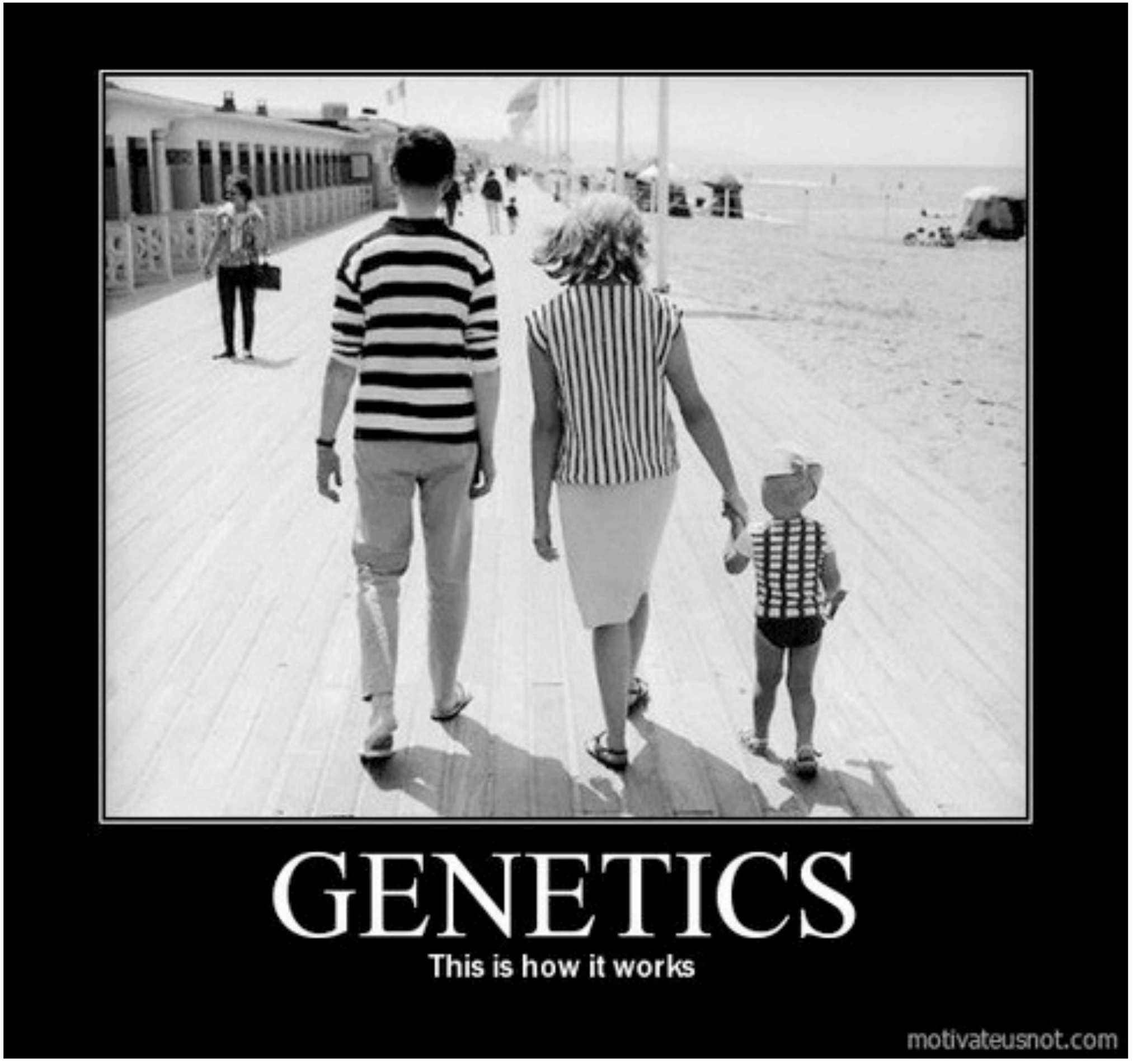
GENETICS

Mendelian & Modern

Principles


GENETICS
This is how it works
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PREFACE

- I would argue that mankind has a fundamental understanding and even an innate interest heredity.
- For centuries humans have observed a dichotomy that exists in sexual reproduction of offspring...
  - *Each offspring is both unique and yet at the same time exhibits identical traits found in its parents.*
- For years many explained heredity by the **"blending" hypothesis**, an idea that each parent donated genetic material that would blend like two color paints.
- However, everyday observations and breeding results contradict the predictions if this hypothesis were true.

PREFACE

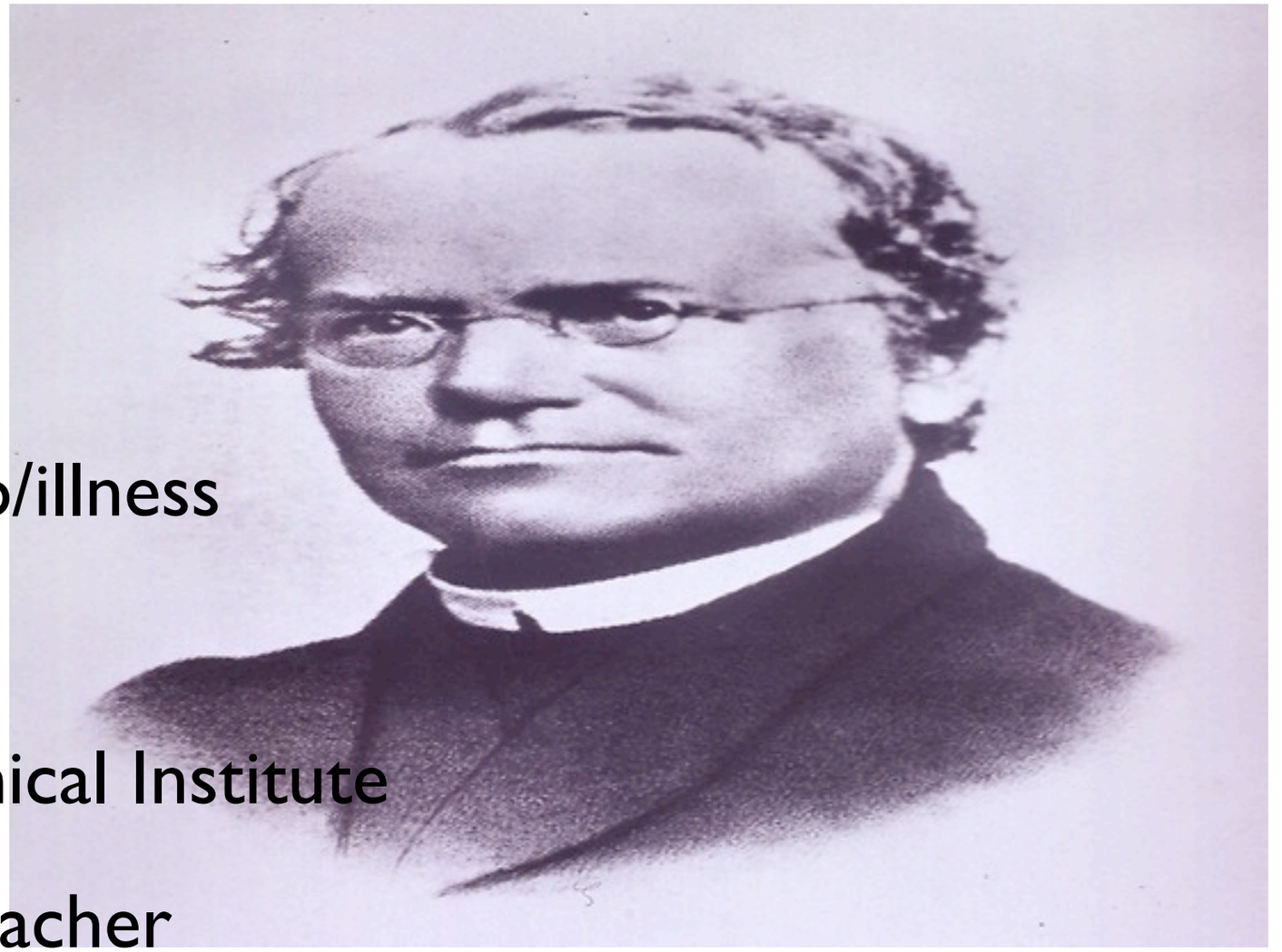
- The alternative to the blending hypothesis is the **particulate hypothesis**, where parents pass on discrete units of hereditary information that retain their identity in the offspring.
    - like dealing cards from deck of cards rather than mixing two colors of paint
- The conformation of this idea and consequently the foundation of all genetic understanding began in an abbey garden by a monk studying the common pea plant.
- **Ironically, this monk, (Gregor Mendel) laid down the foundation of genetic principles before anyone knew about DNA, genes, chromosomes and meiosis.**

Mendelian Genetics

I.

Main Idea: Mendel discovered the basic principles of heredity through carefully planned experiments, meticulous data collection / analysis and a little luck.

Historical Mendel



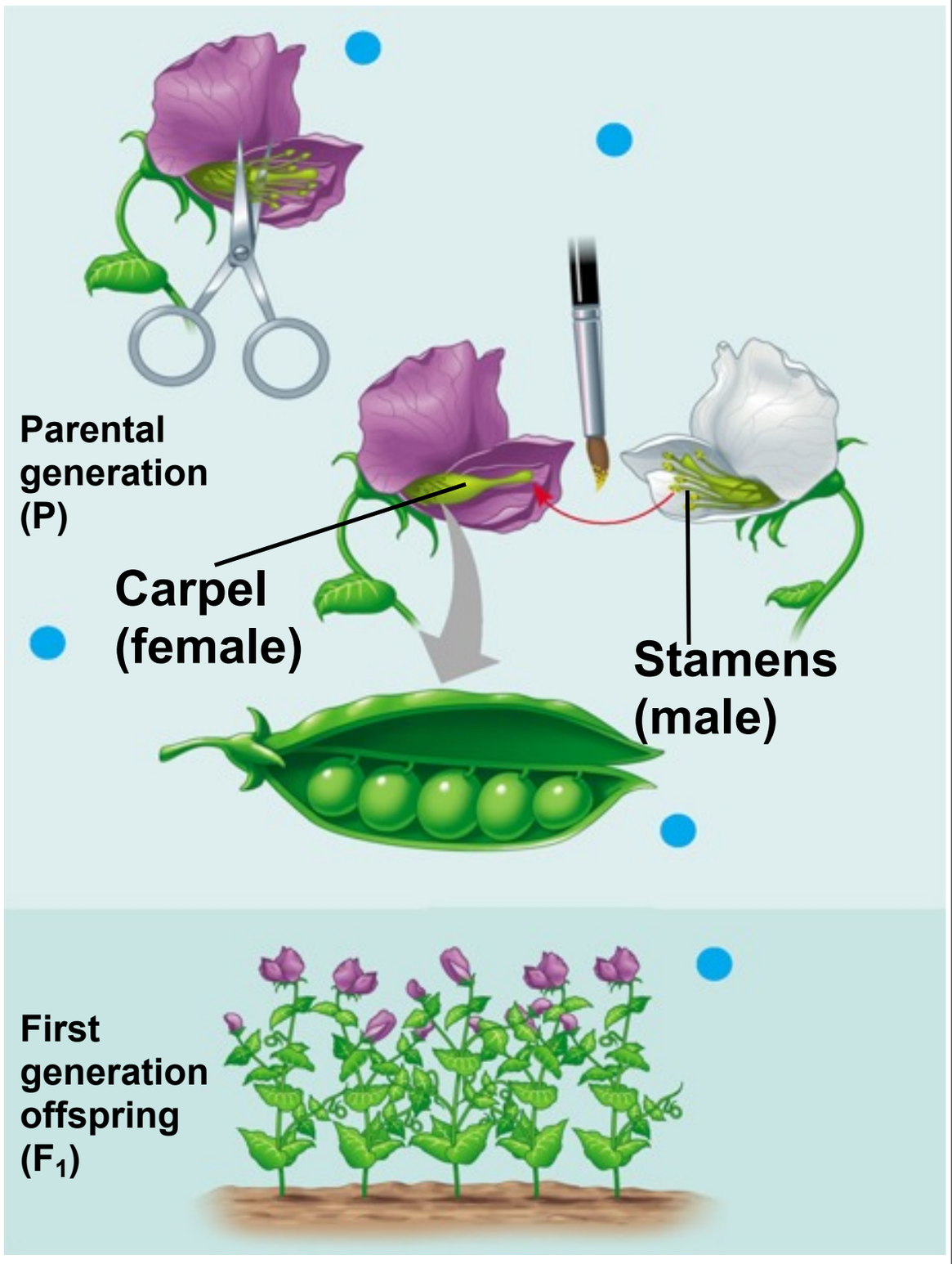
- Born in Austria
- Grew up on parent's farm
- Had agricultural training
- Overcame financial hardship/illness
- Excelled in high school
- Attended Olmutz Philosophical Institute
- Failed exam to become a teacher
- Entered Augustinian monastery at age 21
- Left monastery at 29 to study physics and chemistry at University of Vienna
- Two particular professors had a profound influence on Mendel

Historical Mendel

- One professor, a physicists, emphasized learning science through experimentation and mathematics
- The other professor, a botanist, sparked Mendel's curiosity in plant heredity
- Returns to the monastery
- Teaches at a local school
- Other teaching monks also interested in breeding plants
- In 1857 at the age of 35 Mendel begins breeding pea plants

Choosing Pea Plants

- Pea plants are a wise choice for genetic studies:
  - 1. many varieties
  - 2. short generation time
  - 3. numerous offspring
  - 4. easy to control mating
  - 5. easy to count new seeds

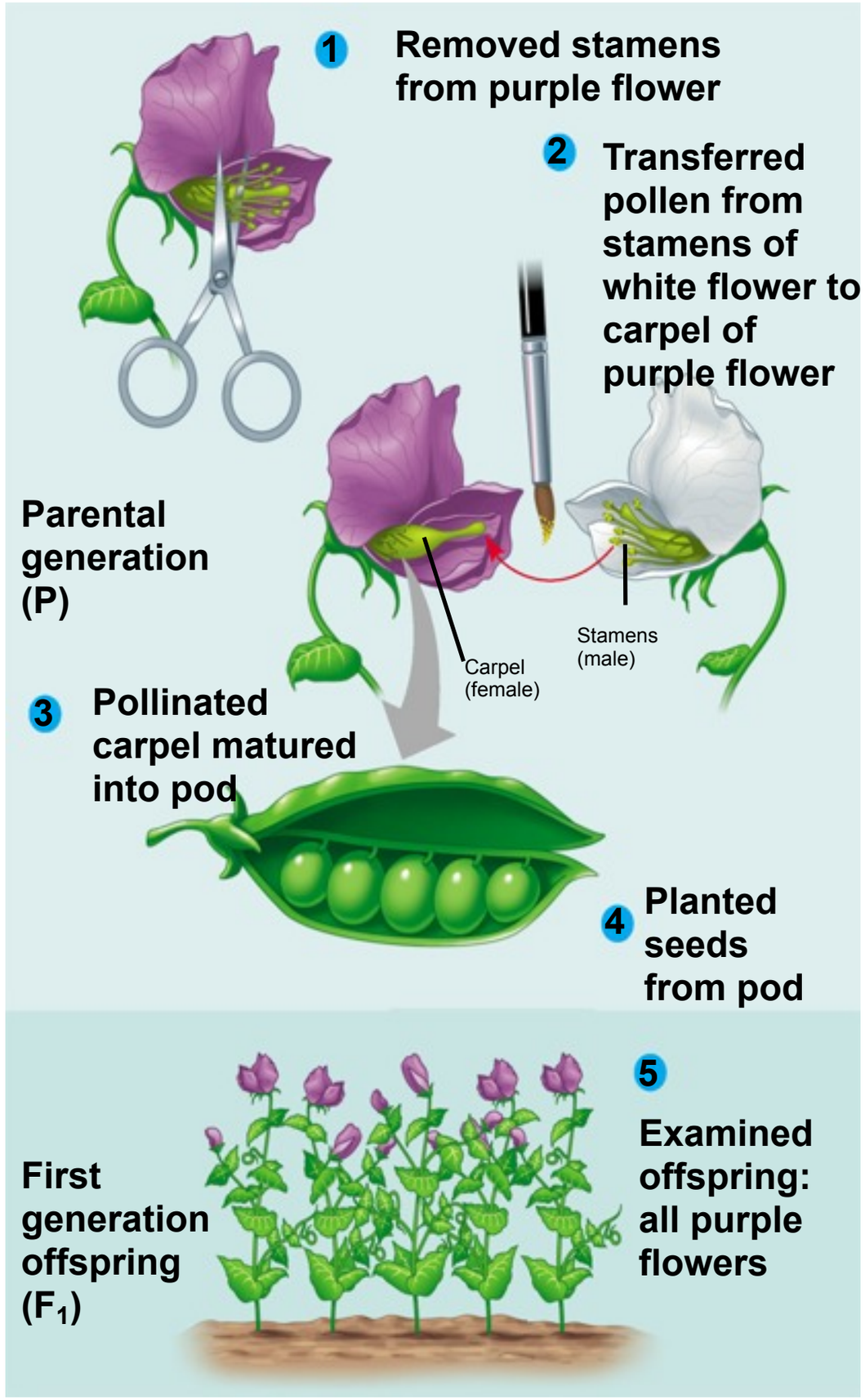


Crossing Pea Plants

APPLICATION By crossing (mating) two true-breeding varieties of an organism, scientists can study patterns of inheritance. In this example, Mendel crossed pea plants that varied in flower color.

TECHNIQUE See steps to the right.

RESULTS When pollen from a white flower fertilizes eggs of a purple flower, the first-generation hybrids all have purple flowers. The result is the same for the reciprocal cross, the transfer of pollen from purple flowers to white flowers.



Crossing Pea Plants

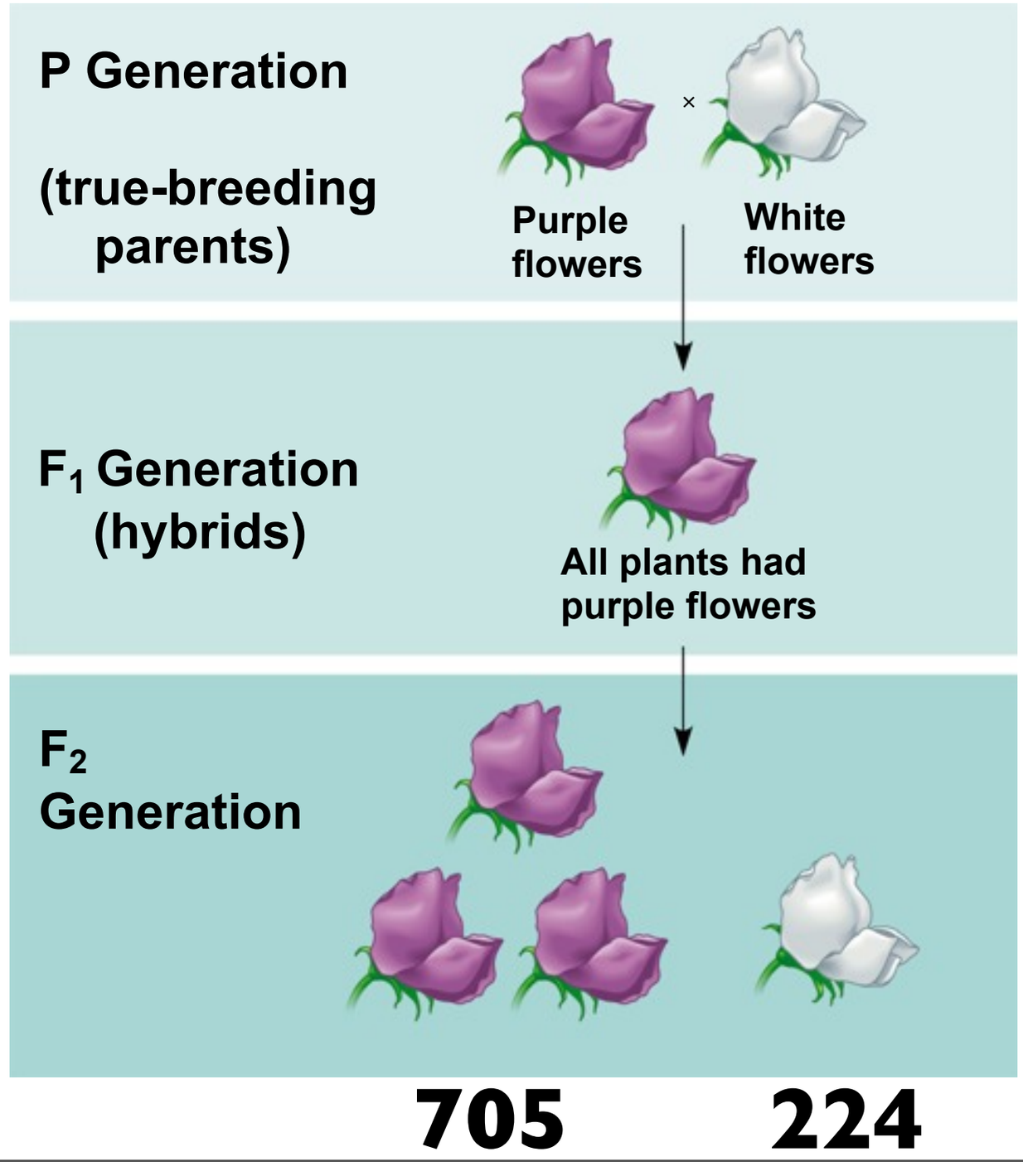
- **Additional important information about Mendel's Crosses:**
  - 1. He chose to track traits that occurred in only two distinct varieties, like flower color (purple or white)
    - *turns out this decision was both fortuitous and lucky as you will learn later*
  - 2. He painstakingly produced plants that he called "true breeding" meaning if they self fertilized they would always produce the same trait as the parent plant, in other words purple flower plants always produced purple flower plants.
  - 3. His typical experiments involved mating two different "true breeding" varieties in what he called "hybridization" and then analyzing the offspring in the further generations.
    - *he made another fortuitous decision to track the trait into 2 or more generations, not just a single generation.*

Crossing Pea Plants

- **Below is a classic Mendelian Cross that illustrates the points made on the last slide(s):**

Experiment

True-breeding purple-flowered pea plants and white-flowered pea plants were crossed (symbolized by ×). The resulting F_1 hybrids were allowed to self-pollinate or were cross-pollinated with other F_1 hybrids. Flower color was then observed in the F_2 generation.



Results

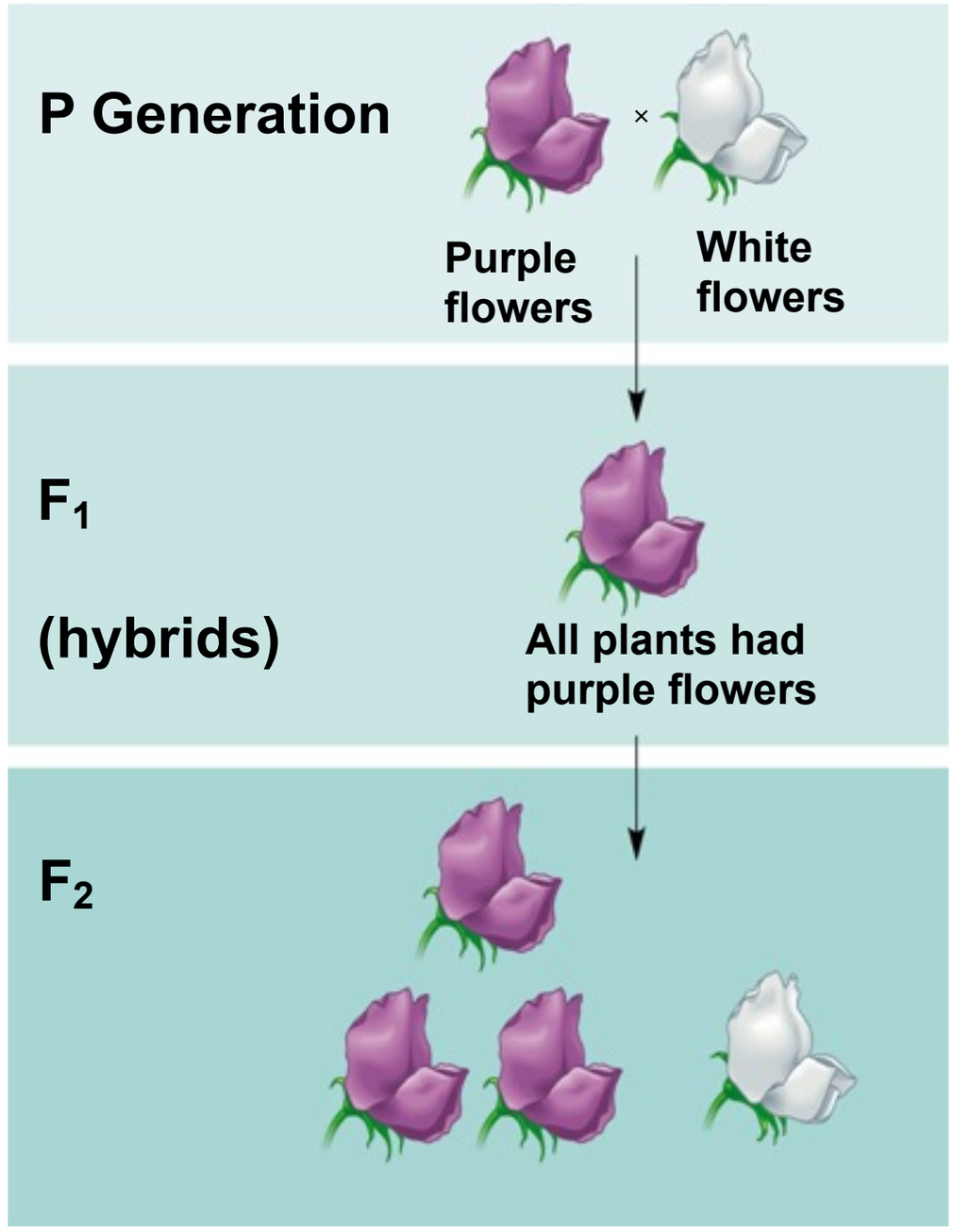
Both purple-flowered plants and white-flowered plants appeared in the F_2 generation. 705 plants had purple flowers, and 224 had white flowers, a ratio of about 3 purple : 1 white.

Crossing Pea Plants

- **This cross and many just like it, provided strong evidence against the blending hypothesis of inheritance.**

Results

If the blending hypothesis were correct then Mendel would expect the F1 hybrids to be purple & white OR lavender in color.



When white colored flowers reappear in the F2 generation, Mendel knew that the "heritable factor" had not been diluted or destroyed.

Mendel reasoned that the white trait was hidden or masked in someway, he called this trait the *recessive trait* and called the purple trait the *dominant trait*.

Table 14.1 The Results of Mendel's F_1 Crosses for Seven Characters in Pea Plants

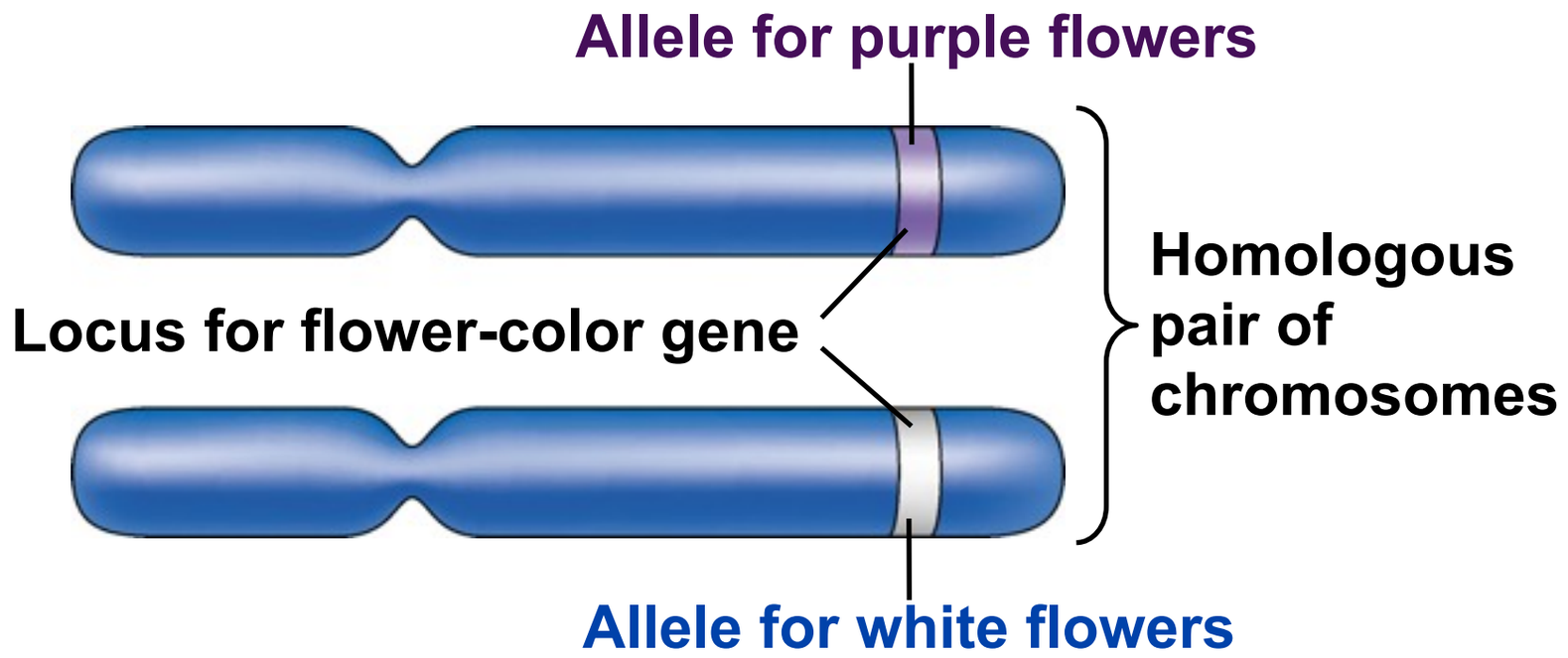
Character	Dominant Trait	×	Recessive Trait	F_2 Generation Dominant:Recessive	Ratio
Flower color	Purple 	×	White 	705:224	3.15:1
Flower position	Axial 	×	Terminal 	651:207	3.14:1
Seed color	Yellow 	×	Green 	6022:2001	3.01:1
Seed shape	Round 	×	Wrinkled 	5474:1850	2.96:1
Pod shape	Inflated 	×	Constricted 	882:299	2.95:1
Pod color	Green 	×	Yellow 	428:152	2.82:1
Stem length	Tall 	×	Dwarf 	787:277	2.84:1

- **Mendel observed this pattern of inheritance in the F1 and F2 generations over and over again.**

Mendel's Model

- **Mendel developed a model to explain this pattern of inheritance in the F1 and F2 generations.**
  - **First:** *Alternative versions of "heritable factors" account for variations in inherited characters.*
  - *NOTE to students Mendel never knew of genes but today we know his "heritable factors" are* ***genes*** *and the alternate forms of genes are called* ***alleles*** *as such I will use these terms exclusively from this point on knowing of course that Mendel did not use terms himself!*

Today we can relate this idea to chromosomes and DNA



Mendel's Model

- **Mendel developed a model to explain this pattern of inheritance in the F1 and F2 generations.**
  - **Second:** *For each character, an organism inherits two copies of a gene, one from each parent.*
    - *The two alleles may be identical or they may be different!*
    - *Identical alleles are today referred to as a* ***homozygous*** *genotype, Mendel used the term "****true breeding****"*
    - *Different alleles are today referred to as a* ***heterozygous*** *genotype, Mendel used the term "****hybrid****"*

Mendel's Model

- **Mendel developed a model to explain this pattern of inheritance in the F1 and F2 generations.**
  - **Third:** *If the two alleles at a locus differ, then one, the* ***dominant allele****, determines the organism's appearance; the other, the* ***recessive allele****, has no noticeable effect on the organism's appearance.*
    - *Capital letters often symbolize dominant alleles (A) while lower case letters often represent the recessive alleles (a).*

Letters are used a symbols to represent the alleles that we can see with the naked eye.

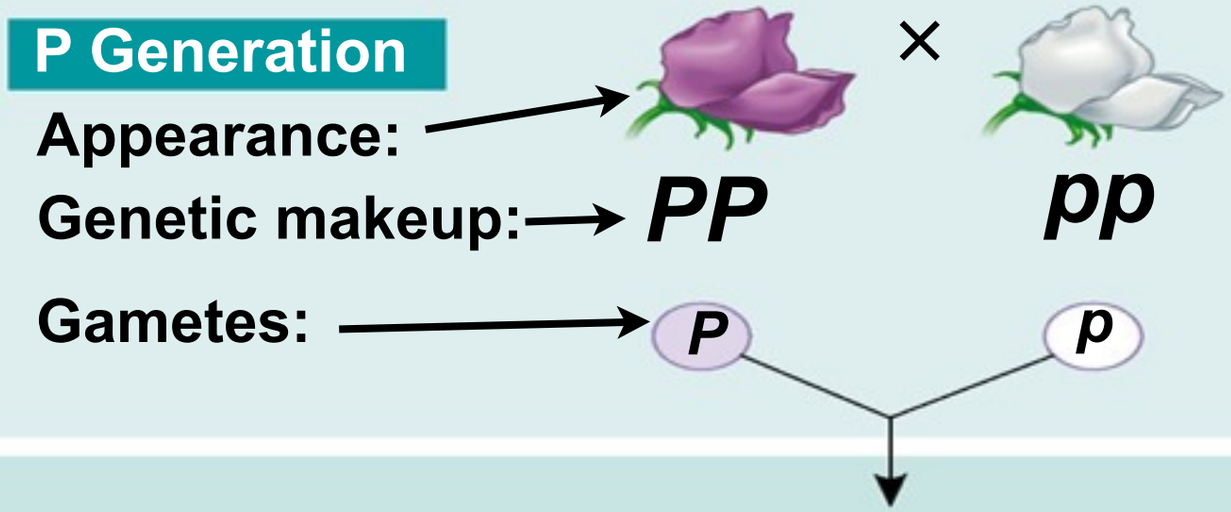
Mendel's Model

- **Mendel developed a model to explain this pattern of inheritance in the F1 and F2 generations.**
  - **Fourth:** *The **Law of Segregation** states that two alleles for a heritable character separate from each other during gamete formation and end up in different gametes.*
    - *Thus sperm and eggs only carry one allele/gene.*
    - *If an organism is true breeding then every gamete will carry the same allele however if the organism is a hybrid the 50% of the gametes will carry one allele while the other 50% carry the other allele.*

Mendel's Model

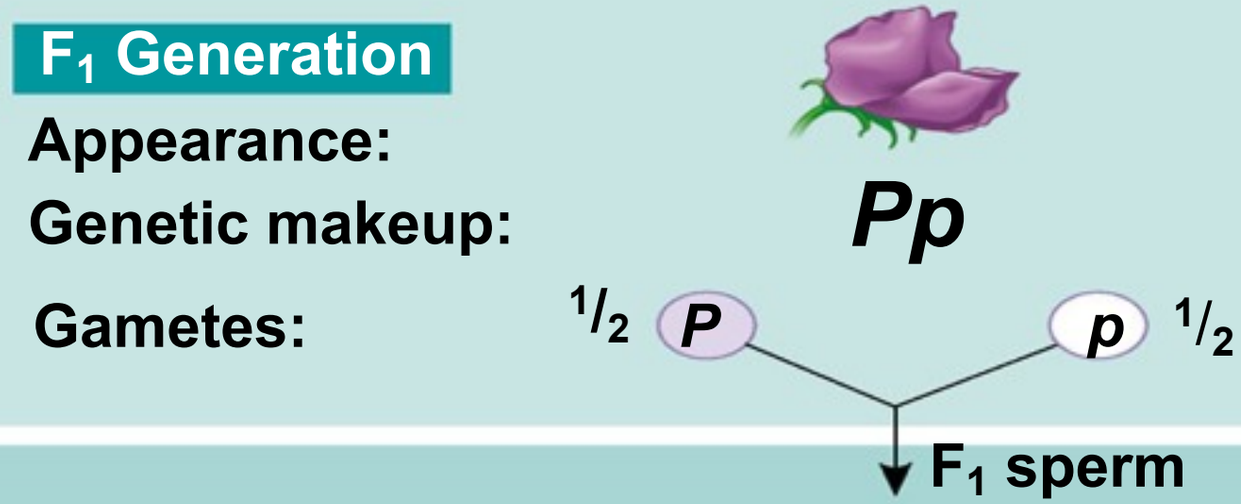
Each true-breeding plant of the parental generation has identical alleles, *PP* or *pp*.

Gametes (circles) each contain only one allele for the flower-color gene. In this case, every gamete produced by one parent has the same allele.



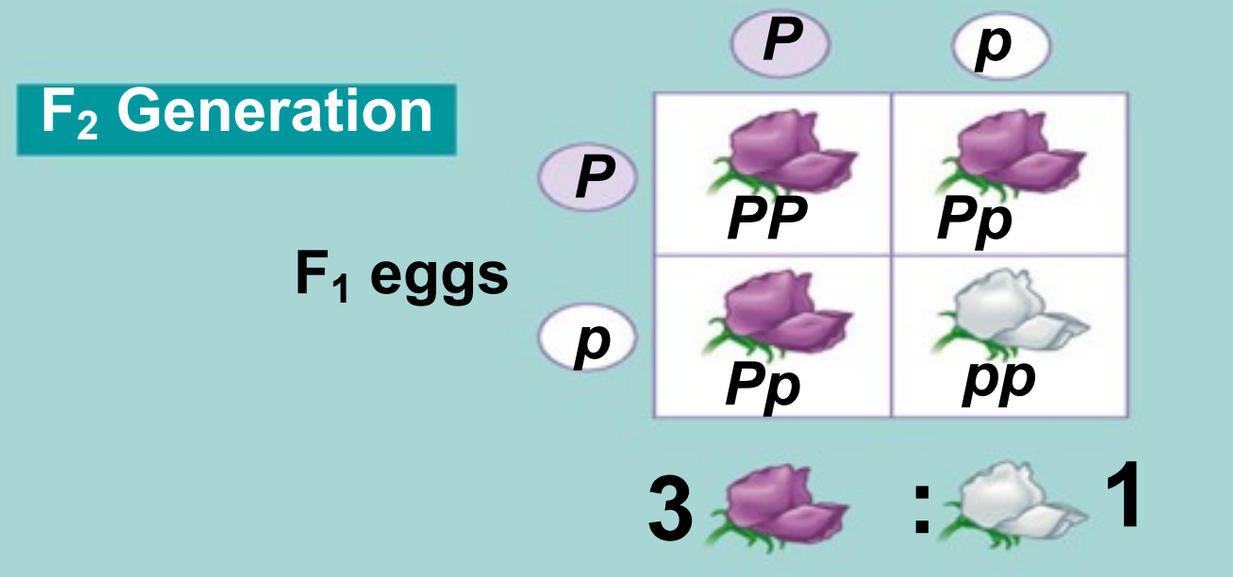
Union of the parental gametes produces F_1 hybrids having a *Pp* combination. Because the purple-flower allele is dominant, all these hybrids have purple flowers.

When the hybrid plants produce gametes, the two alleles segregate, half the gametes receiving the *P* allele and the other half the *p* allele.



This box, a Punnett square, shows all possible combinations of alleles in offspring that result from an $F_1 \times F_1$ (*Pp* × *Pp*) cross. Each square represents an equally probable product of fertilization. For example, the bottom left box shows the genetic combination resulting from a *p* egg fertilized by a *P* sperm.

Random combination of the gametes results in the 3:1 ratio that Mendel observed in the F_2 generation.



Mendel's Model

- **Notice that Mendel's Model lends itself to specific expected results or predictions.**

- ***How do we make conclusions in science?***

  - ***We compare the actual results and the expected results, when the two results are concur then we have support for the hypothesis!***

- ***Does the data and results support Mendel's model?***

  - ***Yes, absolutely!***

Genetic Vocabulary

traits

alleles

	Phenotype		Genotype	
3	Purple		*PP* (homozygous)	1
	Purple		*Pp* (heterozygous)	2
	Purple		*Pp* (heterozygous)	
1	White		*pp* (homozygous)	1
	Ratio 3:1		Ratio 1:2:1	

hybrids

true breeding

The Punnet Square

- **A tool used to predict (<u>future</u>) possible allele compositions of offspring from a cross between parents whose genetic make up is known.**

If we know: **Mom is Aa** and **Dad is Aa**

And we remember that gametes carry only one allele.

Then we can predict possible allele combinations in their offspring using a punnet square.

The Punnet Square

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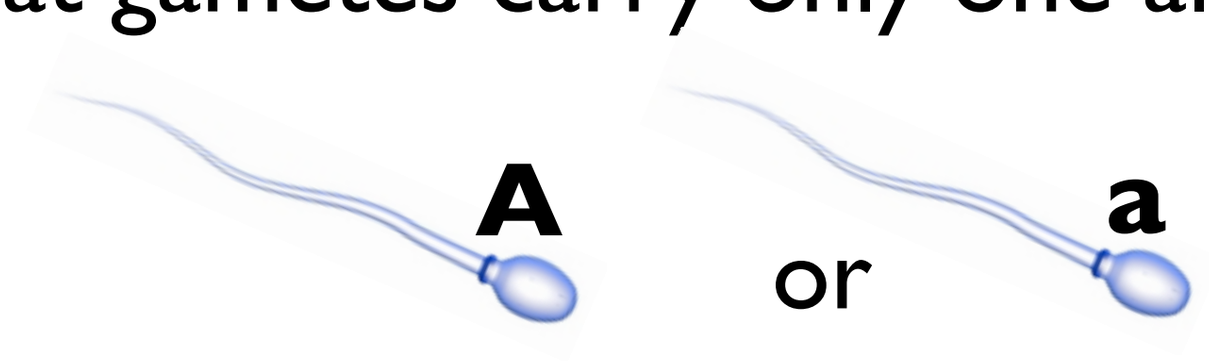
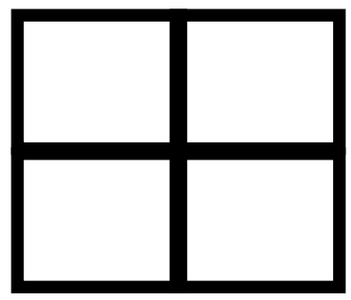


Then we can predict possible allele combinations in their offspring using a punnet square.

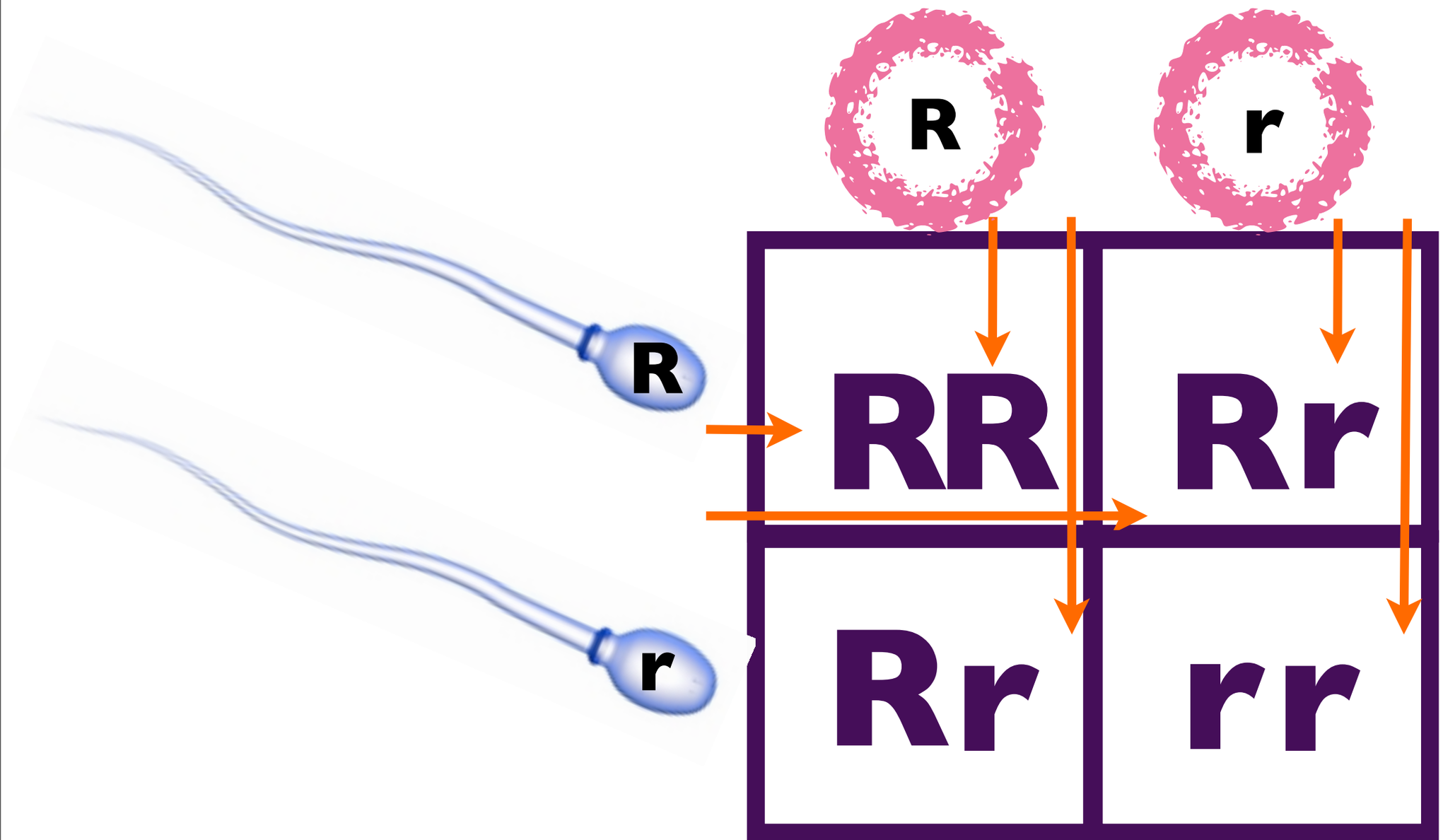


1.) What are the possible sperm?

2.) What are the possible eggs?

3.) What are the possible fertilizations?

4.) What are the possible offspring?



