Mendel and the origin of Genetics

The study of genetics focuses on how traits are passed on from one generation to the next

Like begets like…….

but not always

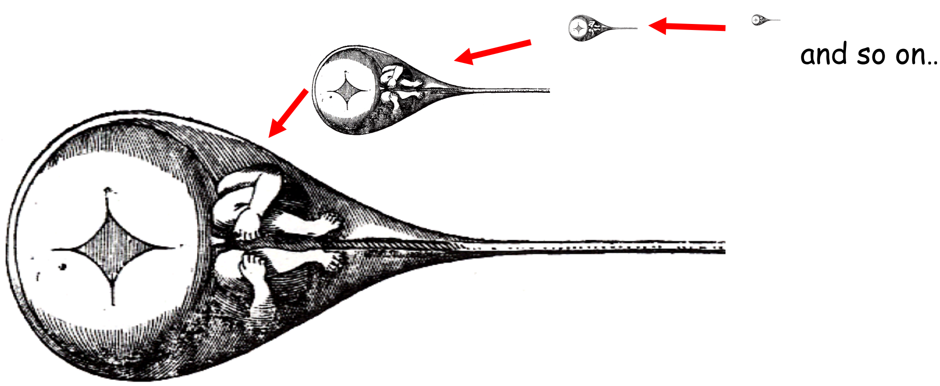
Mendel was the first to successfully address this question

Although Mendel published in 1866, little attention was paid to his findings until 1900. The lack of attention to Mendel's work is still a matter of debate

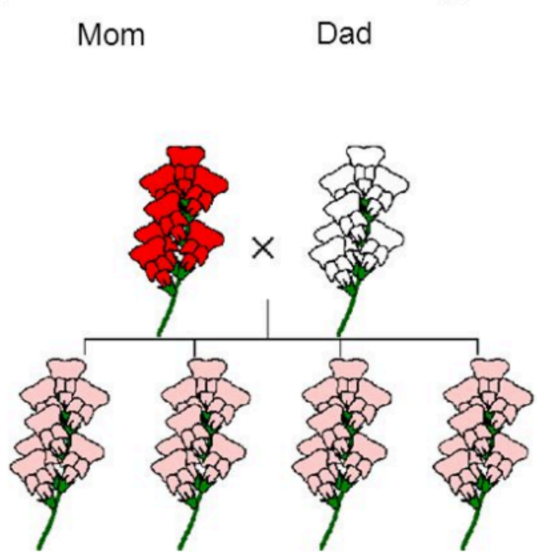
Prevailing theories of inheritance when Mendel performed his experiments

Preformationism: the idea that gamete contains an intact organism, was first proposed in the late 1600s.

A preformed human infant or homunculus contained within a sperm (Male centric view of the world)



Blending inheritance: essences of both sperm and egg mixed to form offspring intermediate between the parents. Strains of plants and animals generated by blending



Charles Darwin proposed his theory of evolution in 1859

A major problem for Darwin was these theories of inheritance could not explain how advantageous traits could be passed on to the next generation

This led Darwin to eventually adopt Lamarckian ideas of inheritance

Lamarckism (or **Lamarckian inheritance**) is the hypothesis that an organism can pass on characteristics that it has acquired during its lifetime to its offspring. It is also known as the heritability of acquired characteristics or soft **inheritance**.

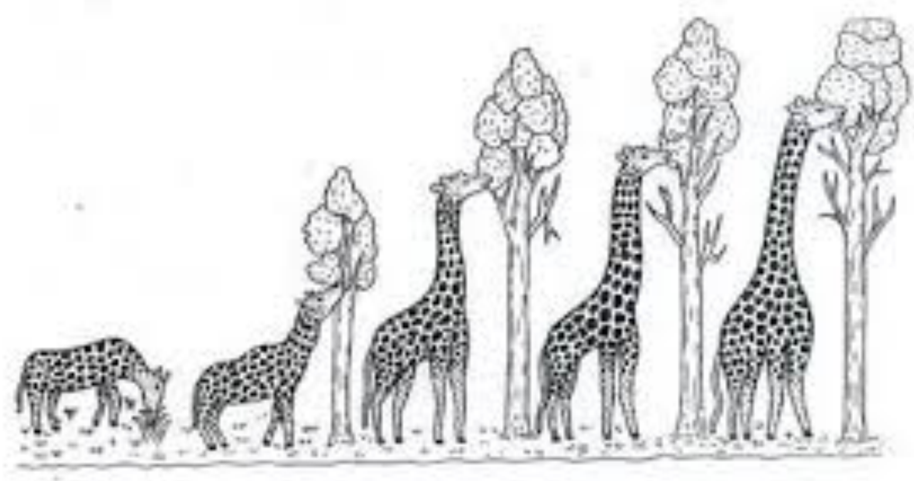


Diagram showing elongation of neck in giraffe according to Lamarck.

So why was Mendel's theory of inheritance ignored?

Mendel's theory did not explain development, it focused solely on transmission of traits.

The origin of genetics: Mendel's inferences

The study of genetics begins when Gregor Mendel, in the 1860's, addressed the question :

"How are characters passed on from one generation to the next?"

Mendel published in 1866. There are often impressions that Mendel was removed from the scientific community, or that his papers were not well circulated. This was not true. Over 200 copies of Mendels papers have been discovered in different libraries.

