Do progeny inherit traits from their parents in predictable ways?

Gregor Mendel (1822-1884) sought to answer this question through careful breeding experiments.

Gregor Mendel and his garden in Brno, Czech Republic
(formerly Brunn, Moravia)

Prevalent views of inheritance before Mendel

"Preformation" / uniparental inheritance

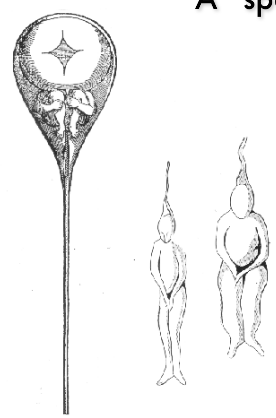
Inherited characteristics were determined by information from just one parent (the female if you were an "ovist," the male if you were a "spermist").

However, various qualities could be modulated by their environment, just as plants grown in different soils will appear different and produce different yields.

Blended inheritance

Offspring somehow merge information from both parents, resulting in a unique version of information and a change of the original information.

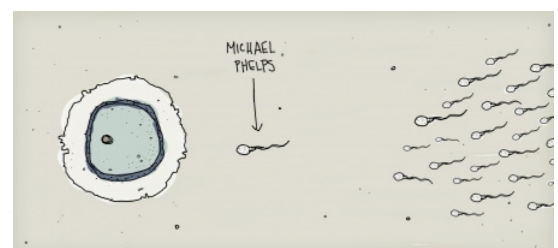
A "spermist" view of inheritance



Nicolas Hartsoeker - 1695

Microscopic observation of rapidly-moving "spermatozoa" (seed animals) seemed to validate the spermists' view that sperm were alive, while the egg seemed relatively passive.

Michael Phelps - In the beginning



Patrick Moberg - 2008

Are there still spermists among us?

Problems with existing theories...

- Lacked explanatory or predictive power

Why do offspring sometimes look like a blend of their parents, and sometimes "favor" one or the other?

How do some traits "skip" generations, but then reappear later?

Why does the putative "blending" of traits result in such obvious differences among the offspring of the same parents?

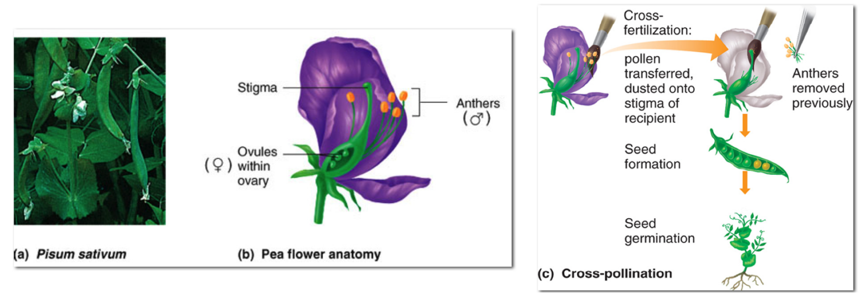
Why are some traits - for example, gender - essentially binary?

Why peas?

Due to favorable anatomical properties, pea plants can easily be mated to others (*outcrossed*) in a controlled fashion, in either direction (♀ x ♂).

Individual plants can also be crossed to themselves (*self-crossed* or just *selfed*).

There is little chance of accidental contamination with pollen (♂) from another plant.



(a) *Pisum sativum* (b) Pea flower anatomy (c) Cross-pollination

Matings produce large numbers of seeds (progeny), permitting robust statistical analysis.

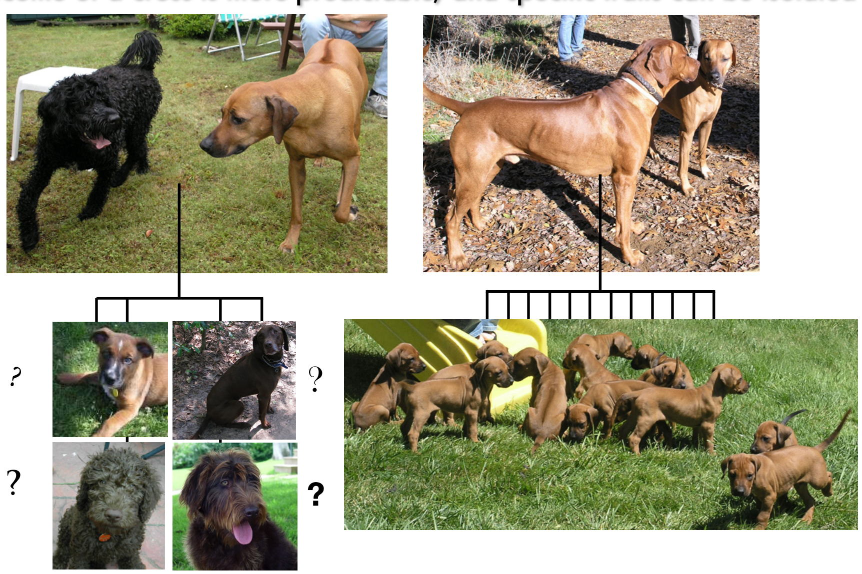
The generation time is short (2 months*), making it possible to do lots of experiments.