Punnett's Squares

These show the 2 alleles of each parent plant crossed with each other and the resulting 4 possible offspring with T = tall, t = short. TT = dominant tall, tt = recessive short, Tt = mixed hybrid

TT = dominant tall (genotype tall, phenotype tall)
Tt = mixed hybrid (genotype hybrid, phenotype tall)
tt = recessive short (genotype short, phenotype short)

	T	T
T	TT	TT
T	TT	TT

Both parents are dominant tall so all offspring are tall.

	T	t
T	TT	Tt
t	Tt	tt

Both parents are mixed hybrids so offspring are a 3:1 ratio.

	T	T
T	TT	TT
t	Tt	Tt

One parent is dominant tall and one is mixed hybrid so all offspring are tall.

	t	t
t	tt	tt
t	tt	tt

Both parents are recessive short so all offspring are short.

What are the parents in cross?

What does the single "T or t" on the outside of the punnet square represent?

What are the genotypic ratios of each? Phenotypic?

Which punnet square shows a monohybrid cross?

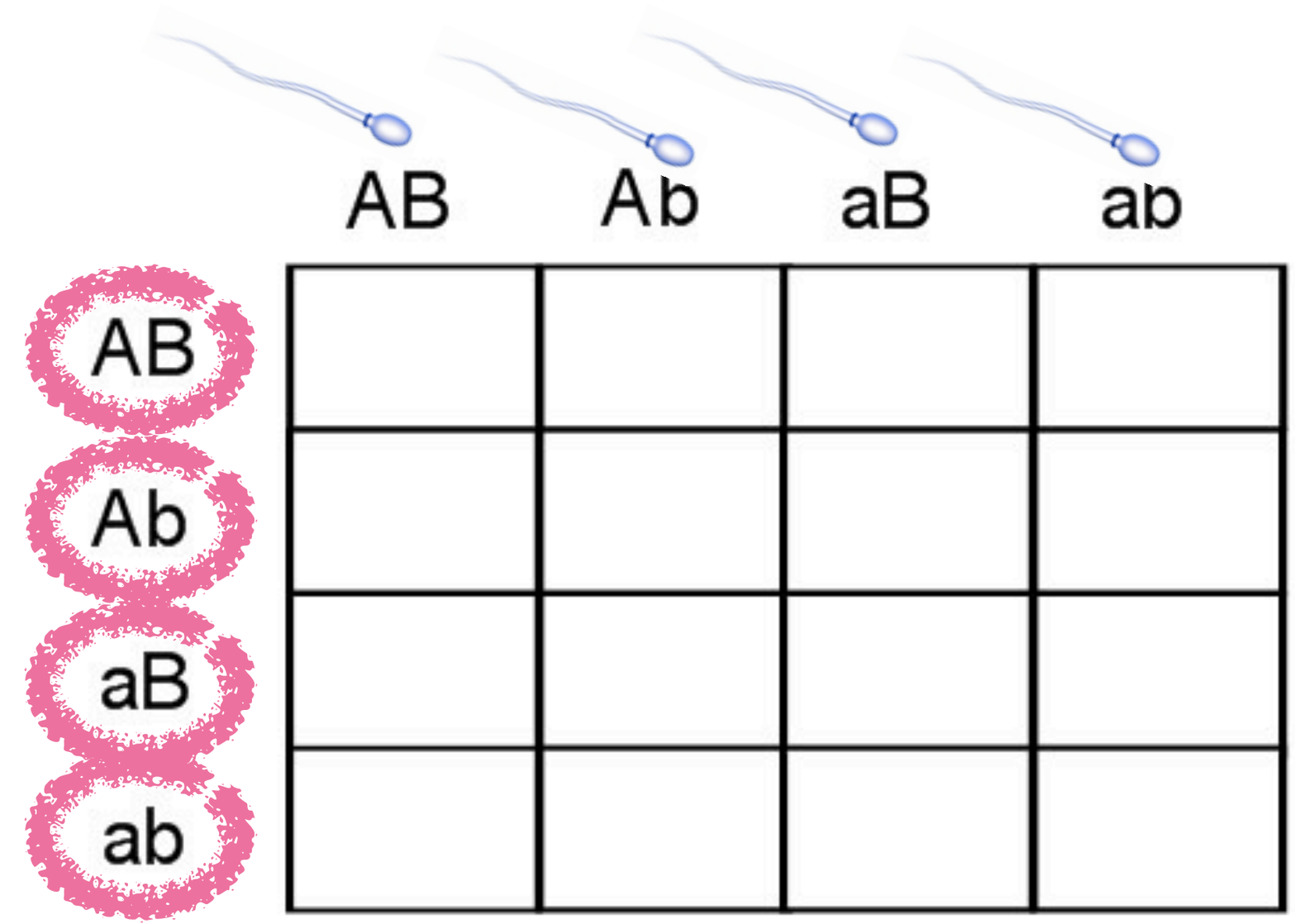
The Punnet Square

- **We can use the punnet square to track multiple alleles at the same time.**

What **If** we know: **Mom is AaBb** and **Dad is AaBb**

You must remember that every gamete must have one of each allele

You can use the "foil" technique from your math class to determine possible gametes



The Punnet Square

- **We can use the punnet square to track multiple alleles at the same time.**

What **If** we know: **Mom is AaBb** and **Dad is AaBb**

What is the phenotypic ratio?

9:3:3:1

Genotypic?

4:2:2:2:2:1:1:1:1

We will come back to this later in the meantime...

possible sperm

possible eggs

	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	Aabb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

Mendel's Model Continues

- **Mendel also looked at two traits at one time.**
- However asked himself the follow question, a question that you should have asked yourself on the last slide.
- ***Do the "a" alleles and the "b" alleles travel separately or as a package?***

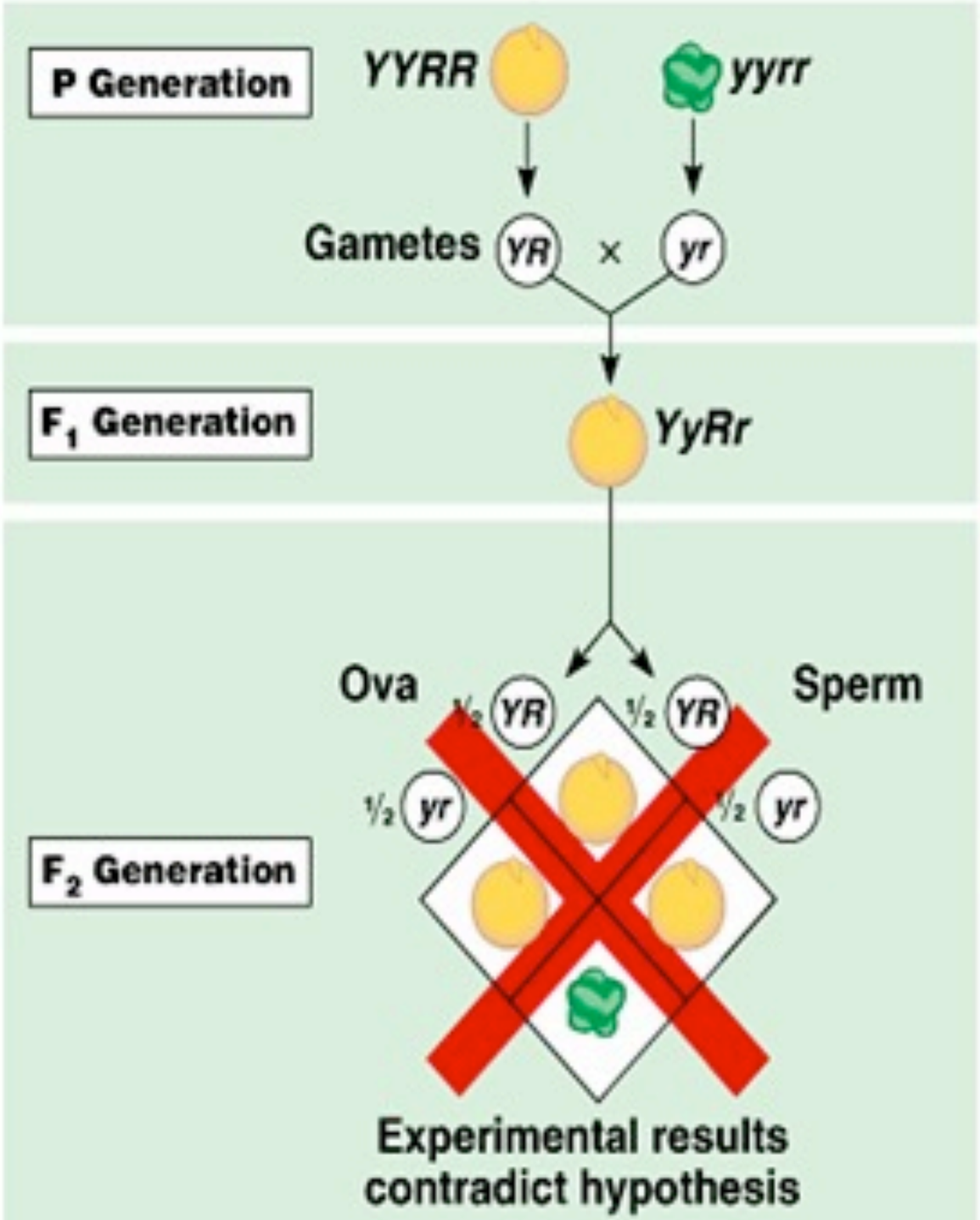
- ***In modern terms: Do the "a" alleles and the "b" alleles travel on the same chromosome or on different chromosomes?***

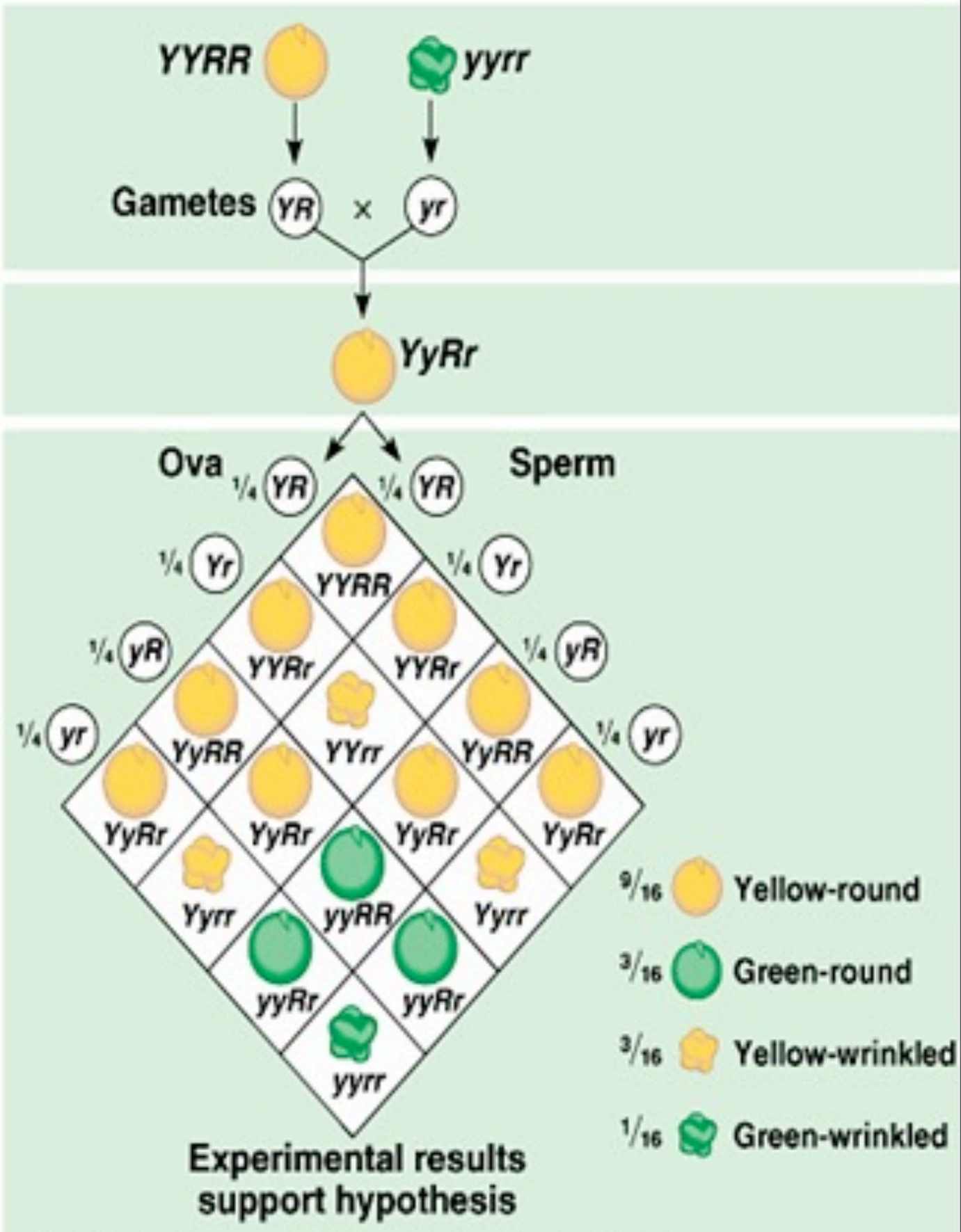
The answer to this question very much matters and as you will see it led Mendel to his 2nd Law of Inheritance!

Mendel's Model Continues

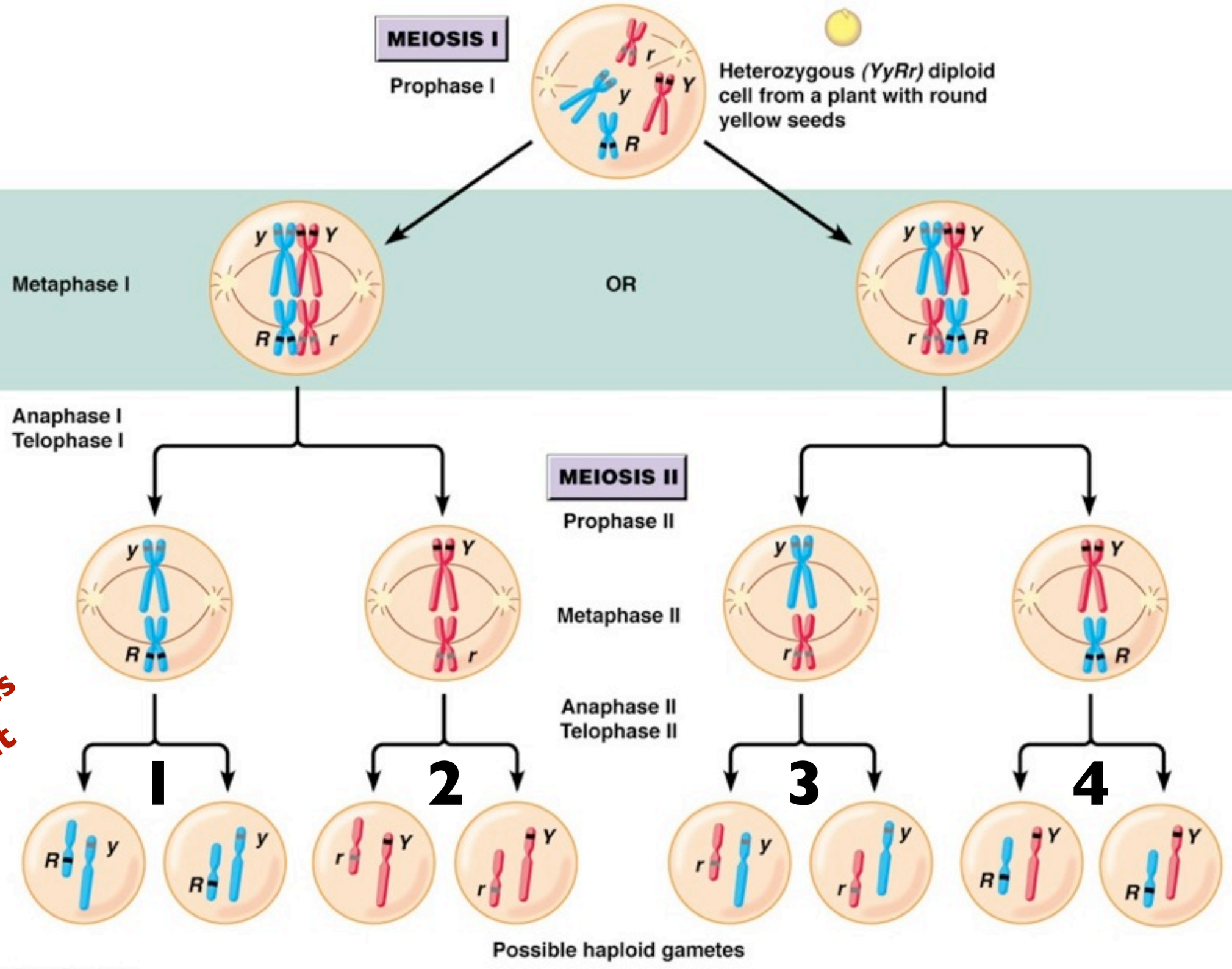
- **Mendel crossed two plants both true breeding. *The first plant was a true plant with Yellow, Smooth seeds and the other true breeding plant produced Green, wrinkled seeds.***

- *Mendel realized and so should you that the F1 hybrids can only produce Yellow, smooth seeds.*
- *The F2 generation is were it gets interesting!*


P Generation
YYRR
yyrr
Gametes
YR
×
yr
F1 Generation
YyRr
Ova
Sperm
½ YR
½ YR
½ yr
½ yr
F2 Generation
Experimental results
contradict hypothesis
(a) Hypothesis: dependent assortment


YYRR
yyrr
Gametes
YR
×
yr
YyRr
Ova
Sperm
¼ YR
¼ YR
¼ Yr
¼ Yr
¼ yR
¼ yR
¼ yr
¼ yr
YYRR
YYRr
YYRr
YyRR
YYrr
YyRR
YyRr
YyRr
YyRr
YyRr
Yyrr
yyRR
Yyrr
yyRr
yyRr
yyrr
9/16 Yellow-round
3/16 Green-round
3/16 Yellow-wrinkled
1/16 Green-wrinkled
Experimental results
support hypothesis
(b) Hypothesis: independent assortment

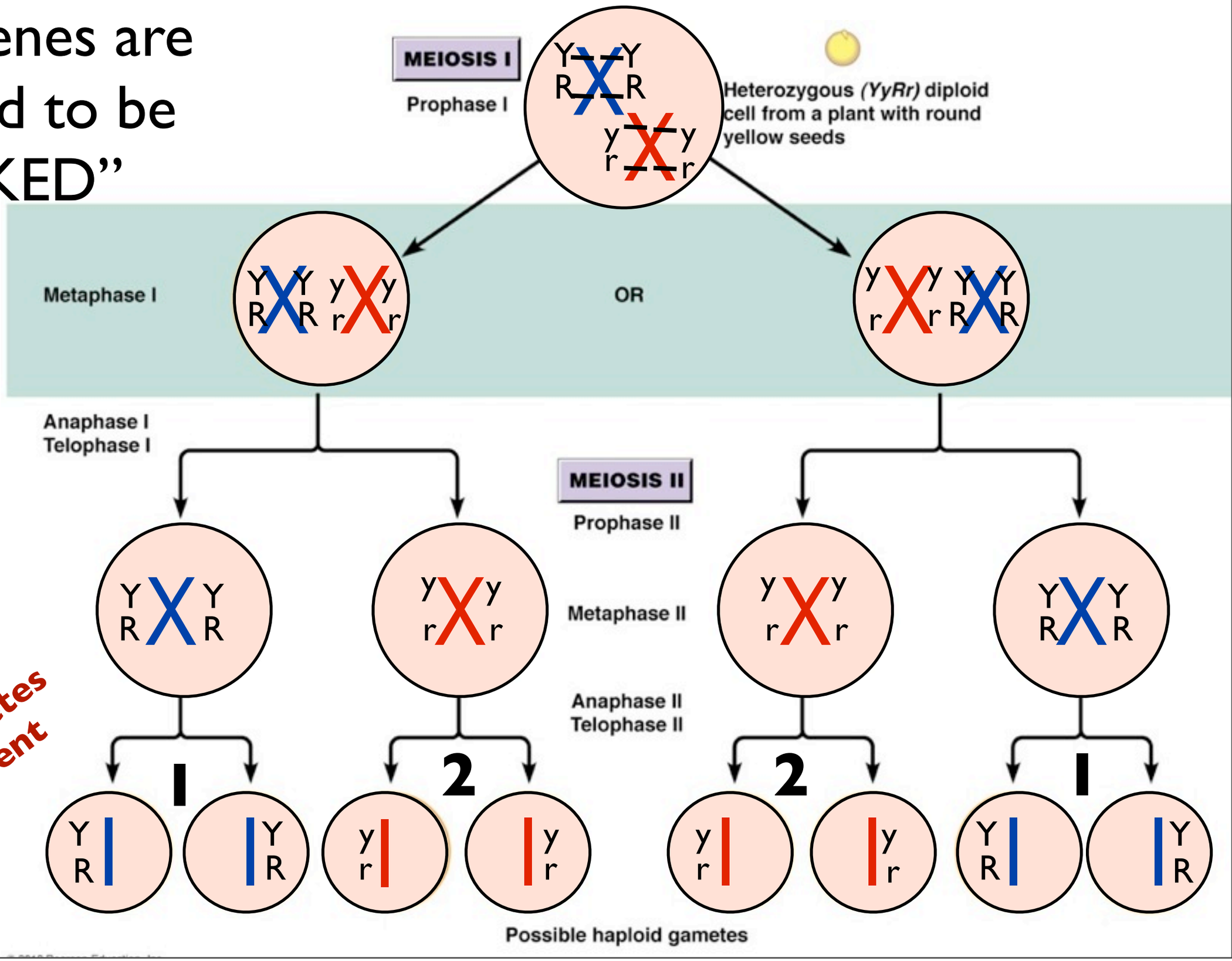
Mendel's results are supported when the different alleles (a and b) are carried on different chromosomes.



4 possible gametes for each parent

Now redraw the formation of gametes, put the different alleles on the same chromosome.

These genes are now said to be "LINKED"

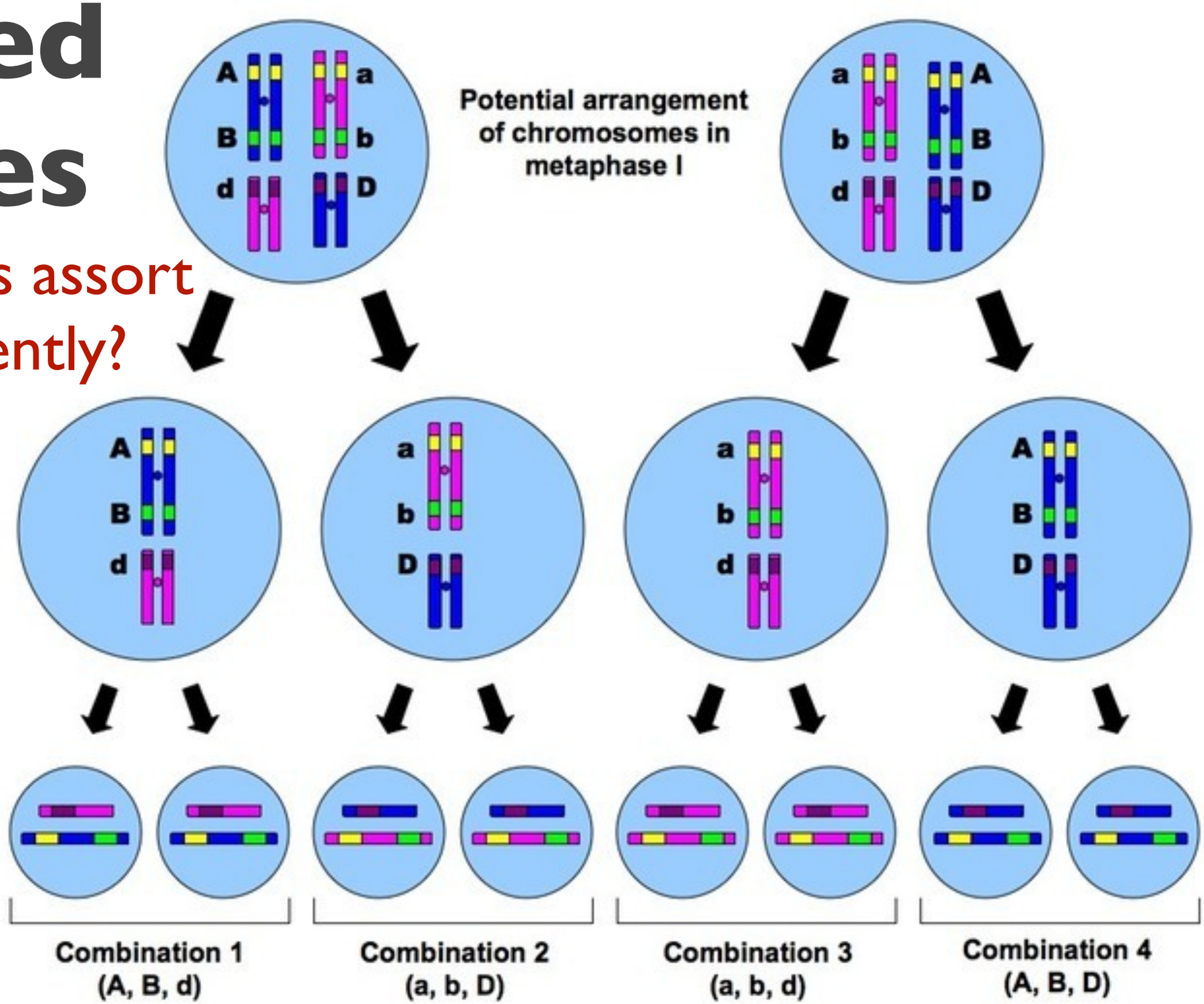


2 possible gametes for each parent

Linked Genes

Which genes assort independently?

Which genes are linked?



Mendel's Model Continues

- **From this Dihybrid cross, Mendel formed his 2nd Law of Inheritance.**
- The **Law of Independent Assortment** states that each pair of alleles separate independently of each other pair of alleles during gamete formation.

PLEASE NOTE: This law only applies to allele pairs that are located on different chromosomes.

Earlier I said that Mendel was a little lucky. He was able to generate this law because every time he tracked two different allele pairs they happen to be on different chromosomes. Do think every allele pair has its own chromosome? I hope not! What would happen if Mendel had picked two allele pairs on the same chromosome? (rhetorical)

Review: Mendel's Laws

P Generation

Starting with two true-breeding pea plants, we follow two genes through the F_1 and F_2 generations. These two genes are on different chromosomes.

Yellow-round seeds (*YYRR*)

Green-wrinkled seeds (*yyrr*)

Meiosis

Fertilization

Gametes

Gametes

F_1 Generation

All F_1 plants produce yellow-round seeds (*YyRr*)

Meiosis

LAW OF SEGREGATION

The *R* and *r* alleles segregate at anaphase I, yielding two types of daughter cells for this locus.

Each gamete gets one long chromosome with either the *R* or *r* allele.

Two equally probable arrangements of chromosomes at metaphase I

LAW OF INDEPENDENT ASSORTMENT

Alleles at both loci segregate in anaphase 1, yielding four types of daughter cells depending on the chromosome arrangement at metaphase 1. Each gamete gets a long and a short chromosome in one of four allele combinations.

Gametes

1/4 – *YR* 1/4 – *yr* 1/4 – *yr* 1/4 – *yR*

F_2 Generation

Fertilization among the F_1 plants

Fertilization recombines the *R* and *r* alleles at random.

9 : 3 : 3 : 1

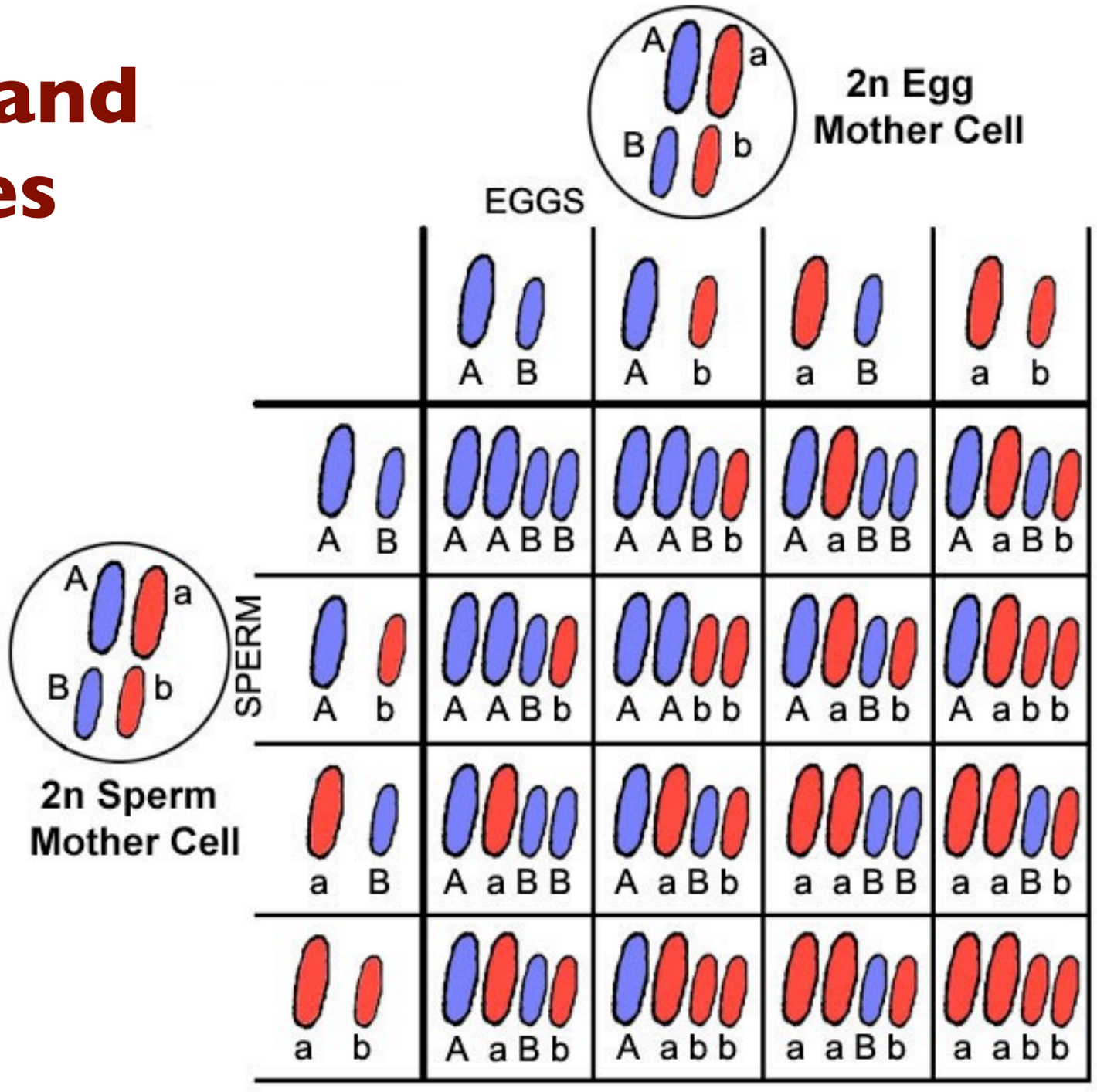
Fertilization results in the 9:3:3:1 phenotypic ratio in the F_2 generation.

...Back to Punnet Squares

If we know: **Mom is AaBb** and **Dad is AaBb**

What do the blue and red chromosomes represent?

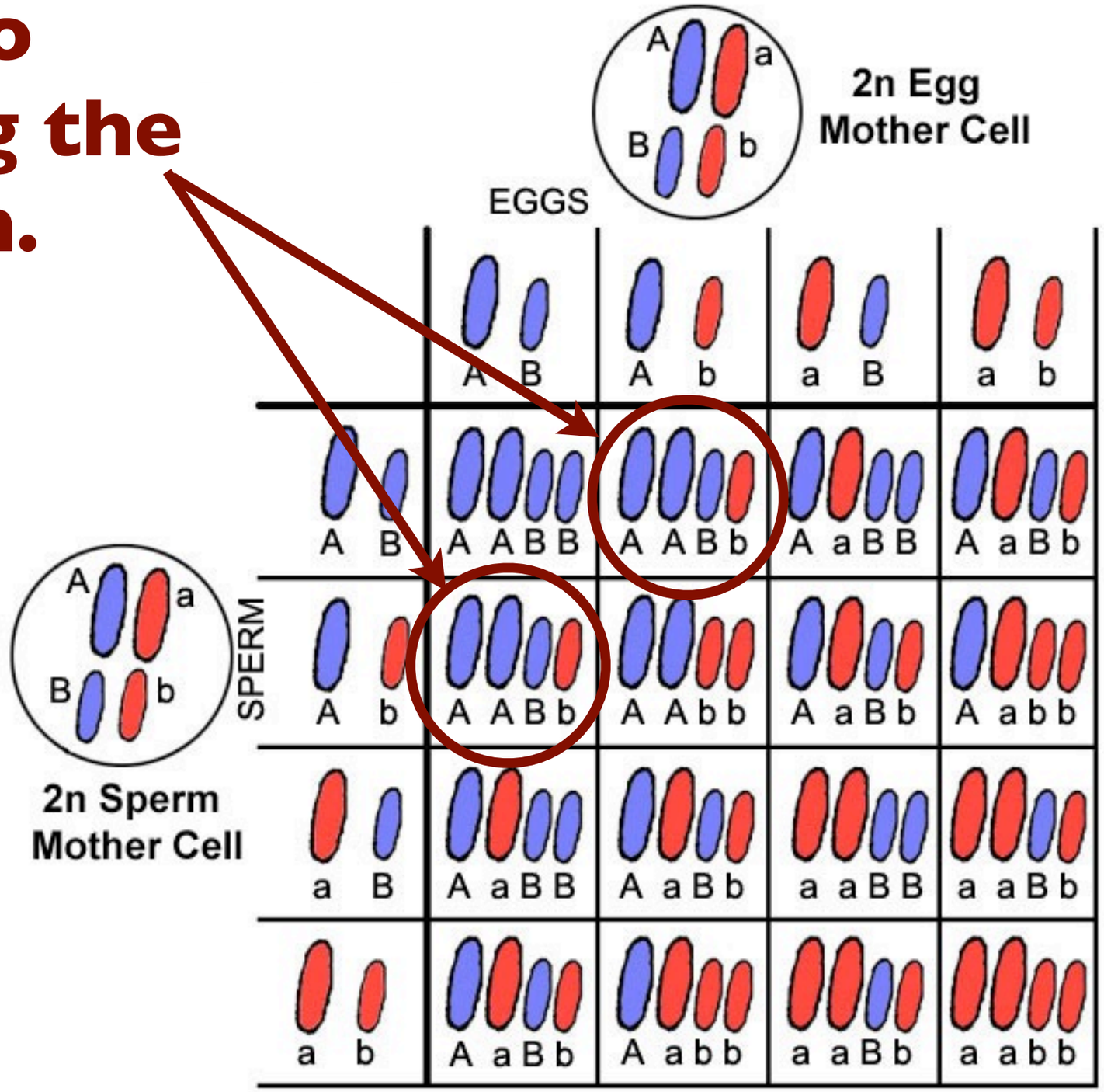
The blue chromosomes are from the paternal lineage and the red ones of the maternal lineage.



If we know: **Mom is AaBb** and **Dad is AaBb**

Are these two possible offspring the same? Explain.

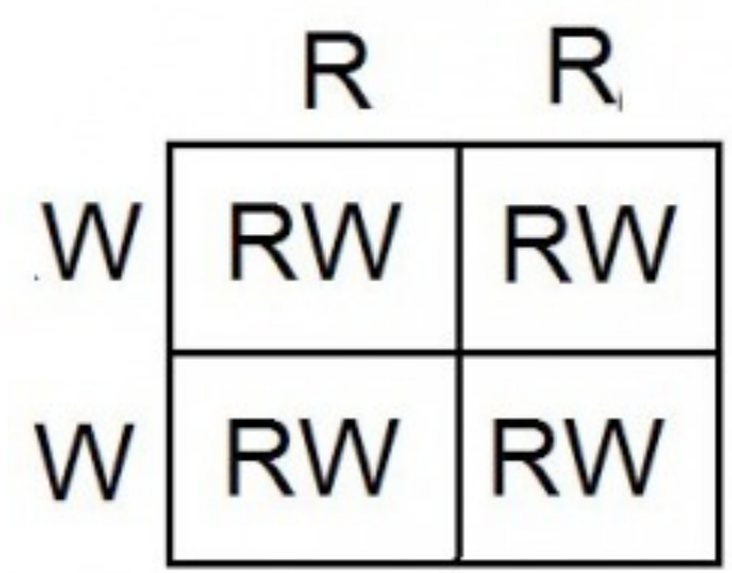
Yes and No, With respect to the traits controlled by these specific alleles (Aa and Bb)...YES both offspring will exhibit the dominant trait but each chromosome comes from either a maternal and paternal lines and thus the other genes on each chromosome are inevitably different...so NO



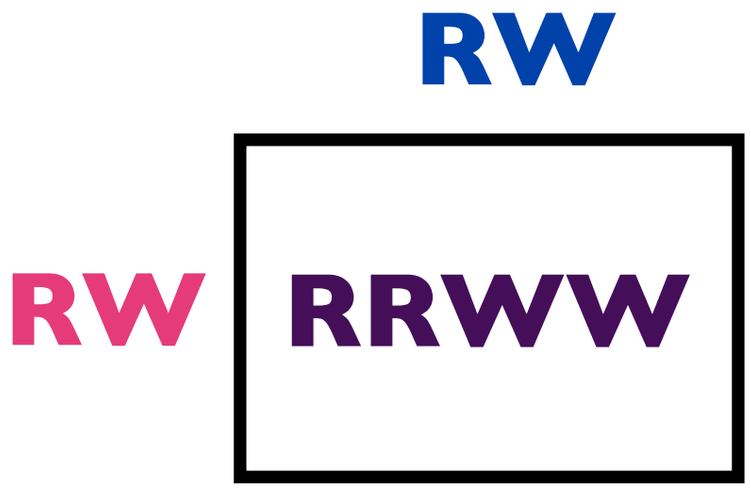
If we know: **Mom is RRWW** and **Dad is RRWW**

What is wrong with this punnet square?

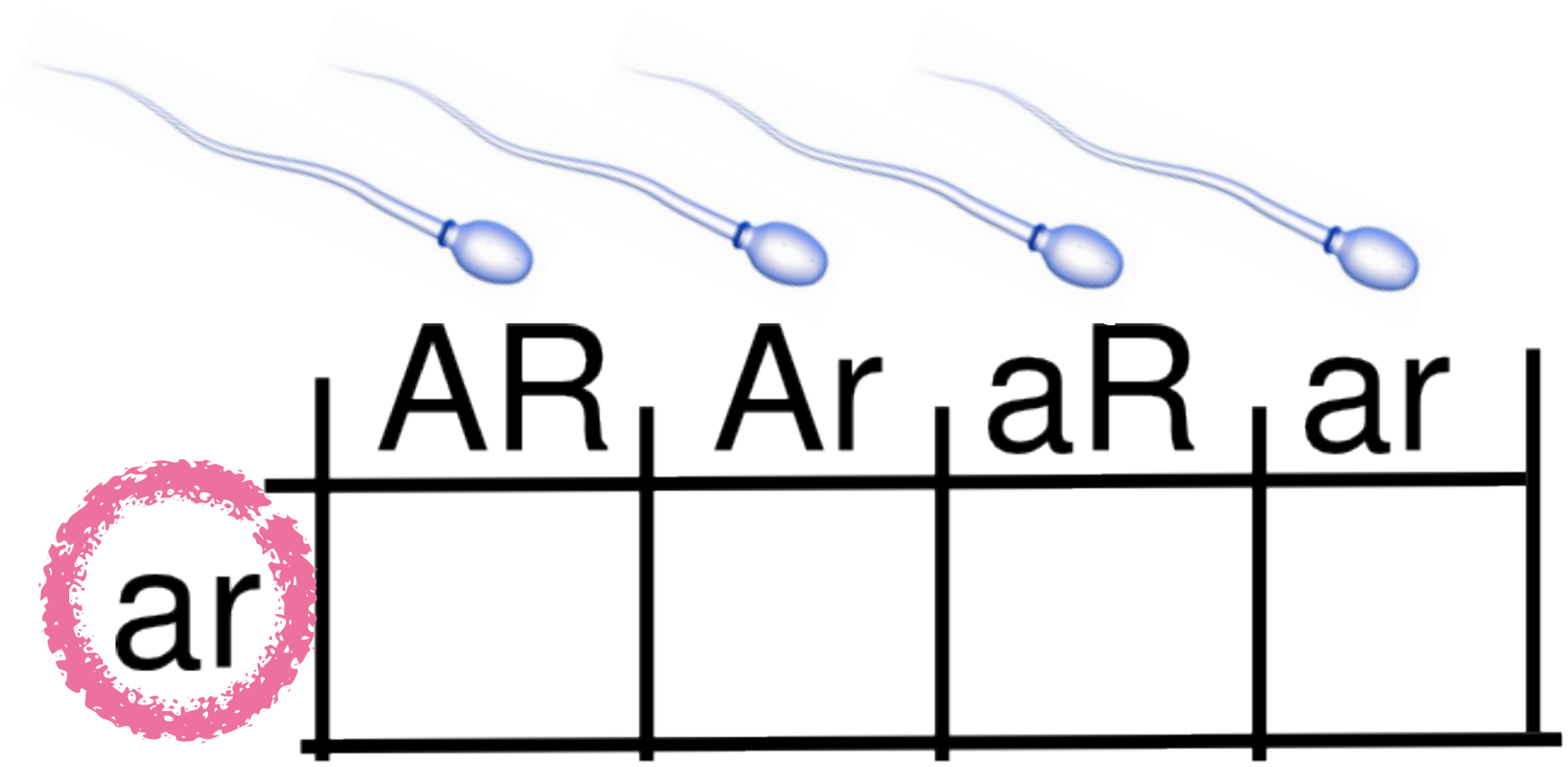
One parent is not donated a "W" allele and the other parent is not donating an "R" allele



Can you fix it?



What are the parent's genotypes?



Mom is aarr and **Dad is AaRr**

What is the probability that these parents produce a submissive long tailed lion?

3/16 or 18.75%

Now, can you do it without the pictures?

Dihybrid Cross

Cross the Nittany Lion with a southern cougar


A for aggressive and victorious

a for submissive and defeated


B for long tailed


b for tailless

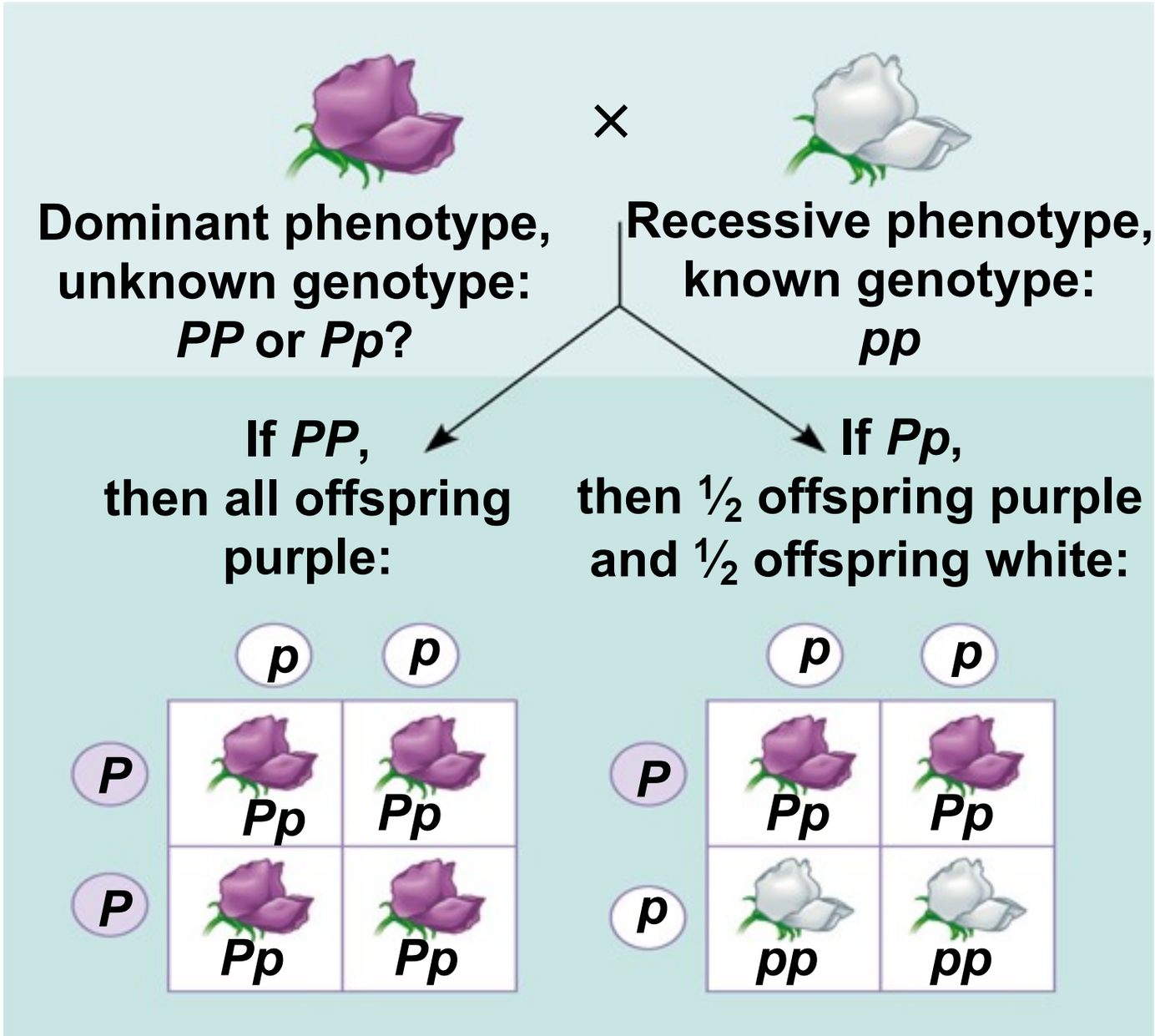
	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAbb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

The Test Cross

What if we find an organism with a dominant phenotype but we do not know its genotype. Can we determine whether its a hybrid or true-bred?