Mendel was the first to make a serious attempt of experimentally answering the question of heredity.

Based on his experiments, he inferred that:

1:There are two factors for each trait in an individual

2: During gamete formation the paired factors separate, each gamete receives only one of the two factors

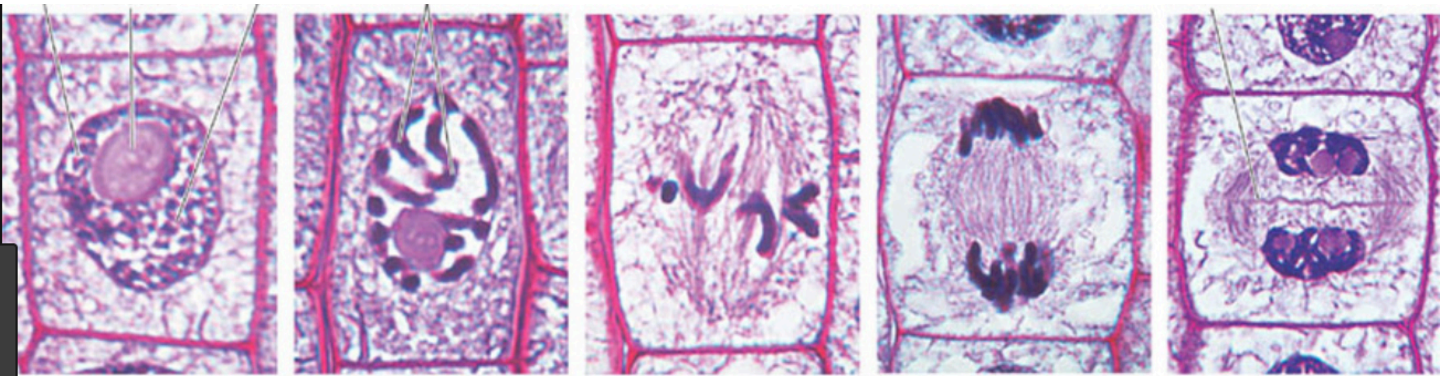
3: Sperm and egg then randomly combine reforming a organism with two factors

4: Segregation of factors for one trait during gamete formation is independent of the segregation of factors for another trait.

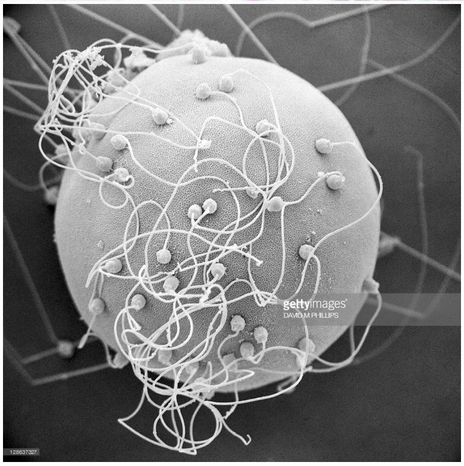
Not only were his answers correct, they were a complete and compelling proof.

Cytology-
The study of cells usually by microscopic observations

1873 Mitosis described in detail- nuclear and chromosome dynamics described



1883 Fertilization in sea urchin showed that sperm and ovum fuse. This links parents to offspring.



Problem of ploidy:. Nuclei of parents and progeny are diploids. If the nuclei of the sperm and egg fuse, chromosome number should double every generation

1885 Meiosis described- Reductional division of Chromosomes in germ cells keeps number of chromosomes constant. No similar phenomenon seen in any other cellular organelle

Cytology's contribution to understanding Mendel's work

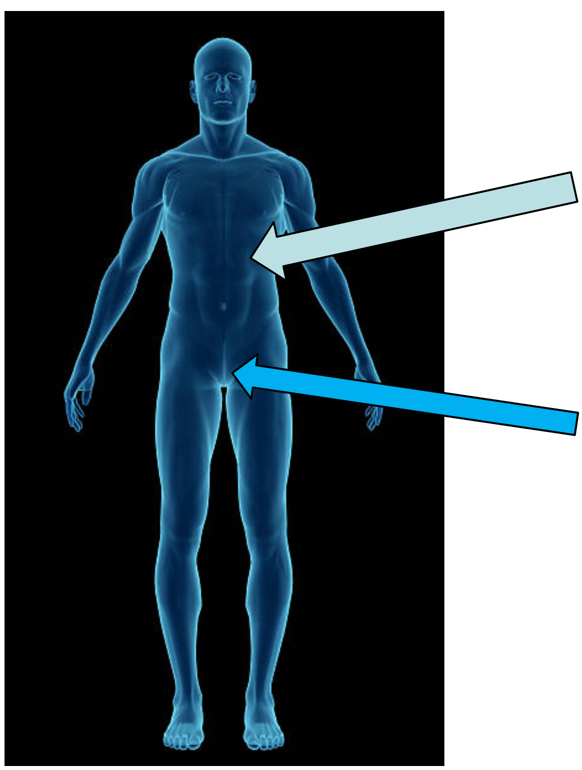
Mendel published in 1866. Little attention was paid to his work until 1900.

During this period cytology contributed towards a better understanding of the inheritance of genetic traits.