Many plants can be cultivated in a small space, and they are easy to grow.

Hybrids between different variants are generally robust and fertile.

*Gurney's Seed and Nursery Co.

When the parents are "purebred" or "inbred" or "true-breeding," the outcome of a cross is more predictable, and specific traits can be isolated



In addition to picking an excellent experimental organism, Mendel also made some prescient decisions about which phenotypes ("characters") to study

He observed a distinction between two types of characters:

1. The hybrid plant is intermediate in phenotype between two parents. For example, the offspring of a tall and a short plant might be intermediate in height.

2. The hybrid plant has a phenotype like one of the parents. For example, a cross between green x yellow seeded plants yields only yellow seeded plants.

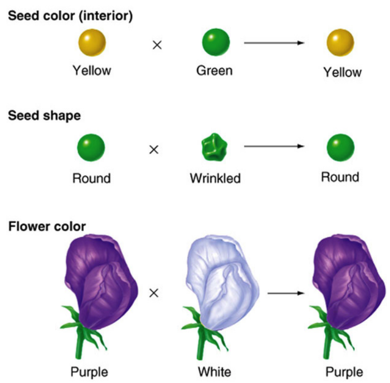
Mendel chose to study traits of the latter type – a judicious decision.

We now know that the laws he discovered also apply to "type 1" traits, but this type of quantitative inheritance is considerably more difficult to follow.

Mendel focused on 7 traits, each of which satisfied 2 criteria:

1. The trait showed two discrete states in two pure-breeding parental lines
2. A breeding between two plants consistently produced "hybrid" offspring that emulated one of the parents, rather than some intermediate or alternate state

Parental (P_0) appearance — F_1 hybrid



Monohybrid crosses revealed units of inheritance and the Law of **Segregation**.

Generation

Parental (P)
true-breeding

First filial (F_1)
hybrid

all yellow

Second filial (F_2)

6022 yellow
2001 green
= 3:1

Mendel's deductions:
Traits have *dominant* and *recessive* forms.

- Disappearance of traits in F1 generation and reappearance in the F2 generation disproves the hypothesis that traits blend.
- Trait must have two forms, each of which can breed true.
- One form must be hidden when plants with each trait are interbred.
- Trait that appears in the F1 generation is dominant.
- Trait that is hidden in the F1 generation, but reappears, is recessive.

- *Nota bene*: dominant and recessive are operationally defined with respect to specific alleles and their interactions. An allele that is dominant in combination with a particular allele might be recessive or semidominant with another allele.

Mendel's first law: **Segregation of Traits**

yellow pea
from a pure-breeding stock
YY

grows into plant → produces eggs and pollen → Y, Y

green pea
from a pure-breeding stock
yy

grows into plant → produces eggs and pollen → y, y

pollen + egg

Y + y

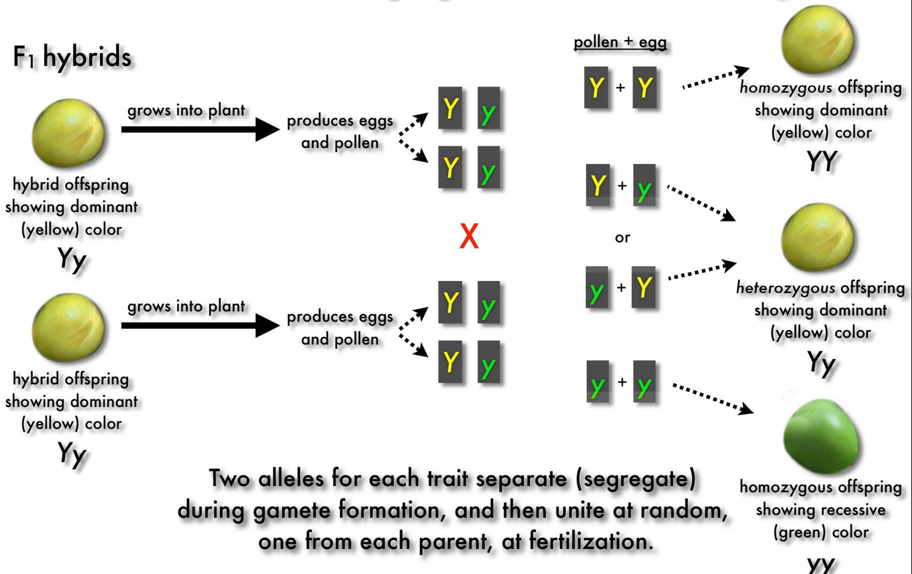
or

y + Y

hybrid offspring showing dominant (yellow) color
Yy

Two alleles for each trait separate (segregate) during gamete formation, and then unite at random, one from each parent, at fertilization.