An organism that exhibits a dominant trait, such as purple flowers in pea plants, can be either homozygous for the dominant allele or heterozygous. To determine the organism's genotype, geneticists can perform a testcross.

In a testcross, the individual with the unknown genotype is crossed with a homozygous individual expressing the recessive trait (white flowers in this example). By observing the phenotypes of the offspring resulting from this cross, we can deduce the genotype of the purple-flowered parent.



Mendelian Genetics

II.

Main Idea: Laws of probability govern Mendel's laws of inheritance.

PREFACE

OK, I feel like we need to catch our breath and look at the big picture before we continue...lets review

- Genetics is the study of inherited traits.
- In a very general way genetics allows us to predict the pathway of traits into the future or allows us to track the pathway from which they came.
- Geneticists use punnet squares to look into the future and pedigrees to look into the past. (we will learn about pedigrees shortly)
- We have to understand Meiosis, Mendel's Model and the Laws of Inheritance if we are to effectively use these tools: punnet square and pedigrees.

PREFACE

- Punnet squares can be cumbersome and time consuming to use.
- As it turns out the Laws of Probability govern inheritance and thus we can use math to predict outcomes of future fusions between gametes.
- The Rule of Multiplication and the Rule of Addition are often less cumbersome and require far less time.
- Solving genetic problems mathematically will greatly increase your ability to quickly and correctly solve many of commonly asked questions in genetics.

Simple Probability

Probability of an event occurring $=$ $\dfrac{\textbf{the \# of desired events}}{\textbf{total \# of events}}$

Chance of flipping "tails" on a coin. $= \dfrac{1}{2}$

Chance of picking an "ace" in a deck of cards. $= \dfrac{4}{52}$ or $\dfrac{1}{13}$

Chance of picking an "ace of hearts" in a deck of cards. $= \dfrac{1}{52}$

Simple Probability

Important lesson about probability!

Outcome of one event does not affect the outcome of second event when those outcomes are independent. The first toss of a coin has no effect on the second toss.

Chance of flipping "tails" on a coin. $= \frac{1}{2}$

Chance of flipping "tails" on a coin for a second flip. $= \frac{1}{2}$

The segregation of alleles into gametes are also independent events, as we will see shortly.

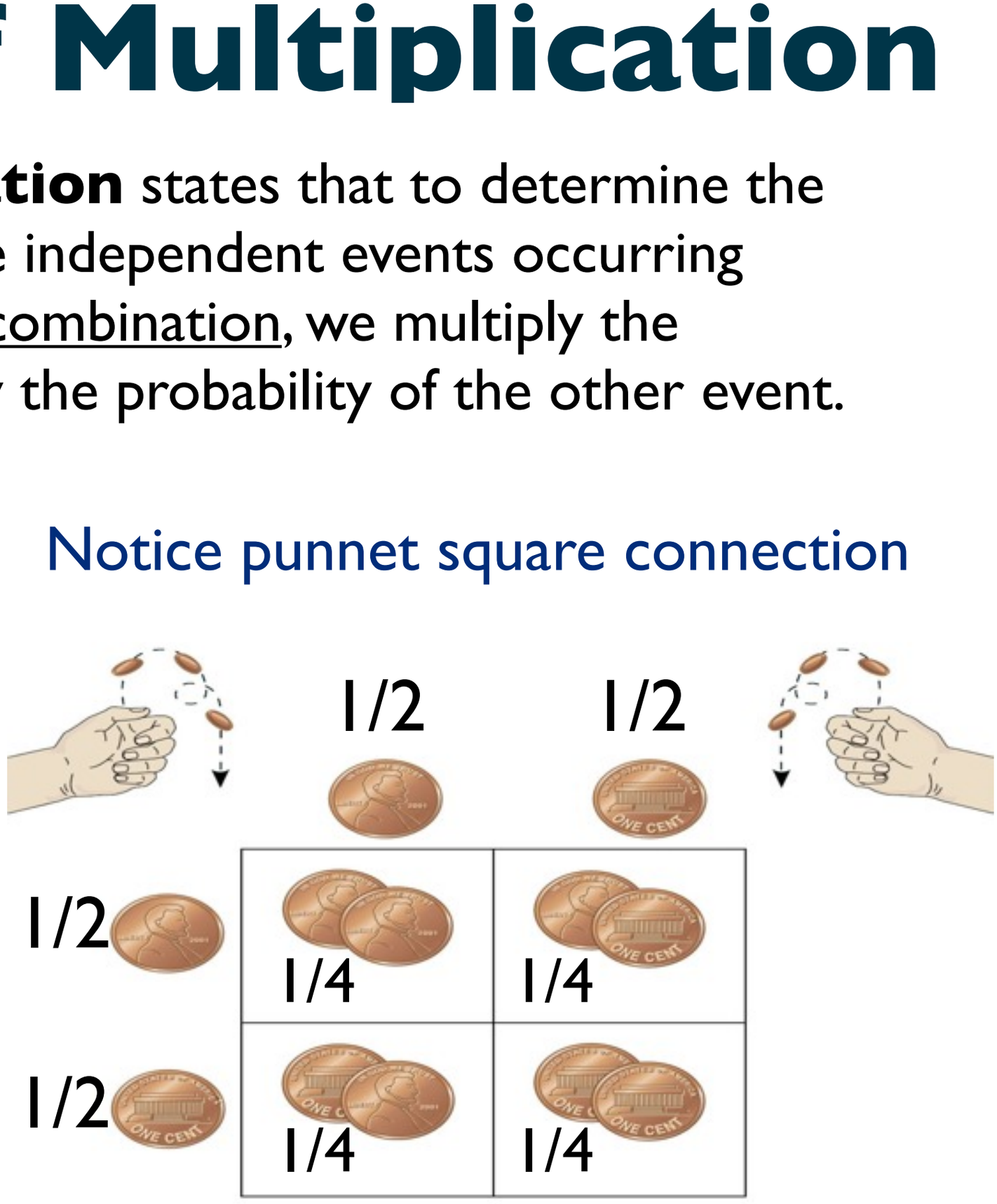
The Rule of Multiplication

- The **Rule of Multiplication** states that to determine the probability of two or more independent events occurring together in some specific combination, we multiply the probability of one event by the probability of the other event.

Chance the coin lands on tails, on two consecutive flips.

$$\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$$

Notice punnet square connection



The Rule of Multiplication

- Notice...If the **order is specified** then you use the rule of multiplication.

Chance you flip tail, then another tail.

Chance you flip tail, then a head.

Chance you flip head, then a tail.

$$ALL = \frac{1}{4}$$

Chance you flip head, then another head.

- In all four cases above the order is specified thus (1/2)(1/2)=1/4.

Chance you flip one tail and one head.

- Notice...The **order is NOT specified.** Now we need to use another rule along with the rule of multiplication.

The Rule of Addition

- The **Rule of Addition** states that to determine the probability of two or more mutually exclusive events occurring together is calculated by adding their individual probabilities.

Chance you flip one tail and one head.

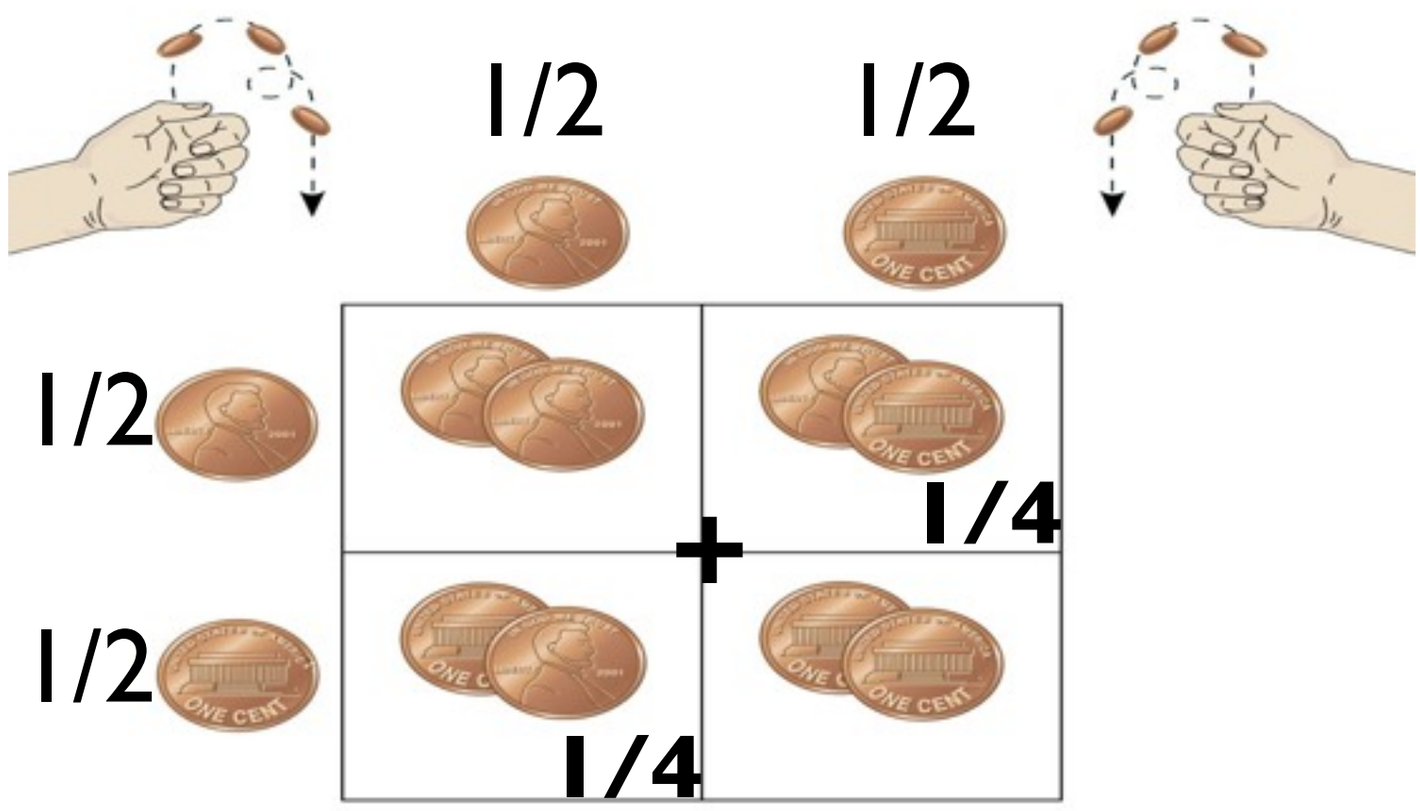
$$\underset{\text{head}}{\frac{1}{2}} \times \underset{\text{tail}}{\frac{1}{2}} = \frac{1}{4}$$

$$\underset{\text{tail}}{\frac{1}{2}} \times \underset{\text{head}}{\frac{1}{2}} = \frac{1}{4}$$

$$+$$

$$\frac{}{1/2}$$

Notice punnet square connection



Math Applied to Genetics

Chance of homozygous recessive. (1/2)(1/2) = 1/4

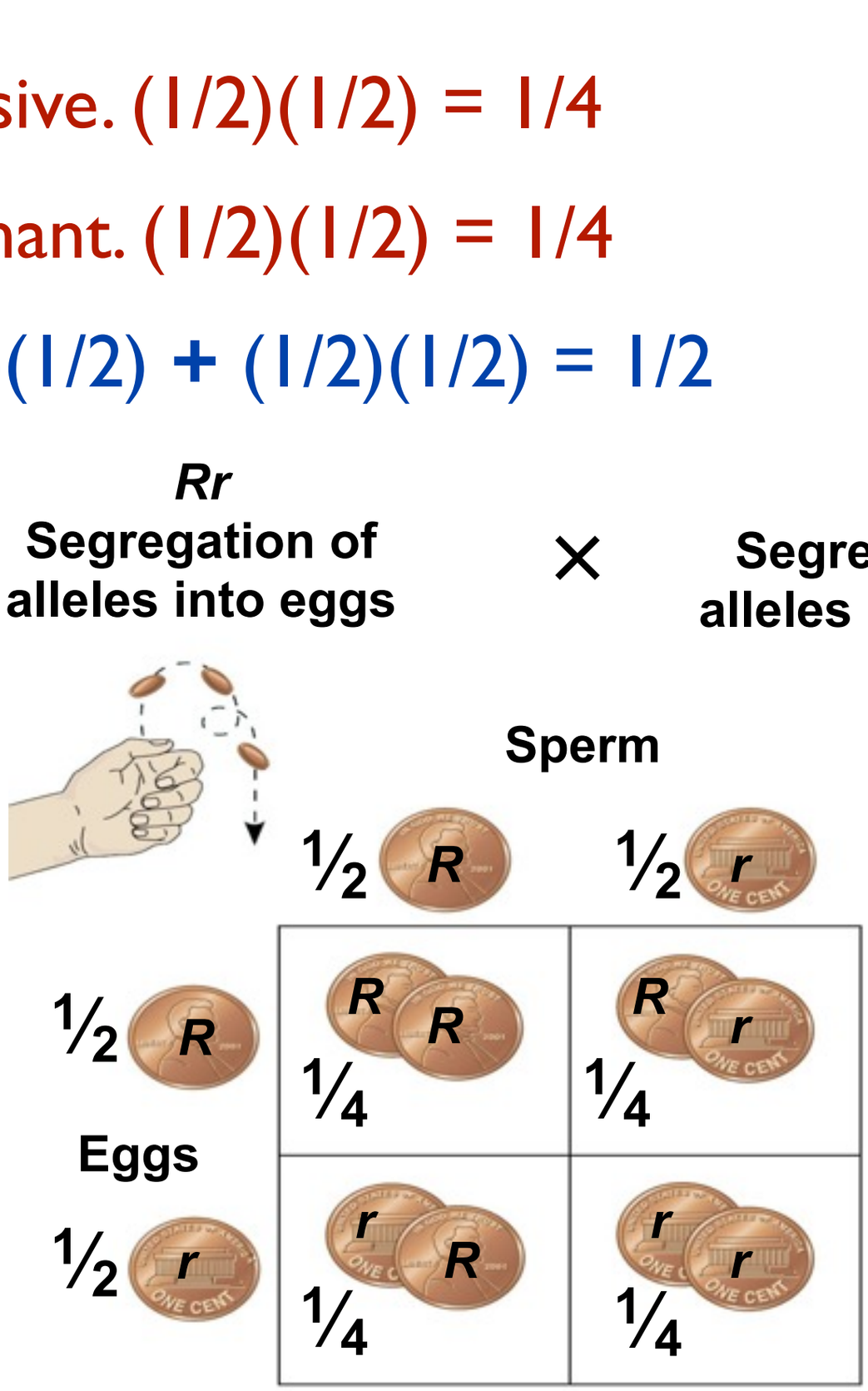
Chance of homozygous dominant. (1/2)(1/2) = 1/4

Chance of heterozygous. (1/2)(1/2) + (1/2)(1/2) = 1/2

Rr
Segregation of alleles into eggs

×

Rr
Segregation of alleles into sperm



Remember this Problem, solve it with math.

What is the probability that these parents produce a submissive long tailed lion?

Start by writing out the genotypes you "desire"

aaBB

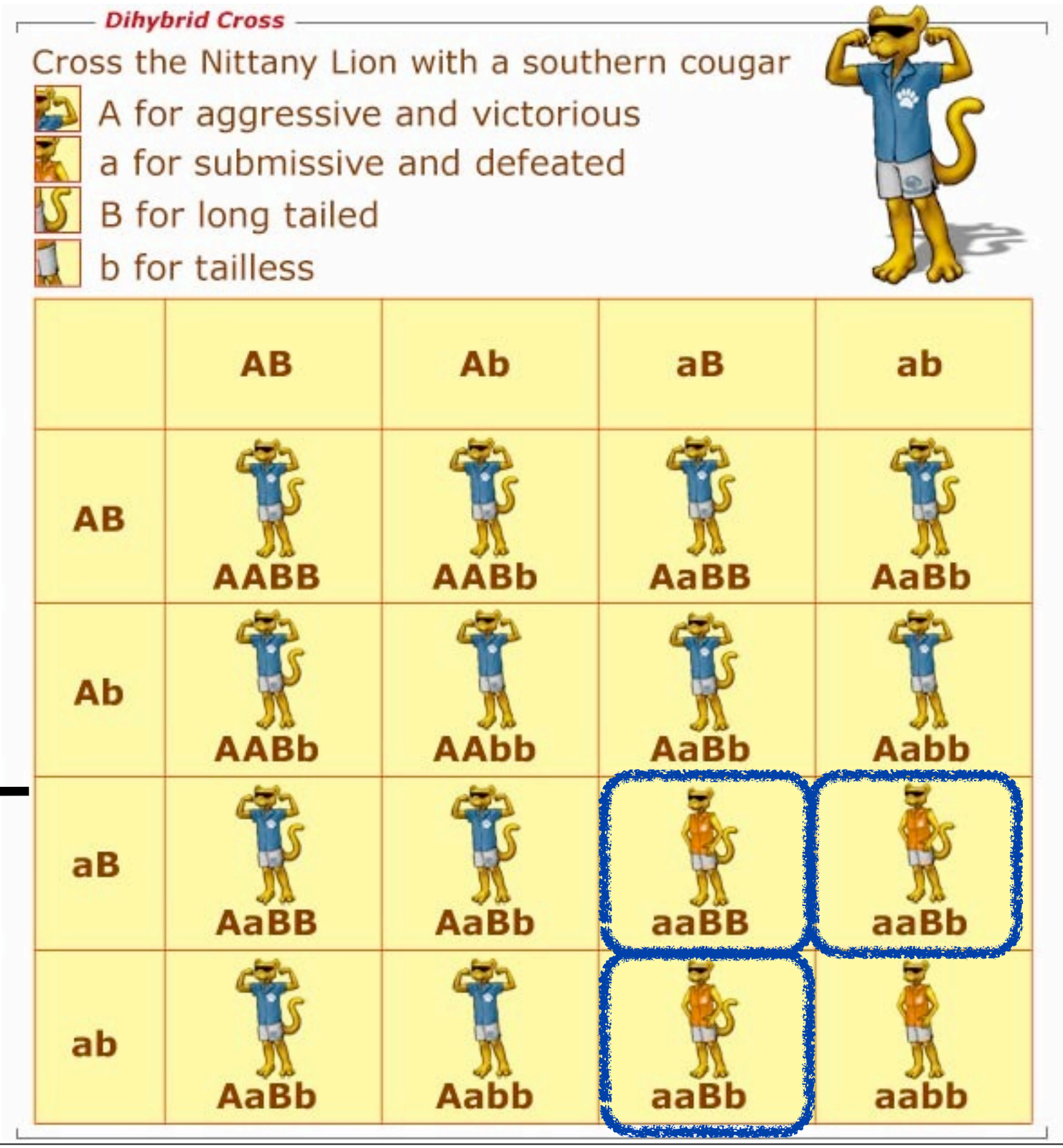
(1/2)(1/2)(1/2)(1/2)=1/16

aaBb

(1/2)(1/2)(1/2)(1/2)(2)=2/16

+

3/16 or 18.75%



Same problem solved differently

What is the probability that these parents produce a submissive long tailed lion?

Treat the problem as separate single factor crosses.

Aa x Aa

chance of aa = (1/2)(1/2)=1/4

Bb x Bb

chance of BB = (1/2)(1/2)=1/4
chance of Bb = (1/2)(1/2)=1/4
chance of Bb = (1/2)(1/2)=1/4
+ =3/4

---

chance of aaBB or aaBb (1/4)(3/4)=

3/16 or 18.75%

Dihybrid Cross

Cross the Nittany Lion with a southern cougar

A for aggressive and victorious

a for submissive and defeated

B for long tailed

b for tailless

	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAbb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

Same problem solved differently... yet again

What is the probability that these parents produce a submissive long tailed lion?

Treat the problem as separate single factor crosses.

Aa x Aa

chance of aa =1/4

can you visualize these probabilities in your head

Bb x Bb

chance of BB or Bb = 3/4

---

chance of aaBB or aaBb (1/4)(3/4)=

3/16 or 18.75%

Dihybrid Cross

Cross the Nittany Lion with a southern cougar


A for aggressive and victorious


a for submissive and defeated


B for long tailed


b for tailless

	AB	Ab	aB	ab
AB	 AABB	 AABb	 AaBB	 AaBb
Ab	 AABb	 AAbb	 AaBb	 Aabb
aB	 AaBB	 AaBb	 aaBB	 aaBb
ab	 AaBb	 Aabb	 aaBb	 aabb

Solve this Problem, using math.

What **If** we know: **Mom is AaBb** and **Dad is AaBb**

What are the chances the offspring is recessive in both traits?

We want...aabb?

Aa x Aa

aa = (1/2)(1/2) = 1/4

Bb x Bb

bb = (1/2)(1/2) = 1/4

aabb = (1/4)(1/4) = 1/16

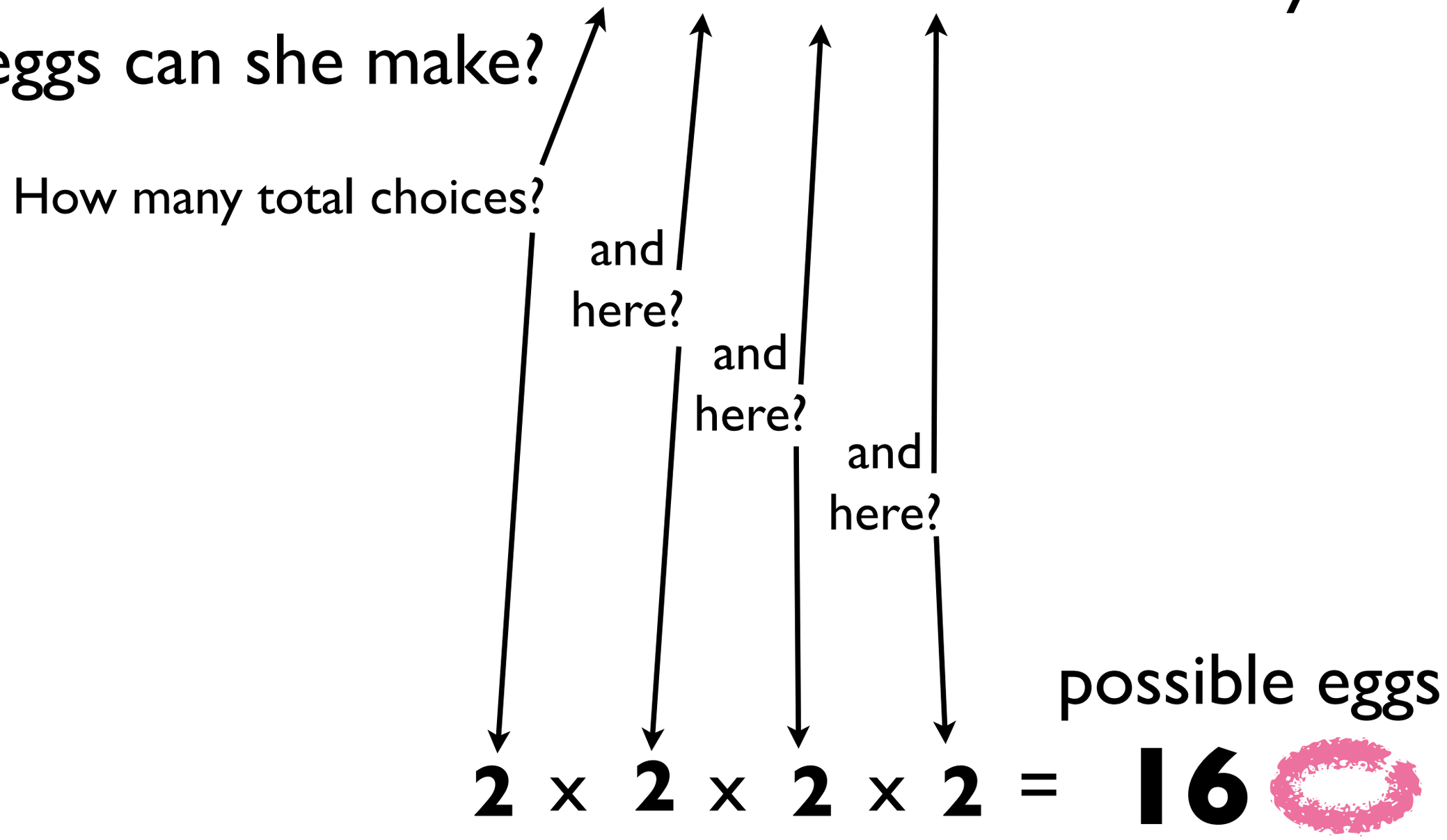
possible sperm

possible eggs

	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	Aabb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

We can use math calculate possible gametes as well.

What **If** we know: **Mom is AaBbCcDd** How many different eggs can she make?



OR...ask yourself the following:

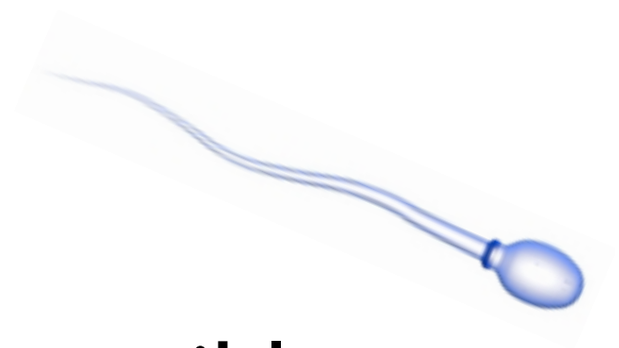
How many choices at each position? = (2) How many positions? = (4)

$$2^4 = 16$$

Lets try one more...

What **If** we know: **Dad is AaBBccdd** How many different sperm can he make?

How many total choices? and here? and here? and here?



2 x 1 x 1 x 1 = **2** possible sperm

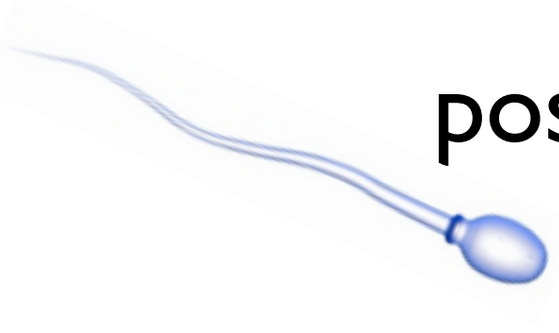
OR...ask yourself the following:

How many choices at each position? = (2) How many positions? = (1)

$$\mathbf{2^1 = 2}$$

AaBBccddEEFFGghh X aaBbccDDeeFFGghh

Draw a empty punnet square for this cross? How many Boxes?
How many different offspring can this couple make? Phenotypically? Genotypically



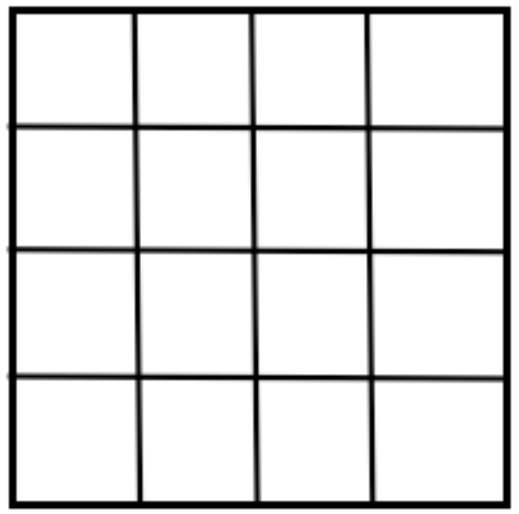
possible sperm

$2^2 = 4$

possible eggs

$2^2 = 4$

16 boxes

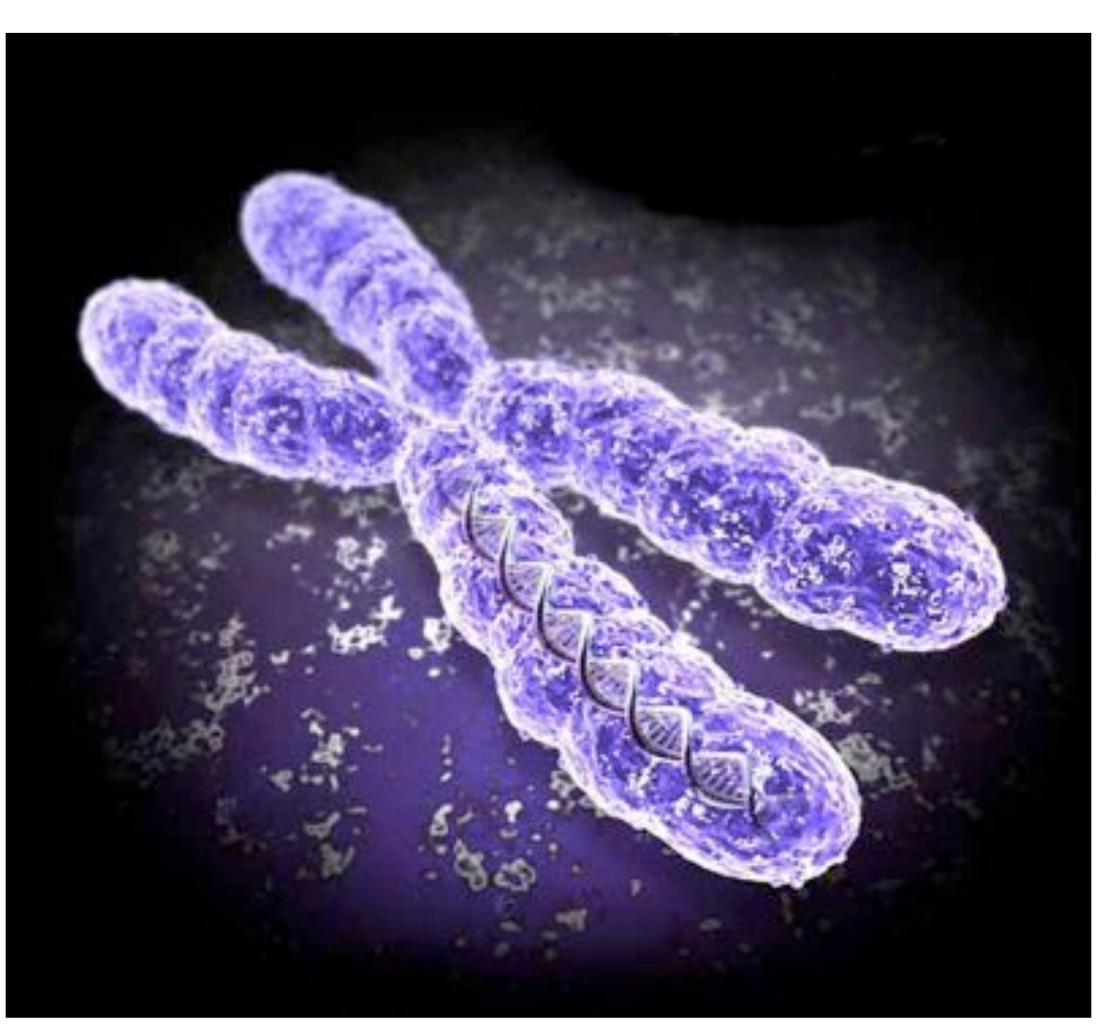


(2)(2)(1)(1)(1)(3)(1) = 12 different genotypes
(2)(1)(1)(1)(1)(2)(1) = 4 different phenotypes

Genetics

III.

Main Idea: Today we know that inheritance patterns are often more complex than those predicted by Mendelian genetics.



PREFACE

- We know today and Mendel knew himself that his models could explain all patterns of observed inheritance.
  - *We know today that relationship between genotype and phenotype is not always straightforward.*
  - *We know that dominant and recessive genes are not always straightforward.*
  - *We know that some traits are controlled by more than two alleles.*
  - *We know that some genes control multiple traits.*
  - *We know that some genes control other the expression of other genes.*
- Although we know that patterns of inheritance extend beyond patterns described by Mendelian models his Law of Segregation and the Law of Independent Assortment hold true and are applicable to even the most most complicated patterns of

Degrees of Dominance

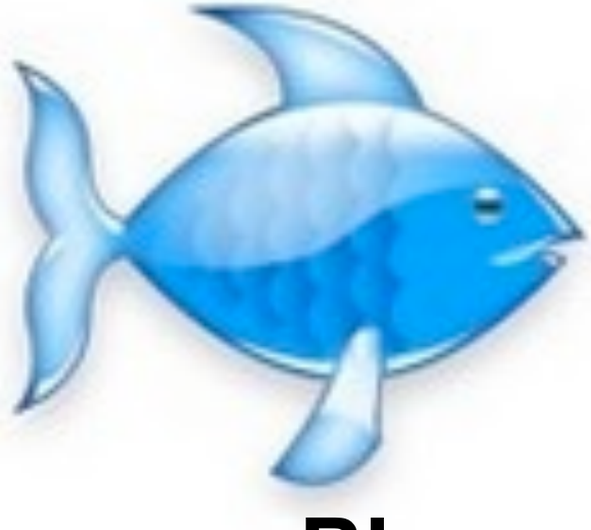
- Alleles can show different degrees of dominance.
- The alleles that Mendel worked with happen to be exhibit **complete dominance**; were the phenotypes of the heterozygous and homozygous dominant are no different.
- In other cases alleles are **incompletely dominant** and as a result the heterozygous condition shows a phenotype that is somewhere between the homozygous dominant and the homozygous recessive genotypes.
- In yet in other cases both alleles may be dominant. **Codominance** results in the heterozygous condition exhibiting a phenotype that is mix of both the homozygous dominant and the homozygous recessive genotypes.

Codominance

Red

C^RC^R

X



Blue

C^BC^B

Red & Blue

C^RC^B

Red & Blue

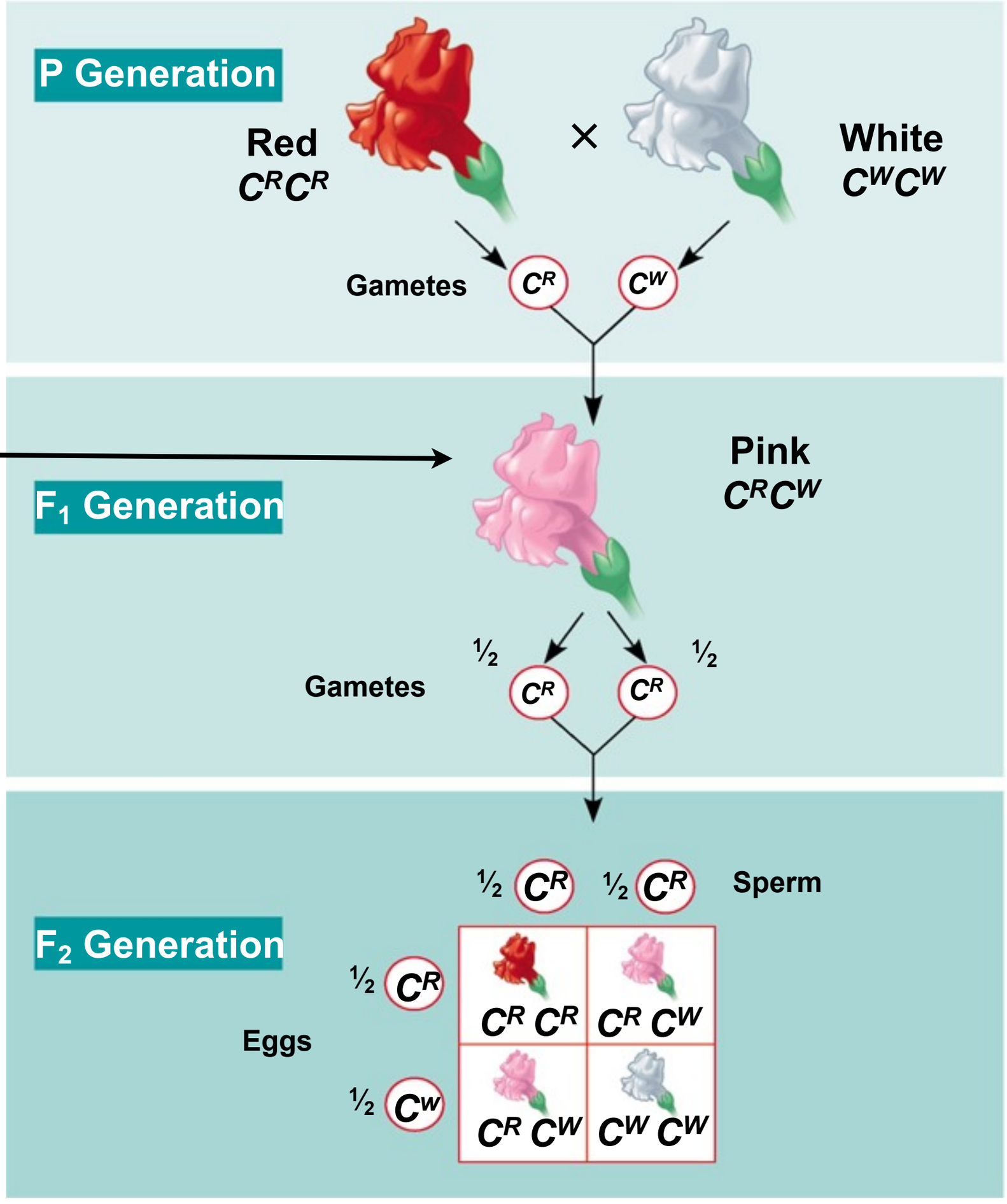
C^RC^B

Notice the change in symbolic representation, now we must use all capital letters to show that recessive alleles do not exist and we use superscripts to differentiate between the two

Incomplete Dominance

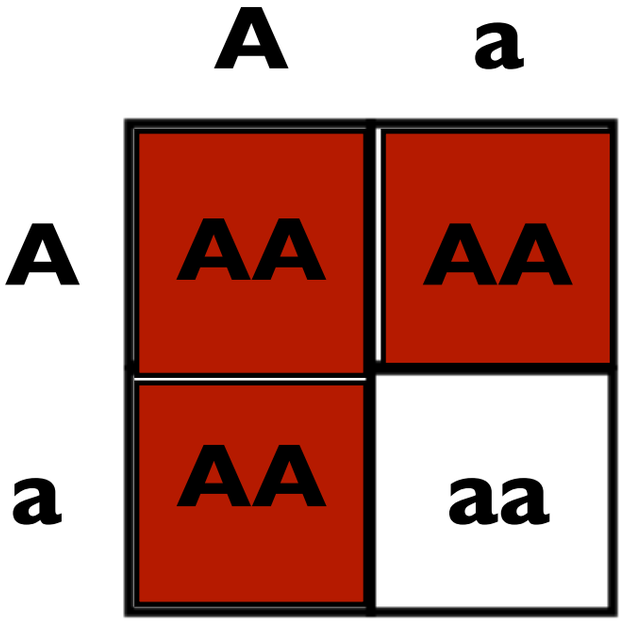
This looks like the blending hypothesis! Why does this not support that idea?

If the blending hypothesis were correct all F2 offspring would be pink, instead red and white both reappear.



Comparison of Degrees

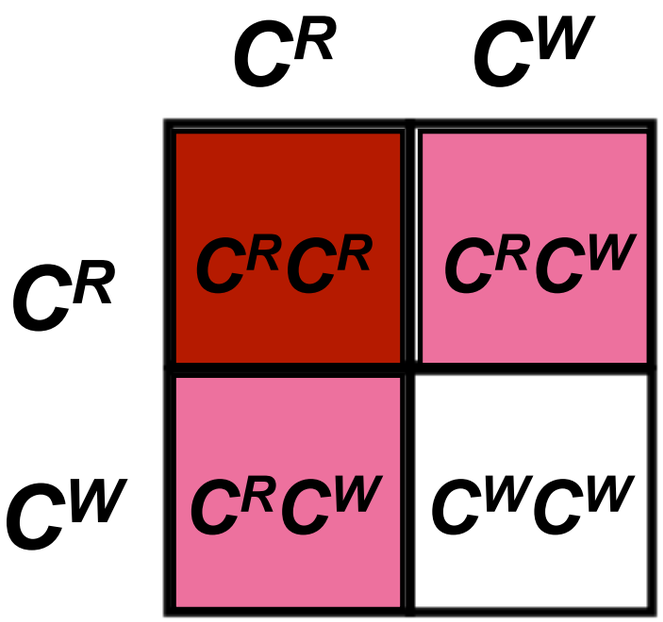
Complete Dominance



Genotype- 1:2:1

Phenotype- 3:1

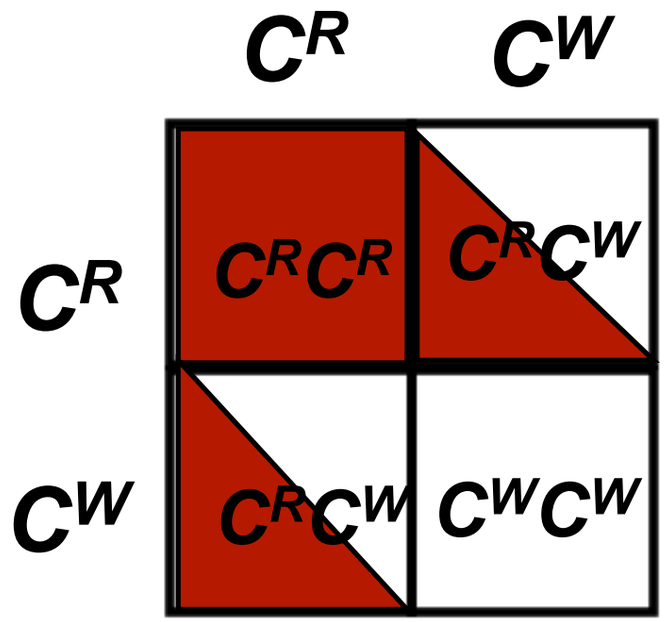
Incomplete Dominance



Genotype- 1:2:1

Phenotype- 1:2:1

Codominance



Genotype- 1:2:1

Phenotype- 1:2:1

Music is "Cathedral" from Van Halen's Diver Down album...What is the connection to this slide?

Dominance & Phenotype

- We have seen a range of dominance from complete to incomplete to codominance.
- Understand that alleles are not dominant because they somehow subdue the other gene.
- A dominant gene is simply the gene that is shows up in the phenotype
- Remember alleles are variations in nucleotide sequences, so when a dominant and recessive alleles coexist they do not even actually interact.
- Thus it is the pathway from genotype to phenotype that dominance comes into play

Dominance & Phenotype

Unbranched Starch

r= ↓ **Defective Enzyme**

Unbranched Starch

↓

Excessive Water Enters

↘

seed dries

Having one dominant allele results in 50% of the "enzymes" being effective. As we can see having at least 50% of the enzymes effective converts enough unbranched starch that we see the smooth phenotype.

Unbranched Starch

R= ↓ **Effective Enzyme**

Branched Starch

↓

Normal Amount Water Enters Seed

↙

seed dries

Dominance & Phenotype

- In fact this relationship is even more intriguing.
- For any character, the observed dominant/recessive relationship of alleles depends on the level at which we examine the phenotype.
- Consider **Tay-Sachs Disease**, an inherited disorder in humans that results in seizures, blindness, degeneration of motor and mental skills all followed by death because a faulty enzyme in brain cells allows lipids to accumulate to dangerous levels.

Tay-Sachs Genetics

Consider a carrier for the disease: **Aa**

- Organismal Level: The genotype of **Aa** is free of disease,
  - *thus the **A** to **a** relationship is simple and complete dominance.*
- Biochemical Level: The **AA** shows no lipid accumulation, the **aa** shows deadly levels of lipid accumulation and the **Aa** shows lipid accumulation but not to deadly levels,
  - *thus the **A** to **a** relationship is incomplete dominance.*
- Molecular Level: The **AA** shows 100% effective enzymes, the **aa** shows 0% effective enzymes and the **Aa** shows 50% effective enzymes,
- *thus the **A** to **a** relationship is codominance.*

Frequency of Dominant Alleles

- **Dominant alleles are NOT necessarily more common in population.**
- Consider polydactyly, a condition where humans are born with extra toes or fingers.
- Some cases of polydactyly are caused by a dominant allele.
- Only 1 in 400 babies are born with this condition, thus most people are homozygous recessive.
- Same is true of blood group alleles, the recessive gene "i" is more common globally than either of the dominant forms.
    - *About 63% of all people worldwide carry the recessive "i" allele.*

Multiple Alleles

- As stated in the preface, we know today that some traits are controlled by more than two alleles.

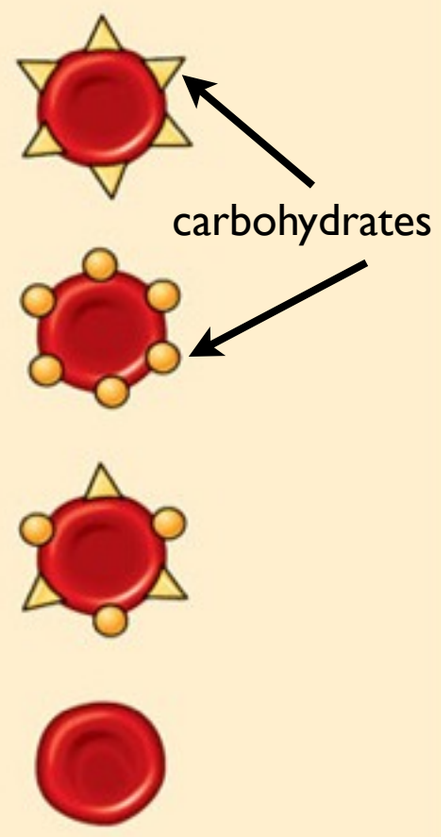
- Some traits are controlled by more than two alleles for instance the ABO blood groups.