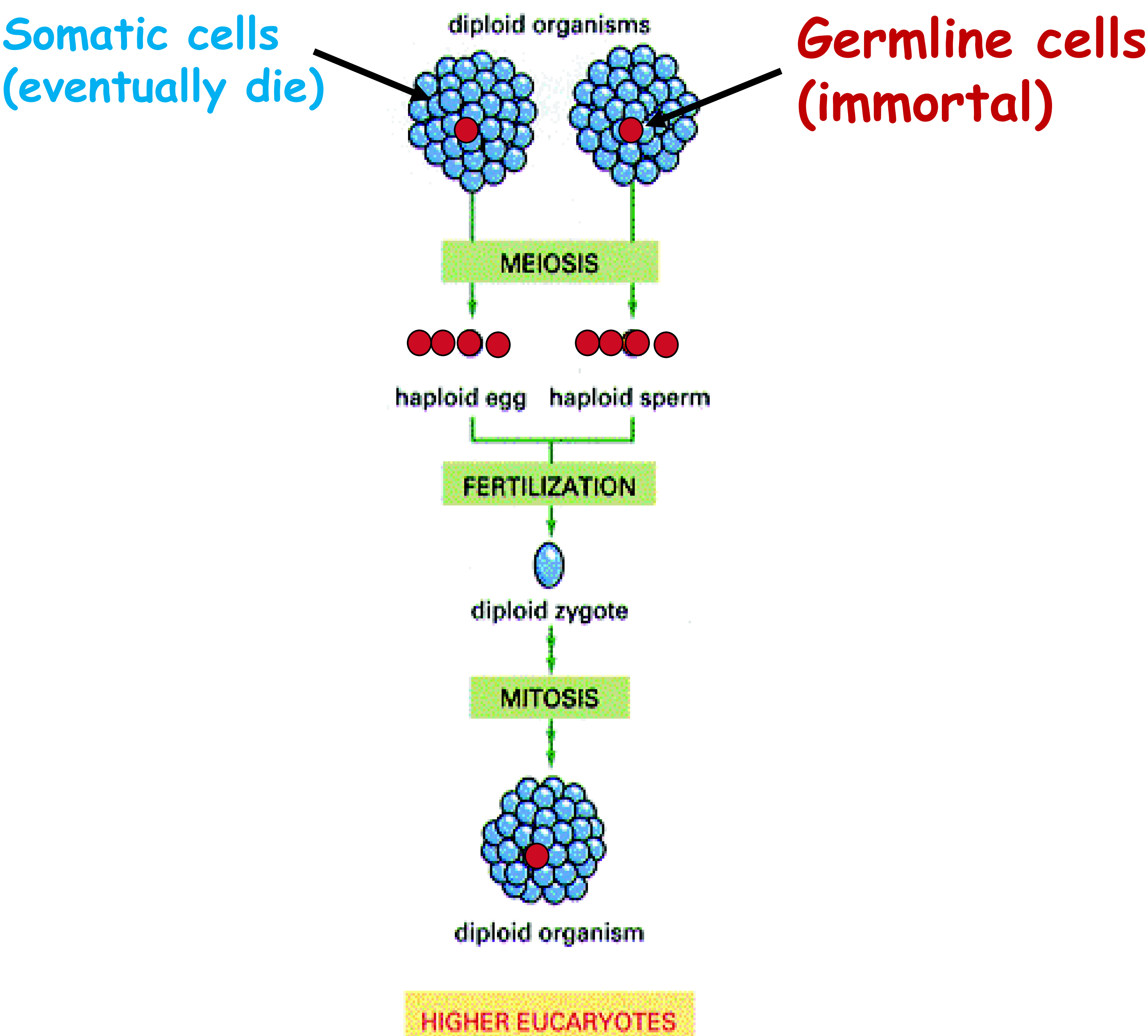
Heredity is a consequence of genetic continuity

Germ cells are the vehicle of transmission of traits from one generation to the next.

Germline versus the Soma



Perhaps the most significant question in biology: the immortality of the germline



Little is known concerning the mechanisms that “refresh” and maintain germline immortality

Germ cells produce cells (gametes) that contain half the number of chromosomes found in somatic cells

Somatic cells= 2 copies of each chromosome (diploid)
Gametes (sperm/eggs)= 1 copy of each chromosome (haploid)

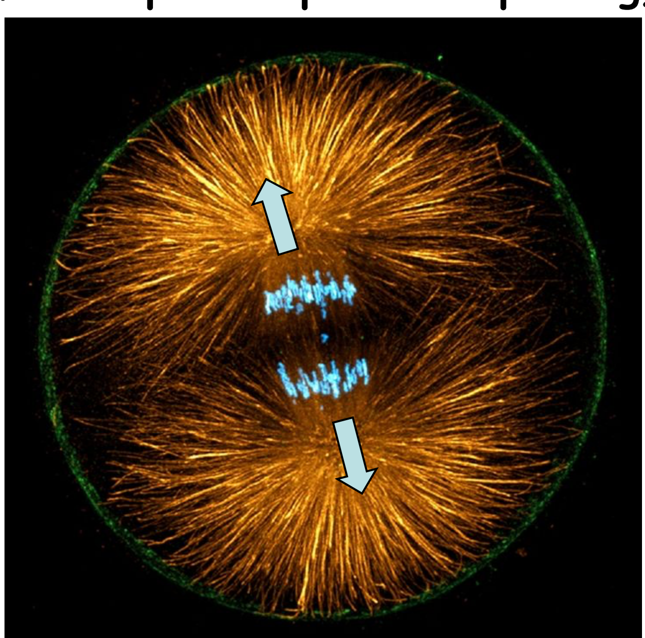
Fertilization involves union of sperm and eggs. Fertilization involves union of nuclei.

