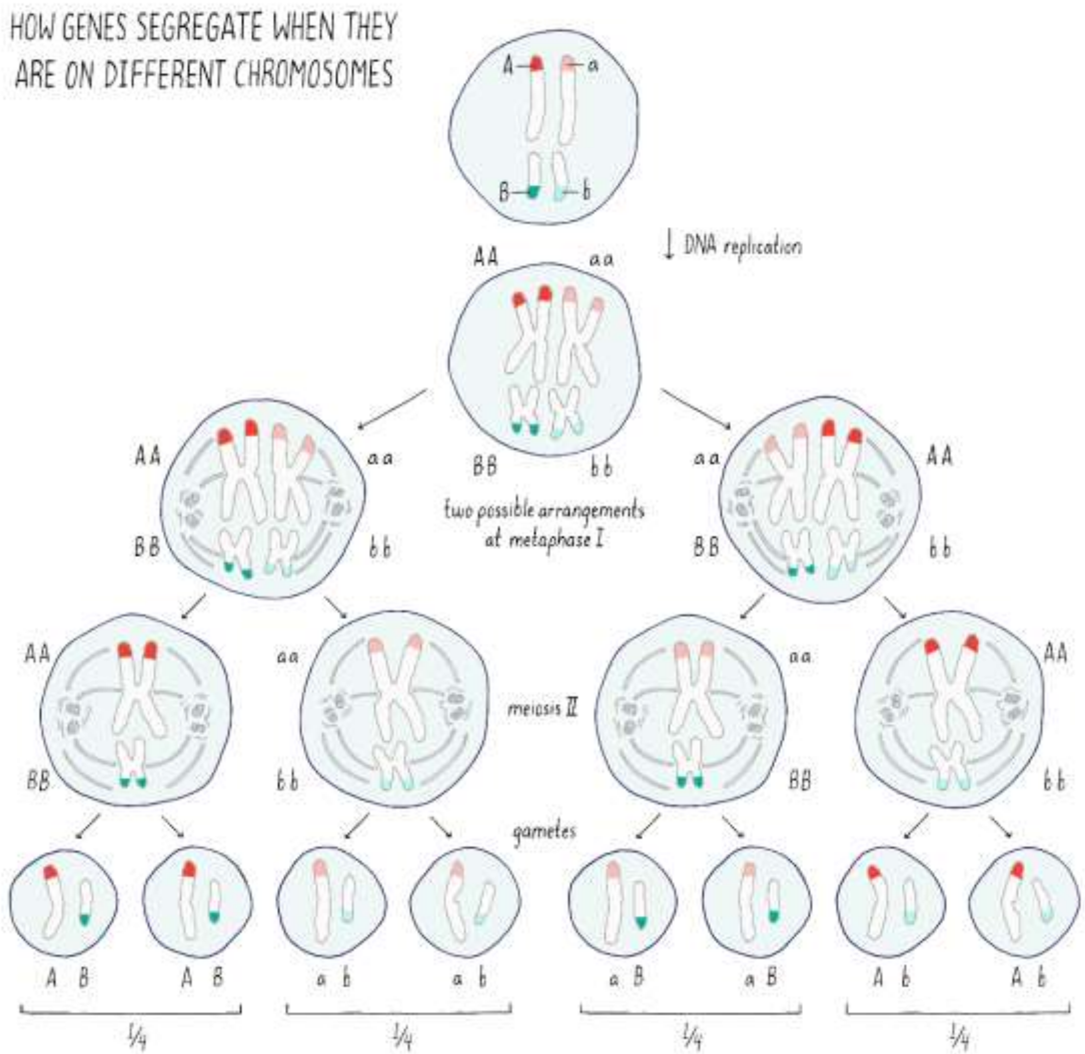


These are genes consisting of DNA

- Each pea plant harbors 2 copies of a gene
- Dominant allele has the effect but recessive has not

HOW WAS DNA DISCOVERED TO BE THE GENETIC MATERIAL? NEXT LECTURE

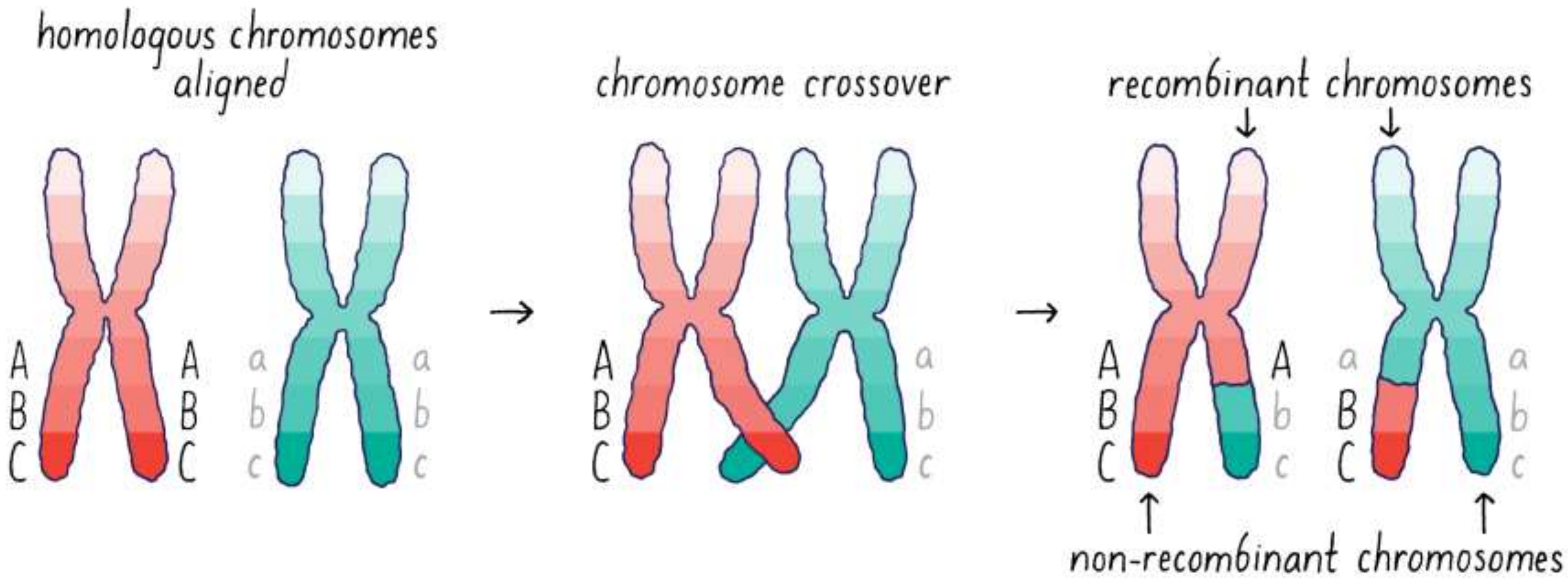
Crossing of plants is still used for making new crops with desired traits