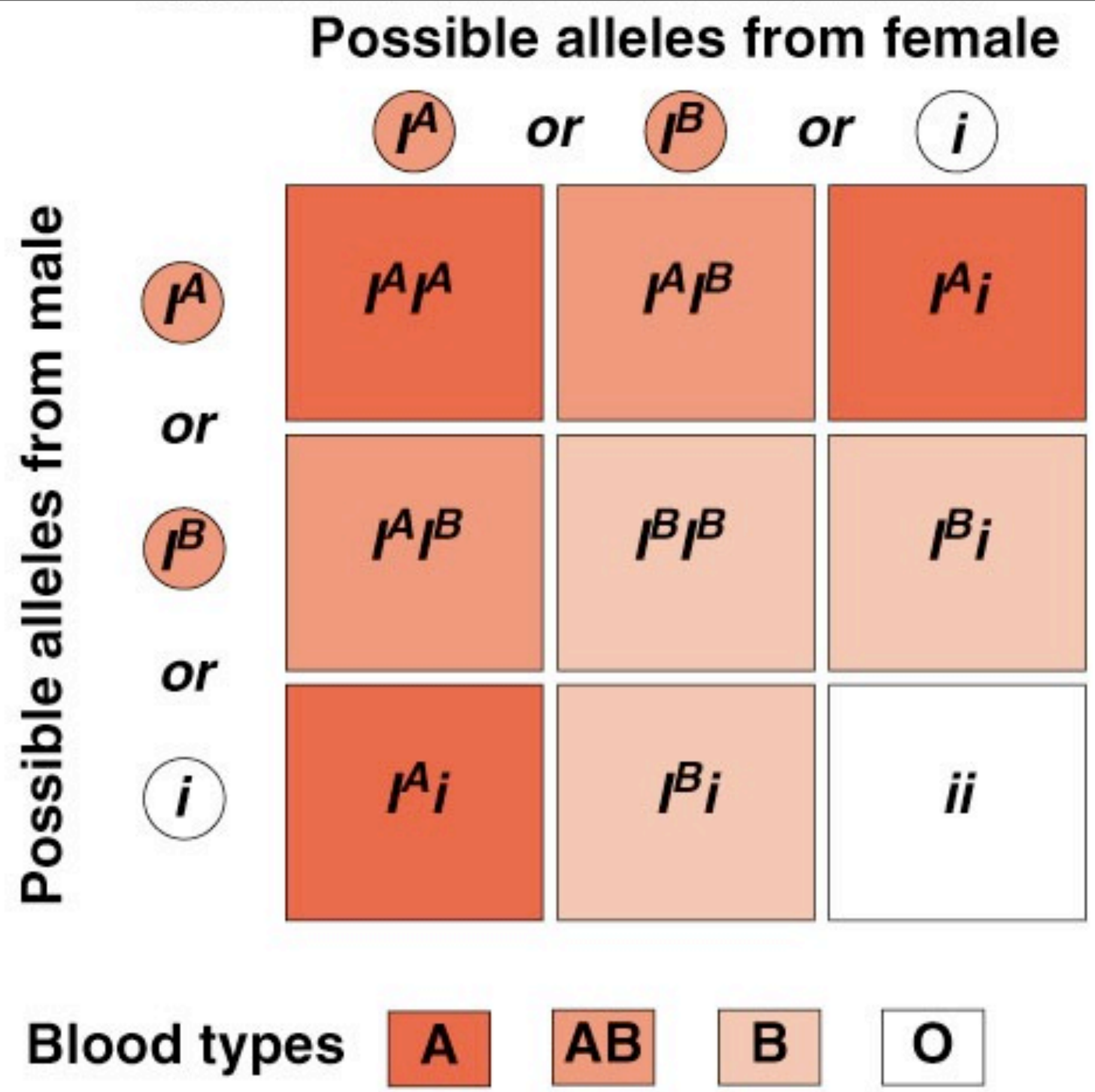
- The ABO blood groups are controlled by two codominant alleles and one recessive allele.

Type "O" used to be called "C" but was later changed to reflect the german word "ohne" meaning without.

Determination of ABO Blood Group by Multiple Alleles

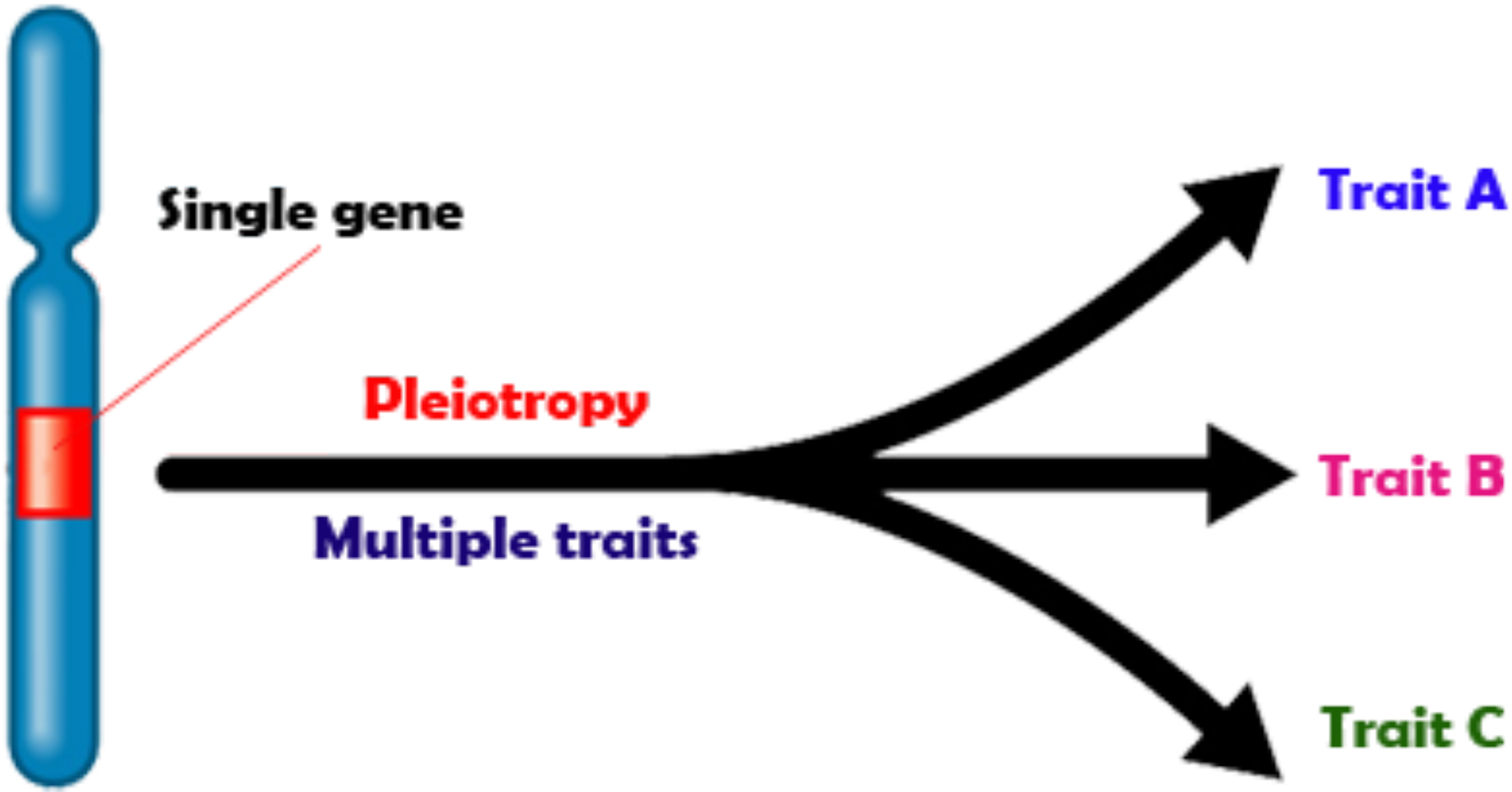
Genotype	Phenotype (Blood Group)	Red Blood Cells
$I^A I^A$ or $I^A i$	A	
$I^B I^B$ or $I^B i$	B	
$I^A I^B$	AB	
ii	O	




Possible alleles from female
I^A
or
I^B
or
i
Possible alleles from male
I^A
or
I^B
or
i
$I^A I^A$
$I^A I^B$
$I^A i$
$I^A I^B$
$I^B I^B$
$I^B i$
$I^A i$
$I^B i$
ii
Blood types
A
AB
B
O

Pleiotropy

- Most genes have multiple phenotypic effects, a property called **pleiotropy**.



Pleiotropy

The gene that affects pigmentation in cats also affects hearing.

Approximately 40% of white fur, blue eyed cats are deaf.

The gene that causes Frizzle feathered trait also effects the chickens: metabolic rate, body temp, digestive capacity, blood flow and the number of eggs they lay.

Epistasis

- In **epistasis**, the phenotypic expression of a gene at one locus alters that of a gene at a second locus.

B- E- bb E- B- ee bb ee

B- black pigment
b- brown pigment

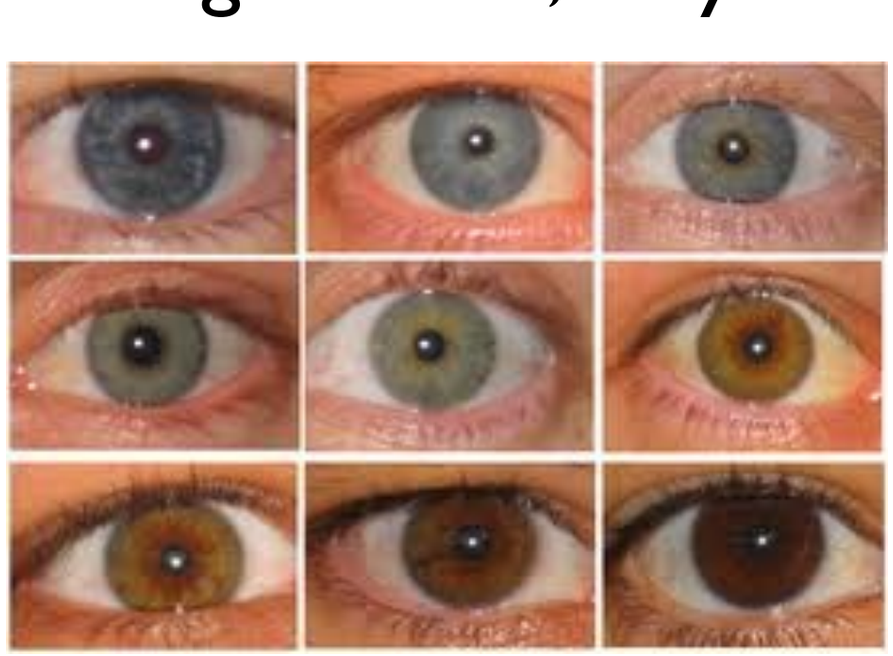
E- controls/allows pigment deposition
e- controls/ does not allow pigment deposition

Epistasis

	AB	Ab	aB	ab
AB	 AABB Walnut	 AABb Walnut	 AaBB Walnut	 AaBb Walnut
Ab	 AABb Walnut	 AAbb Rose	 AaBb Walnut	 Aabb Rose
aB	 AaBB Walnut	 AaBb Walnut	 aaBB Pea	 aaBb Pea
ab	 AaBb Walnut	 Aabb Rose	 aaBb Pea	 aabb Single

Polygenic Inheritance

- Mendel studied traits that could be described as "either-or traits".
  - *smooth OR wrinkled seeds, purple OR white flowers*
- Many characters can not be described in this manner because they display themselves in a continuum or gradation, they are called **quantitative characters**.

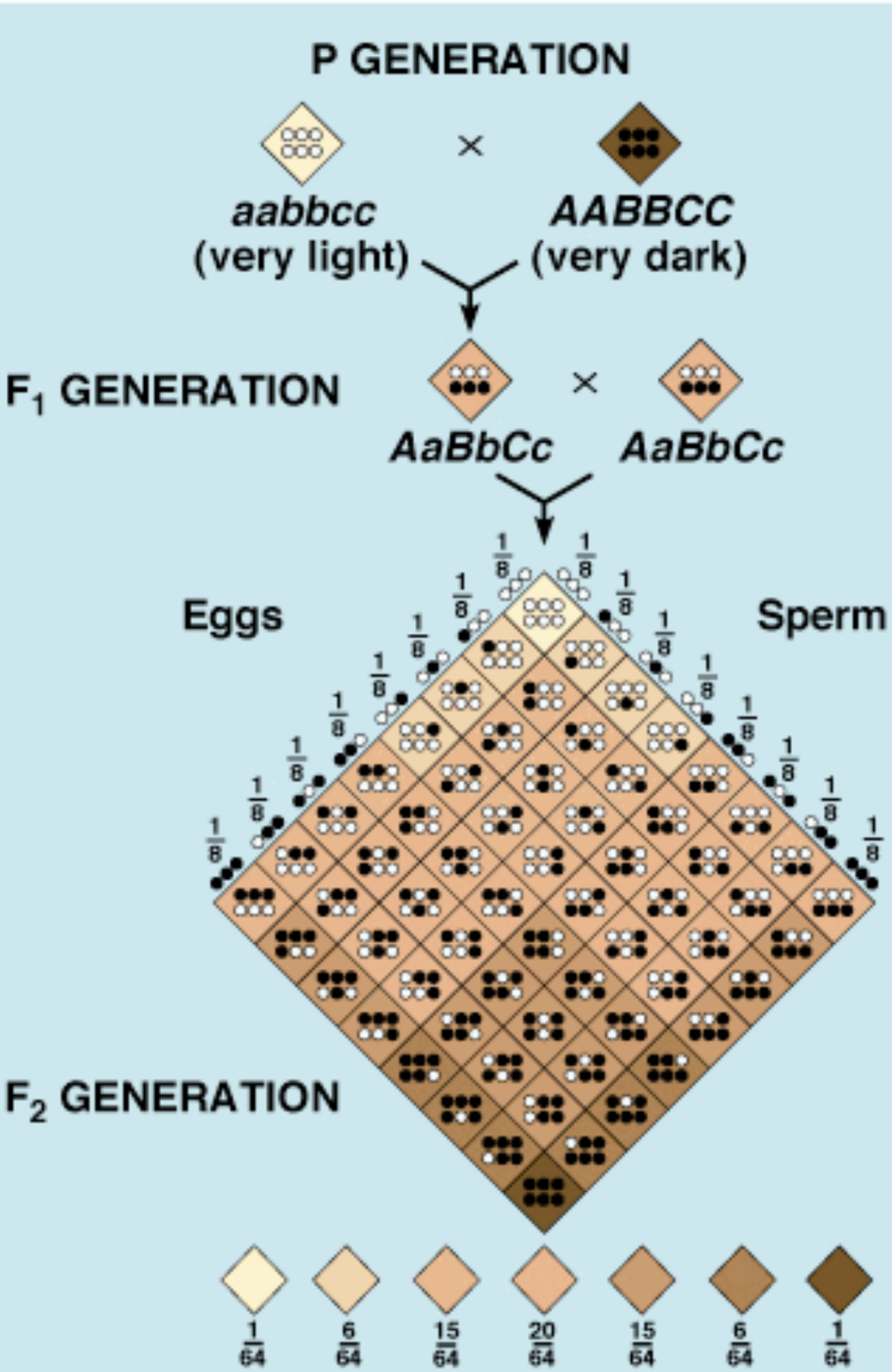


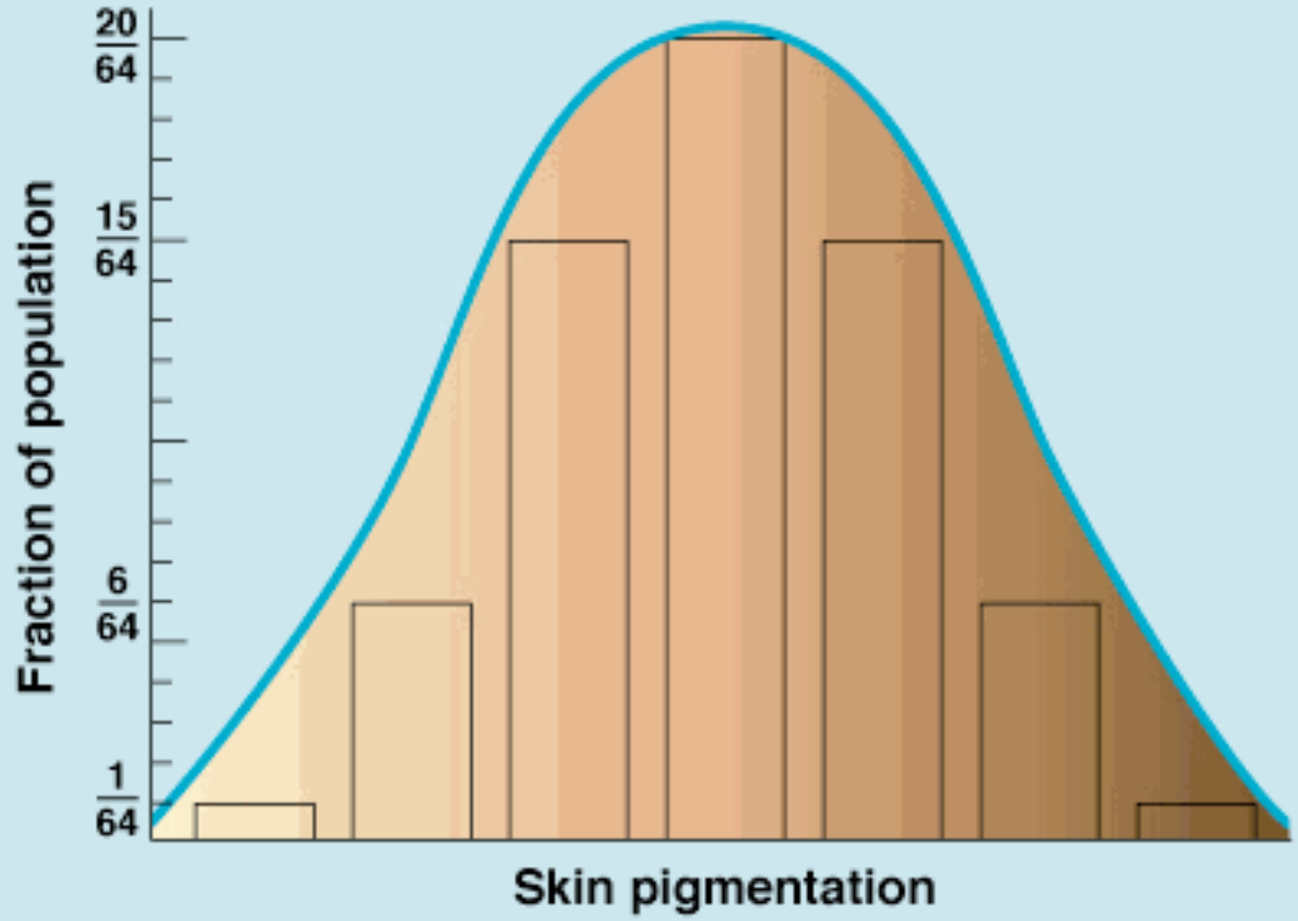
- Quantitative characters usually indicates **polygenic inheritance**, an additive effect of two or more genes on a single phenotypic character.

Polygenic Inheritance

- Multiple genes are necessary to generate all these phenotypes.

Skin Color is Polygenic





Note: The environment can also play a role skin color.

Environmental Impact on Phenotypes

- Another departure from simple Mendelian inheritance occurs when the environment and the genotype work together to produce the phenotype..
- A TREE, is born with certain and specific genes but its overall shape, branch characteristics and leaf characteristics vary depending on environmental conditions.
- For example, the number, shape and greenness of its leaves depend on wind, sun, water and nutrient availability.

Nature vs. Nurture

- A HUMAN Being is born with certain and specific genes but many characteristics from skin color to intelligence to height to athletic ability vary depending on environmental conditions.
    - Identical twins although genetically the same develop phenotypic differences through their life.
- The question of whether "WE" are more a product of our genes or our environment is very old and hotly contested.
- Biology can say that genotypes are generally not associated rigidly with a phenotype.
- Rather a "phenotypic range" for a genotype exists due to environmental conditions called the **norm of reaction.**

Norm of Reaction

- Some traits have a very narrow norm of reaction like ABO blood groups.
  - If your genotype is "ii" then you will have O blood.
- Other traits have a broad norm of reaction like blood cell count.
  - The number of blood cells varies widely due to altitude, physical fitness and infections.
- Generally norm of reaction is broadest in polygenic traits and are consequently termed **multifactorial characters** by many geneticists.

Sex Linked Inheritance

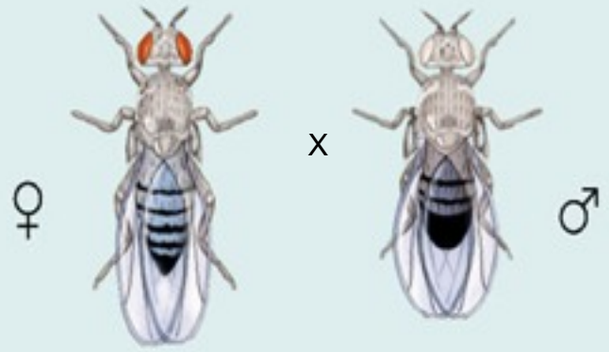
- Thomas Hunt Morgan, an embryologist from Columbia University, provided the first solid evidence that genes were in fact located on chromosomes.
    - *Like Mendel his discovery was both insightful and a little lucky.*
- After years of tedious work with fruit flies, Morgan provided the first support for the **chromosome theory of inheritance**, that specific genes are carried on specific chromosomes.
    - *fruit flies breed quickly and have only 4 chromosomes*
- In addition, he showed that genes located on the sex chromosomes exhibit a unique pattern of inheritance.

Morgan's Experiment

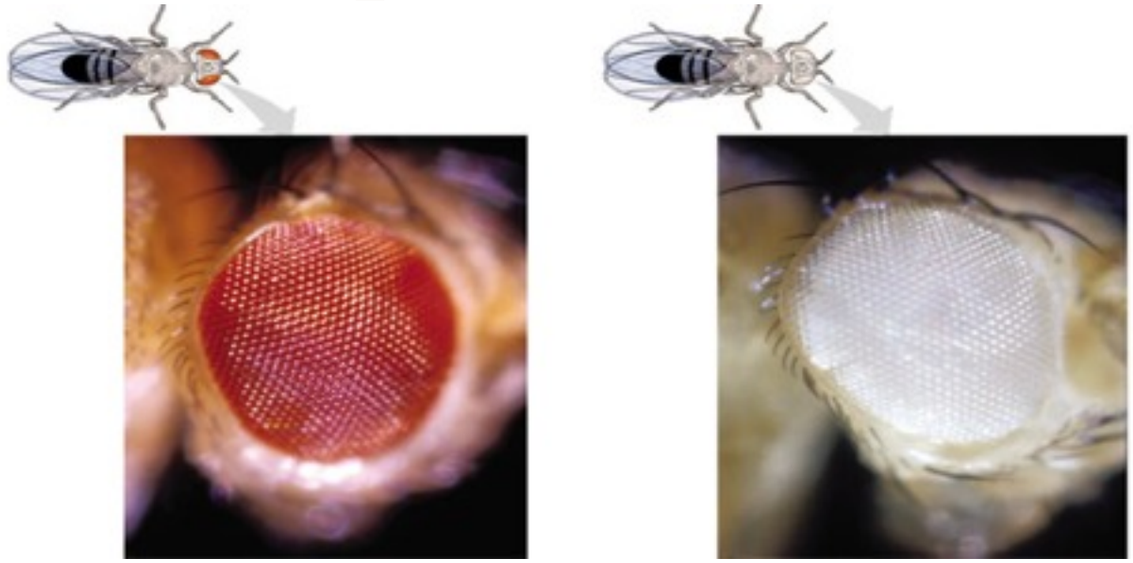
Morgan mated a wild-type (red-eyed) female with a mutant white-eyed male. The F_1 offspring all had red eyes.

EXPERIMENT

P Generation



F_1 Generation



Morgan then bred an F_1 red-eyed female to an F_1 red-eyed male to produce the F_2 generation.

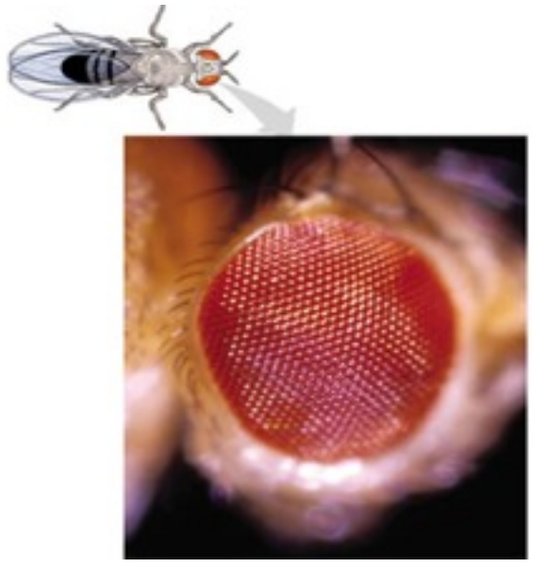
RESULTS

F_2 Generation

The F_2 generation showed a typical Mendelian 3:1 ratio of red eyes to white eyes. However, no females displayed the white-eye trait; they all had red eyes. Half the males had white eyes, and half had red eyes.

Fruit Fly Genetic Symbols

Now called "wild type" instead of dominant



w^+

(+) superscript now used instead of capital letter

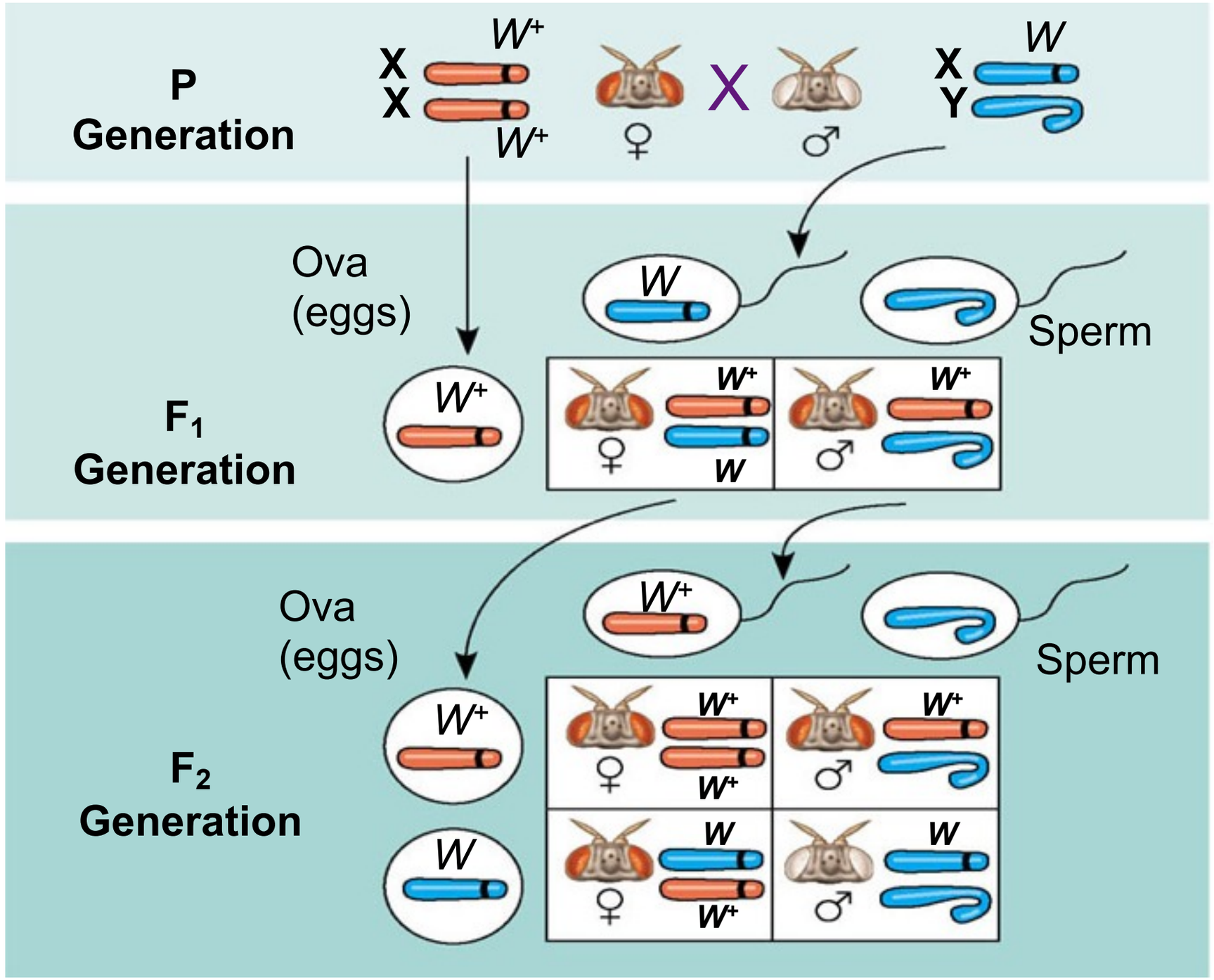
w

lower case letters still used for recessive allele

Now called "mutant" instead of recessive

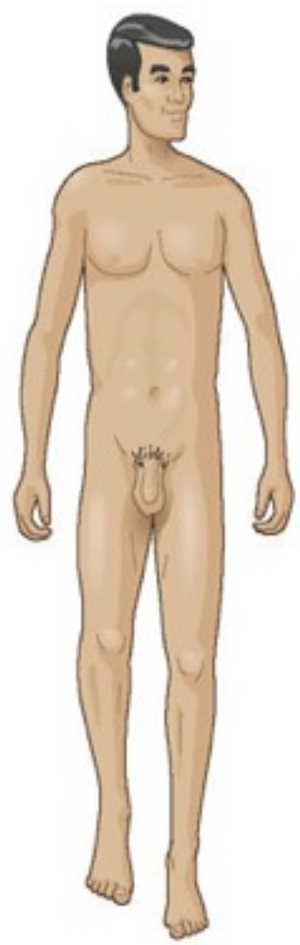
CONCLUSION

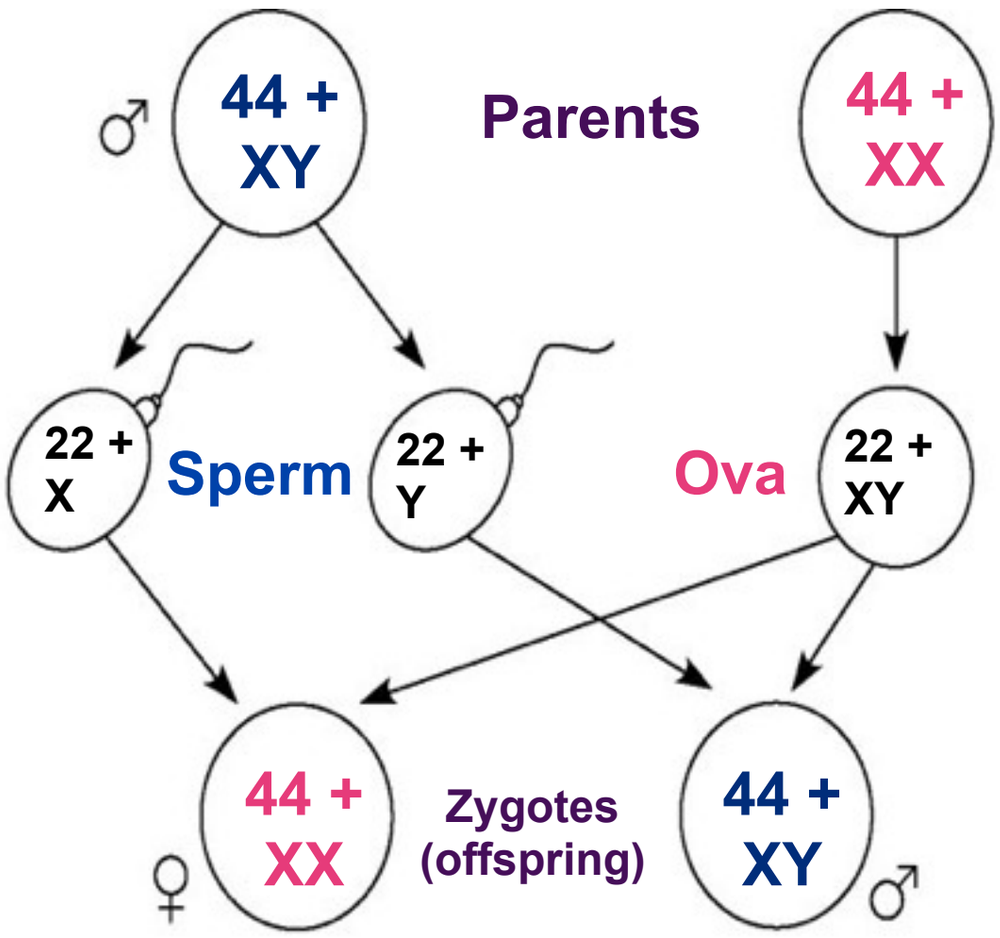
Since all F_1 offspring had red eyes, the mutant white-eye trait (*w*) must be recessive to the wild-type red-eye trait (w^+). Since the recessive trait—white eyes—was expressed only in males in the F_2 generation, Morgan hypothesized that the eye-color gene is located on the X chromosome and that there is no corresponding locus on the Y chromosome, as diagrammed here.



Chromosomal Basis of Sex

- There are two varieties of sex chromosomes X and Y.
- An organisms sex is determined by the presence or absence of certain sex chromosomes.





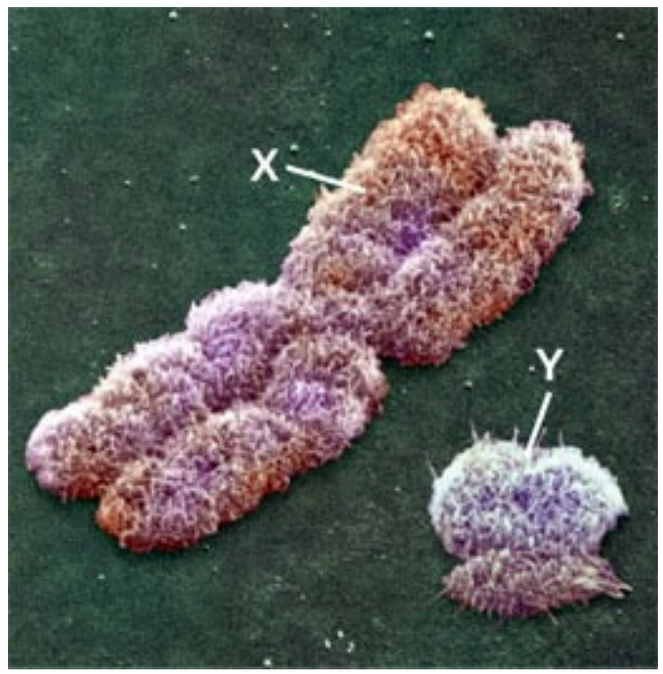
The X-Y system

XX= Girl

XY= Boy

Y chromosome carries about 78 genes

X chromosome carries about 1,100 genes



Other Systems of Sex Determination

22 + XX

♀

22 + X

♂

The X–0 system

76 + ZW

♀

76 + ZZ

♂

The Z–W system

16 (Diploid)

♀

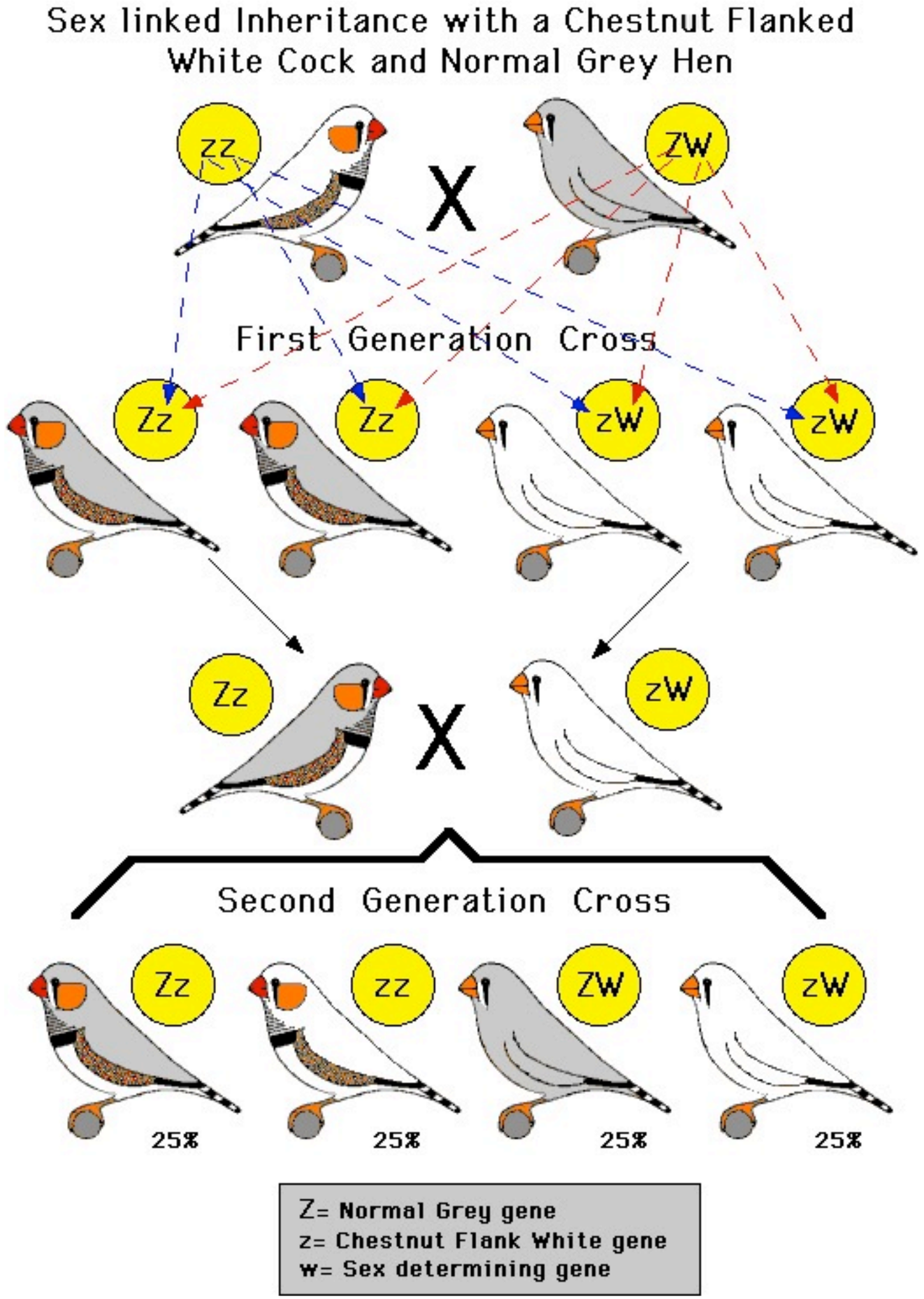
16 (Haploid)

♂

The haplo-diploid system

A gene located on any sex chromosome is said to be sex linked

Sex Linked Example on the ZW System

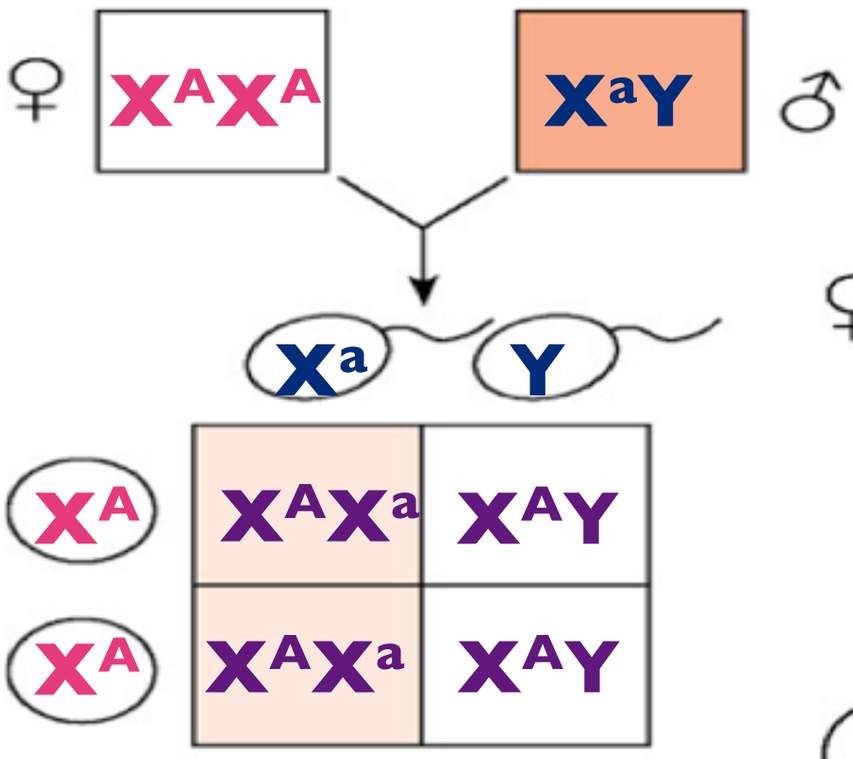


A gene located on any sex chromosome is said to be sex linked

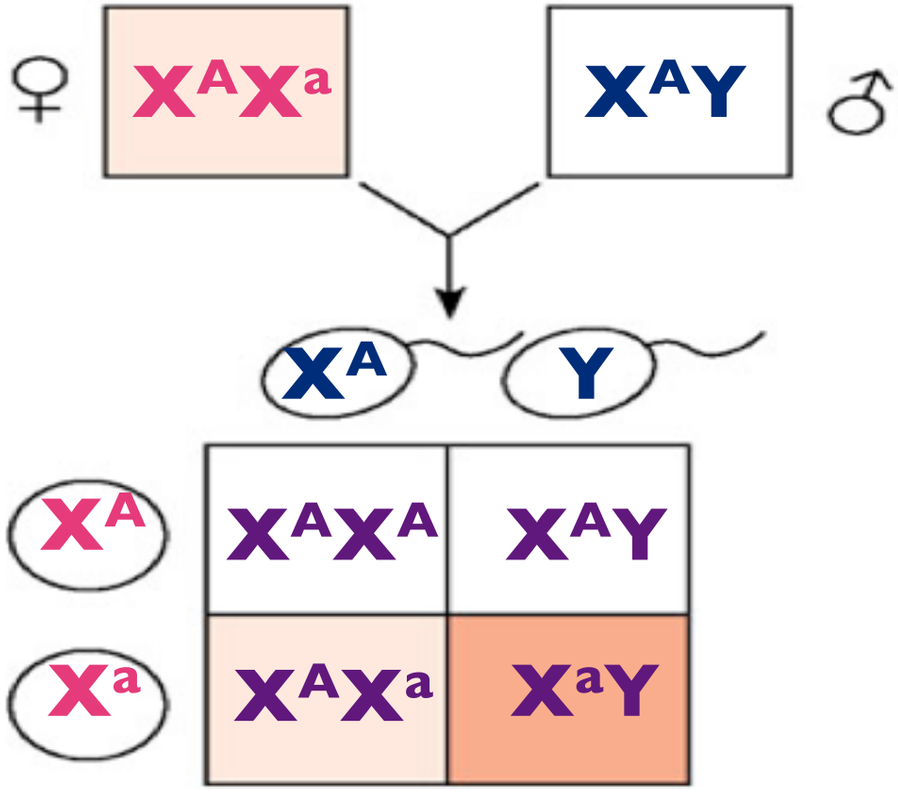
Inheritance of Sex Linked Traits

- Although a sex linked trait can be found on the X or Y chromosome, **most** genetic problems you will encounter will be "X-linked" traits.
  - *Y linked traits are few and mainly sex determinate*
- X-linked traits are far more numerous and some diseases are carried on this chromosome consequently most genetic problems are X-linked.
  - *Duchenne Muscular Dystrophy, Hemophilia & Color Blindness*
- **Most importantly X-linked traits follow a unique pattern of inheritance, the same pattern seen in Morgan's fruit flies.**

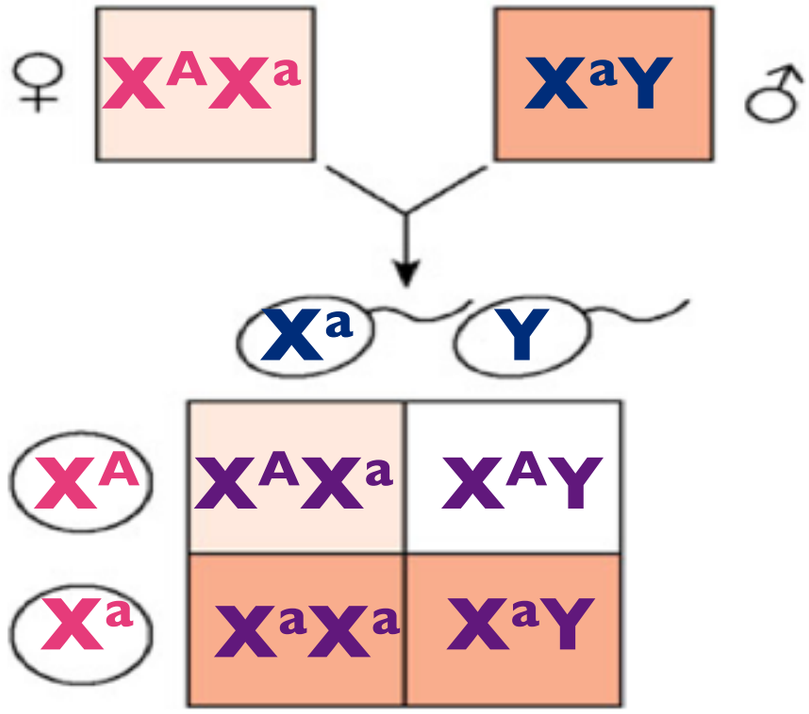
Inheritance of Sex Linked Traits



A father with the disorder will transmit the mutant allele to all daughters but to no sons. When the mother is a dominant homozygote, the daughters will have the normal phenotype but will be carriers of the mutation.



If a carrier mates with a male of normal phenotype, there is a 50% chance that each daughter will be a carrier like her mother, and a 50% chance that each son will have the disorder.