The result of fertilization is the the embryo possesses 2 copies of each chromosome

That is the two haploid gametes fuse to produce a diploid zygote

Chromosomes do not lose their individuality.
They are inherited intact- one copy from each parent.

During division they split lengthwise and separate from one another (must replicate prior to splitting).



Mendel’s background

Gregor Mendel was born on 20th July, 1822 in Heizendorf (today Hynice in the Czech Republic).

From 1851 to 1853, Mendel studied Physical and Biological sciences at the University of Vienna.

He studied botany under Prof. Unger where he learned genetic crosses

He studied physics under Prof. Doppler where he learned statistics

Mendel returned to Brno and began his experiments with the hybrid cultivation of pea plants in 1856.

After spending eight years carrying out experimental work in the monastery garden, he reported on the results of his observations at the meetings of the Association for Natural Research in Brno on the evenings of February 8th and March 8th, 1865 and published in 1866

Why Peas?

Perfect Propagation Properties of Pea Plants

Mendel choose the common garden pea as a model system to study patterns of inheritance because of the following properties:

Diversity- a wide array of varieties available with distinct shapes and colors

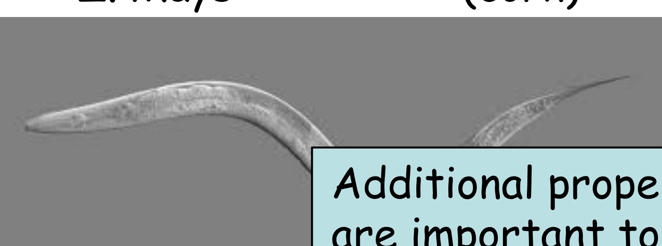
Easy to self and cross pollinate

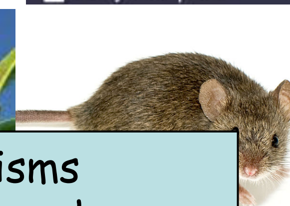
Short generation time

Cheap easy to grow

Model genetic organisms currently used include

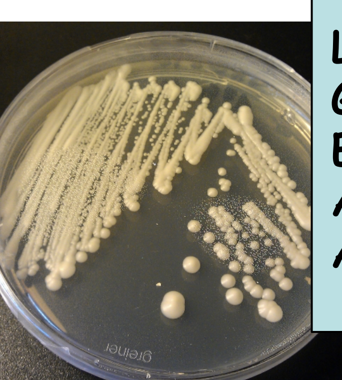
A. thaliana	(small flowering plant)
E. coli	(gut bacteria)
S. cerevisiae	(bakers yeast)
D. melanogaster	(fruit fly)
C. elegans.	(worm)
B. rerio	(zebrafish)
M. Musculus.	(mouse)
Z. Mays	(corn)

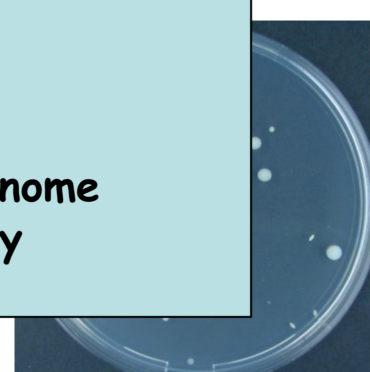




Additional properties of model organisms are important to modern genetic research:

Location in evolutionary tree
Genome size
Ease of cloning a gene
Ability to insert DNA back into genome
Ability to manipulate experimentally





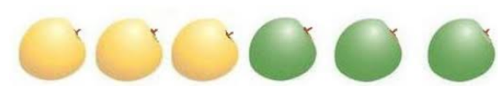
The first two years of Mendel's studies were devoted to identifying and selecting over 30 lines that breed true for a given trait

For example he identified plants that produced only round seeds and plants that produced only wrinkled seeds

We say these plants are pure-breeding for the wrinkled or round trait

Mendel also created pure-breeding lines for

Seed color- yellow versus green



Seed shape- round versus wrinkled

Flower color- red versus white

Mendel's work site and garden

Mendel's first crosses

P yellow male X green female ----> All yellow

Reciprocal cross

P yellow female X green male ----> All yellow

These results do not fit with:

Blending theory of inheritance
(should have gotten a blend between yellow and green colored seeds)

Preformation theory of inheritance
(reciprocal crosses would not be expected to produce the same result)

Mendel's second cross:

Pure-breeding yellow pea plants were crossed to pure-breeding green pea plants

All of the progeny were yellow pea plants

The yellow plants were selfed:

The progeny consisted of 6022 yellow and 2001 green

The standard way of diagramming Mendel's crosses are:

P: green x yellow	P= Parental
F1: yellow	F1= 1st filial generation
F2: 6022 yellow, 2001 green	F2= 2nd filial generation

Although others were doing similar experiments at the time, Mendel's approach was unique because he:

1. Generated pure breeding lines
2. Analyzed individual characters rather than the plant as a whole (ignored development)
3. Counted the progeny

Key results:

--In all crosses, the F1 generation showed only one of two alternative traits
--It did not matter which parental variety was male and which was female: the results were the same (these are known as reciprocal crosses
--The trait not present in the F1 reappeared in the F2 and was always present in about 25% of the offspring

Conclusions:

1. Traits do not blend
2. Each parent makes an equal contribution to the genetic make-up of the organisms

Some terms:

Dominant and Recessive

The trait that is expressed in the F1 is dominant and the trait that is hidden but re-expressed in the F2 is recessive

P: **green** x **yellow**
F1: all **yellow**
F2: 3 **yellow** to 1 **green**
In this cross, **yellow** is dominant, **green** is recessive

Phenotype and Genotype:

It is necessary to make a distinction between the appearance of an organism and its genetic make-up. Phenotype refers to the appearance of an organism and genotype refers to its genetic make-up.