This is the ¼ we saw in Mendel's dihybrid cross

https://explorebiology.org/collections/genetics/plant-genetics-and-the-future-of-food

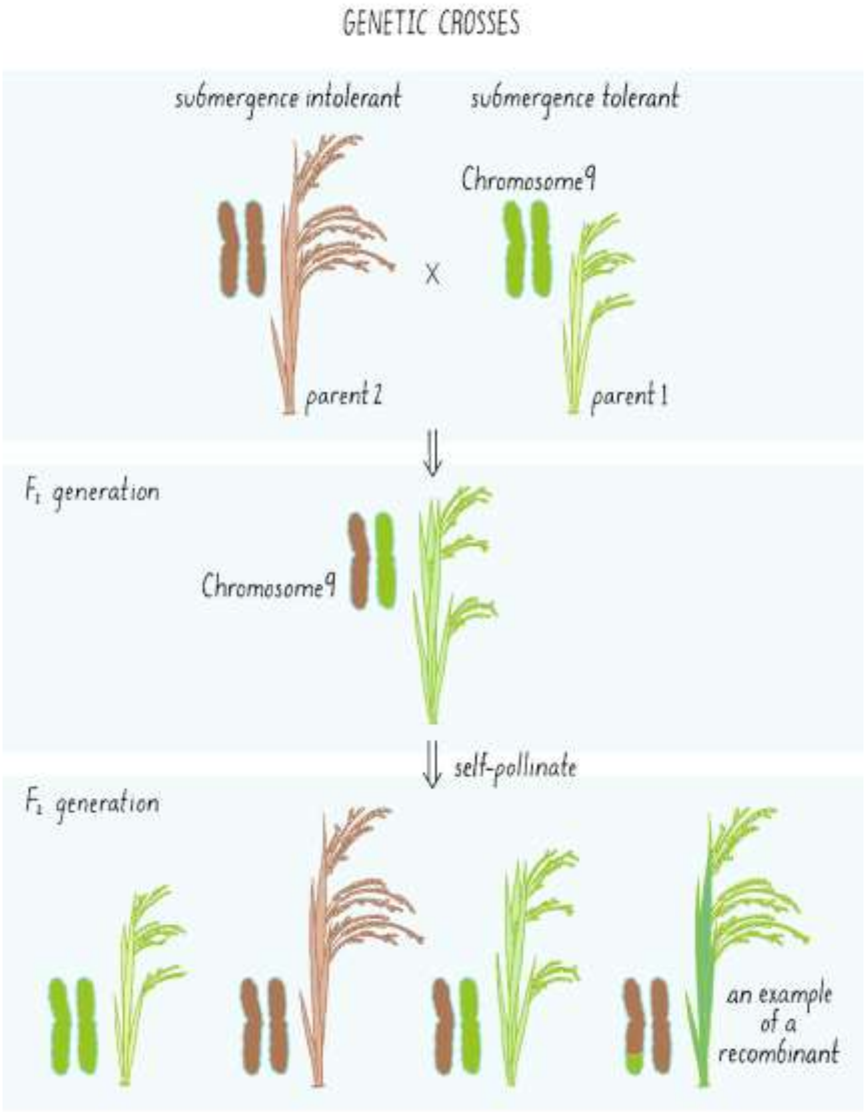
New concept: recombination or crossing over



During formation of gametes (seeds and pollen in plants), the chromosomes exchange their DNA

https://explorebiology.org/collections/genetics/plant-genetics-and-the-future-of-food

Crossing of plants is still used for making new crops with desired traits



Rice that is tolerant to being submerged in water was crossed with the local variety of rice (having phenotype for food grains) to generate the “Scuba” rice.

Scuba rice has been adopted by farmers in Bangladesh and India, resulting in a huge impact on their livelihood.

https://explorebiology.org/collections/genetics/plant-genetics-and-the-future-of-food

Do you think Mendel was lucky?

Mendel’s numbers were too close to the perfect 3:1 ratio (Fischer, a statistician and population geneticist)

Mendel chose traits in his dihybrid crosses that did not undergo recombination (luck or choice?)

Imagine the future……..

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You will use your newly acquired knowledge about cells and heredity to answer questions about this scenario during the tutorial.