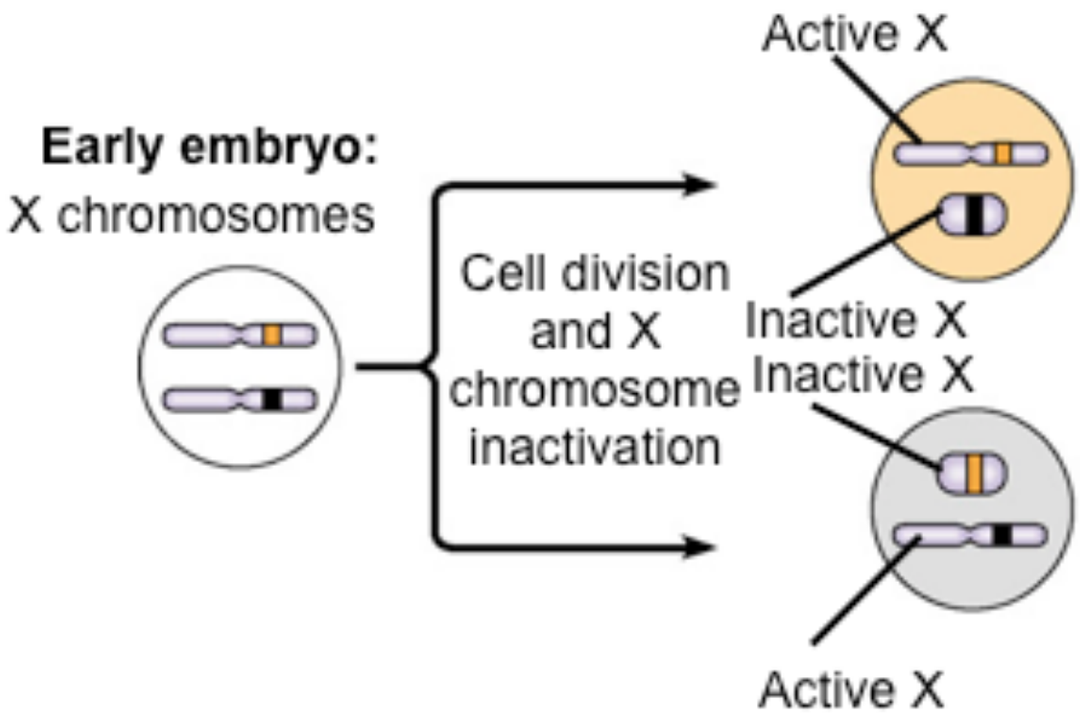
If a carrier mates with a male who has the disorder, there is a 50% chance that each child born to them will have the disorder, regardless of sex. Daughters who do not have the disorder will be carriers, where as males without the disorder will be completely free of the recessive allele.

X Inactivation in Female Mammals

- Females receive 2 "X" chromosomes compared to males who only get 1.
  - *If females used both chromosomes then their effective gene dose would be double that of males!*
- When a gene on the X chromosome makes its protein product females would have 2X the normal amount or if that amount was normal then males would only ever get 1/2X the normal amount.
  - *To make the gene dose equal females only use 1 of their X chromosomes.*

X Inactivation in Female Mammals

- **Every cell in a female mammal will randomly select and inactivate one of the two X chromosomes there by making the gene dose equal to that in males.**
- The inactivate X chromosome is called the **Barr Body** and lies just inside the edge of the nuclear envelope.

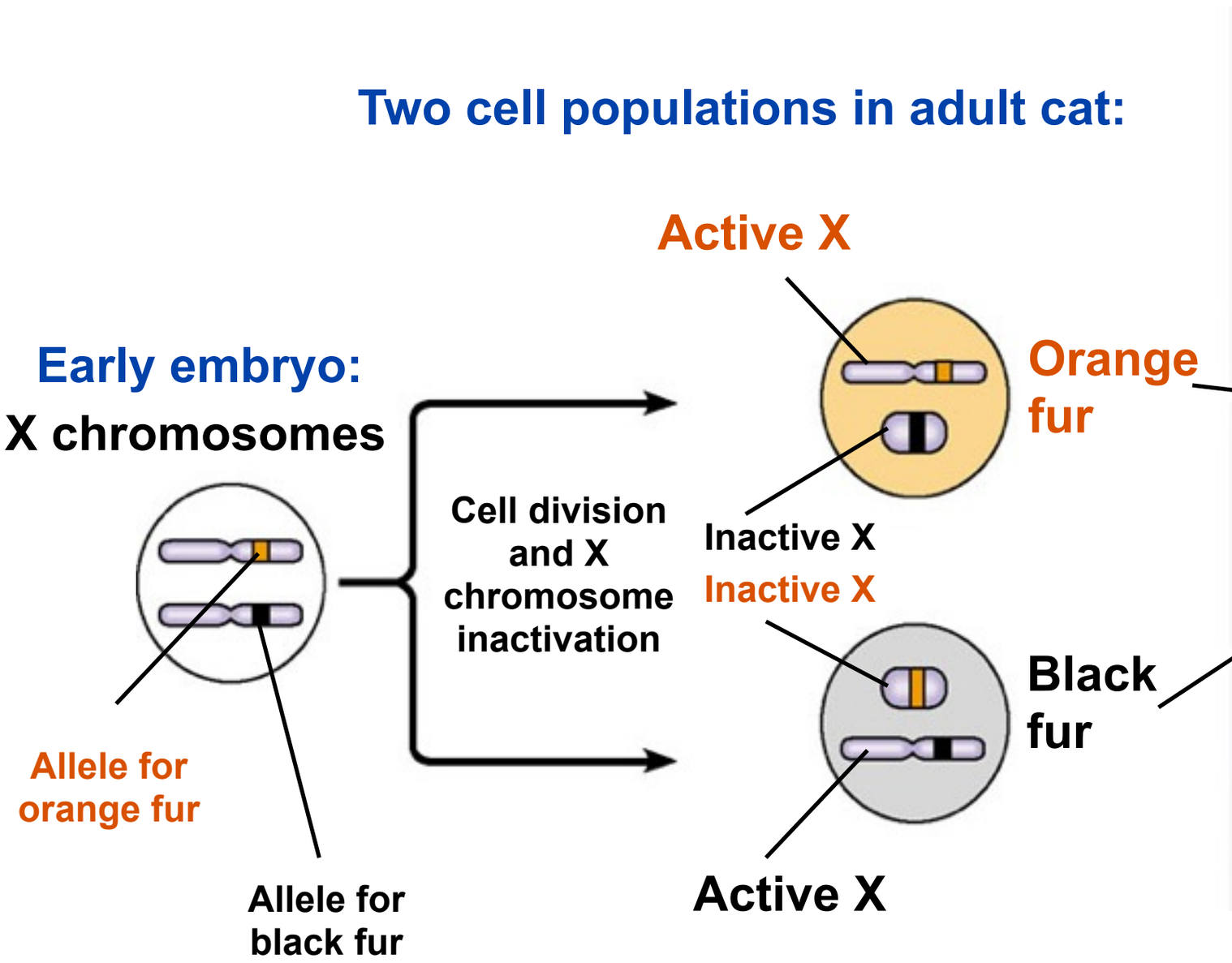


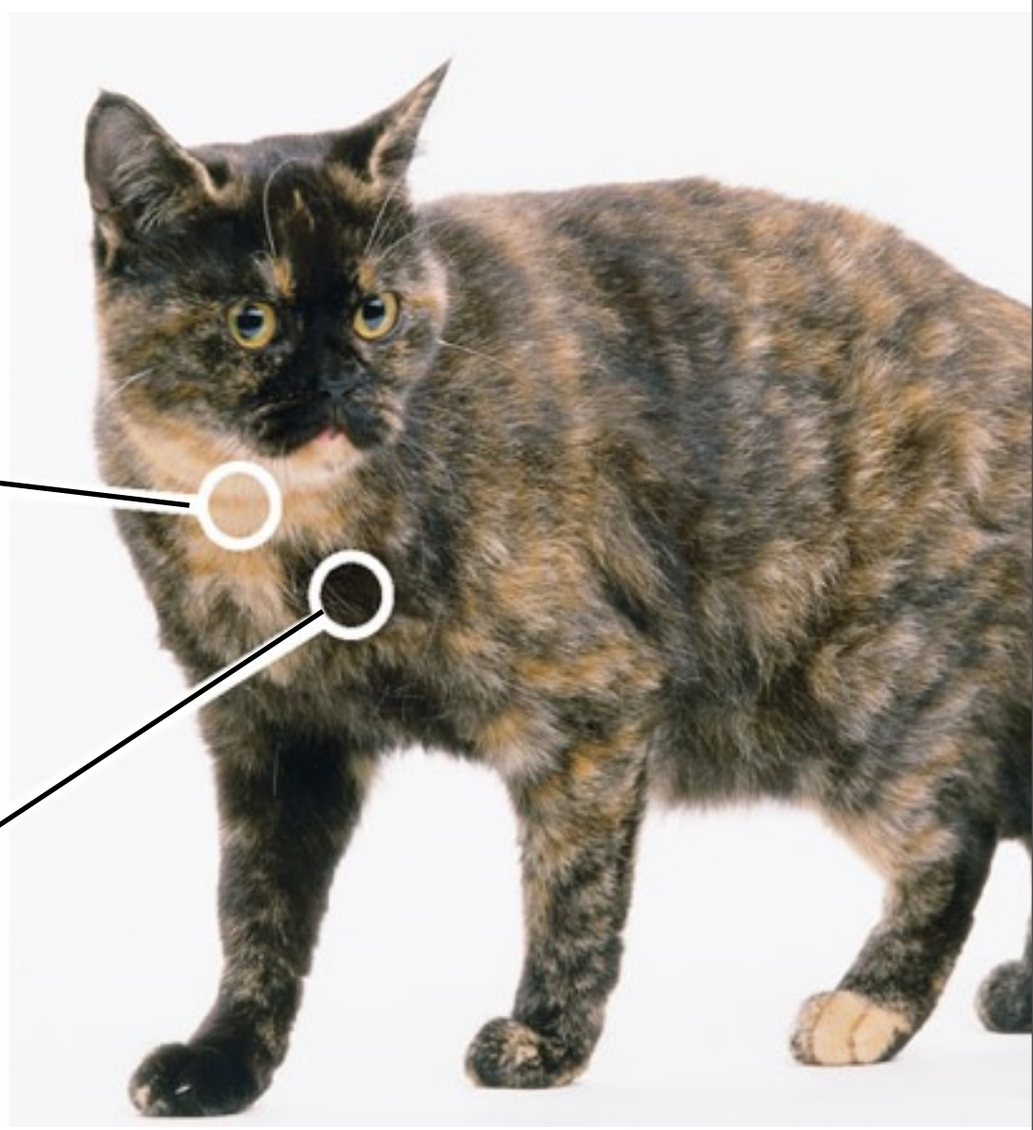
What one and only cell type reactivates the Barr Body?

...germ cells, that give rise to ova

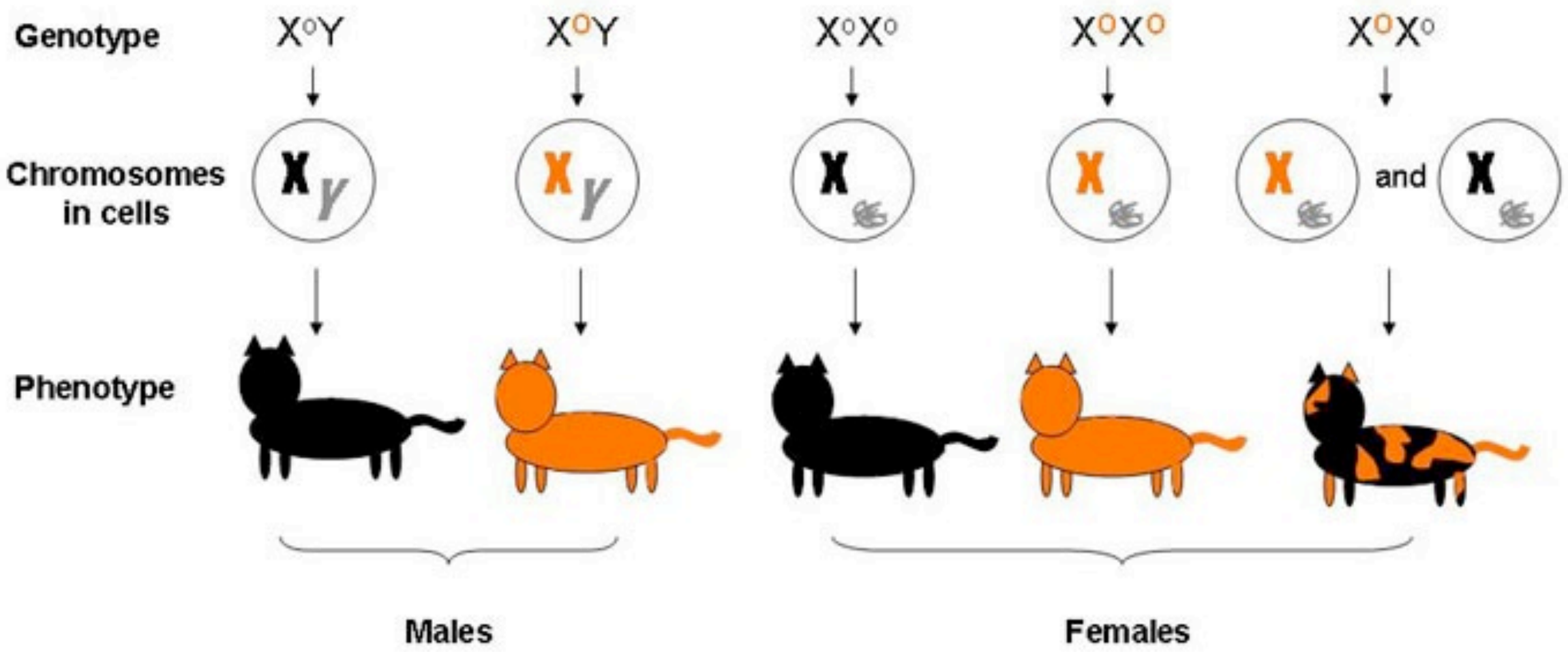
Mosaic Female Phenotypes

- Although the chromosomes are both "X" chromosomes, one came from dad and one came from mom therefore the genes on each are likely mostly different.





Sidebar: Some human females exhibit a mosaic pattern of sweat glands around their body, patches of skin sweat while other patches do not.



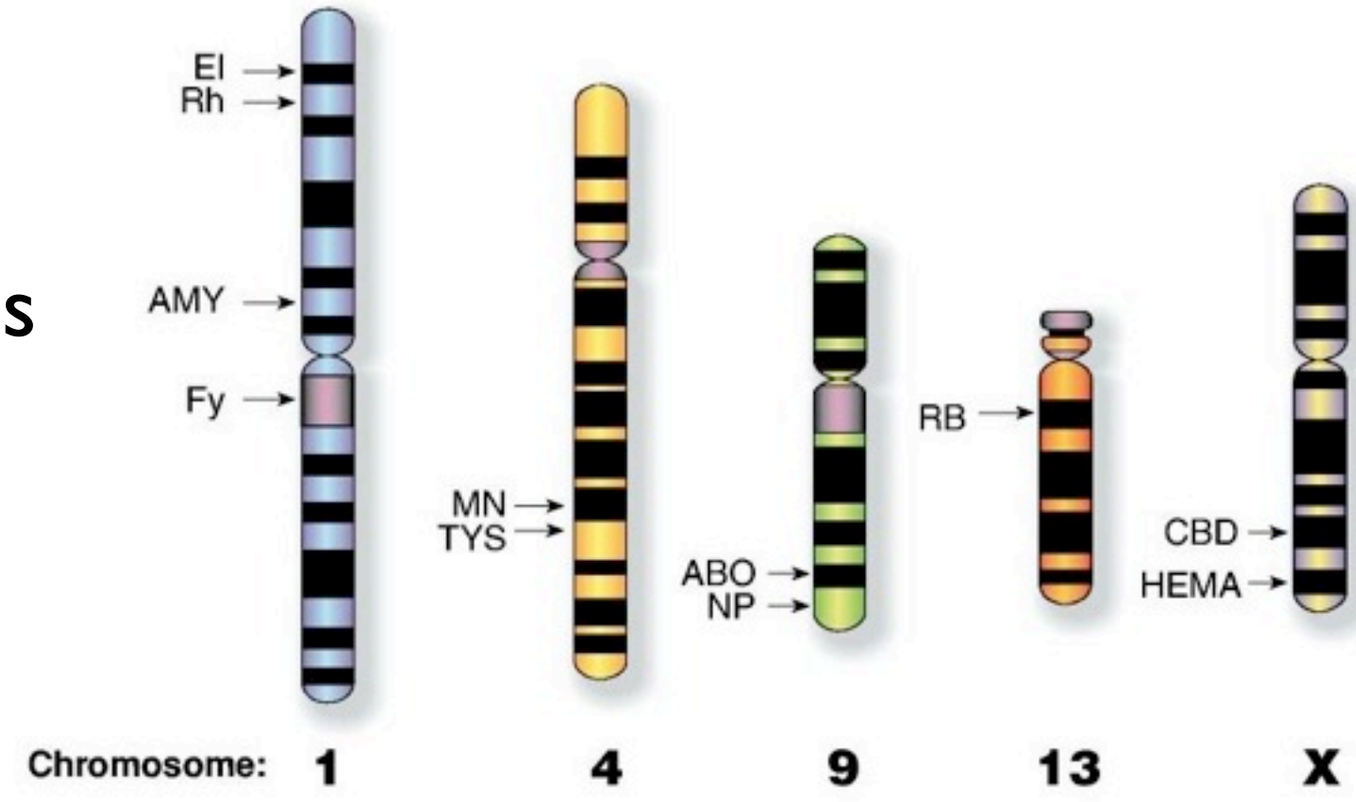
Can a male calico cat exist?

= inactivated X chromosome, also called a Barr body

No & Yes, Under normal circumstances No but if nondisjunction occurs in meiosis then a male could get 2 "X" chromosomes along with his Y, if this occurs then... Yes

Autosomal Gene Linked Traits

- **IF** there are far more genes then chromosomes,
- **and** chromosomes carry genes,
- **then** each chromosome must carry multiple genes.
- **And they do!**



GENE SYMBOLS	
ABO	ABO blood type
AMY	Production of amylase enzyme
CBD	One form of colour blindness
El	Shape of red blood cells
Fy	Duffy blood type
HEMA	Production of a blood clotting factor
NP	Structure of nails and kneecaps
Rh	Rhesus blood type
RB	Retinoblastoma (a cancer of the eye)
MN	MN blood type
TYS	Skin structure

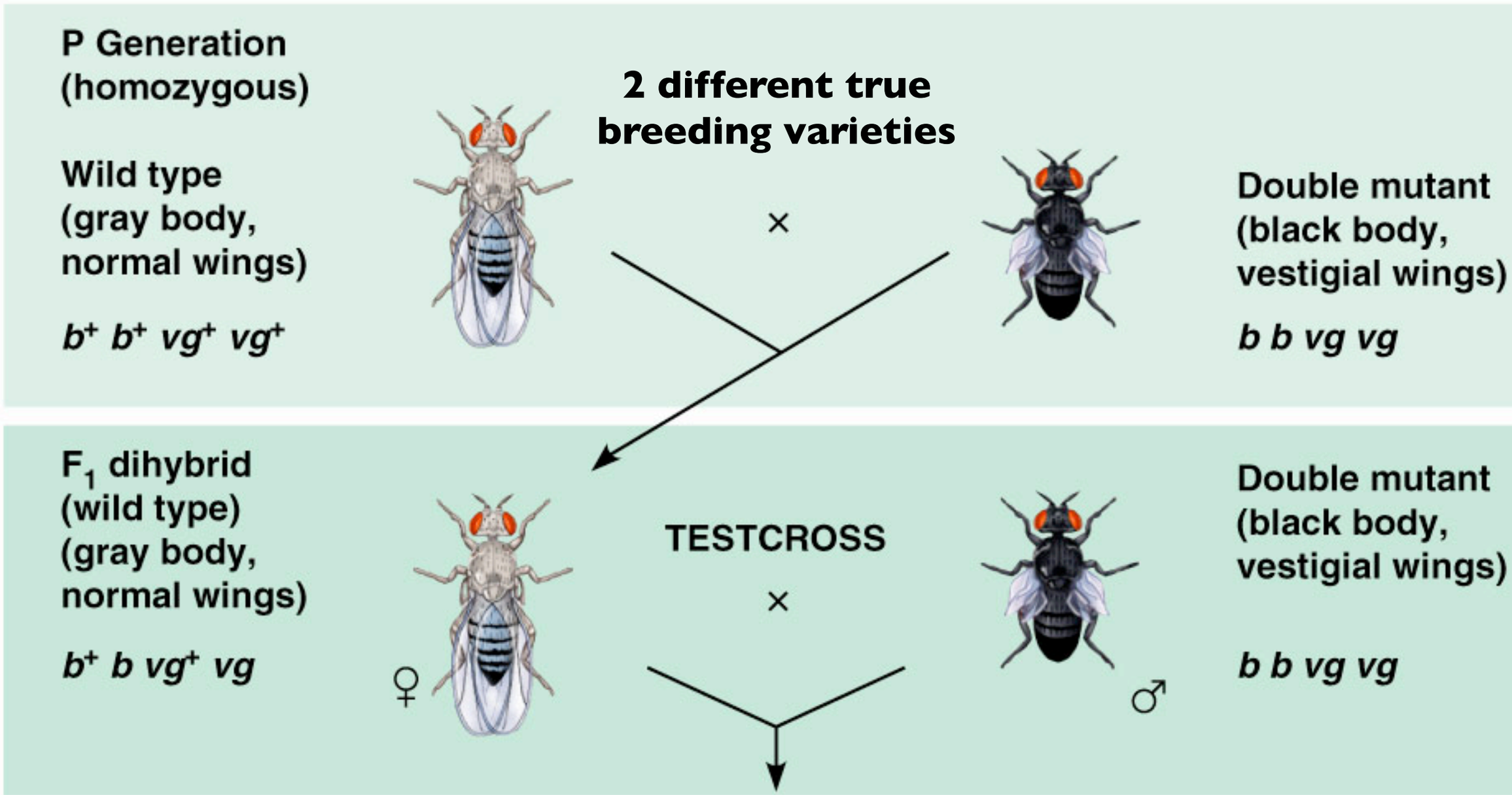
Autosomal Gene Linked Traits

- Genes on the same autosomal (*non sex chromosome*) chromosome are said to be linked.
- **Because linked genes travel together the results of breeding experiments deviate from those expected from Mendel's Law of Independent Assortment.**

Autosomal Gene Linked Traits

- Genes on the same autosomal (*non sex chromosome*) chromosome are said to be linked.
- **Because linked genes travel together the results of breeding experiments deviate from those expected from Mendel's Law of Independent Assortment.**
- Thomas Hunt Morgan, explored the idea of gene linkage by running a series of breeding experiments with fruit flies.

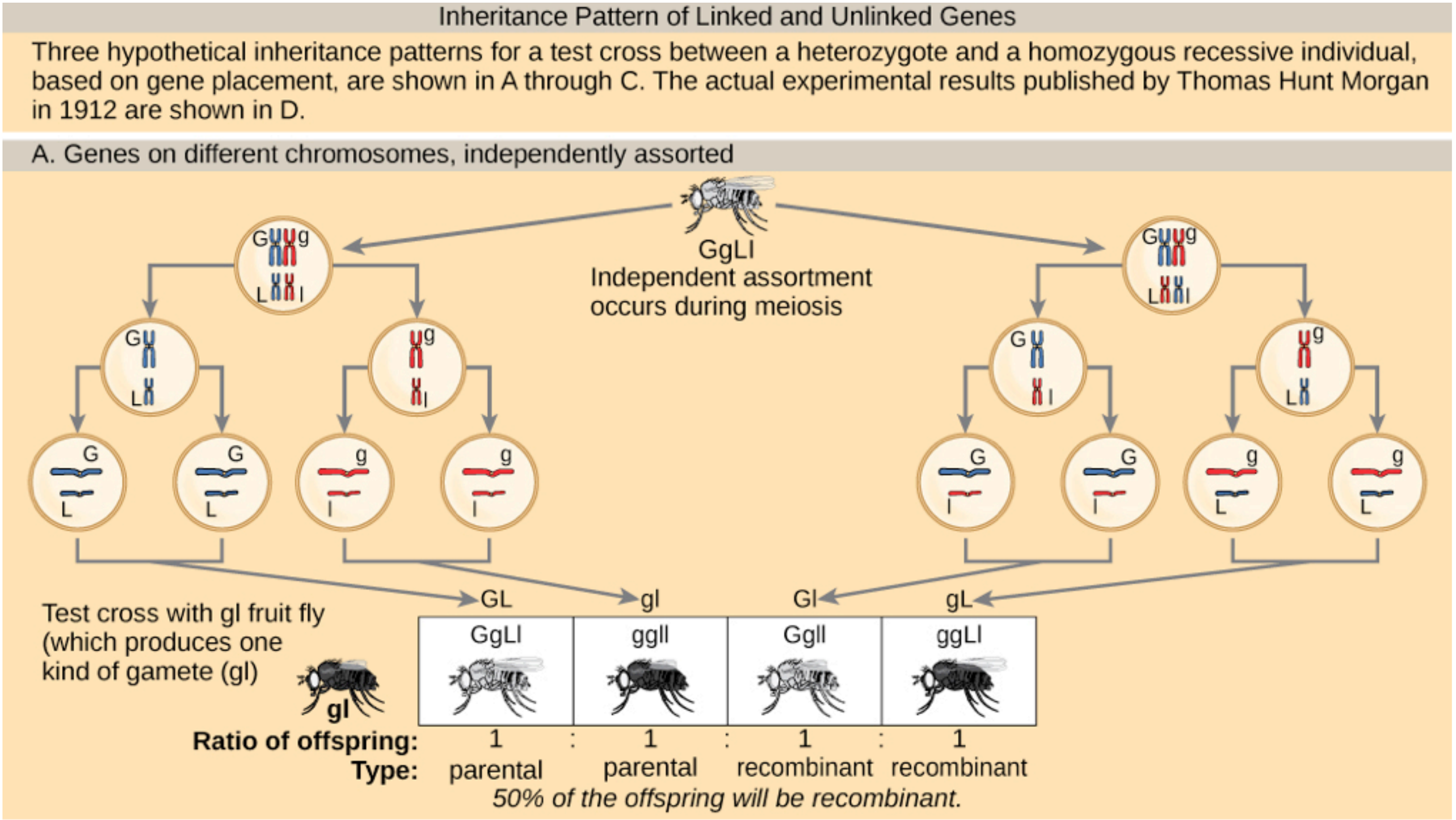
Morgan's Gene Linkage Work



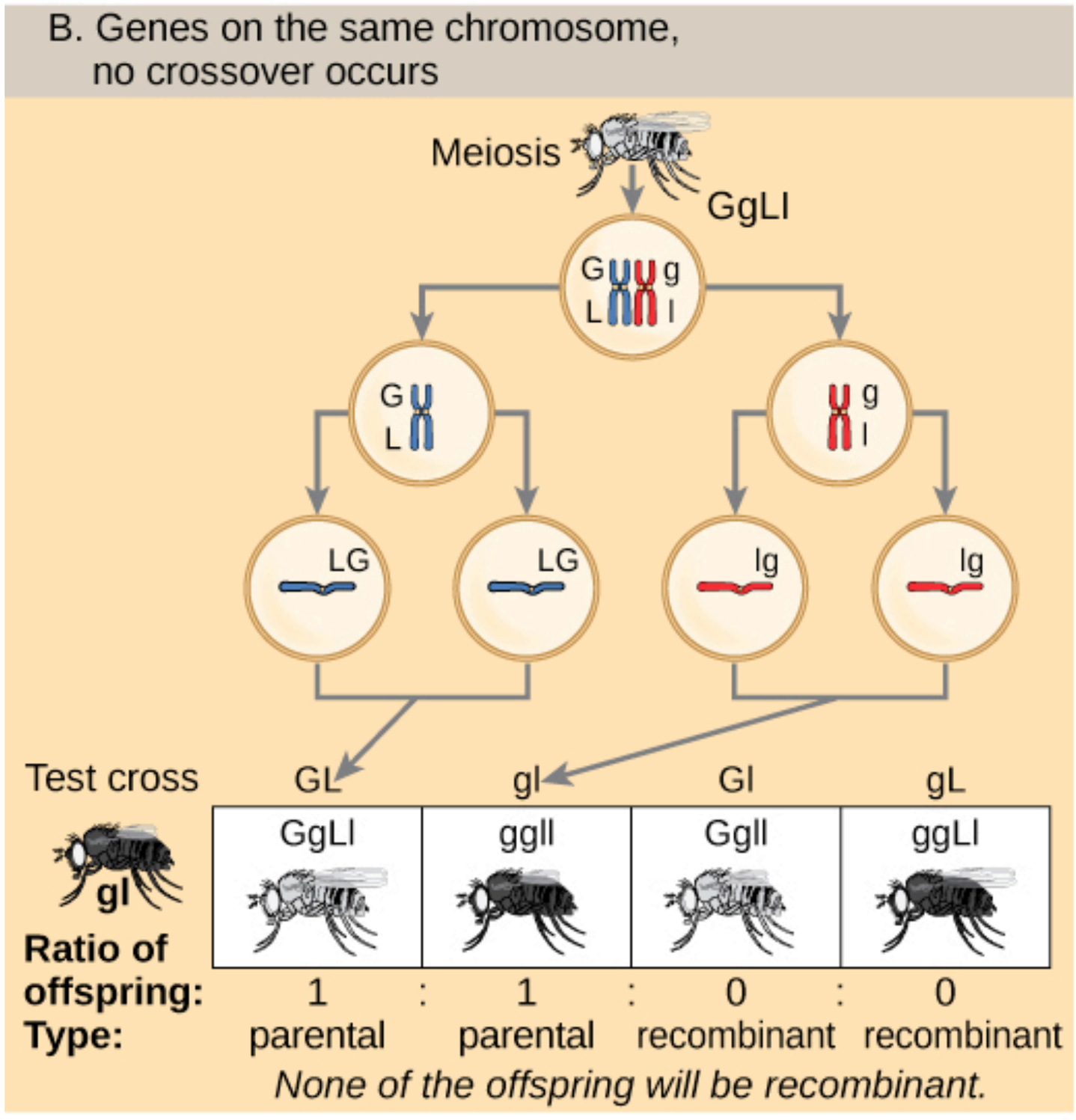
What do you think Morgan was expecting in the F2 generation?

1:1:1:1

He assumed and that the genes were on separate chromosomes and thus they would assort independently from each other resulting in the predicted 1:1:1:1 ratio



He also considered the alternative... that the genes were on the same chromosome and thus they would not assort independently from each other resulting in the predicted 1:1 ratio



So at this point Morgan is expecting either a

1:1:1:1 ratio

or

1:1 ratio

So... which did he get?

NEITHER

D. Results from Morgan's 1912 experiment

Test cross

	GL	gl	Gl	gL
	GgLl 	ggll 	Ggll 	ggLl 
Number of offspring:	965	944	206	185
Ratio of offspring:	1 :	1 :	.2 :	.2
Type:	parental	parental	recombinant	recombinant

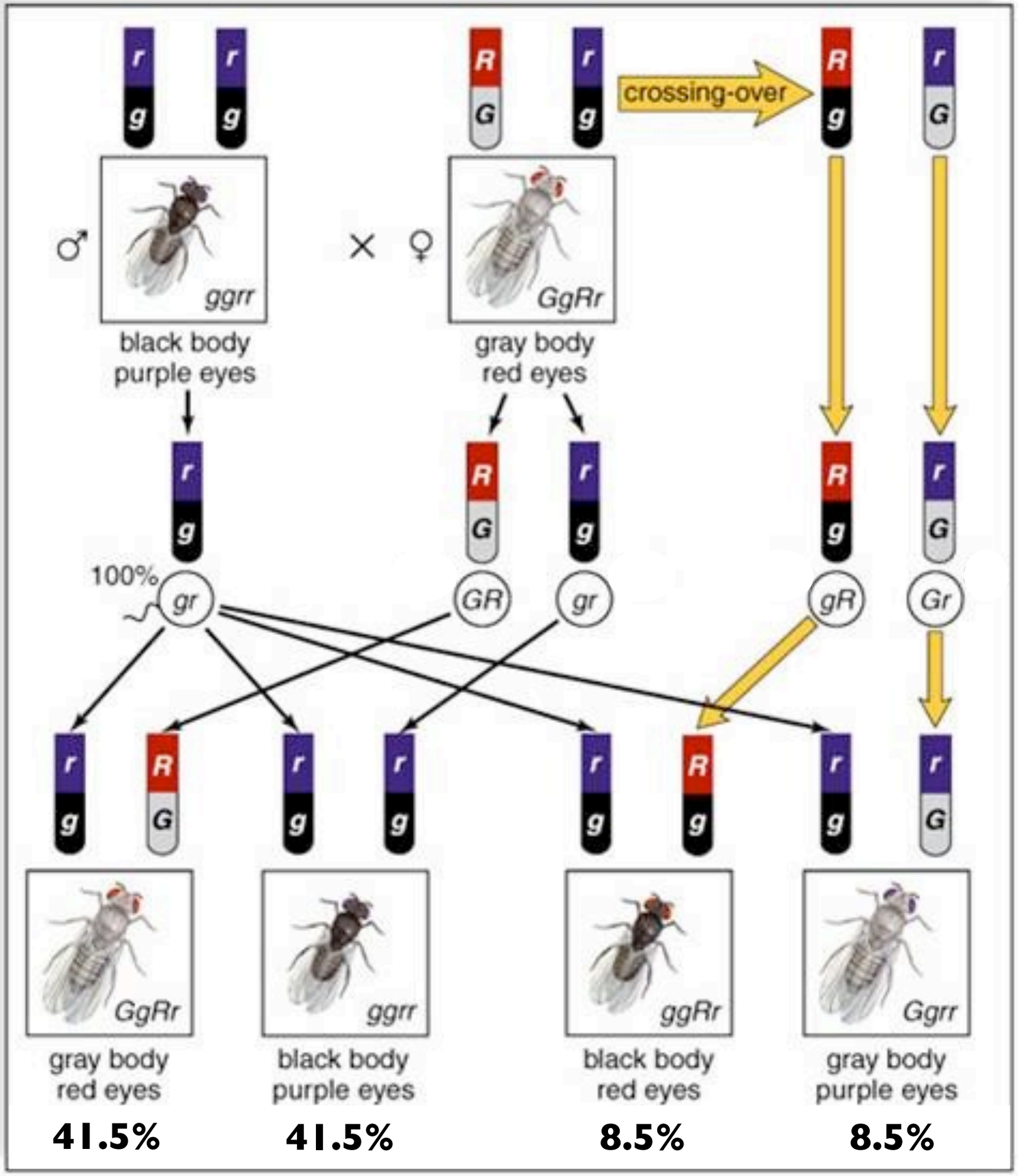
17% of the offspring are recombinant, indicating that the genes are on the same chromosome and crossover occurs some of the time.

Morgan correctly concluded that the genes were linked!
First, most offspring resembled the parents a result expected if genes were linked
Second, the results more resembled a 1:1ratio also expected if genes were linked.

BUT, How would he explain the unexpected 17% that he called recombinants?

Remember Crossing Over?

- Morgan proposed that some process must occasionally break the physical connection between specific alleles of genes on the same chromosome.
- Subsequent experiments have confirmed and demonstrated this process which is today known as **crossing over.**
- Crossing would account for the recombination of genes and consequently the 17% recombinant phenotypes in Morgan's experiment.
  - here is what it would look like...



This explanation and these results lead to further questions...

If this experiment is repeated will you always get 17% recombinants?

Why 17%? Why not some other %?

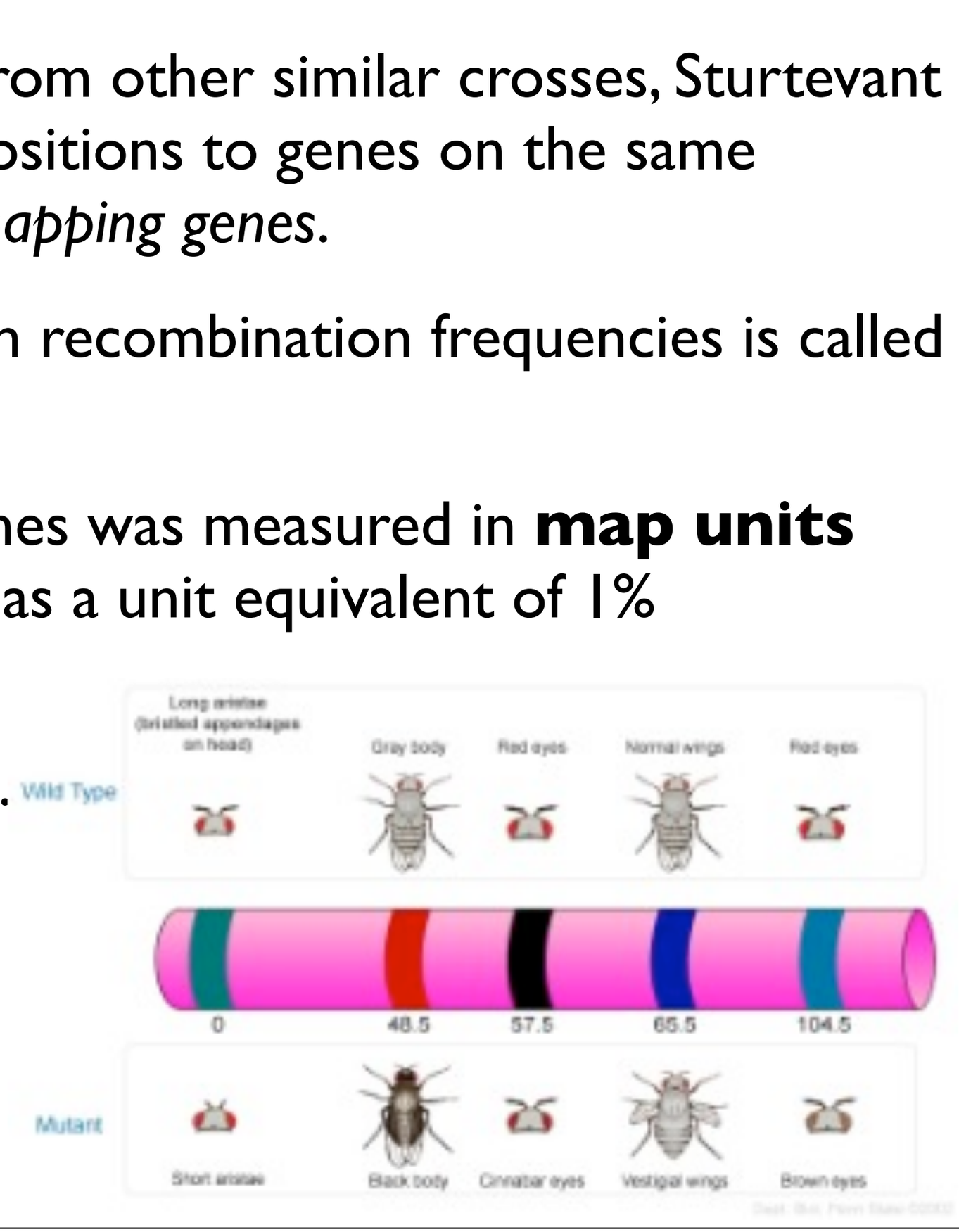
Will other linked genes give the same % of recombinants?

Recombinant Frequency

- The answers to these questions came later from one of Morgan's students none the less.
- Alfred H Sturtevant assumed that crossing over was random and hypothesized that *recombination frequency* (the 17%) was dependent upon the distance between the two linked genes.
- He reasoned and predicted that the farther apart two genes are, the higher the probability that a crossover will occur between them and therefore the higher the recombination frequency.

Gene Mapping

- Using recombinant data from other similar crosses, Sturtevant began assigning relative positions to genes on the same chromosome, he began *mapping genes*.
- A genetic map based upon recombination frequencies is called a **linkage map**.
- The distance between genes was measured in **map units** which Sturtevant defined as a unit equivalent of 1% recombination frequency.
- lets take a closer look...



Gene Mapping

APPLICATION

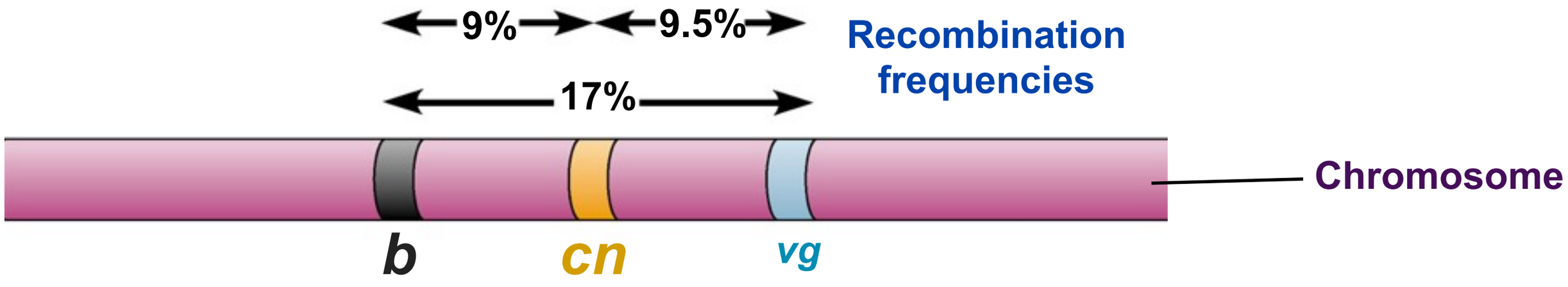
A linkage map shows the relative locations of genes along a chromosome.

TECHNIQUE

A linkage map is based on the assumption that the probability of a crossover between two genetic loci is proportional to the distance separating the loci. The recombination frequencies used to construct a linkage map for a particular chromosome are obtained from experimental crosses, such as the cross depicted in Figure 15.6. The distances between genes are expressed as map units (centimorgans), with one map unit equivalent to a 1% recombination frequency. Genes are arranged on the chromosome in the order that best fits the data.

RESULTS

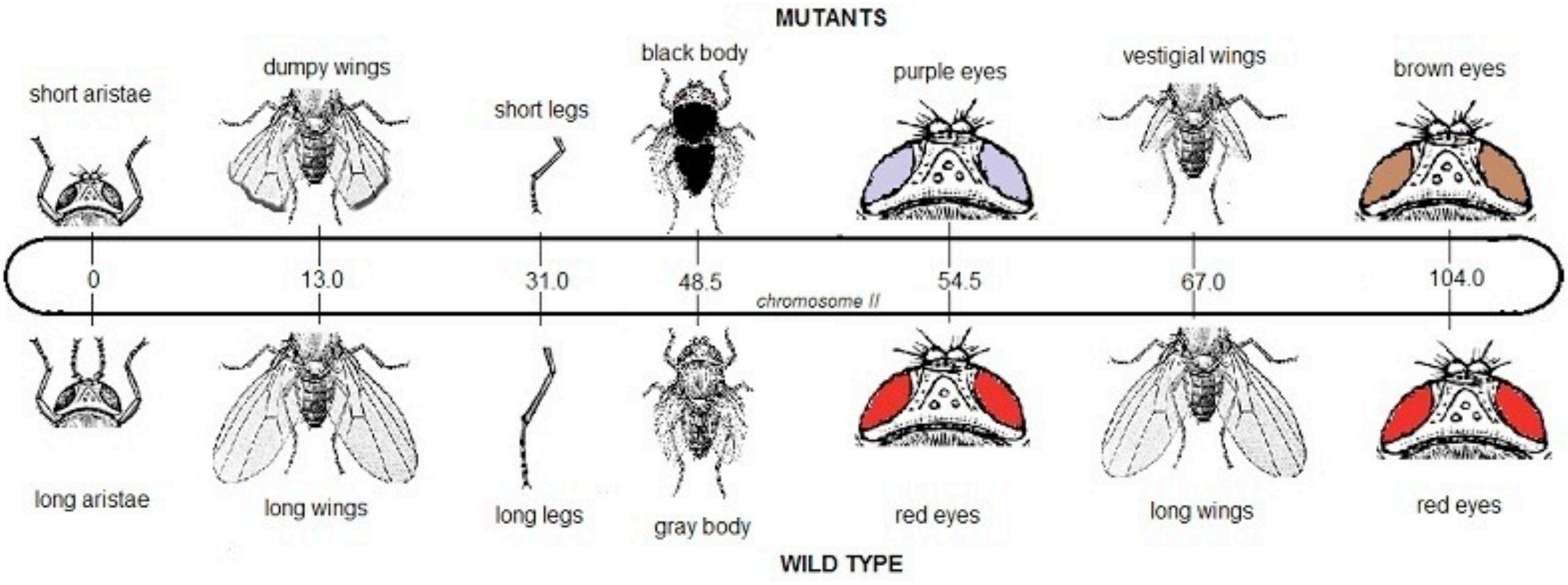
In this example, the observed recombination frequencies between three *Drosophila* gene pairs (*b–cn* 9%, *cn–vg* 9.5%, and *b–vg* 17%) best fit a linear order in which *cn* is positioned about halfway between the other two genes:



The *b–vg* recombination frequency is slightly less than the sum of the b–cn and *cn–vg* frequencies because double crossovers are fairly likely to occur between *b* and *vg* in matings tracking these two genes. A second crossover would "cancel out" the first and thus reduce the observed *b–vg* recombination frequency.