For example Mendel's experiments revealed that while the Parental **yellow** pea plants and the F1 **yellow** pea plants have the same phenotype, they have different genotypes

Parental **yellow**

yellow x yellow

↓

All yellow
(they are pure-breeding)

F1 **yellow**

yellow x Yellow

↓

yellow and green progeny

How many factors are involved in determining seed color?

1. Since yellow and green are both present in the F2, Mendel concluded that each trait must be determined by at least one factor.

2. Reciprocal crosses produce the same results suggesting that the male and female contribute equally.

With these assumptions, the simplest model is that the F1 contains Two hereditary factors: one for green and another for yellow

Some nomemclature:

Uppercase **Y** represents dominant yellow factor
Lowercase **y** represents the recessive green factor

P: Phenotype	**yellow** pea	x	**Green** pea
Genotype	**YY**	x	yy
Gametes	**Y**		y
F1: Phenotype	**yellow**		
Genotype	**Y**y		

The Principle of Segregation

According to Mendel, while the parents have two factors they produce gametes containing only a single factor

Mendel correctly reasoned that without a mechanism to half the number of factors each generation, the factors would double with each generation

Therefore his model included the proposition that during gamete formation, the paired factors separate and each gamete receives one of the two factors

Mendel's assumption of each individual possessing two factors that segregate during gamete formation makes a strong prediction concerning the genetic make-up of the F1 and F2 pea plants

Phenotype	Genotype		
P: **yellow x green**	**YY**	x	yy
Gametes	(1/2**Y**, 1/2**Y**)		(1/2y, 1/2y)
F1: **all yellow**	**Y**y		

If these F1 plants are allowed to self-fertilize

yellow male × yellow female

Yy × Yy

1/2**Y** 1/2y
Male gametes

1/2**Y** 1/2y
Female gametes

These male and female gametes randomly combine to produce The F2 progeny. The process is often diagrammed with a Punnett square:

	1/2**Y**	1/2y
1/2**Y**	1/4**YY**	1/4**Y**y
1/2y	1/4**Y**y	1/4yy

So the F2 genotype and phenotype ratios are as follows

Genotype: 1/4**YY** 1/2**Y**y 1/4yy

Phenotype; **3/4 yellow** **1/4 green**

Genotype: 1/4YY 1/2Yy 1/4yy

Phenotype; **3/4 yellow** **1/4 green**

Based on his segregation model, Mendel inferred genotypes from the observed phenotypes.

For example , the model predicts that of the F2 yellow plants, there should be a 2:1 ratio of **Yy: YY**

That is: 2/3 should be **Y**y and 1/3 should be **YY**

Mendel tested this model by selfing each of the F2 plants

Genotypes of the yellow F2 plants: 1/3 **YY** and 2/3 **Y**y

YY **Y**y **Y**y

Each of these yellow plants is selfed

What are the predicted phenotypes and ratios?

If instead of selfing the F2 plants, they are crossed to pure-breeding green plants (yy), what are the expected outcomes?

Crossing unknown *genotype* to the homozygous recessive is known as a <u>Testcross:</u>

<u>F2 genotypes</u> <u>Expected phenotypes</u>

$\mathbf{YY} \times yy$

$\mathbf{Y}y \times yy$

$\mathbf{Y}y \times yy$

$\mathbf{Y}y \times yy$

These crosses provided convincing evidence that the inheritance of the green and yellow traits in peas was determined by two factors that segregated during gamete formation

Therefore underlying the 3:1 (yellow to green) phenotypic ratio in the F2 was a 1:2:1 genotypic ratio ($\mathbf{YY}$: $\mathbf{Y}y$: yy)

Some terms:

Mendel's factors are now known as *genes*
We say there is a gene for seed color
"gene" coined in 1909 referring to an abstract unit of inheritance. Now has a very concrete definition: a linear segment of DNA

Alternate forms of a *gene* that determine different phenotypes of a *given* trait are known as alleles
The *gene* encoding seed color has distinct alleles for green and yellow

Individuals with two identical alleles of a *given gene* are said to be homozygous for that *gene*
True breeding green plants are homozygous for the recessive green allele

Individuals with two different alleles of a *given gene* are said to be heterozygous for that *gene*
Non true breeding yellow plants are heterozygous for the yellow allele

The dihybrid cross and the principle of independent assortment

Mendel also investigate the pattern of inheritance for two two set of traits

Pea shape: **Smooth**, wrinkled
(**Smooth** is dominant to wrinkled)

Cotyledons color: **Yellow**, green
(**Yellow** is dominant to green)