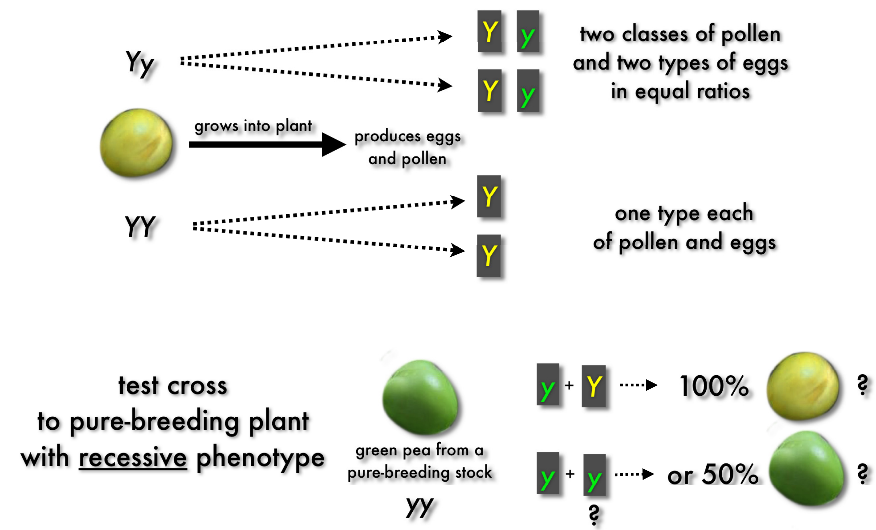
Mendel's first law: **Segregation of Traits**



Two alleles for each trait separate (segregate) during gamete formation, and then unite at random, one from each parent, at fertilization.

This gives rise to a 3:1 phenotypic ratio among the F$_2$ progeny.

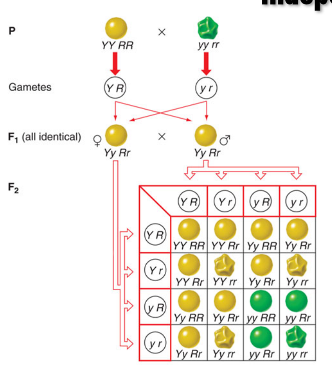
How can you tell whether an F$_2$ expressing a dominant trait is homozygous (YY) or heterozygous (Yy)?



On your own (or in discussion sections):

Go through the discussion of "dihybrid crosses" (crosses involving two different traits) in the textbook and make sure that you understand how Mendel derived his second law:

Independent Assortment



Type	Genotype	Phenotype	Number	Phenotypic Ratio
Parental	Y– R–	yellow round	315	9/16
Recombinant	yy R–	green round	108	3/16
Recombinant	Y– rr	yellow wrinkled	101	3/16
Parental	yy rr	green wrinkled	32	1/16

Ratio of yellow (dominant) to green (recessive) = 12:4 or 3:1
Ratio of round (dominant) to wrinkled (recessive) = 12:4 or 3:1

It is difficult to overstate the brilliance or significance of Mendel's insights

He demonstrated for the first time, in a single paper,* that:

- the units of inheritance are "particulate," not blended
- phenotypes are determined by a combination of two discrete particles, one from each of the reproductive cells that give rise to an organism
- it is inconsequential whether a particular particle is inherited through the pollen or the ovum
  - that is, both sexes make equal contributions to the progeny
- distinct traits are determined independently of each other

He did all of this with no knowledge of DNA, meiosis, or chromosomes, and no understanding of the biochemical basis for the traits he studied.

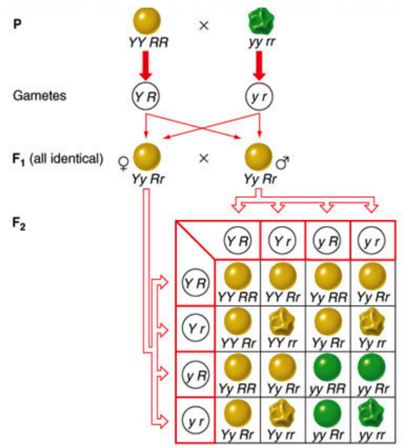
Not only did he design, execute and interpret a set of painstaking, clever, and completely novel experiments, but he also had to invent a vocabulary and notation system to describe and document his findings.