Gene Mapping

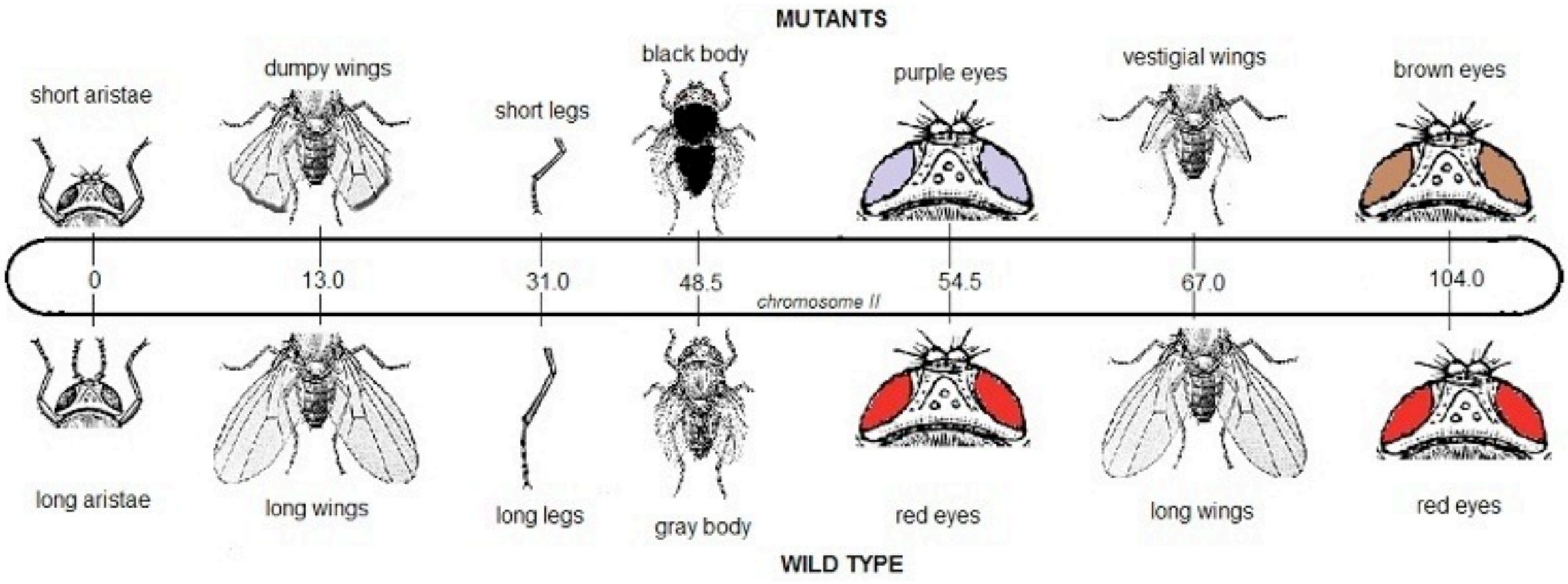
- In practice gene mapping can be a bit more complicated.
- Recall Morgan's prediction for "unlinked genes".
  - *He predicted a 1:1:1:1 ratio (25% of each phenotype)*
  - *The prediction also stated that 50% of the offspring would have a different phenotype than the parents, in other words 50% would be recombinants.*
- A problem arises because two genes far apart are virtually guaranteed to cross over resulting in 50% recombination frequency.
- **SO... When we get 50% recombinants we can not tell if they are assorting independently on different chromosomes OR whether they are far apart on the same chromosome.**



Notice **body color** and **eye color** are more 50 map units away from each other thus your breeding experiment looked at these two traits you would 50% recombinants and could not tell if they are assorting independently on different chromosomes OR whether they are far apart on the same chromosome.

However, if you cross **eye color** and **wing length** then you would get 37% recombinants, evidence that the genes controlling these traits are on the same chromosome, they are LINKED.

Now cross **body color** and **wing length**, you would get 18.5% recombinants, evidence that the genes controlling these traits are on the same chromosome, they are LINKED.



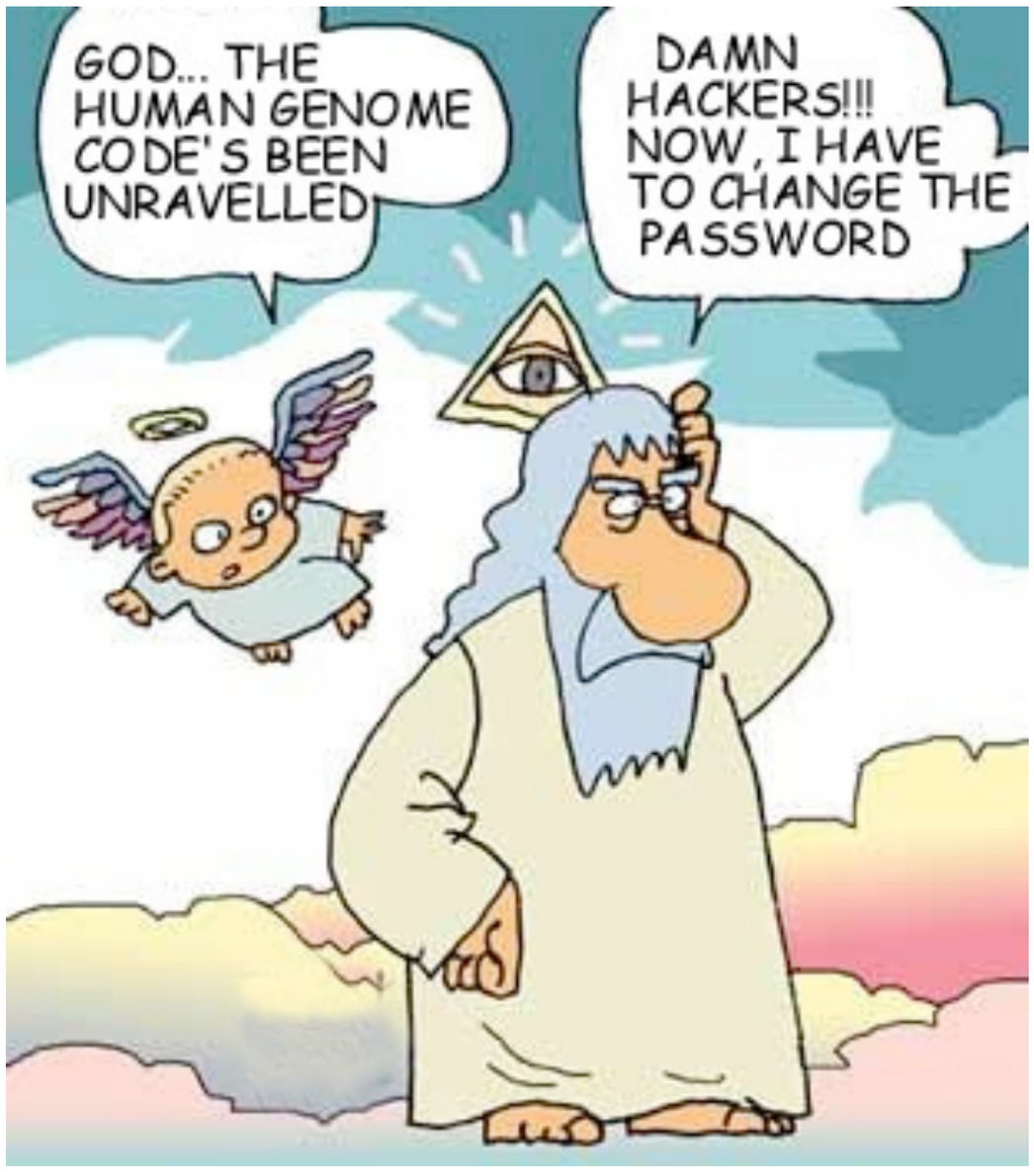
IF the genes for **eye color** and **wing length** are linked **AND** the genes for **wing length** and **body color** are linked **THEN** the genes controlling **eye color** and **body color** are on the same chromosome, they are **LINKED**.

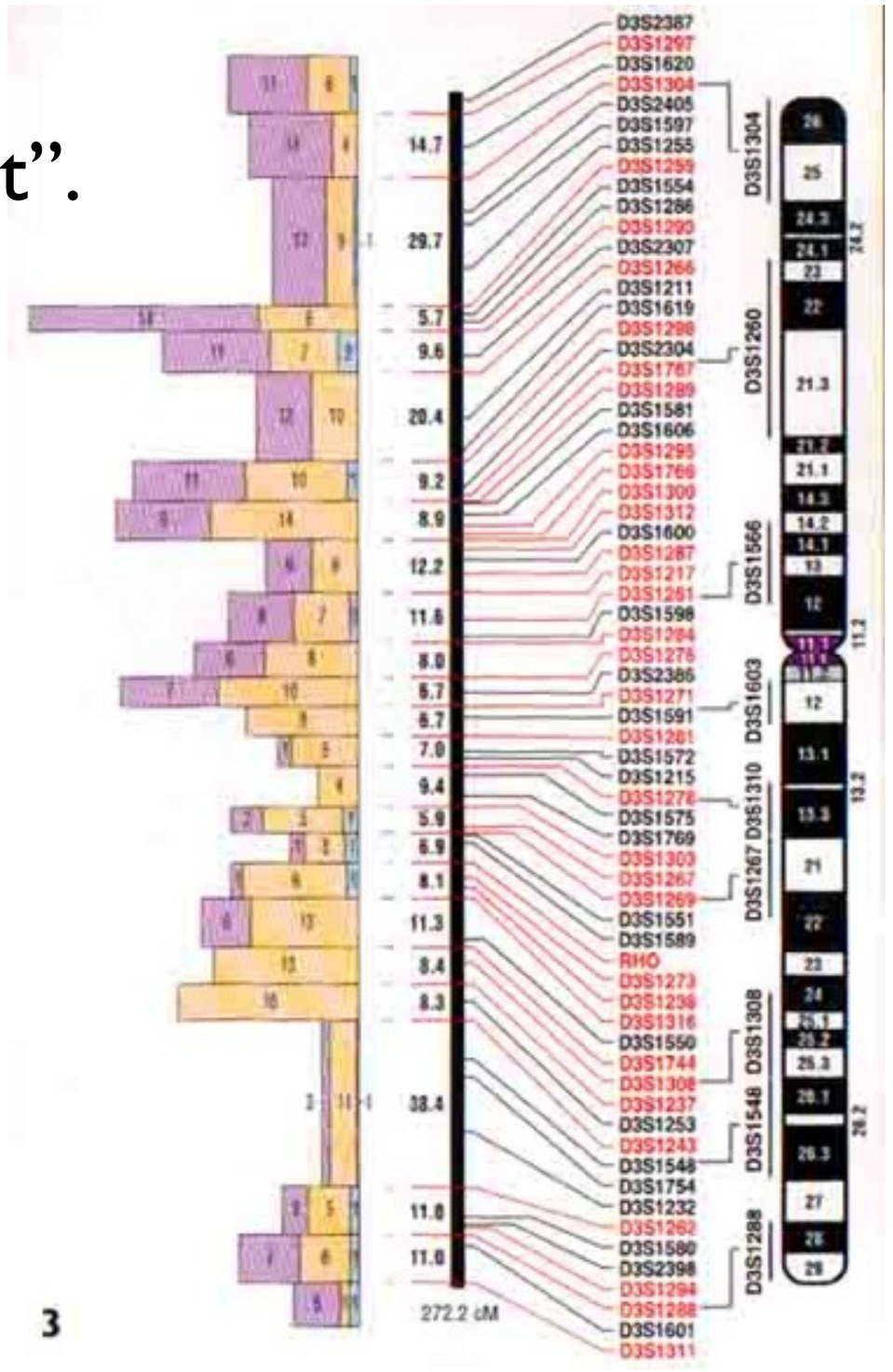
Human Genome Project

- Gene mapping has come a long way since.
- In 1990, an international effort began to sequence the entire human genome.
- The Goal was to identify and map from a physical and functional standpoint the nearly 25,000 genes from the 3 billion bases found in human DNA samples.
- The potential applications and benefits would include a better understanding of human evolution and the treatment of disease.

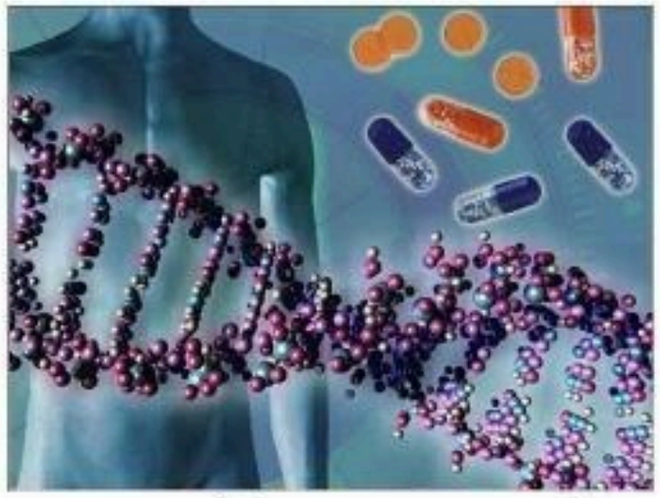
Human Genome Project

- The project, a public and private effort, was announced complete in April of 2003.
  - Today there is even an "App for that".





Human Genome Project through its sequencing of the DNA can help us understand diseases including genotyping of specific viruses to direct appropriate treatment; identification of oncogenes and mutations linked to different forms of cancer; designing medications and predicting its response better; advancement in forensic applied sciences; biofuels and other energy applications; agriculture, livestock breeding, bioprocessing; risk assessment; bioarcheology, anthropology, evolution. Another proposed benefit is the commercial development of genomics research related to DNA based products, a multibillion dollar industry. [genomics.energy.gov]



Human Genome Project vs F-35 Project

One of the largest projects in the history of science

Cost: $3,000,000,000
$9 per US citizen

Status: Completed ahead of schedule.

Benefit To Humanity: Helps us avoid disease, discomfort, aging and death. The commercial development of this technology has already generated $140 for every $1 spent on the project.

It can take off like a helicopter*

Cost: $1,904,000,000,000 (and counting)
$6110 per US citizen

Status: Doesn't work. The plane went into production years before being fully designed or tested. $8 billion has already been spent maintaining a growing stockpile of non-functional planes. The F-35 may never see combat but continues to be produced.

Benefits To Humanity: It's a plane that can take off like a helicopter*

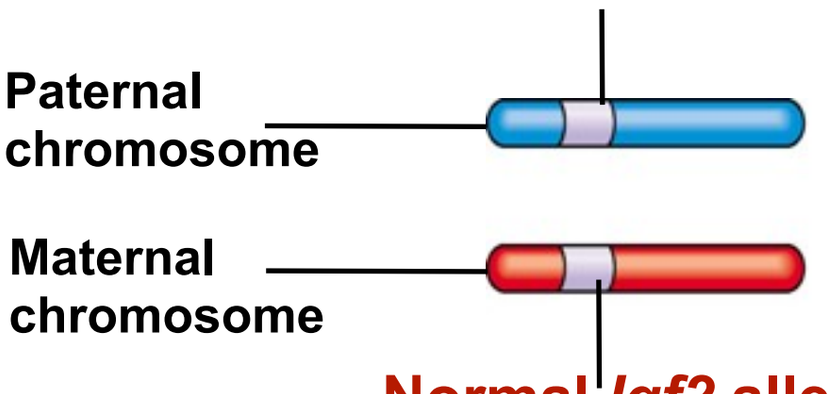
***this feature is currently unavailable**

Genomic Imprinting (mammals)

- For most inherited traits the given allele would will have the same effect whether it comes from the mother or the father.
- In recent years, geneticists have uncovered 2 to 3 dozen traits where the phenotype not only depends on the alleles but also which parent donated them.
- **Genomic Imprinting**- describes inheritance where the phenotype varies depending on which parent donated which allele.
  - *most imprinting occurs in autosomes*

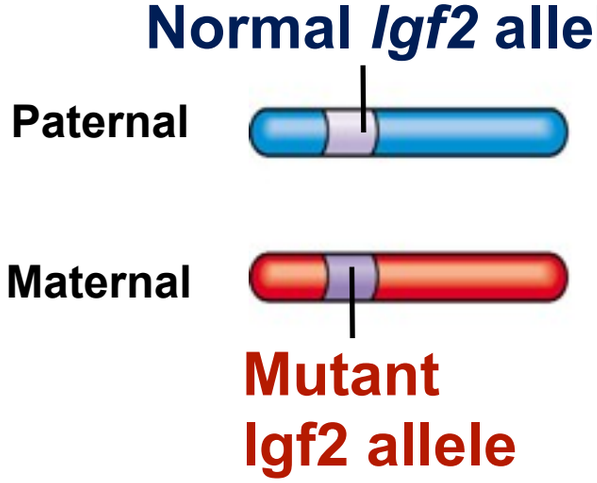
Genomic Imprinting

- Genomic Imprinting occurs during gamete formation and results in the silencing of certain alleles.
    - *roughly similar to X inactivation where a chromosome is silenced, here a single allele is silenced.*
- Since sperm and eggs imprint differently the zygote only ever expresses one of the two alleles.
- As the zygote divides each daughter cell carries the same imprint, only when that sexually mature organism makes its own gametes will the old imprints be erased new imprints be made.
    - *All members of the same species the same genes are imprinted in the same way.*



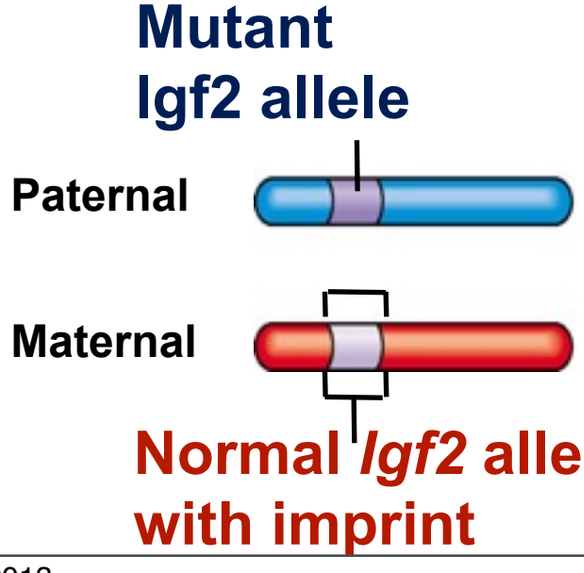
A wild-type mouse is homozygous for the normal *Igf2* allele.

Wild-type mouse (normal size)



When a normal Igf2 allele is inherited from the father, heterozygous mice grow to normal size.

Normal size mouse



But when a mutant allele is inherited from the father, heterozygous mice have the dwarf phenotype.

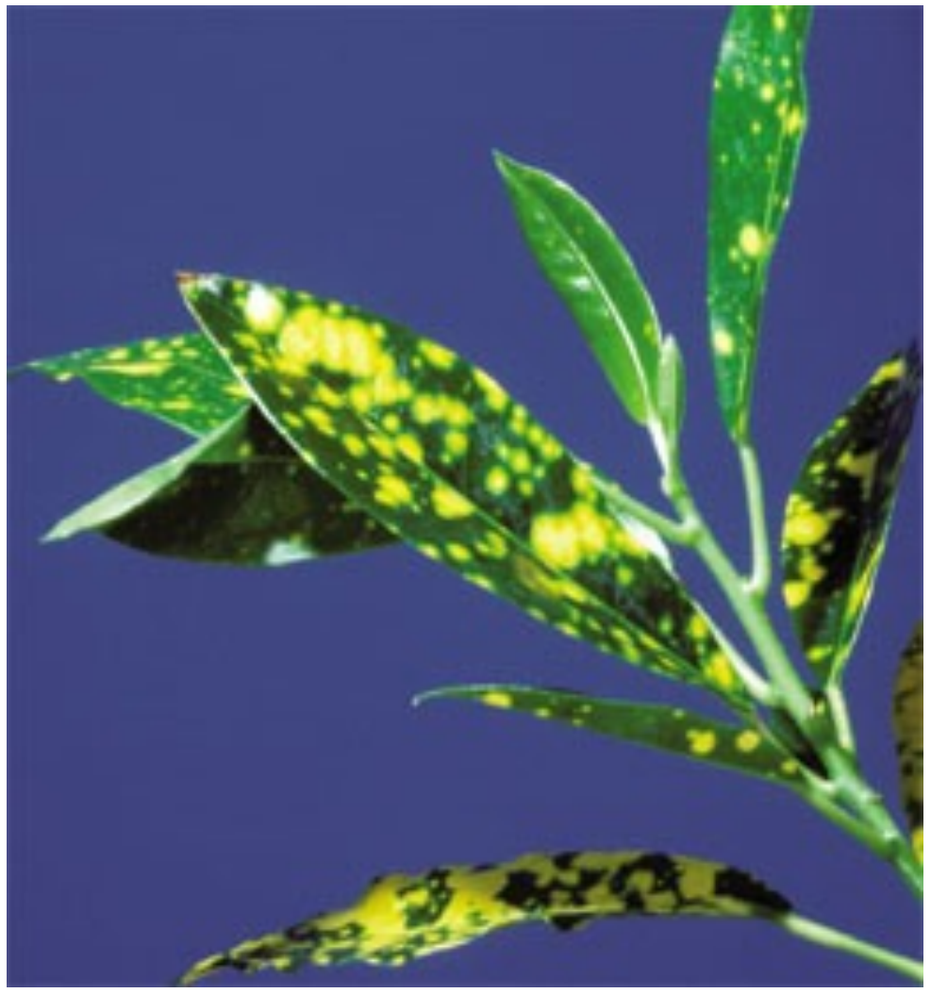
Dwarf mouse

Genomic Imprinting

- Genomic Imprinting accomplished through DNA methylation, a process we will learn about later.
  - *in most cases DNA methylation turns off genes but here it actually turns on the genes (another story all together).*
- Although genomic imprinting occurs in few genes, it plays critical roles in embryological development.
  - *Apparently a single gene dose is key in these cases.*

Inheritance of Organelle Genes

- Not all genes are located in the nuclear chromosomes, or even the nucleus they are located in organelles.
  - *these genes are often called extranuclear or cytoplasmic genes.*
  - *specifically these genes are located in the mitochondria and chloroplasts.*
- These genes do not follow Mendelian Laws of Inheritance.
  - *The first of this came in 1909, when a German scientist, Karl Correns noticed yellow/white spots on otherwise green leaves.*
  - *He later determined that the inheritance of the spots was strictly due the eggs/mother.*

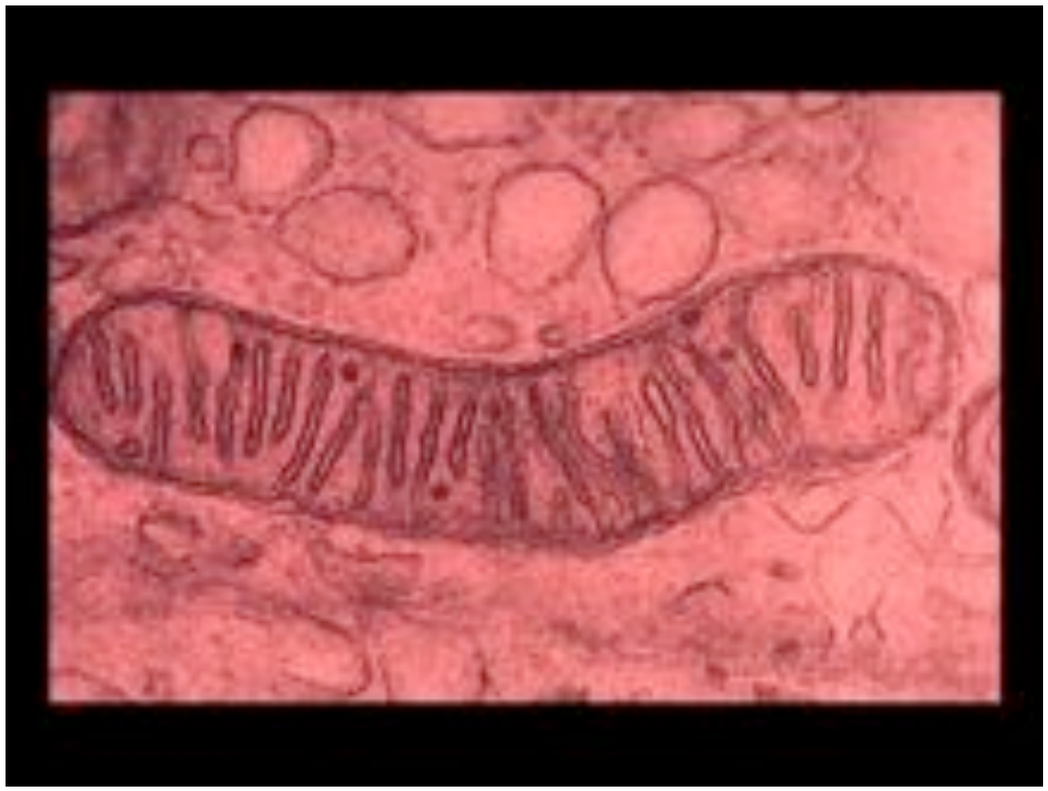


Turns out the spots are due to a mutations in plastid genes that control pigment.

Plastid genes are located in the chloroplast's genes

Since sperm only contribute the haploid set of chromosomes, the egg supplies all organelles including the chloroplasts

The egg may contain plastids with different alleles, these plastids are randomly distributed to daughter cells, the color variation is due to the ratio of wild-type & mutant plastids in various tissue



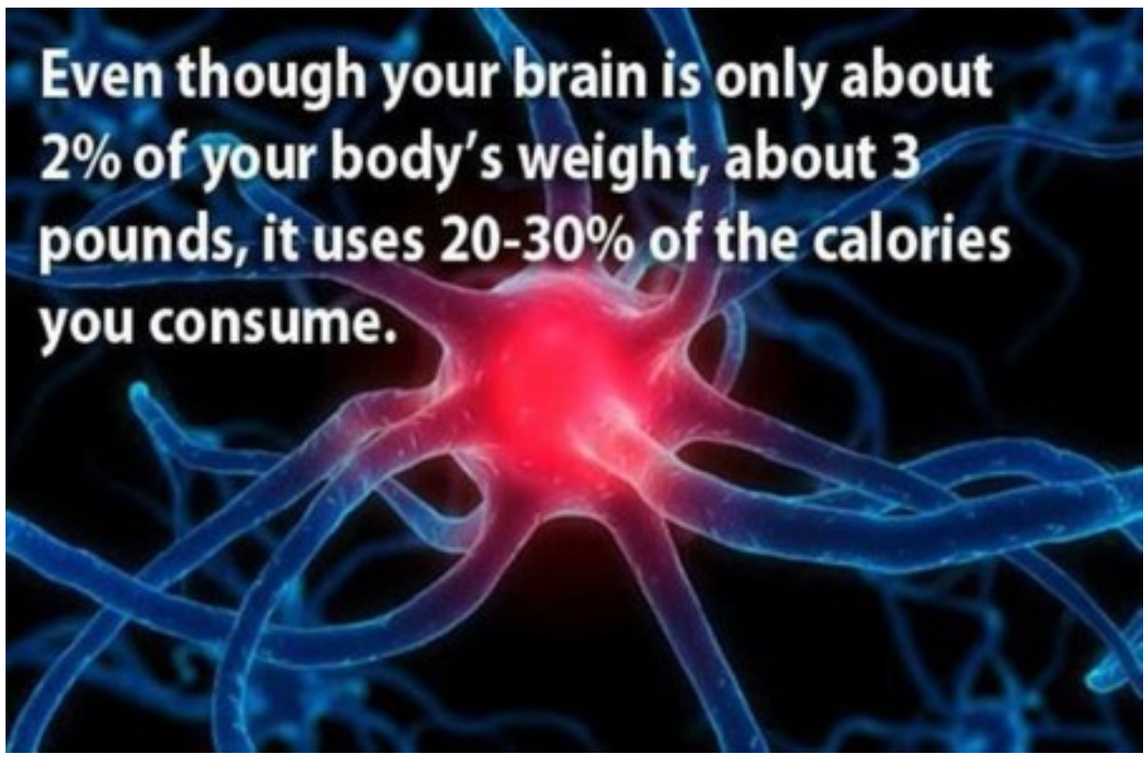
Maternal inheritance is also the rule for the mitochondria, the egg supplies the mitochondria for the zygote.

What do you think most mitochondrial genes code for?

proteins that make up the electron transport chain and the ATP synthase, components of oxidation phosphorylation

What tissues would be most affected by mutations in mitochondrial DNA? What general effects would you expect?

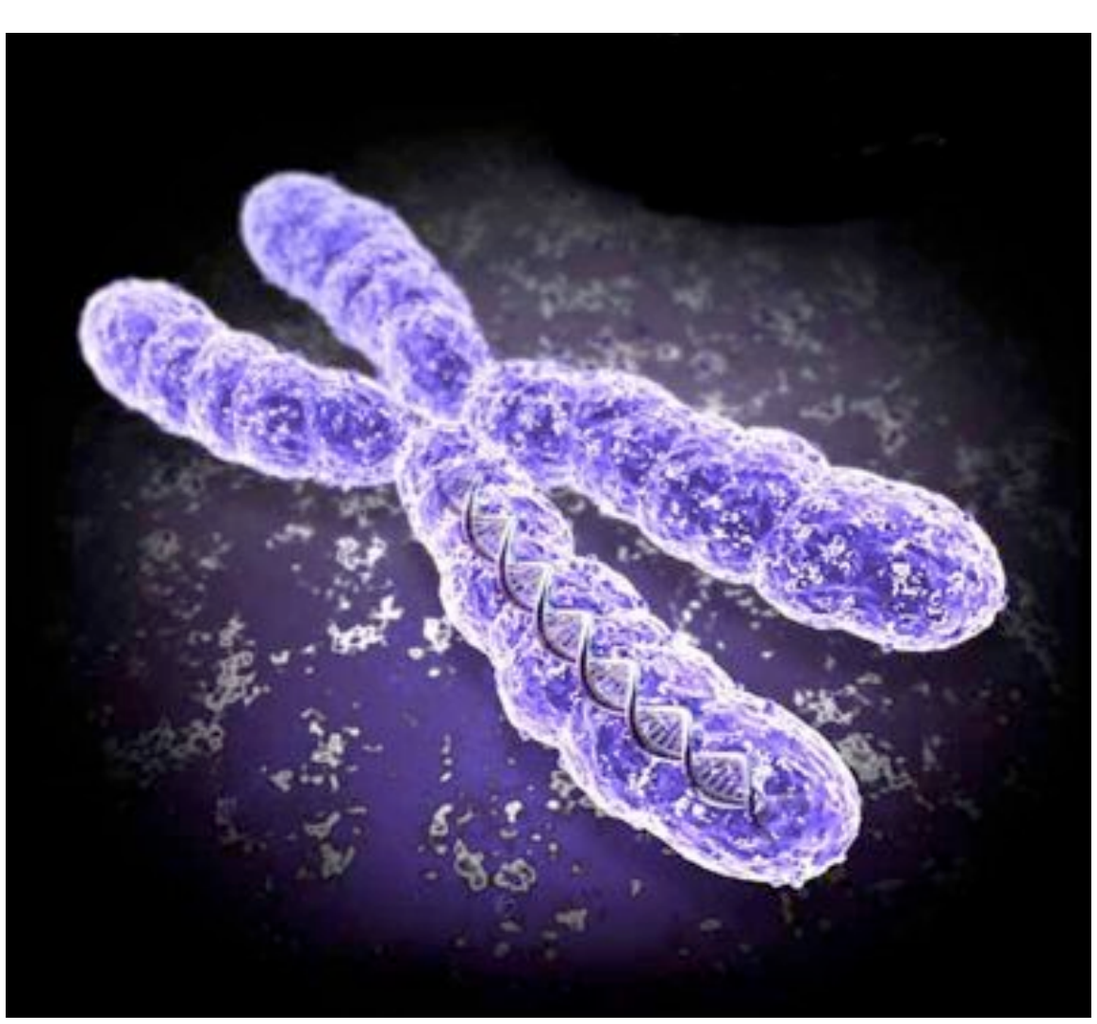
muscles and the nervous system, weakness, intolerance to exercise, muscle deterioration



Human Genetics

IV.

Main Idea: Human traits follow Mendelian patterns of inheritance but studying human inheritance has its own unique obstacles and tools to overcome those obstacles.



PREFACE

- Peas and fruit flies are convenient subjects for genetic research, humans are not.
  - Humans have a long generation span (~ 20 years)
  - Humans produce few offspring to analyze.
  - Breeding humans is unethical.

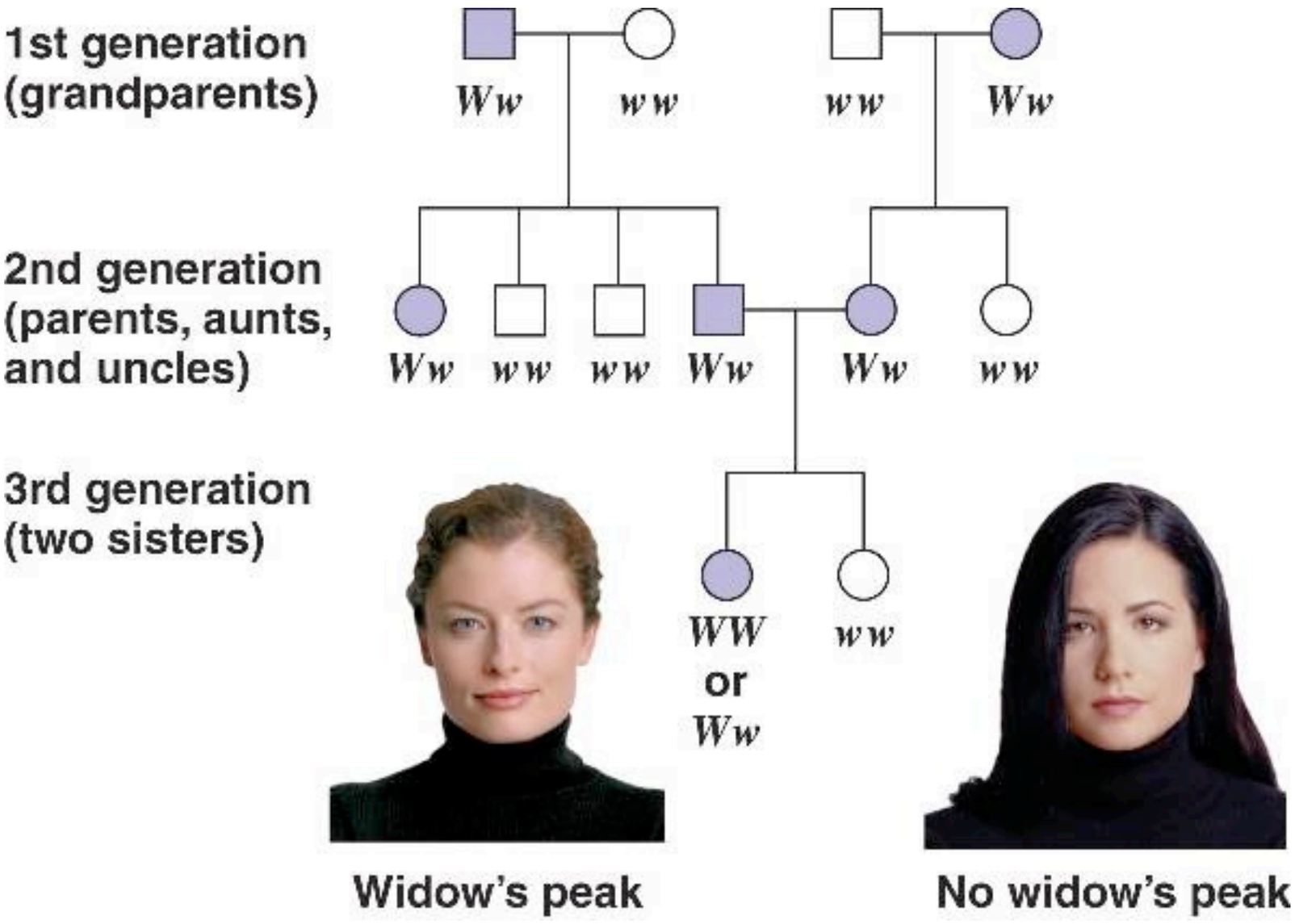
- In spite of these difficulties our desire to understand human inheritance is strong.
- Much of our desire is driven by need to understand human disease and consequently the potential to cure those diseases.
- New techniques and discoveries have lead to our increasing body of knowledge in human genetics.

Pedigrees

- Unable to manipulate human mating, geneticists analyze matings that have already occurred.
- They do so by collecting information about a families history for a particular trait and assembling that information into a "family tree".
- The family tree describing the trait(s) of parents and offspring across generations is called a **pedigree**.
- *If the punnet square was our tool to look into the future, then the pedigree is our tool for looking into the past.*

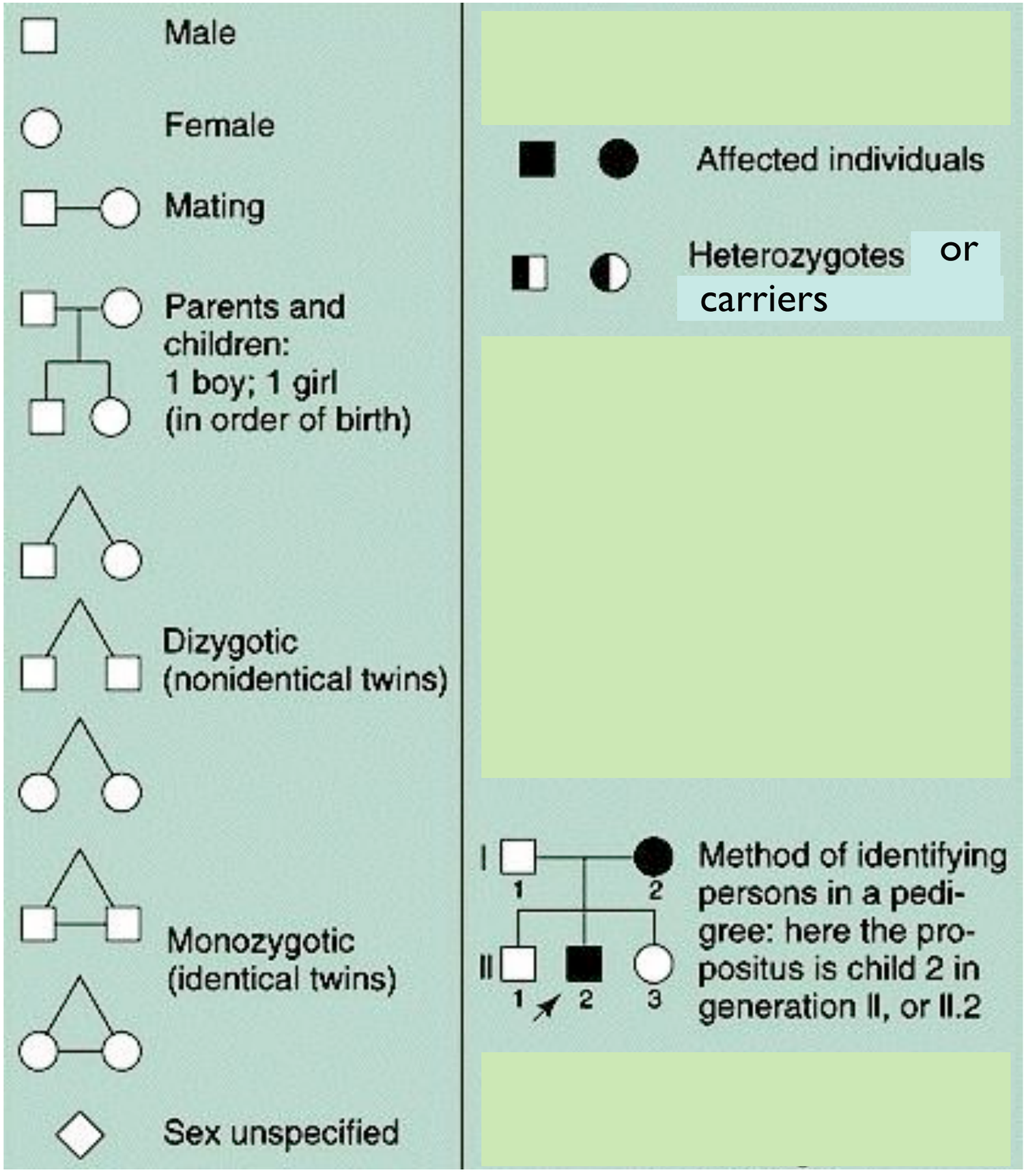
Pedigrees

- As is this case with many tools, becoming proficient with a tool requires a knowledge of its parts and lots of practice.
- Let's start by taking a look at a pedigree.

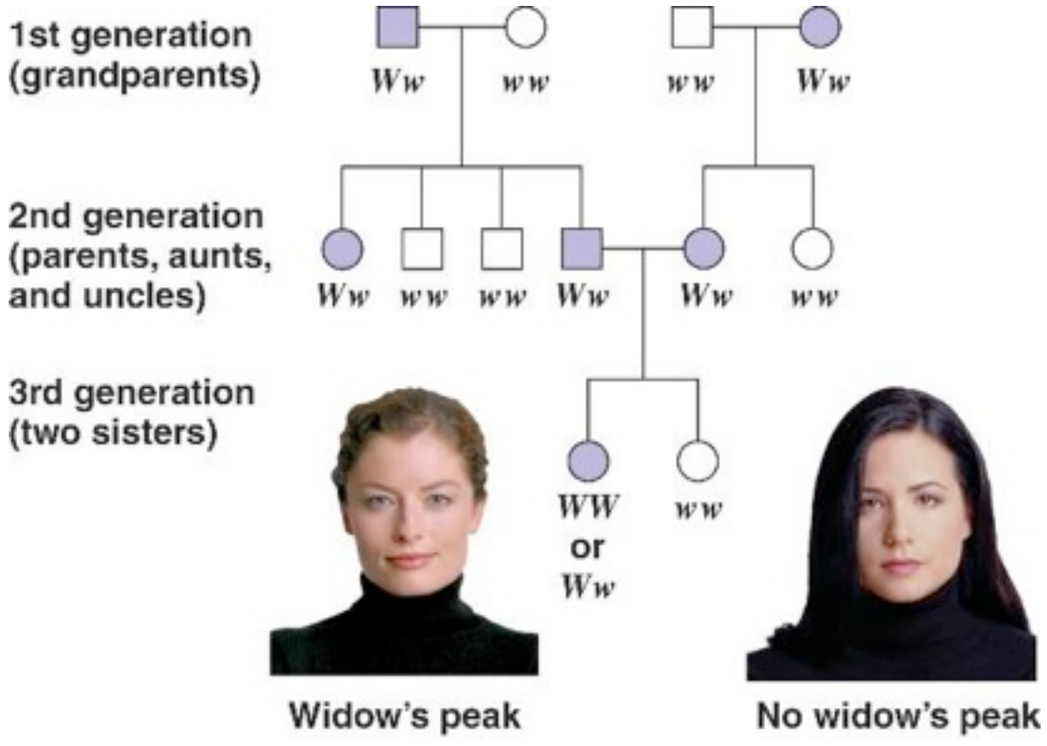


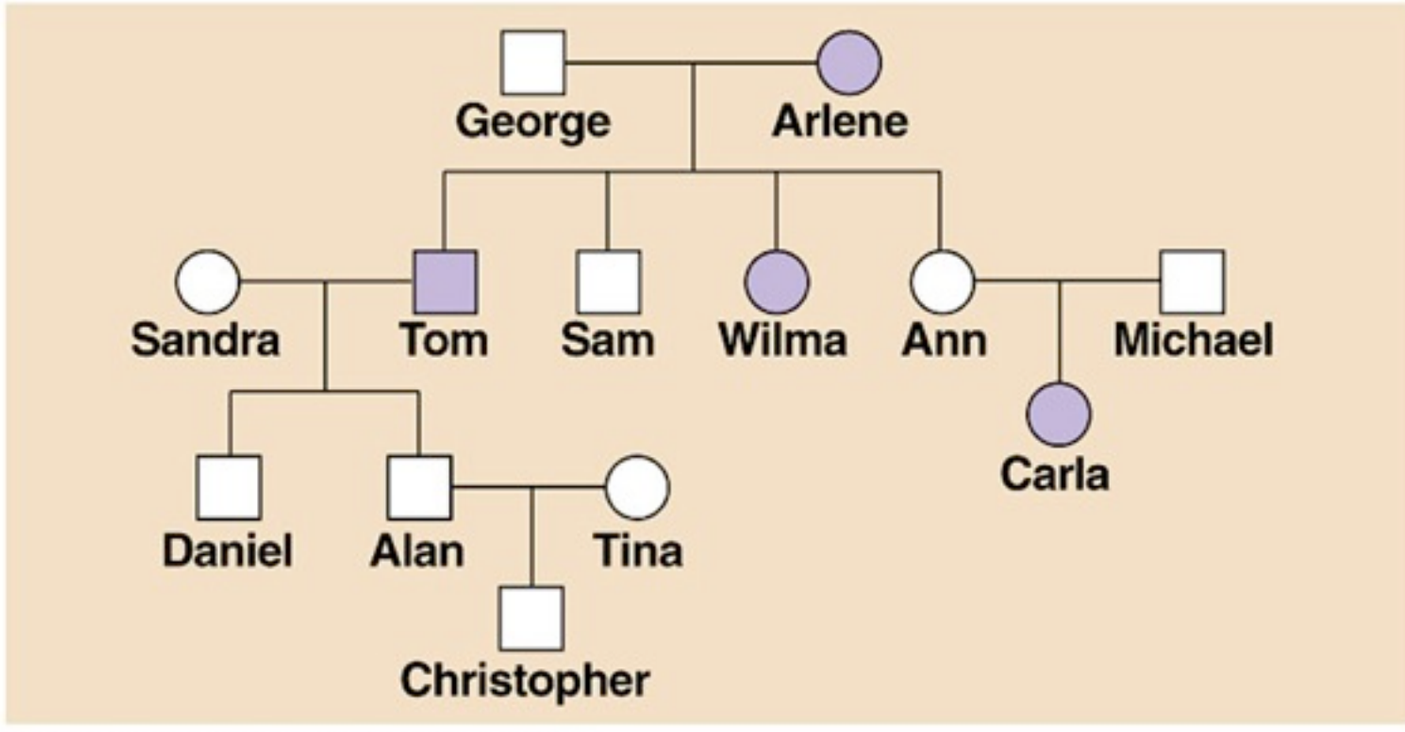
Every pedigree is unique but they will all look similar and use the same types of symbols

- Below is a table depicting the common symbols and their meanings.
- Sometimes you will encountered slight variations but fundamentally they are the same.
- Also, I have blocked out some symbols that are beyond the scope of this class, the rest you may encounter this year.