Cotyledons are the embryonic leaves of seed-bearing plants

P: **Smooth**, Yellow X wrinkled , green

F1: **Smooth**, Yellow

(Self fertilize)

F2:			**Ratio**
Smooth,	Yellow	315	9
Smooth,	green	108	3
wrinkled,	Yellow	101	3
wrinkled ,	green	32	1

The 9:3:3:1 ratio is much more complex than the 3:1 ratio of the crosses involving a single trait (mono-hybrid)

Embedded in this dihybrid ratio is the classic 3:1 ratio of the monohybrid cross

P: **Smooth**, Yellow X wrinkled , green

F1: **Smooth**, Yellow

(Self fertilize)

			Ratio
F2:	**Smooth**, Yellow	315	9
	Smooth, green	108	3
	wrinkled, Yellow	101	3
	wrinkled , green	32	1

To determine the mode of inheritance of the two genes in this dihybrid cross Mendel examined each of the traits separately: If we examine seed shape (smooth, wrinkled) and ignore cotyledon color (yellow, green), in the F2, we expect to find 3/4 smooth and 1/4 wrinkled:

	Ratio
Smooth: 315 + 108 = 423	**3**
wrinkled: 101 + 32 =. 108	**1**

If we examine only cotyledon color, we expect to find…….

The 9:3:3:1 ratio of the dihybrid cross provides strong evidence for the principle of independent assortment

That is the wrinkled trait and the green trait behave as a standard recessive found in monohybrid cross

Therefore the origin of the 9:3:3:1 ratio can be diagrammed as follows;

3/4 Smooth	3/4 Yellow	3/4 x 3/4= 9/16
	1/4 green	3/4 x 1/4= 3/16
1/4 wrinkled	3/4 Yellow	3/4 x 1/4= 3/16
	1/4 green	1/4 x 1/4= 1/16

What is the biological significance of the 9:3:3:1 ratio?

This ratio is only produced if the different gene pairs assort independently during gamete formation

That is, the presence of the allele of one gene in a gamete does not influence the probability of the allele of another gene being found in that gamete. The events are independent.

This is similar to flipping coins. The outcome of flipping one coin does not affect the outcome of flipping a second

This cross can be diagrammed as follows:

P: SS**YY** × ssyy

Smooth, **Yellow** — wrinkled, green

Gametes: S**Y** — sy

F1: Ss**Y**y

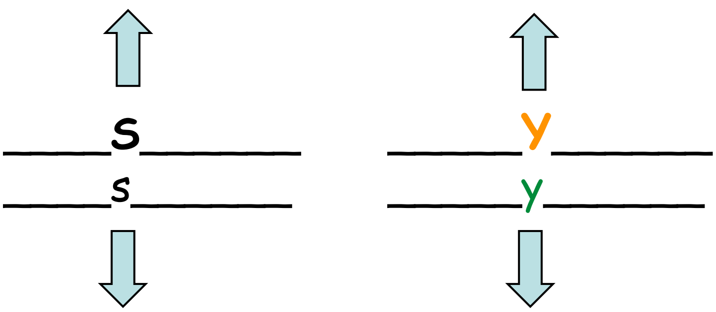
(selfed)

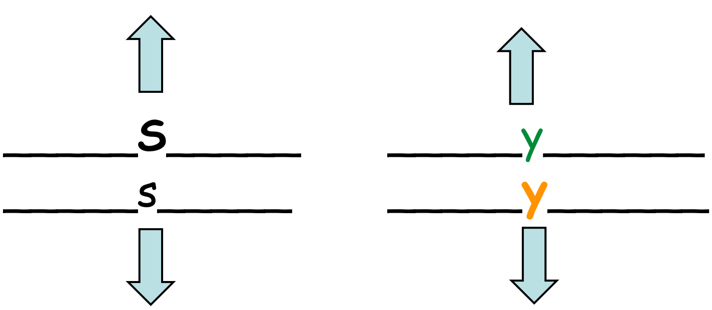
Ss**Y**y × Ss**Y**y

If independent assortment is occurring, four different kinds of gametes will be produced in equal frequencies.

The key rule is that S and s segregate into separate gametes and **Y** and y segregate into separate gametes (that is one does not get an Ss-bearing gamete or a **Y**y-bearing gamete

Because genes are on chromosomes, a better way of diagramming this is:





The punnett square provides a means of calculating the Progeny and ratios from a dihybrid cross

Given this pattern of segregation, SyYy males and females will produce four types of gametes in equal frequencies

SY Sy sY sy

The male and female gametes randomly combine during fertilization and diploidy (two copies of each gene) is restored.