Why, then, was his work lost in obscurity for 35 years, until 16 years after his death?

Some of this was circumstantial - he was a monk, and a failed academic.

* This paper is well worth reading and can be found online in English translation at http://www.mendelweb.org/Mendel.html

The Punnett Square is a very useful tool to consider the possible outcomes of a genetic cross systematically



As the number of possible gamete classes gets large, this representation becomes unwieldy.
At this point it may be better to use a more abstracted, mathematical approach.

Calculating the probabilities of *combinations* of independent events

In many of the problems for Chapter 2, you are asked to figure out the likelihood that a particular combination of circumstances will arise.

Usually it is not difficult to calculate the probability of each individual event occurring, based on Mendel's laws

The probability that *both* event A *and* event B will occur

= the product of their probabilities (P_A x P_B)

Calculating the probabilities of *combinations* of independent events

The probability that *either* A or B will occur...

If A and B are *mutually exclusive events*, then
$P_{(A \text{ or } B)}$ = the sum of their individual probabilities = (P_A + P_B)

NOTE: in the lecture I only dealt with the case where A and B are mutually exclusive events.

If A and B are *not* mutually exclusive, then
$P_{(A \text{ or } B)} = P_A + P_B - P_{(A \text{ and } B)}$
$= P_A + P_B - (P_A \times P_B)$

This formula includes a correction for that fact that when you add P_A and P_B, the occasions on which both A and B occur are counted twice, so you need to subtract one set of those occasions.

Calculating the probabilities of *combinations* of independent events

How would you calculate the probability that *neither* A *nor* B will occur??

First, you might realize that "neither A nor B" is logically equivalent to "(not A) *and* (not B)"

Then you might recognize that the probability that A *will not* occur can be easily related to the probability that A *will* occur:
The probability that *either* (A will occur) *or* (A will not occur) is 1

written mathematically: $P_A + P_{(not\ A)} = 1$

Thus: $P_{(not\ A)} = 1 - P_A$

So, the probability of [(not A) *and* (not B)] occurring
= $(1 - P_A) \times (1 - P_B)$

Calculating the probabilities of *combinations* of independent events

These general rules of probability can be extended to more than two independent events

For example:
The probability that either A or B will occur *and* C will *not* occur
$= [P_A + P_B - (P_A \times P_B)] \times (1 - P_C)^*$

*if A and B are mutually exclusive, you would drop the $-(P_A \times P_B)$ term

Very often, solving a genetics problem primarily involves translating the language of the problem into logical operators (*and, or, not, etc.*) so that it can be formulated using these basic mathematical functions

A liver-nosed male Rhodesian Ridgeback dog (Cooper) was bred to a black-nosed Ridgeback female (Mizani).

Both parents had obvious back ridges and were negative for a defect called *dermoid sinus*, which often occurs in this breed of dogs.

(All Ridgebacks that lack a ridge or have dermoid sinus are neutered by breeders.)

<u>12 puppies resulted from this mating</u>

8 were male (♂); 4 were female (♀)

10 had ridges, 2 (1 ♂, 1 ♀) did not

All 12 had black noses

None had dermoid sinus (phew!)

What can you deduce about the inheritance of the ridged-back trait and nose color?
What were the likely genotypes of the parents?
Why might dermoid sinus continue to be a problem in this breed, if dogs that show it are never bred?

For a answers, see the next slide...

A liver-nosed male Rhodesian Ridgeback dog (Cooper) was bred to a black-nosed Ridgeback female (Mizani).

Both parents had obvious back ridges and were negative for a defect called *dermoid sinus*, which often occurs in this breed of dogs.

(All Ridgebacks that lack a ridge or have dermoid sinus are neutered by breeders.)

What can you deduce about the inheritance of the ridged-back trait and nose color?

Answer: The fact that ridgeless puppies emerged from a breeding between two ridged parents indicates that the ridge is dominant over the ridgeless phenotype, since recessive traits can be "hidden" by dominant traits.
The fact that all puppies had black noses indicates that a black nose is likely to be dominant over a liver nose.

<u>12 puppies resulted from this mating</u>

8 were male (♂); 4 were female (♀)

10 had ridges, 2 (1 ♂, 1 ♀) did not

All 12 had black noses

None had dermoid sinus (phew!)