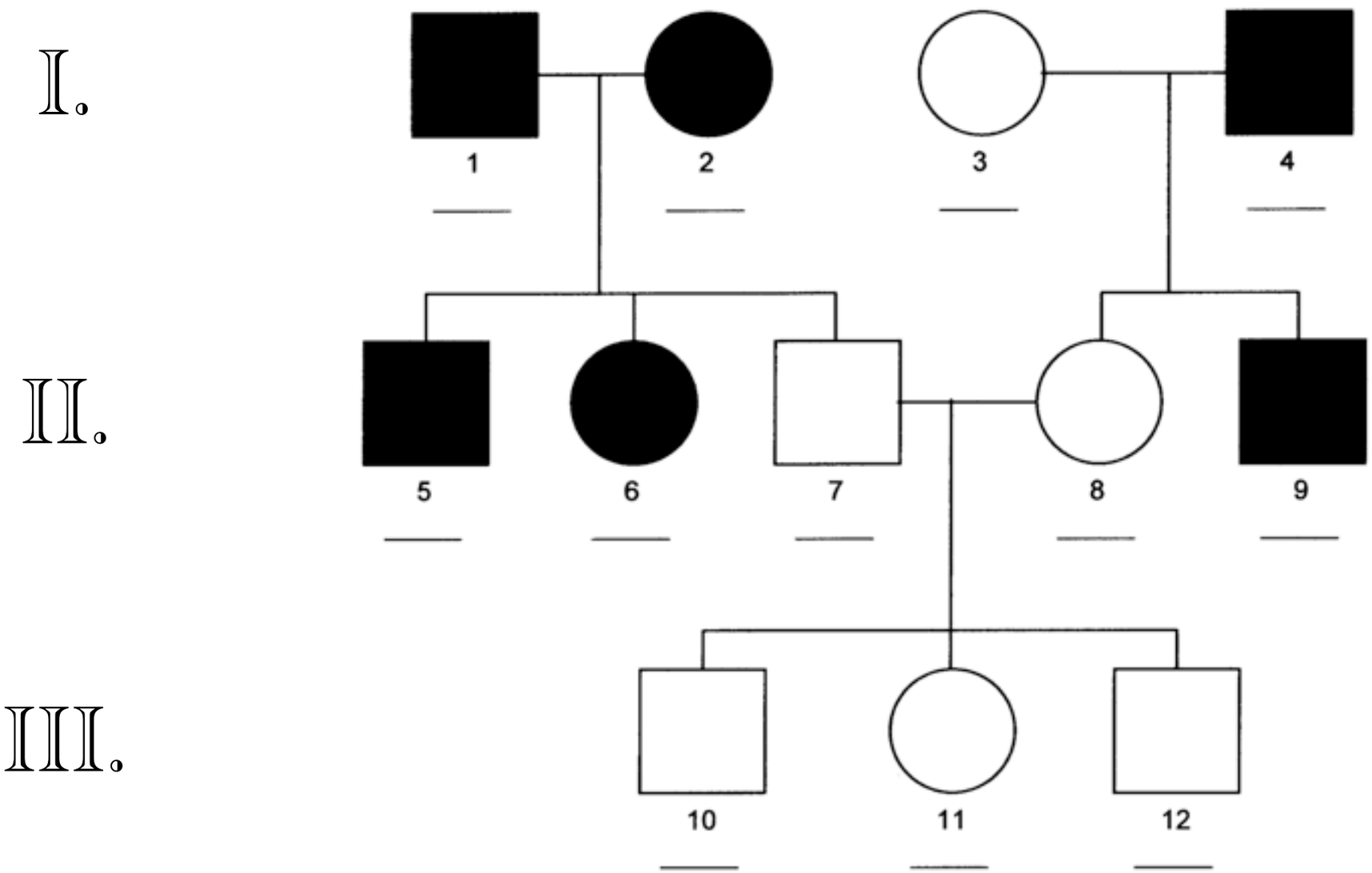
- Most pedigrees you encounter will not look the one on the left but rather like the one on your right.
- In order to read and interpret a pedigree and then answer questions using a pedigree you will need to know:
  - 1. the meanings of the symbols
  - 2. an understanding of simple Mendelian inheritance
  - 3. the rules of probability and be able to use them





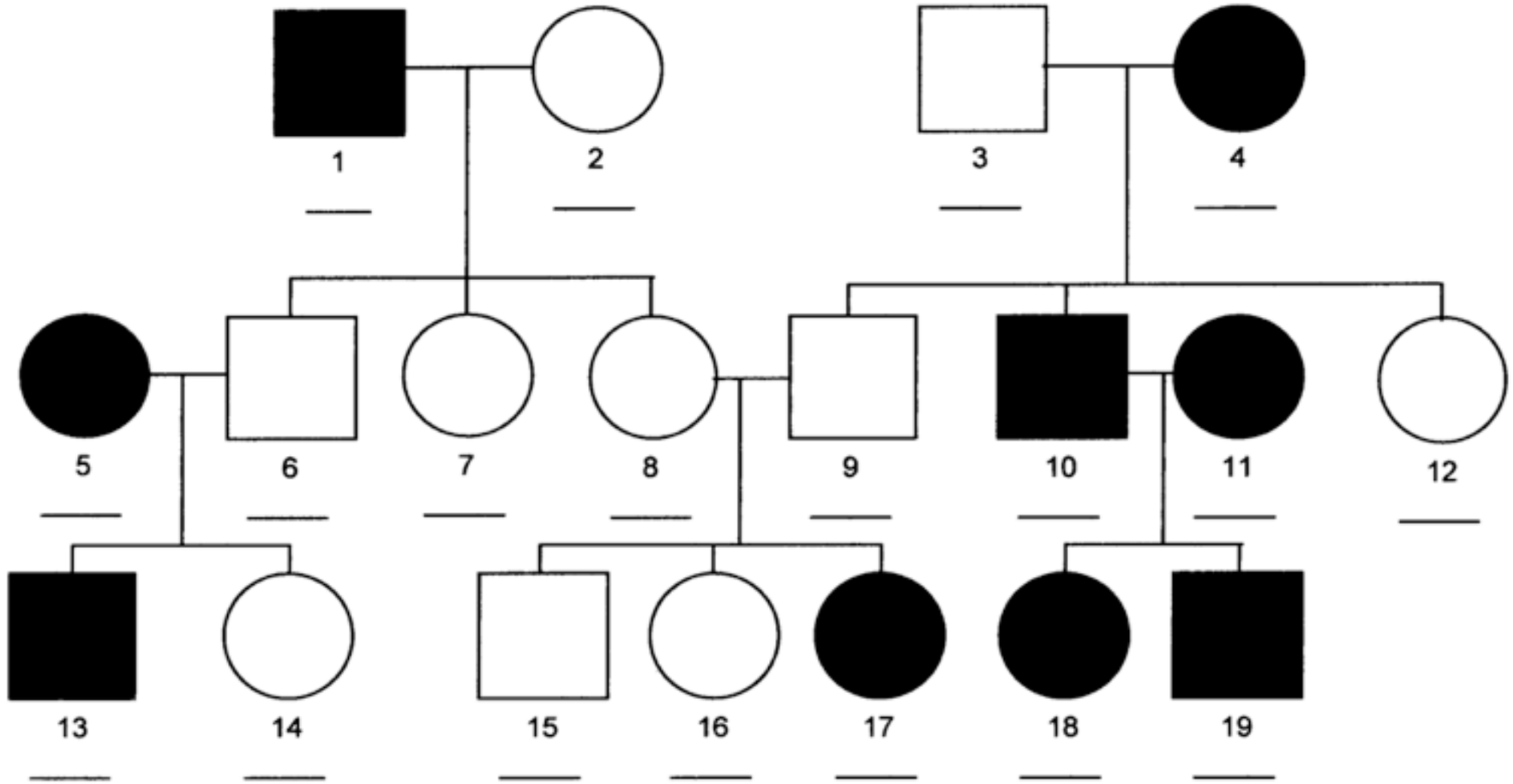
- **Fortunately the pedigrees you will encounter in this class are limited.**
  - They will follow Mendelian Laws of Inheritance.
  - They will likely track traits that exhibit complete dominance.
  - They will be smaller and more manageable.
  - They will likely track one of four possible types of traits
    - autosomal dominant
    - autosomal recessive
    - sex-linked dominant
    - sex-linked recessive

Autosomal Dominant



1. affected offspring have at least one affected parent
2. trait passed directly from affected individual to affected individual
3. trait is present in each generation
4. about 1/2 of the progeny of an affected individual exhibit the trait (rare trait)
5. two affected individuals may have an unaffected child (trait may not breed true)
6. both sexes are equally affected

AUTOSOMAL RECESSIVE

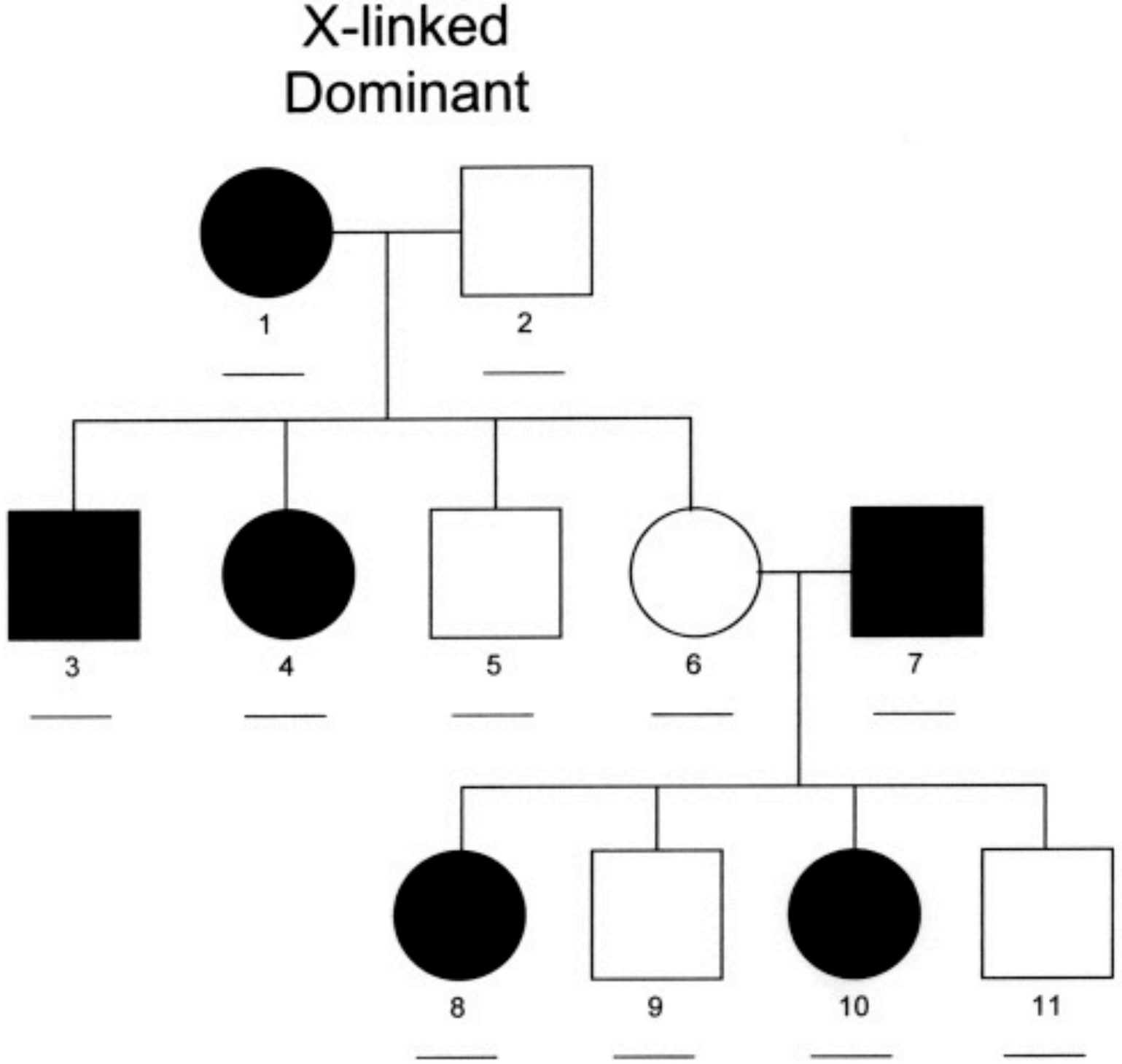


1. trait appears in progeny of unaffected parents
2. about 1/4 of a sib group is affected
3. the trait breeds true
4. both sexes are equally affected
5. some degree of inbreeding is present (rare trait)

I.

II.

III.

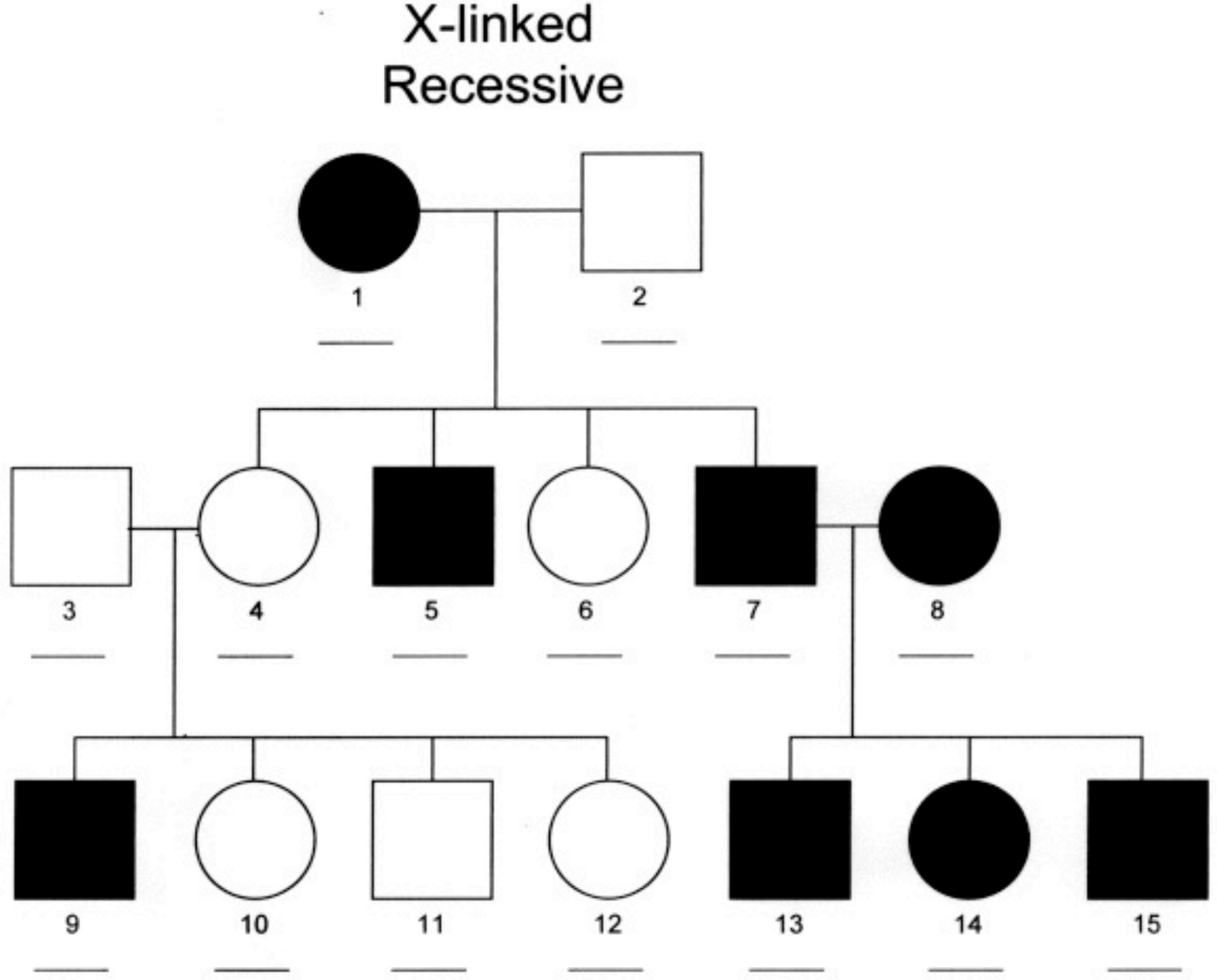


1. affected males produce all affected daughters and no affected sons
2. a heterozygous female will transmit the trait to about half of her sons and half of her daughters

I.

II.

III.

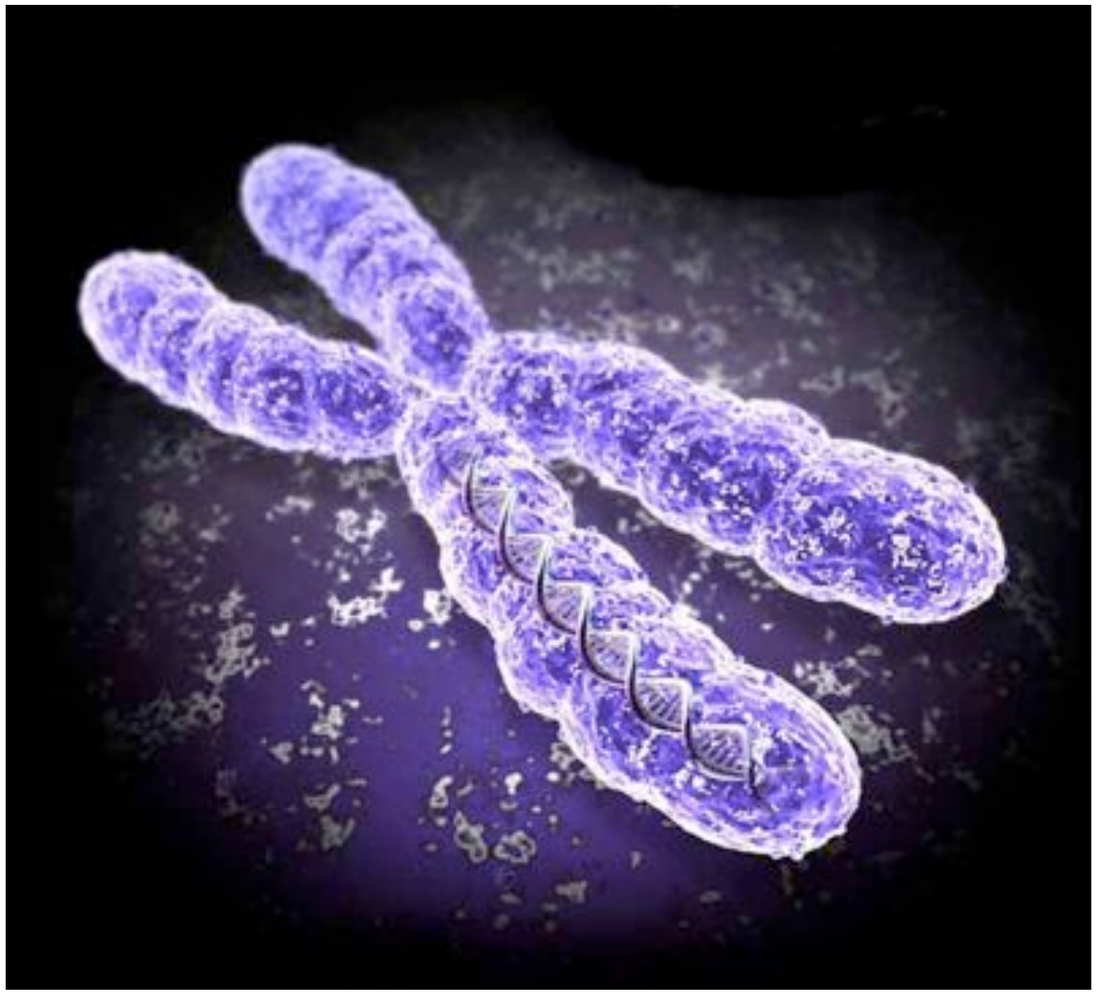


1. all daughters of affected males are carriers; all sons of affected females are affected
2. the phenotype is not transmitted from father to son but rather from father to grandson
3. phenotypic expression is higher in males than in females
4. affected female will have an affected father

Human Genetic Diseases

V.

Main Idea: Many human diseases and disorders have a genetic basis. Understanding the genetic basis of disease helps us better predict and manage the disease in the future.



PREFACE

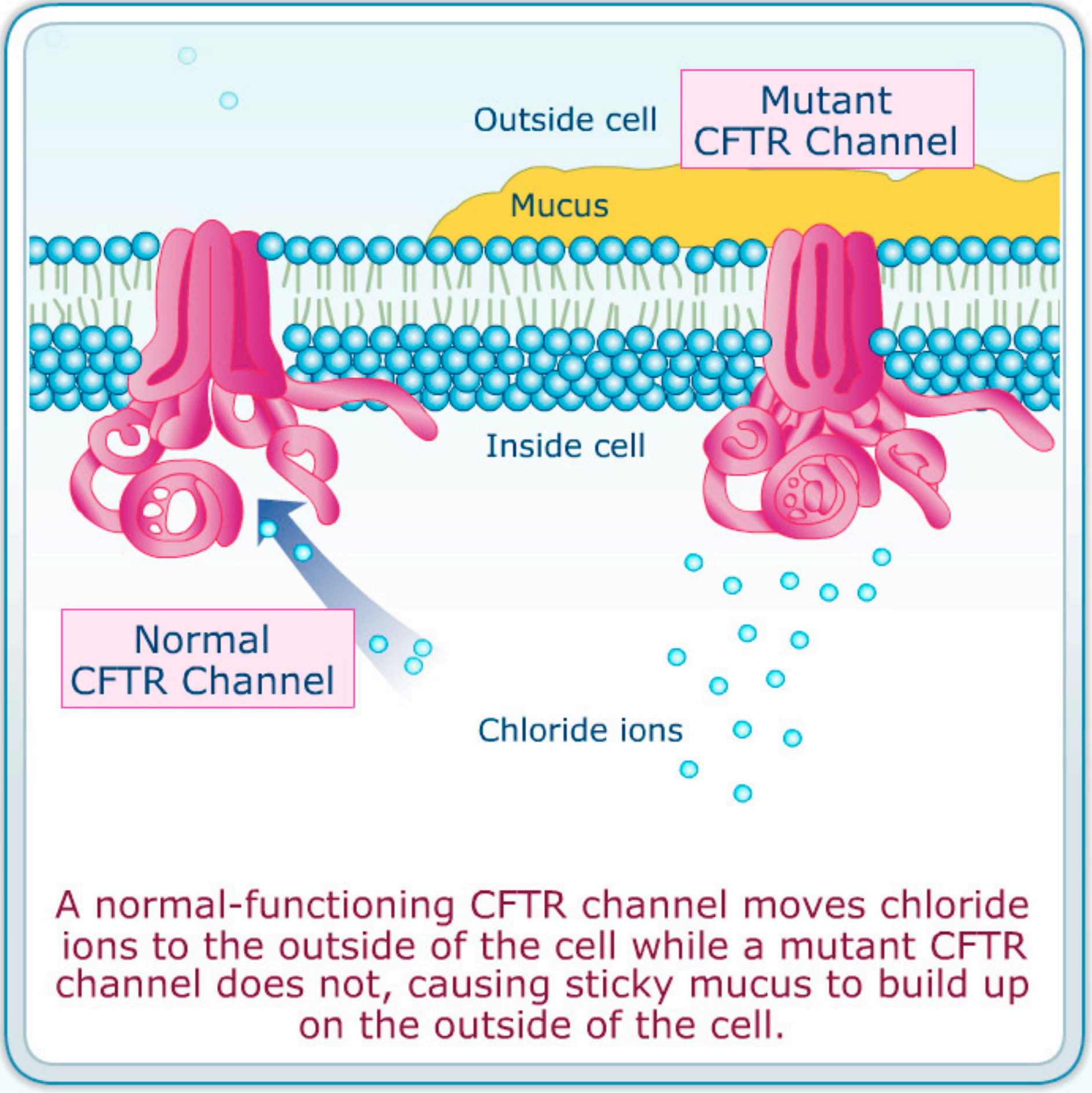
- Genetic disease and disorders range from mild phenotypes, like color blindness, to life threatening like Tay-Sachs disease.
- Some genetic disease occurs at the gene level, where a mutation results in a detrimental protein or level of protein.
  - These diseases can be dominant or recessive.
  - They are found on autosomes and sex chromosomes
- Other genetic disorders occur at the chromosomal level, where a mutation results in a too many chromosomes, too few chromosomes or broken chromosomes.

Recessive Disorders

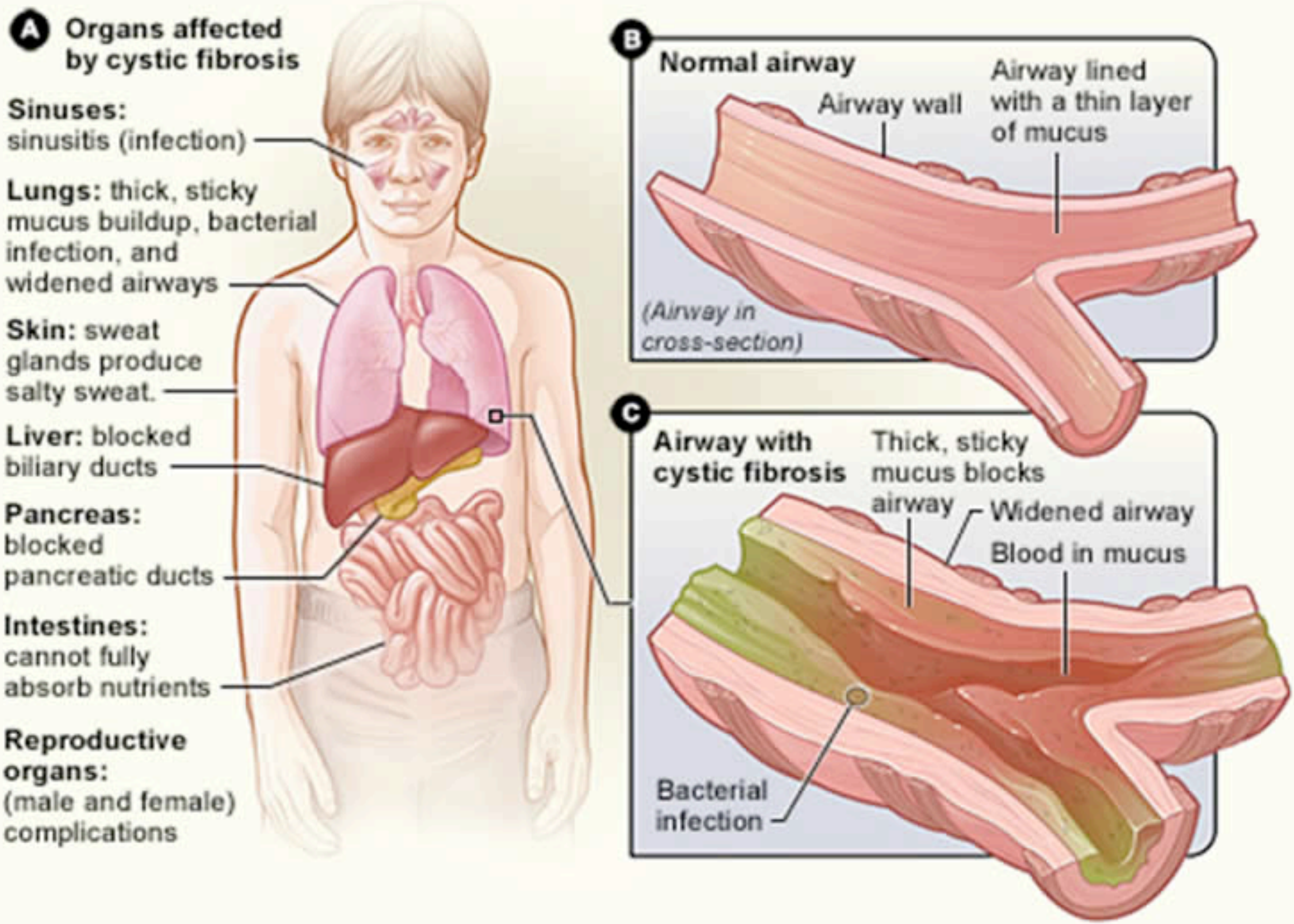
- In general genetic disorders are not evenly distributed among all groups of people.
- When a disease causing allele is rare, it is unlikely that two carriers meet and mate.
- Because people with recent common ancestors are more likely to carry the same recessive alleles than unrelated people mating of close relatives produce more homozygous recessive offspring (diseased).
  - *most societies and cultures have laws or taboos forbidding* ***consanguineous*** *marriages which may have evolved from empirical evidence over time.*
  - *many pure bred dog breeds today are so inbred they have greater incidence of physical and behavioral problems*

Cystic Fibrosis

- The most common lethal genetic disease in the United States, strikes 1in 2500 people of European descent.
- 4% of people with European descent are carriers for the trait.
- If untreated most children die before the age of 5.
- With treatment, more than 50% of those in the U.S. live into their 20's or 30's.
    - Treatment includes: antibiotics, daily pounding on the chest to clear mucous and other preventive treatments



A normal-functioning CFTR channel moves chloride ions to the outside of the cell while a mutant CFTR channel does not, causing sticky mucus to build up on the outside of the cell.


A Organs affected by cystic fibrosis
Sinuses: sinusitis (infection)
Lungs: thick, sticky mucus buildup, bacterial infection, and widened airways
Skin: sweat glands produce salty sweat.
Liver: blocked biliary ducts
Pancreas: blocked pancreatic ducts
Intestines: cannot fully absorb nutrients
Reproductive organs: (male and female) complications
B Normal airway
Airway wall
Airway lined with a thin layer of mucus
(Airway in cross-section)
C Airway with cystic fibrosis
Thick, sticky mucus blocks airway
Widened airway
Blood in mucus
Bacterial infection

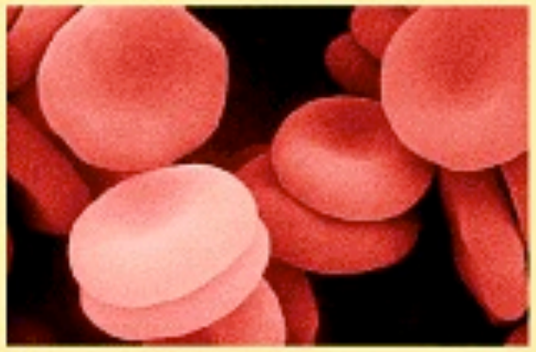
Sickle Cell Anemia

- The most common genetic disease in people of African descent, strikes 1 in 400 people.
- About 1 in 10 African-Americans carry the trait.
- The high incidence stems from the partial resistance to malaria conferred by carrying the sickle cell trait thus being selected for in Africa where malaria is common.
- Regular blood transfusions can ward off brain damage in children and new drugs can help prevent and treat the disease other related problems but there is no cure.

Two copies of the sickle-cell allele

All hemoglobin is the sickle-cell (abnormal) variety

Abnormal hemoglobin crystallizes when oxygen content of blood is low, causing red blood cells to become sickle-shaped



Normal cells

Sickled cells

Breakdown of red blood cells

Clumping of cells and clogging of small blood vessels

Accumulation of sickled cells in spleen

Physical weakness

Anemia

Heart failure

Pain and fever

Brain damage

Damage to other organs

Spleen damage

Impaired mental function

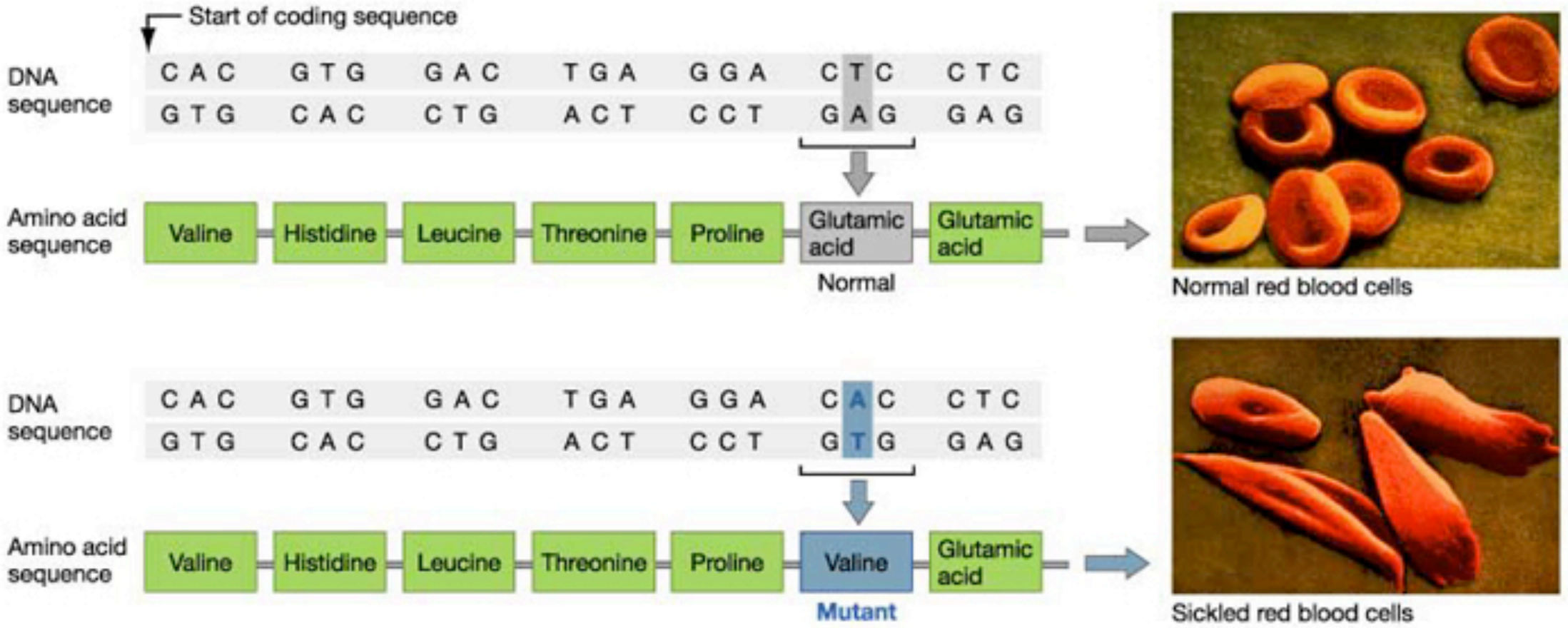
Paralysis

Pneumonia and other infections

Rheumatism

Kidney failure

Sickle Cell Trait & Malaria



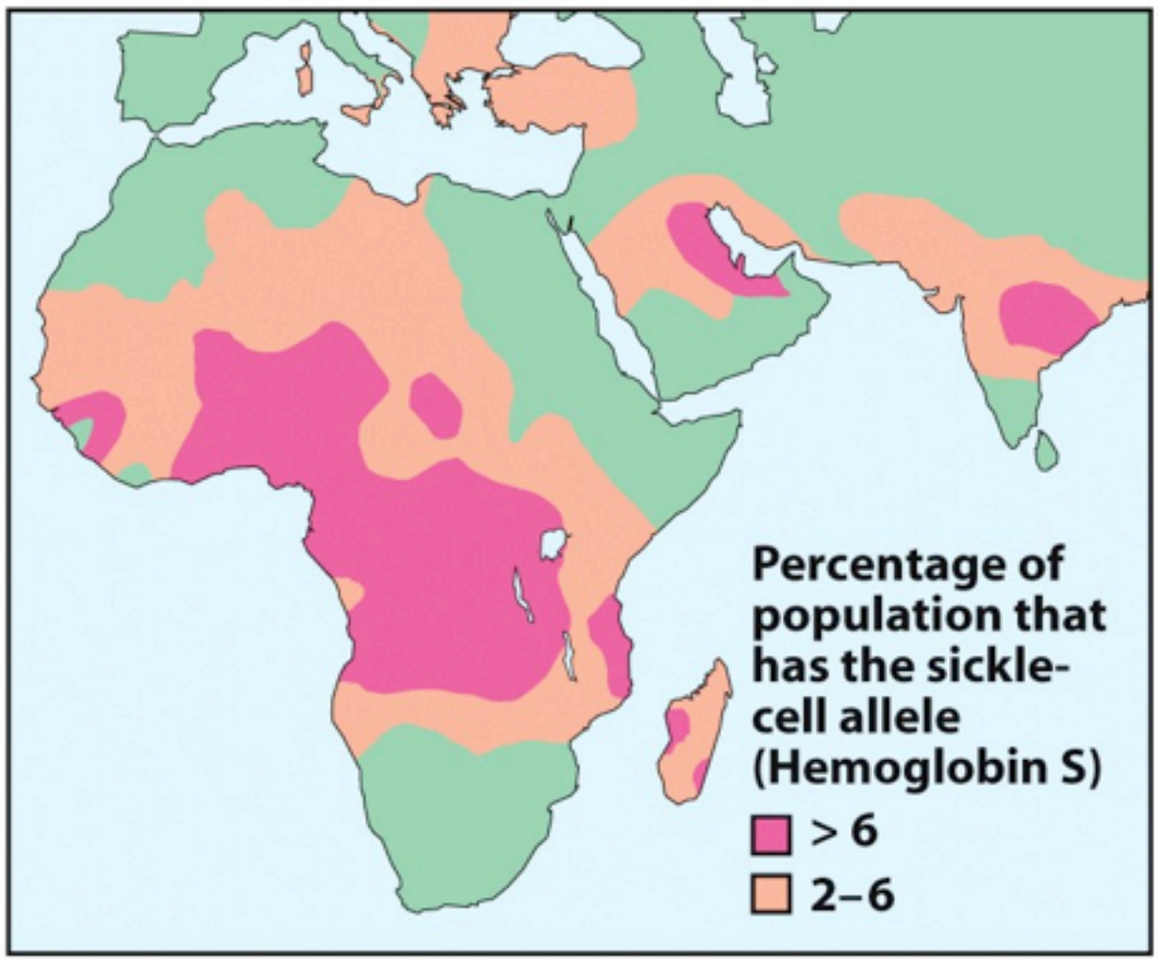
The change in amino acid sequence causes hemoglobin molecules to crystallize when oxygen levels in the blood are low. As a result, red blood cells sickle and get stuck in small blood vessels.

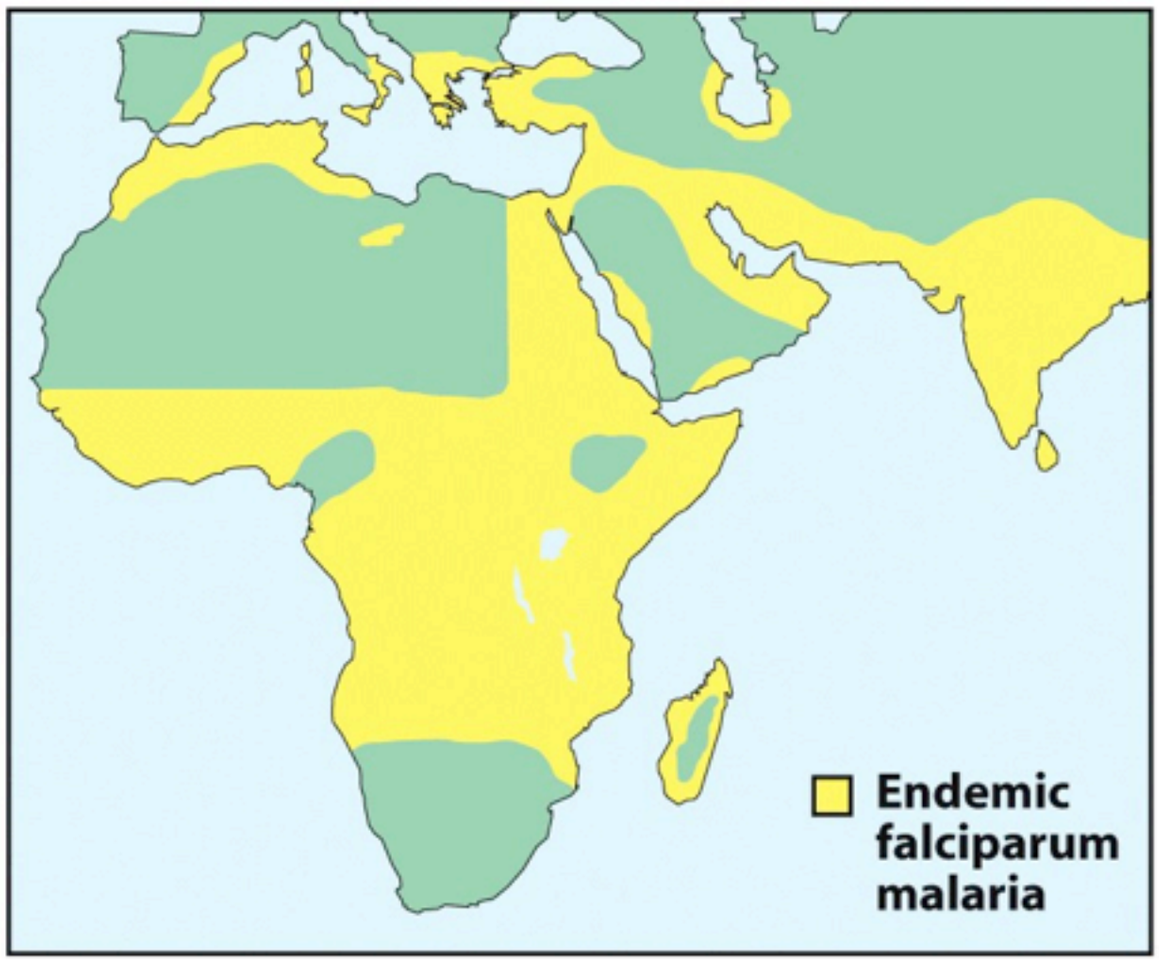
This is a "substitution" mutation notice the thymine was switched with alanine.

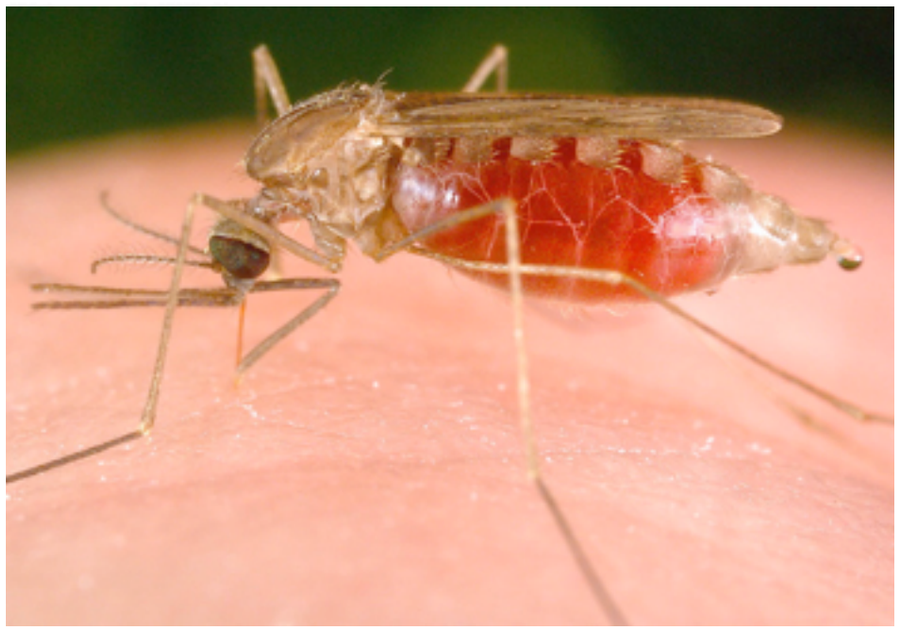
The normal beta subunit consists of 438 nucleotides and 146 amino acids.

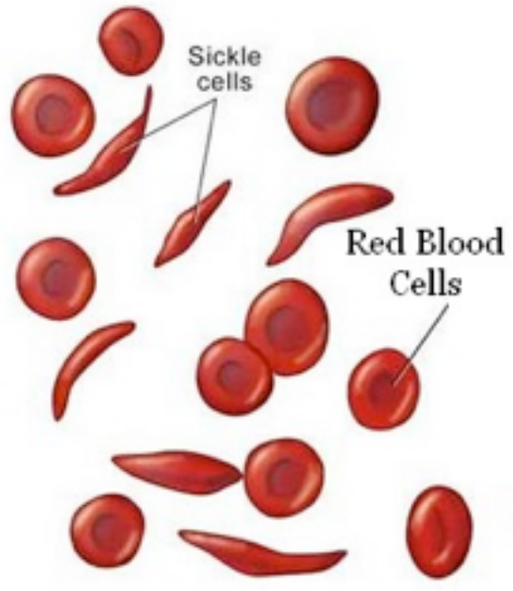
A change in 1 nucleotide, changes 1 amino acid resulting in sickle cell disease

Sickle Cell Trait & Malaria









	A	a
A	AA	Aa Carrier
a	Aa Carrier	aa Child has Sickle Cell Anemia

a — Sickle cell allele

Dominant Disorders

- Although many harmful alleles are recessive, a number genetic diseases are due to dominant alleles.

Achondroplasia

- A form of dwarfism that occurs in 1 in 25,000 people.
- The heterozygous individuals(Aa) are dwarfs, thus 99.9+% of the population is homozygous recessive(aa).
- The high incidence stems from the partial resistance to malaria conferred by carrying the sickle cell trait thus being selected for in Africa where malaria is common.
- Regular blood transfusions can ward off brain damage in children and new drugs can help prevent and treat the disease other related problems but there is no cure.

Huntington's Disease

- A rare lethal dominant allele located on the tip of chromosome #4, that effects 1in10,000 people.
- The timing of the disease expression is crucial in its persistence in the gene pool.
- Most lethal dominant alleles would be quickly eliminated from the gene pool because they offspring would die prior to passing on the trait.
- Huntington's, a degenerative disease of the nervous system has no effect until the person 35-45 years old, who has likely already reproduced and passed the gene on.

Aa X aa

↑

Huntington's

{ Offspring will have a 50% of inheriting the allele and the disease

Multifactorial Diseases

- The genetic disease discussed up to this point are caused by one or both alleles at one genetic locus.
- However many diseases have both a genetic component as well as an *environmental* component.
  - Cardiovascular Disease (#1 killer in U.S.), Cancer (#2), Diabetes (becoming epidemic), Alcoholism, Schizophrenia, Bipolar disorder
- To complicate matters the genetic component is often polygenic.
- So little is understood about the genetic component that the best public health strategy is to educate people about the environmental factors and promote healthy behavior.