The probability of pairing specific male and female gametes during fertilization is often diagrammed in a Punnett square:

	SY	Sy	sY	sy
SY				
Sy				
sY				
sy				

Therefore the 9:3:3:1 phenotypic ratio is a direct outcome of applying Mendel's two laws:

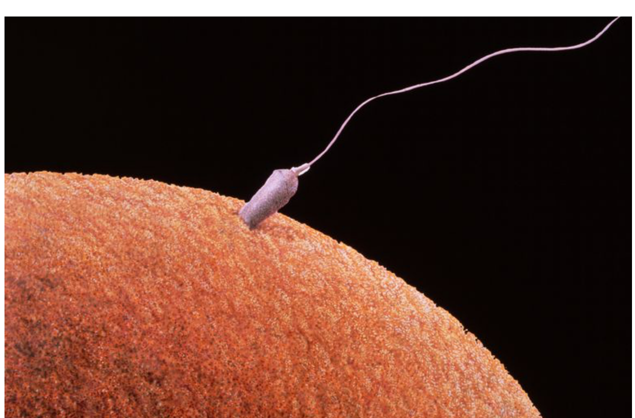
1. The principle of segregation: Each individual two carries two copies of a given gene and these segregate from one another during gamete formation

2. The principle of independent assortment: the segregation of one pair of genes is independent of the segregation of any other gene pair (we will find there are important exceptions to this rule)

By applying these rules, Mendel concluded that SsYy individuals produced the following gametes in a 1:1:1:1 ratio

SY Sy sY sy

Once the gamete ratios are determined, the progeny ratios are simply the probability of random fusion of male and female Gametes (sperm and egg) during fertilization



A more direct method of inferring genotypes and gamete ratios produced from SsYy individuals is through a testcross

These Smooth, Yellow individuals are crossed to wrinkled, green individuals (ssyy). Because they are expressing the recessive traits, we know they are homozygous for the recessive alleles

SsYy × ssyy
(female) (male)

sy

	Genotype	Phenotype
SY		
Sy		
sY		
sy		

P:

-------------	x	--ssyy-----
female		male

F1: 50% **Smooth**, **Yellow**

50% **Smooth**, green

Pea shape: **Smooth**, wrinkled
(**Smooth** is dominant to wrinkled)

Cotyledons color: **Yellow**, green
(**Yellow** is dominant to green)

What is the genotype of the female parent

Hint: Answer this by focusing on a single trait at a time

The power of Mendelian ratios to inform us about the number of genes controlling a specific trait

These ratios provide a direct read-out of the number of genes controlling a trait

3:1 ratio= Trait controlled by a single gene

9:3:3:1 = Trait controlled by two genes

For example, what if seed color were controlled by 2 genes: **S**/s and **T**/t

sstt= green   and all other genotypes= yellow

What are the genotypic and phenotypic ratios produced in the F2 of this cross:

P: **SSTT**   x   sstt

F1:   **S**s**T**t
(self)

F2:
9 **S**_ **T**_
3 ss **T**_
3 **S**_ tt
1 ss tt

15 yellow: 1 green
is a simple variant of
9:3:3:1 ratio

These conclusions about Mendelian ratios gene number can be applied to other traits such as:

Behavior   Size   Morphology   Personality

This brings us to dogs and their amazing genetic diversity

Dogs probably originated from the Ancient Wolf at least Two different occasions on opposite sides of the Eurasian continent some 12,000-15,000 years ago.

Through years of intense selective breeding, there are now over 300 breeds of dogs

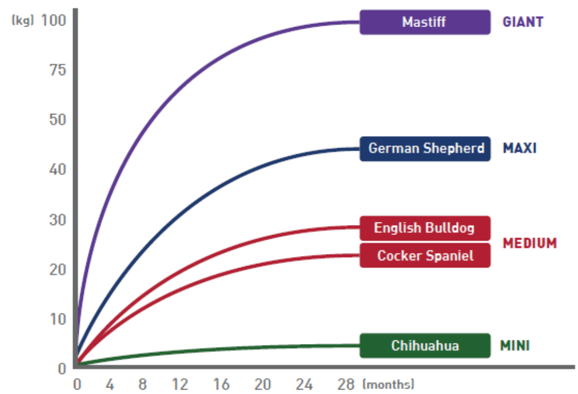
Incredible diversity in

1. Physical make-up:
   coat color, coat hair, height, mass, morphology (snout etc)

2. Intelligence

3. Behavior: Herding, Tracking, Retrieving, Guarding,

Mastiff and Chihuahua differ by 100 fold in weight yet they are the same species!



Also extreme variability in head, snout, body type and coat

Importantly, all breeds can successfully mate with
One another and produce viable offspring

Viable offspring even produced from dog/wolf
dog/coyote matings

How many genes control each of these traits?

A project initiated by Dr. Jasper Rine at UCB is an example of how basic Mendelian principles are currently being used to identify genes that control morphology and behavior

This project takes advantage of the fact that dogs breeds exhibiting tremendous differences in morphology and behavior are able to breed with one another.

The research used Newfoundlands and Border Collies to identify genes controlling behavior

Newfoundlands weigh 140 pounds and are excellent swimmers

Border collies weigh 50 pounds and are natural herders

Questions that can be addressed by geneticists

1. How many genes involved in determining specific behaviors and morphology?

2. What is the identity of the these genes?

3. What is the function of these genes?

The Mendelian principles discussed today enable us to Address the first question

Using these two breeds, we can test two models concerning the swimming trait:

1. One gene controls preference to swim

2. Two genes control the preference to swim

P:

Mom
"Pepper"
- Easygoing
- Affectionate
- Water-loving
- Loyal
- Extra-large
- All black coat

Dad
"Gregor"
- Brainy
- Intense
- Water-avoiding
- Workaholic
- Medium-size
- White marking