What were the likely genotypes of the parents?

Answer: The parents must both be heterozygous for the ridged trait, since they gave rise to homozygous non-ridged (recessive) puppies. The father must be homozygous for the liver-nosed trait, if it is indeed recessive. The mother is very likely to be homozygous for the black nosed trait, since 100% of the puppies inherited a black-nosed allele.

Why might dermoid sinus continue to be a problem in this breed, if dogs that show it are never bred?

Answer: It turns out that dermoid sinus is caused by the same mutation that causes the ridge. Dogs that are homozygous for the ridged trait have a higher probability of dermoid sinus. By selecting for dogs that have a ridge but don't have dermoid sinus, breeders have continually selected for heterozygotes for the ridge trait.

Molecular characterization of the "ridge" mutation

nature genetics

Duplication of *FGF3*, *FGF4*, *FGF19* and *ORAOV1* causes hair ridge and predisposition to dermoid sinus in Ridgeback dogs

Nicolette H C Salmon Hillbertz[1], Magnus Isaksson[2], Elinor K Karlsson[3,4], Eva Hellmén[2,5], Gerli Rosengren Pielberg[6], Peter Savolainen[7], Claire M Wade[3,8], Henrik von Euler[9], Ulla Gustafson[1], Åke Hedhammar[9], Mats Nilsson[2], Kerstin Lindblad-Toh[3,6], Leif Andersson[1,6] & Göran Andersson[1]

The dorsal hair ridge in Rhodesian and Thai Ridgeback dogs is caused by a dominant mutation that also predisposes to the congenital developmental disorder dermoid sinus. Here we show that the causative mutation is a 133-kb duplication involving three fibroblast growth factor (FGF) genes. FGFs play a crucial role in development, suggesting that the ridge and dermoid sinus are caused by dysregulation of one or more of the three FGF genes during development.

Dogs with a characteristic dorsal hair ridge seem to have been present in both Africa and Asia long before European colonization (**Fig. 1**). The Rhodesian Ridgeback dog (**Fig. 1a**), first registered in South Africa in 1924, is most likely a blend of European dogs (brought to Africa by early colonizers) and an extinct indigenous breed of Africa, the ridged Hottentot Khoi dog[1]. The Thai Ridgeback (**Fig. 1b**) and the Vietnamese Phu Quoc dog are two Asian breeds with a dorsal hair ridge closely resembling the one found in Rhodesian Ridgeback dogs.

Histology of the skin from a ridged dog, taken strictly from the dorsal median plane, showed cross-sectioned appendages (that is, hair follicles and sebaceous glands) of normal appearance but lateral orientation (**Fig. 1d**). In contrast, skin from the median plane of a ridgeless dog showed caudally oriented hair follicles (**Fig. 1e**). Ridgeback dogs are affected by the congenital malformation dermoid sinus

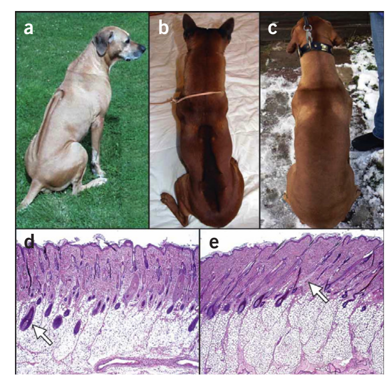


Figure 1 Phenotypes of Rhodesian and Thai Ridgeback dogs. (**a**,**b**) The

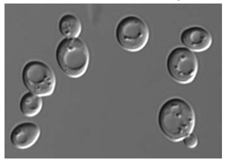
Some organisms are especially well-suited to genetic analysis

- "The value and utility of any experiment are determined by the fitness of the material to the purpose for which it is used..." (Mendel, 1865)

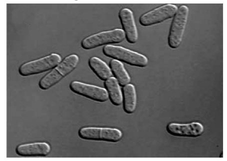
Prokaryotes

The bacterium *Escherichia coli*

Single-celled fungi



The budding yeast (baker's yeast)
Saccharomyces cerevisiae

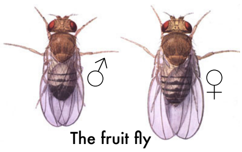


The fission yeast
Schizosaccharomyces pombe

Plants

The flowering plant
Arabidopsis thaliana

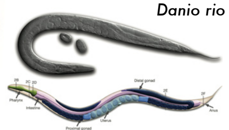
Animals



The fruit fly
Drosophila melanogaster

The zebrafish
Danio rio

The laboratory mouse
Mus musculus



The nematode
Caenorhabditis elegans