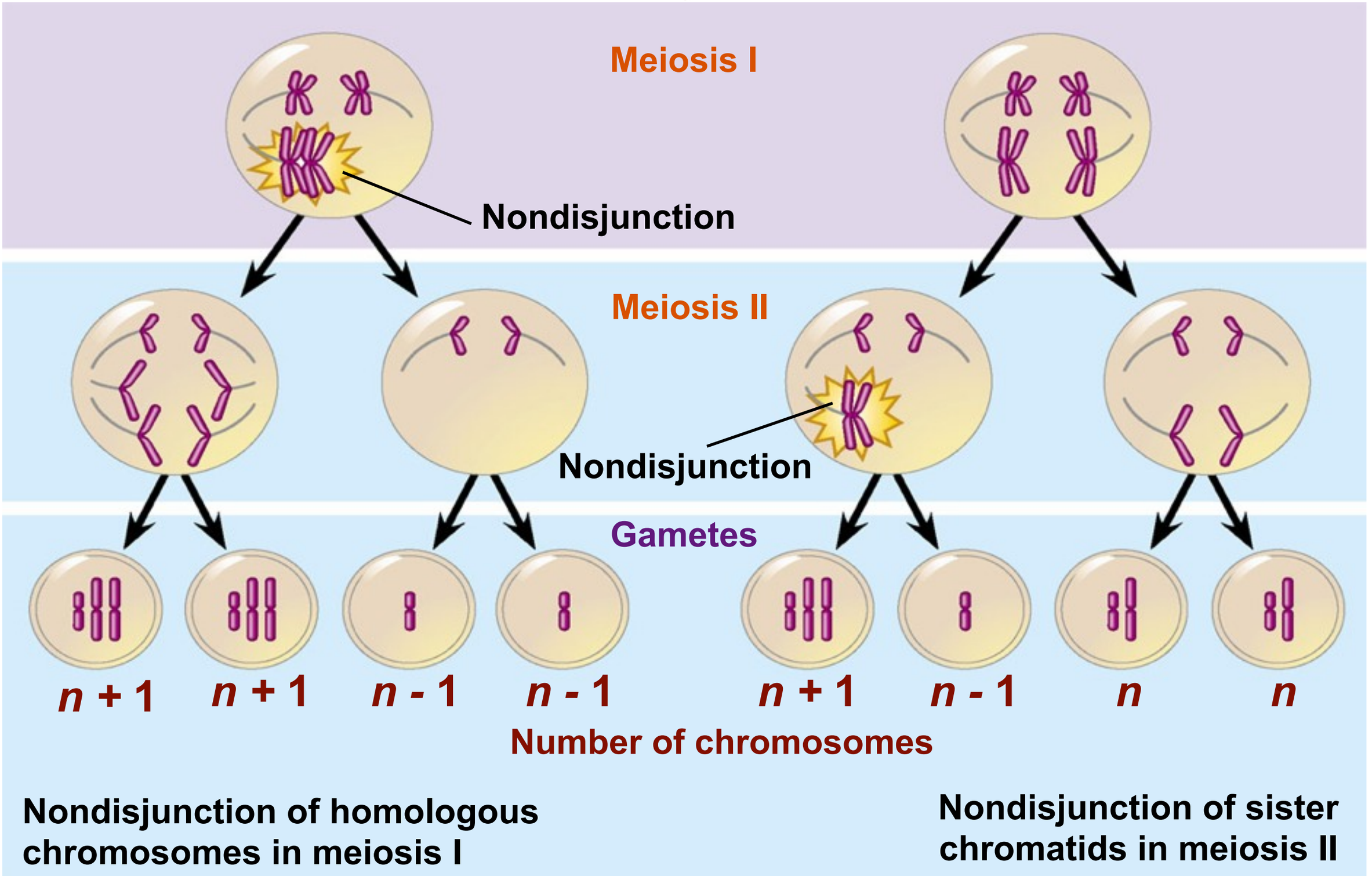
Chromosomal Disorders

- Random mutations result in new alleles that which can lead to new phenotypes and even disease as we just learned.
- However large scale chromosomal changes can also effect an organisms phenotype and result in genetic disorders.
    - Errors in cell division can result in cells have too many chromosomes or too few chromosomes.
    - Physical and chemical disturbances can alter chromosome structure and function as well.
- These changes to the chromosome number or integrity result in genetic disorders.
- The disorders can vary in severity and plants tend to deal with these alterations better than animals.

Alteration in Chromosome Numbers

- Ideally chromosomes are distributed evenly and without error amongst daughter cells during meiosis.
- Occasionally errors occur, when, members of a pair of homologous chromosomes fail to separate during meiosis I or sister chromatids fail to separate during meiosis II it is called **nondisjunction**.
    - These errors in cell division result in some cells having too many chromosomes, while the other cells have too few chromosomes.
- Should any of these gametes fuse with a normal gamete the resulting zygote will also have an abnormal number of chromosomes which in many cases leads to significant effects.

Nondisjunction



Nondisjunction can also occur in mitosis, during embryological development.

Trisomic- zygote will have 3 chromosomes at one position

Monosomic- zygote will have only 1 chromosome at one position

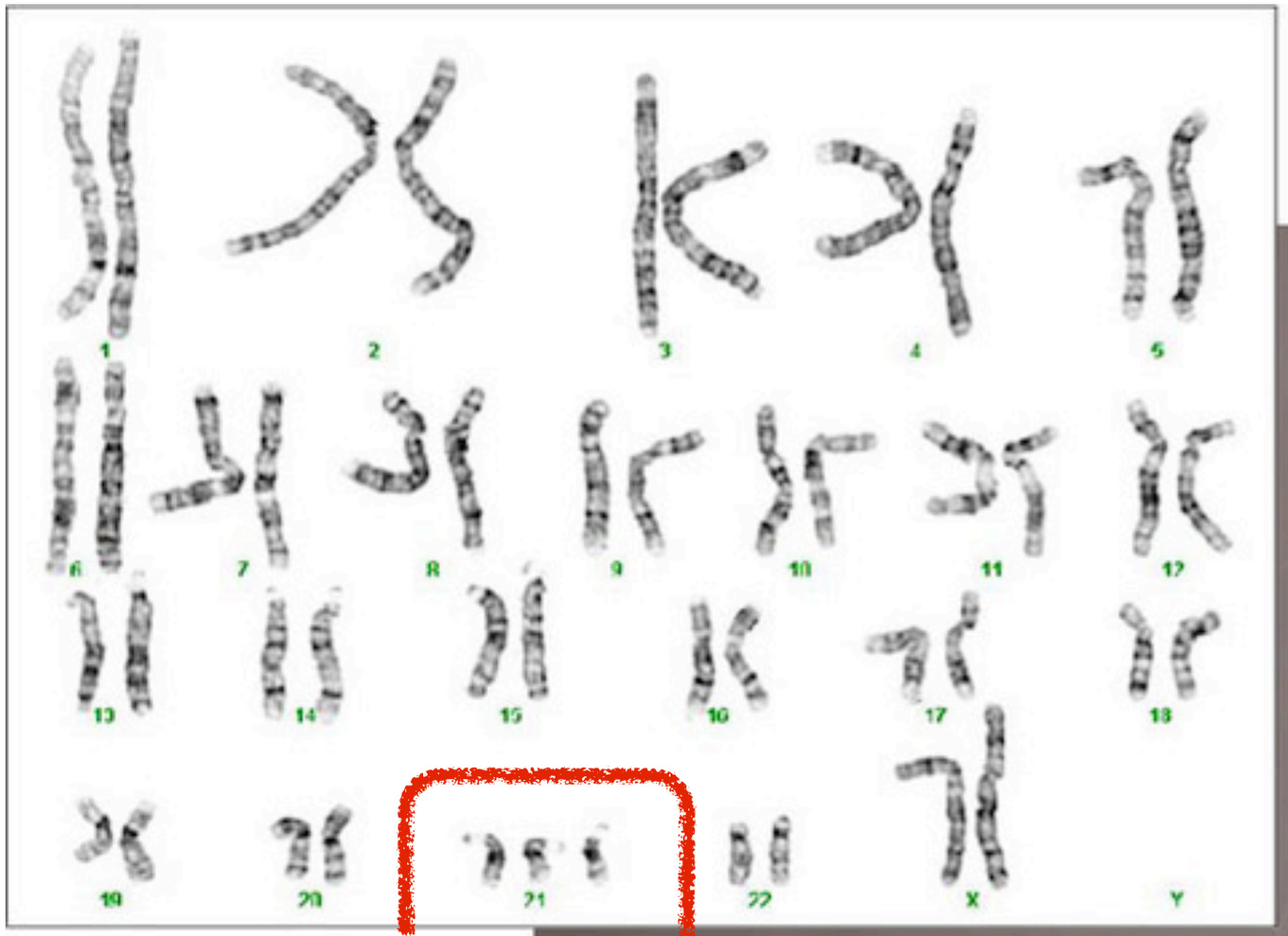
Aneuploidy- a condition where an individual has an abnormal number of chromosomes and it may involve more than one chromosome.

- Mitosis will consequently pass the anomaly to each and every cell of the body during development.

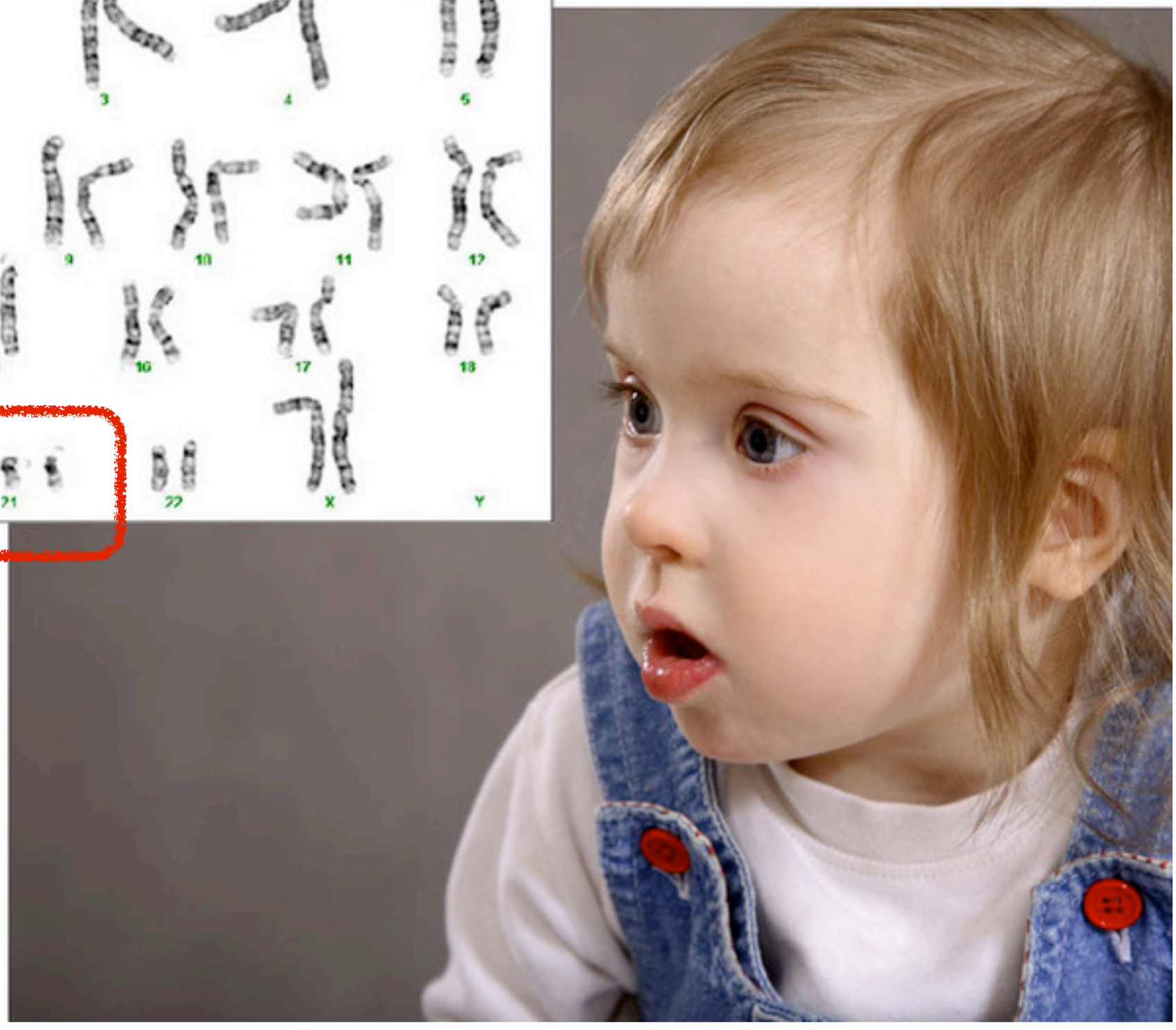
Alteration in Chromosome Number

- These alterations may be quite common but most of the time we never see the results of such alterations because the embryos spontaneously abort well before birth.
- When the embryo survives it results in a **syndrome**, a set of certain traits associated with that specific type of aneuploidy.
- ex. Downs syndrome, Klinefelters, Turners

Downs Syndrome

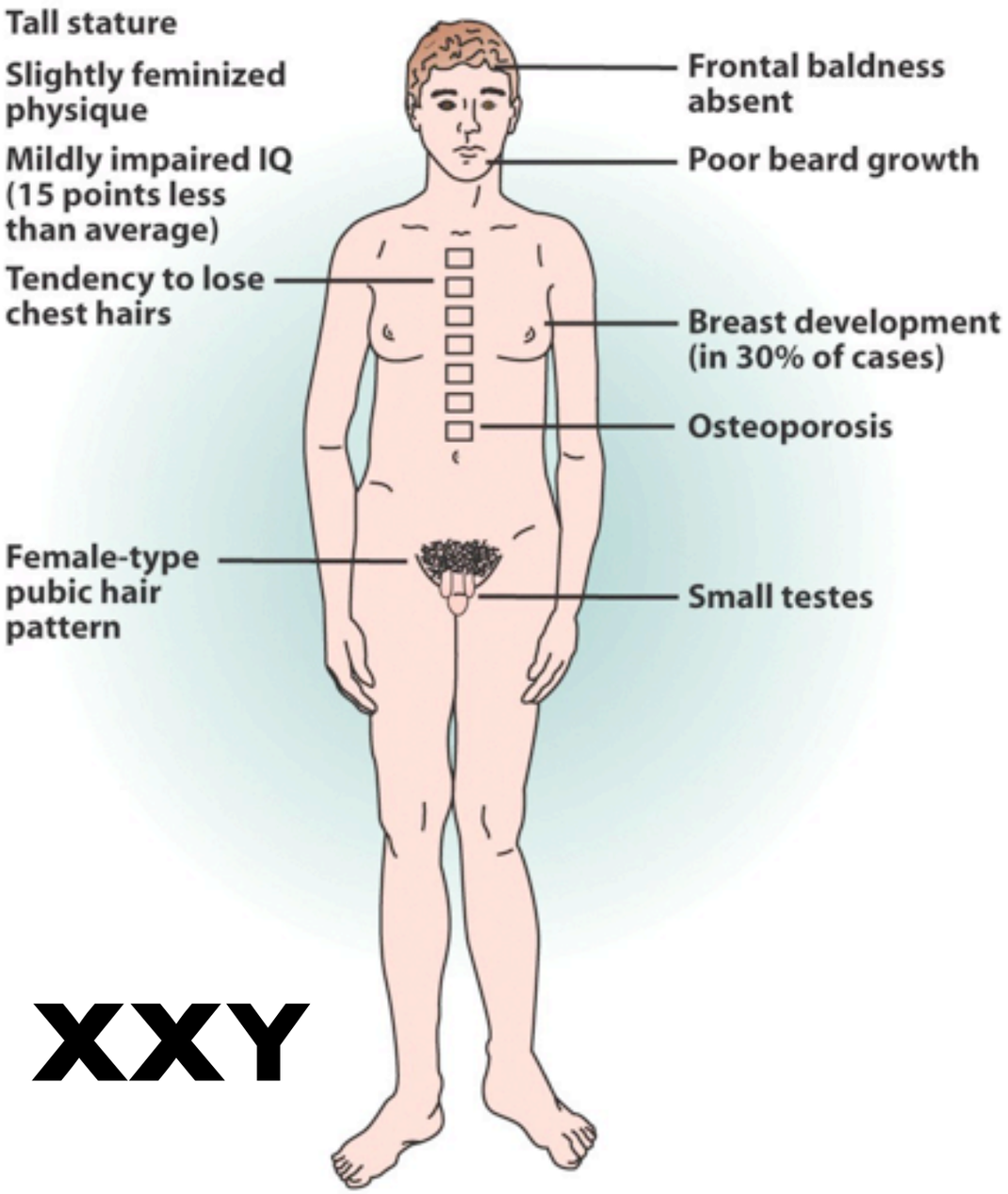


1 in 700 births in U.S.



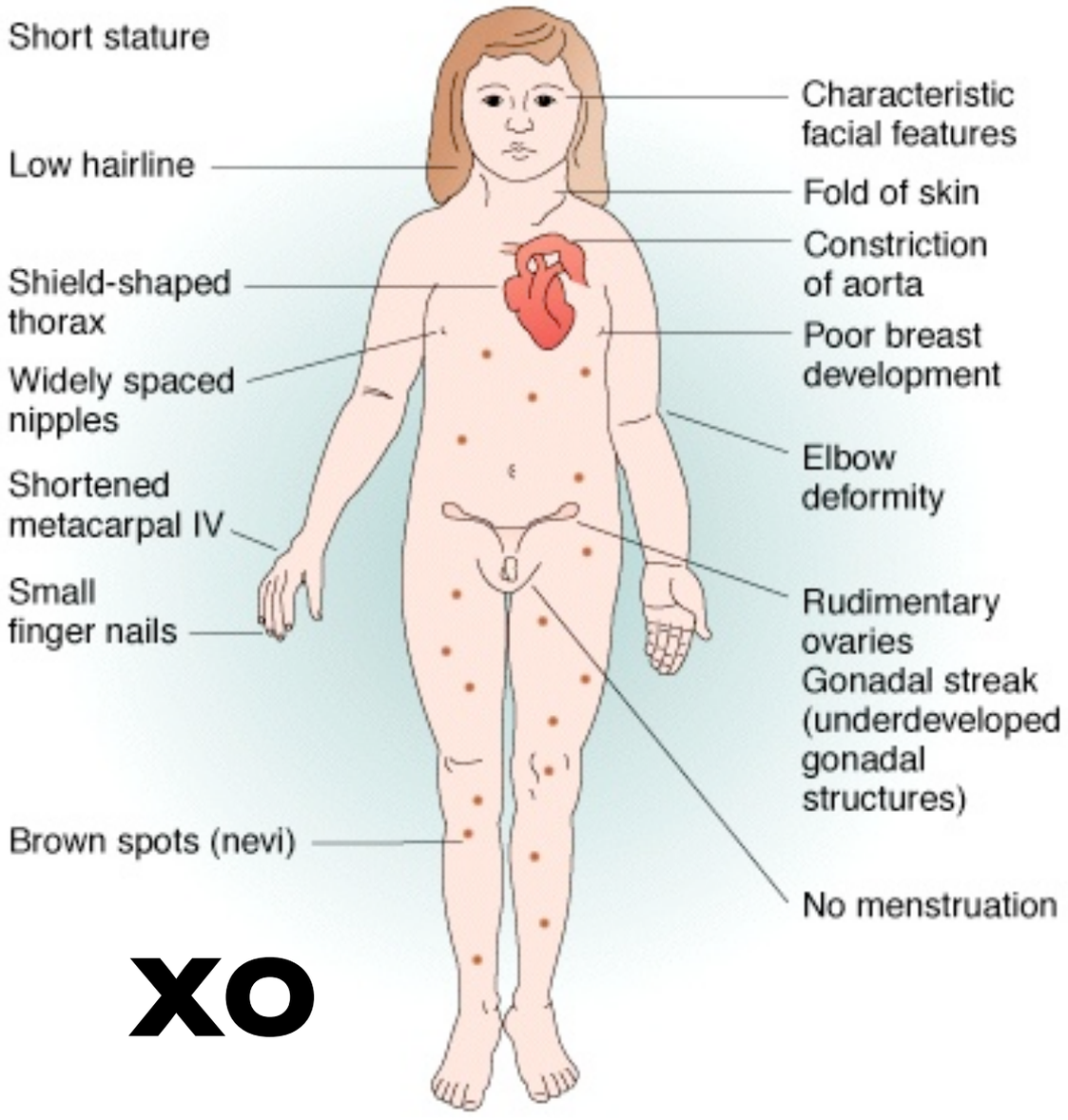
3 copies of chromosome #21

Two or the more common sex chromosome aneuploidy conditions



XXY

Klinefelter Syndrome



XO

Turner Syndrome

Aneuploidy in Sex Chromosomes

Table 1. Main features of numerical sex chromosome anomalies

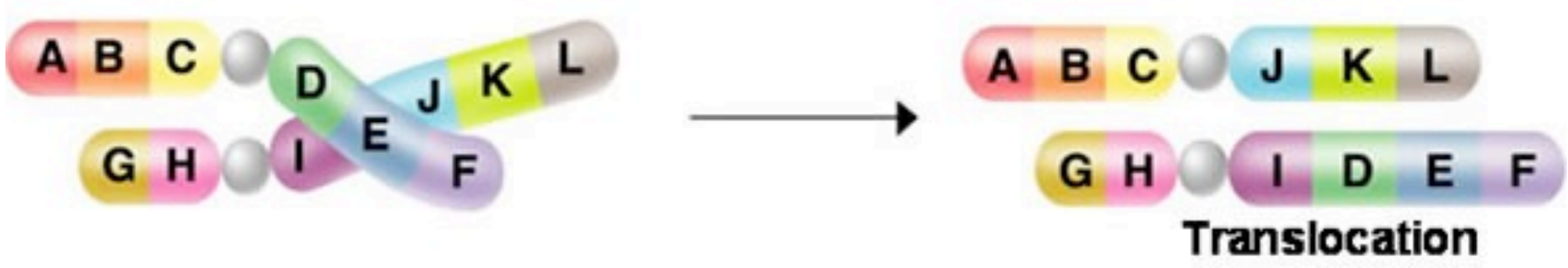
Karyotype	Incidence	Mental retardation	Behavioral disorders	Stature	Gonadal function	Congenital anomalies/ Additional medical problems	Ref.
45,X	1:2,130 F	-	-	Short	Hypergonadotropic hypogonadism	Dysmorphic picture, CV and renal anomalies, autoimmune disorders	1,2
47,XXY	1:576 M	Greater frequency when compared with normal men	Greater frequency when compared with normal men	Tall	Hypergonadotropic hypogonadism	Minor physical findings, varicose veins, DVT, *diabetes mellitus*, autoimmune disorders	1, 2,6
47,XYY	1:851 M	Greater frequency when compared with normal men	Greater frequency when compared with normal men	Tall	Usually normal	Minor physical findings	1,2,6
47,XXX	1:897 F	Greater frequency when compared with normal women	Greater frequency when compared with normal women	Tall	Usually normal Unknown frequency of premature ovarian failure	Minor physical findings, low frequency of genitourinary anomalies and seizures	1,2,6
48,XXXX 49,XXXXX	?	+	Variable	Short	Hypergonadotropic hypogonadism	Dysmorphic picture, CV anomalies	6,16
48,XXYY	1:18,000-1:40,000 M	+	+	Tall	Hypergonadotropic hypogonadism	Dysmorphic picture, CV and renal anomalies, type II diabetes, seizures, DVT	3,6,7
48,XXXY	1:50,000 M	+	+	Tall	Hypergonadotropic hypogonadism	Dysmorphic picture, CV and renal anomalies, type II diabetes, seizures, DVT	4,6,7
49,XXXXY	1:85,000-1:100,000 M	+	+	Short	Hypergonadotropic hypogonadism	Dysmorphic picture, CV and renal anomalies, type II diabetes, seizures, DVT	4,6,7

+ = present; - = absent; CV = cardiovascular; DVT = deep vein thrombosis; F = females; M = males.

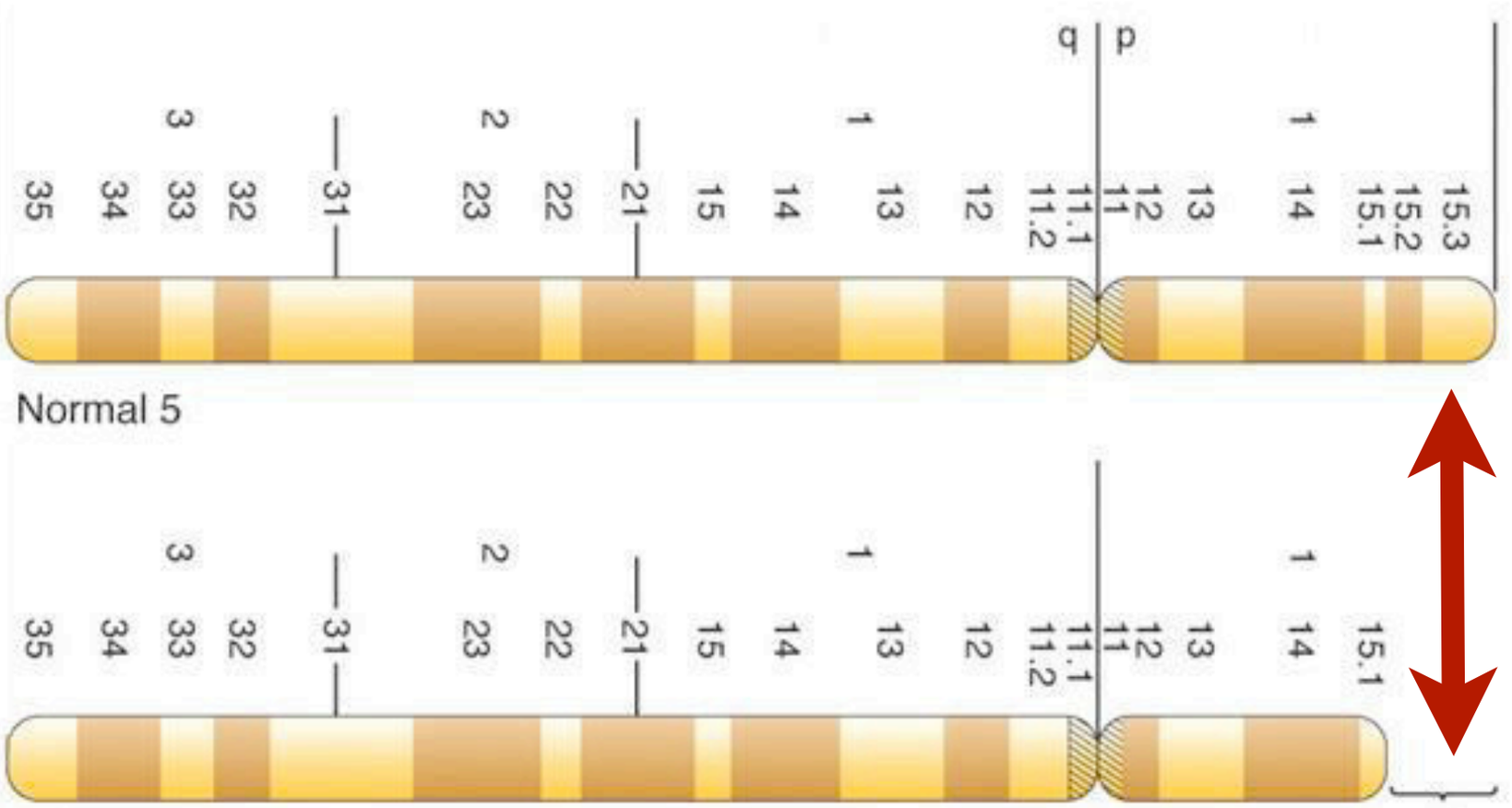
Alteration in Chromosome Structure

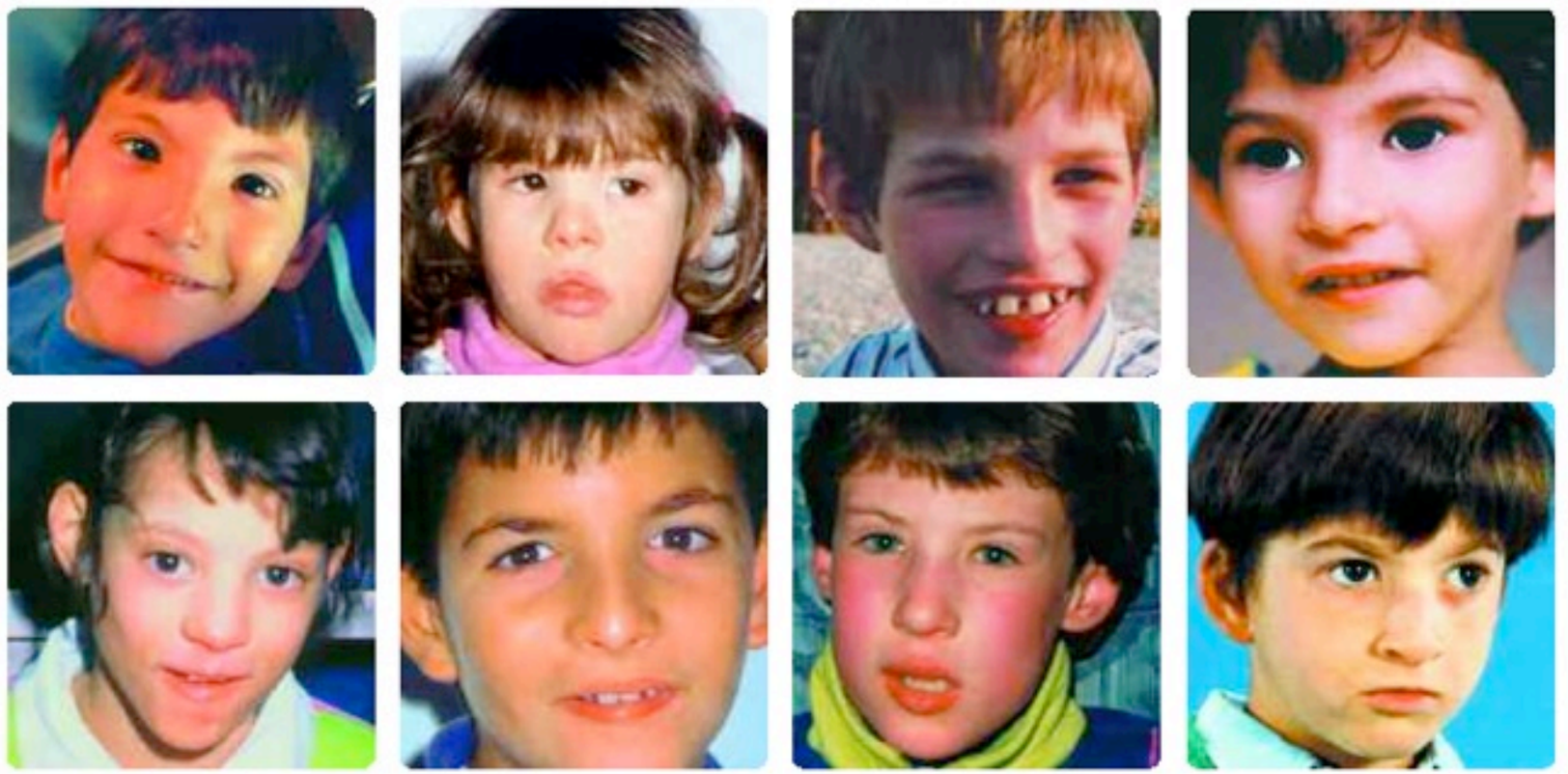
- Errors in meiosis or damaging agents can alter chromosome structure in 1 of 4 ways. (illustrated on next slide)
  - *deletions, duplications, inversions & translocations*
- These alterations may cause severe problems.
  - Cri du Chat, Chronic Myelogenous Leukemia, Burkitt's Lymphoma

Chromosomal Mutations

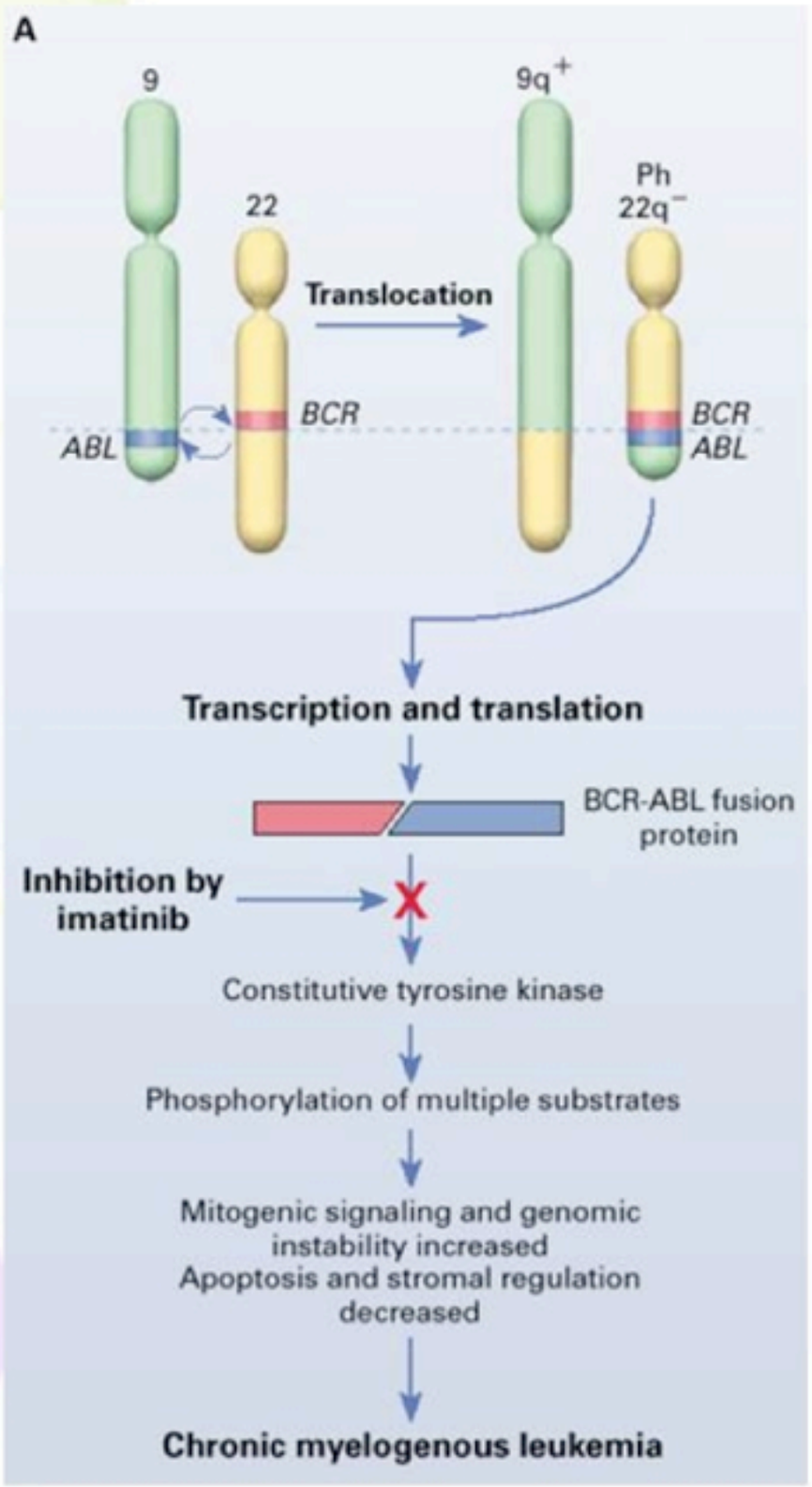


THE CRI DU CHAT SYNDROME





Chronic Myelogenous Leukemia



?

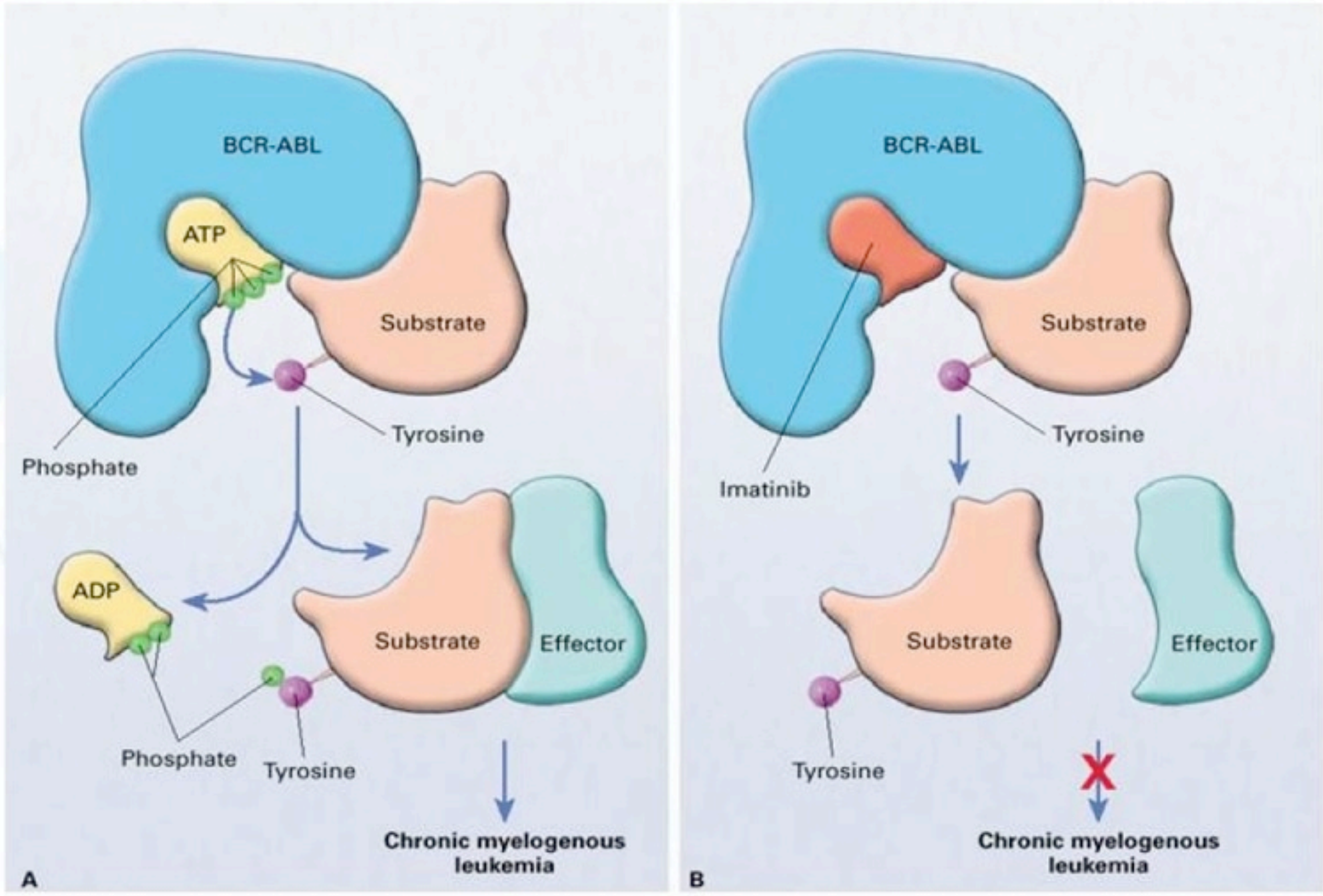
Philadelphia Chromosome

- A shortened chromosome 22 resulting from the translocation between chromosome 9 and chromosome 22

- Produces BCR-ABL oncogene

Can you explain the problem?

Chemotherapy: Gleevec



Can you explain how this drug works?

This figure shows the BCR-ABL oncoprotein with a molecule of ATP in the kinase pocket. The substrate is activated by the phosphorylation of one of its tyrosine residues. It can then activate other downstream effector molecules. When Gleevec in the kinase pocket (Panel B), the action of BCR-ABL is inhibited, preventing phosphorylation of its substrate.

Appendix: Genetic Problems

VI.

Main Idea: Genetic problems are common in many biology classes and exams. In this section I will address common genetic problems by type, offer solution tips and explain how statistical tools are used for evaluating results.

Chi-Squared Test

- Chi square, is a test for difference between two data sets.
- It can only be used on raw count data, not measurements or derived data.
- It should only be used to compare experimental data (actual results) with theoretical data (expected results).
- Is not reliable when sample size is below 20, the more data the better.
- Its goal is to test the **Null Hypothesis**
  - Null Hypothesis (H_0) states that there is no difference between the two data sets.

Side bar...

Know the meaning of the 3 different types of chi-square analysis techniques.

(1) **Goodness-of-fit test** is a chi-square test technique used to study similarities between proportions or frequencies between groupings (or classification) of categorical data. this is our application in genetics

(comparing a distribution of data with another distribution of data where the expected frequencies are known).

(2) **Tests of Independence** is a chi-square technique used to determine whether two characteristics (such as food spoilage and refrigeration temperature) are related or independent.

(3) **Test of Homogeneity** is a chi-square technique used to study whether different populations are similar (or homogeneous or equal) in reference to some characteristic or attribute (such as "do students national identity affects the time spend doing homework?").

Chi-Squared in Genetics

- In many genetic problems we are asked to make a prediction about fate of a certain gene or likelihood that an offspring receives a certain gene.
- Recall that punnet squares and rules of probability are the tools we use to make these predictions
  - For Instance in the dihybrid cross below, a Mendelian pattern of inheritance predicts a 9:3:3:1 phenotypic ratio.

AaBb X AaBb

9 = yellow/round

3 = green/round

3 = yellow/wrinkled

1 = green/wrinkled

Where...

A = yellow

a = green

B = round

b = wrinkled

Chi-Squared in Genetics

- In reality, when crosses are actually carried out in the lab or in your potential genetic problems the actual phenotypic ratio never exactly matches the expected ratio.
- Now consider two possibilities
  - 1. The actual results are "close enough" to the expected ratios to conclude that the assumed pattern of inheritance is at work in this case.
  - OR 2. The actual results are simply due to chance or some other factor, thus assumed pattern of inheritance has no data to support it.

How close is "close enough"?

Hard to say going on instincts alone, our "gut feelings" are too subjective

Using Chi-Squared

- **Chi square is a statistical application that objectively helps us decide between the two alternatives, in other words how close is "close enough".**

- State your two hypotheses.

  - 1. Null Hypothesis (H_0)-There is no difference between the two data sets. Your actual results are the same as your expected results.

  - 2. Alternative Hypothesis (H_A) -There is a difference between the two data sets. Your actual results are not what you predicted(put simply H_A is H_0 is not true).

Now use Chi-square and let it determine which of the two choices above is more likely

$$X^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}$$

Chi-Squared Equation

$$\chi^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}$$

where

χ^2 = Pearson's cumulative test statistic, which asymptotically approaches a χ^2 distribution.

O_i = an observed frequency;

E_i = an expected (theoretical) frequency, asserted by the null hypothesis;

n = the number of cells in the table.

Using Chi-Squared

AaBb X AaBb

PREDICTED

9 = yellow/round
3 = green/round
3 = yellow/wrinkled
1 = green/wrinkled

$$X^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}$$

EXPERIMENTAL

441 = yellow/round
159 = green/round
143 = yellow/wrinkled
57 = green/wrinkled

The predicted ratios assume that two traits are assorting independently and as as result probability of creating a yellow/round seed is 9/16, etc.

The experimental ratios are not perfect matches of the predicted percentages.

SO...

Are these traits following the presumed pattern of inheritance?

Steps:

1. State H_0 and H_A hypotheses
2. Calculate chi squared
3. Calculate degrees of freedom
4. Find P value for your X^2 value
5. Reject or Accept your H_0

Steps:

1. State H_0 and H_A hypotheses

- 1. Null Hypothesis (H_0)-There is no difference between the two data sets. Your actual results are the same as your expected results.

- 2. Alternative Hypothesis (H_A) -There is a difference between the two data sets. Your actual results are not what you predicted (put simply H_A is H_0 is not true).

PREDICTED	EXPERIMENTAL
9 = yellow/round	441 = yellow/round
3 = green/round	159 = green/round
3 = yellow/wrinkled	143 = yellow/wrinkled
1 = green/wrinkled	57 = green/wrinkled

Steps:

$$X^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}$$

2. Calculate chi squared

Expected:
(9/16)(800)= 450
(3/16)(800)= 150
(3/16)(800)= 150
(1/16)(800)= 50

EXPERIMENTAL

Total 800 {
441 = yellow/round
159 = green/round
143 = yellow/wrinkled
57 = green/wrinkled

Category	***O***	***E***	***O-E***	***(O-E)²***	***$\frac{(O-E)^2}{E}$***
yellow/round	441	450	-9	81	0.18
green/round	159	150	9	81	0.54
yellow/wrinkled	143	150	7	49	0.33
green/round	57	50	7	49	0.98
	∑ 800				**2.03**

Steps:

3. Calculate degrees of freedom

df=3

Category
yellow/round
green/round
yellow/wrinkled
green/round

n = 4 categories
degrees of freedom = n-1
thus 4-1 = 3 d.f.

Steps:

4. Find P value for X^2 value

$X^2 = 2.03$

df	$\chi^2_{0.005}$	$\chi^2_{0.01}$	$\chi^2_{0.025}$	$\chi^2_{0.05}$	$\chi^2_{0.10}$	$\chi^2_{0.90}$	$\chi^2_{0.95}$	$\chi^2_{0.975}$	$\chi^2_{0.99}$	$\chi^2_{0.995}$
1	0.000039	0.00016	0.00098	0.0039	0.0158	2.71	3.84	5.02	6.63	7.88
2	0.01	0.0201	0.0506	0.1026	0.2107	4.61	5.99	7.38	9.21	10.6
3	0.0717	0.115	0.216	0.352	0.584	6.25	7.81	9.35	11.34	12.84
4	0.207	0.297	0.484	0.711	1.064	7.78	9.49	11.14	13.28	14.86
5	0.412	0.554	0.831	1.15	1.61	9.24	11.07	12.83	15.09	16.75
6	0.676	0.872	1.24	1.64	2.20	10.64	12.59	14.45	16.81	18.55
7	0.989	1.24	1.69	2.17	2.83	12.02	14.07	16.01	18.48	20.28
8	1.34	1.65	2.18	2.73	3.49	13.36	15.51	17.53	20.09	21.96
9	1.73	2.09	2.70	3.33	4.17	14.68	16.92	19.02	21.67	23.59
10	2.16	2.56	3.25	3.94	4.87	15.99	18.31	20.48	23.21	25.19

Accept H_0

Reject H_0

Steps:

5. Reject or Accept your H_0

$X^2 = 2.03$

df	$\chi^2_{0.005}$	$\chi^2_{0.01}$	$\chi^2_{0.025}$	$\chi^2_{0.05}$	$\chi^2_{0.10}$	$\chi^2_{0.90}$	$\chi^2_{0.95}$	$\chi^2_{0.975}$	$\chi^2_{0.99}$	$\chi^2_{0.995}$
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10	2.16	2.56	3.25	3.94	4.87	15.99	18.31	20.48	23.21	25.19

Accept H_0

Reject H_0

There is no difference between the two data sets.

Your actual results are the same as your expected results.

Analysis of Different Types of Genetic Problems

coming next year...

In the meantime I have sample problems of every type that you may encounter on the test. You can find them on the website under the homework tab.