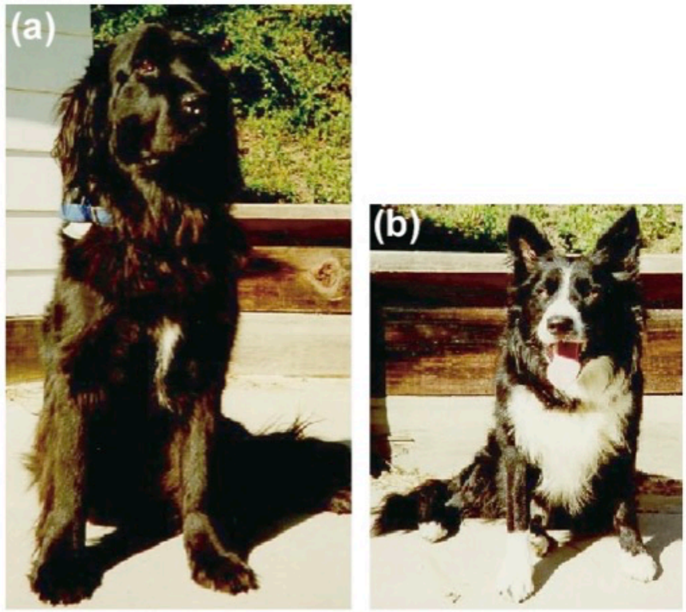


Figure 1
A Newfoundland female **(a)** was bred to a Border Collie male **(b)** to produce animals for the intercross.

F1:

Newfloundland parent

Border Collie parent

Which traits were under investigation?

Trait/behavior	Newfoundland	Border Collie
size	extra large	medium
coat color	all black	black with white markings
showing eye	absent	strong
crouch	absent	strong
eye contact with owner	absent	strong
biddability	absent	strong
tail posture when running	held high	held low
barking at home	moderate	very low
running gait	bounding	sprint
scent vs sight	scent	sight
sensitivity to noise	insensitive	sensitive
water preference	high	low
people in water	attentive/intervening	indifferent
affection demands	high	low
sociability with other dogs	high	low

How many genes control the <u>preference for swimming</u> trait?

Model 1: One gene controls swimming preference and Swimming is dominant to non-swimming

S = swimming. s = non-swimming

Border collies are homozygous for the non-swimming gene
Their genotype is ss

Newfoundlands are homozygous for the swimming gene.
Their genotype is **SS**

P: **SS** x ss
Newfoundland Border Collie

F1: **S**s (Newfoundland/Collie mix)

F2:

	S	s
S		
s		

Model 1: Two genes control swimming preference
Both dominant forms required for swimming

S = swimming.
s = non-swimming

F = swimming
f= non-swimming

P: **SSFF** x ssff
Newfoundland — Border Collie

F1: **S**s**F**f (Newfoundland/Collie mix)

F2: What is the expected ratio of swimmers/ non-swimmers?

More on Hybrid Dogs

The progeny of crosses between different pure-bred dogs
Are usually robust healthy dogs

Retriever: AAbbCCDD (b= hip problems)

Husky: AABBccdd. (c= cataracts/other eye problems)

F1: AABbCcDd

Heterozygous at many genes including those for recessive harmful traits

X

This F1 hybrid is heterozygous for recessive deleterious alleles

What would the F2 look like?

Lets answer that question by specifically focusing on the dog jaw

In dogs, the length of the upper and lower jaws are Controlled by different genes

Upper jaw: T= long t=short

Bottom jaw. B= long b=short

Cross and long snouted dog to a short snouted dog

P: TTBB x ttbb

Gametes: TB tb

	Genotype	Phenotype
F1:	TtBb	Long snout

What about the F2?

The problem with the F2 generation

P: TTBB (long(	x	ttbb (short)
F1:	TtBb (long)	

Gametes: TB Tb tB tb

Punnett Square

	TB	Tb	tB	tb
TB				
Tb				
tB				
tb				

The problem with F2's

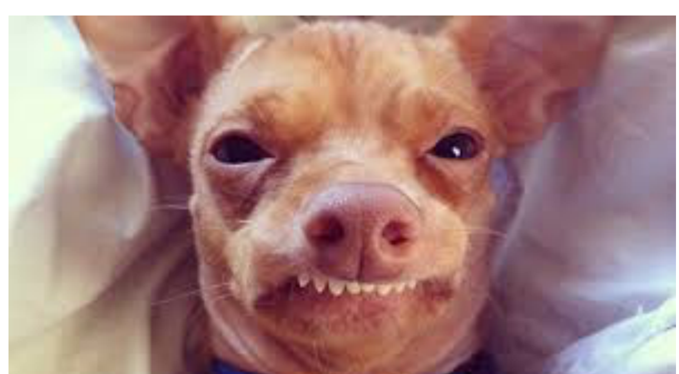
Upper jaw: T= long t=short

Bottom jaw. B= long b=short

What are the potential genotypes for dogs with overbite or Underbite?

Severe Underbite

Severe Overbite



Dogs are becoming model organisms for studying human disease

Because of intensive inbreeding many dog breeds suffer From genetic disorder that also occur in humans

Dobermans are at risk for nacrolepsy

Scotties are at risk for hemophila

Terriers are at risk for copper metabolism defect Known in humans as Menke's disease

Labrador retriever at high risk for hip dysplasia

Beagles at risk for seizures

Dogs are also becoming a model for research in human cancer

VIDEO OF NACROLEPTIC DOG

(https://www.youtube.com/watch?v=jTj3a2nHw8k&t=46s)