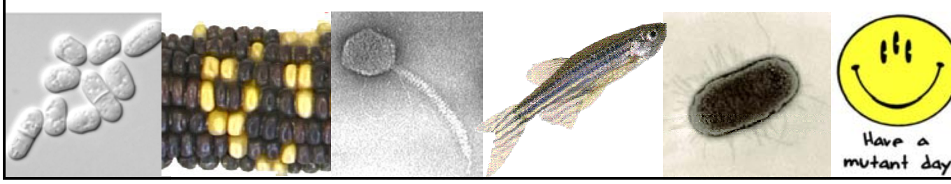
Biology 321 Genetics
Spring 2008

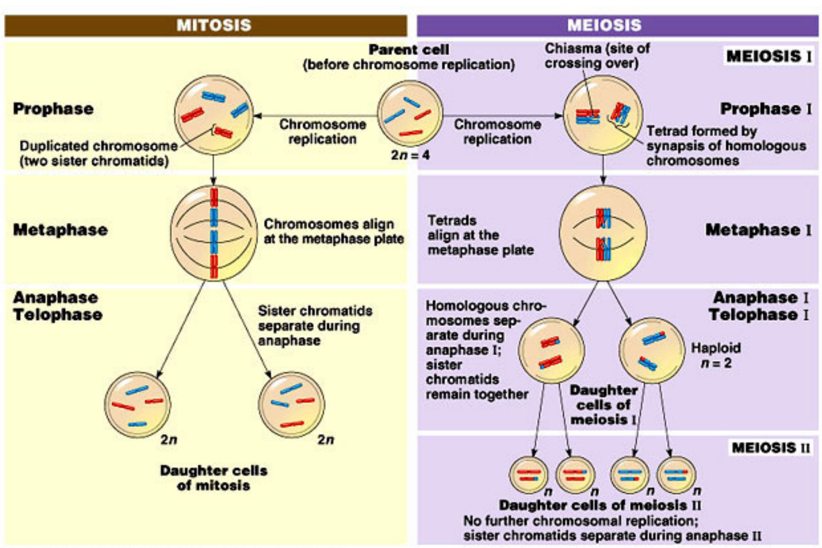
Dr. Sandra Schulze

Office BI409

Office Hours: WF 2:30PM – 3:30PM

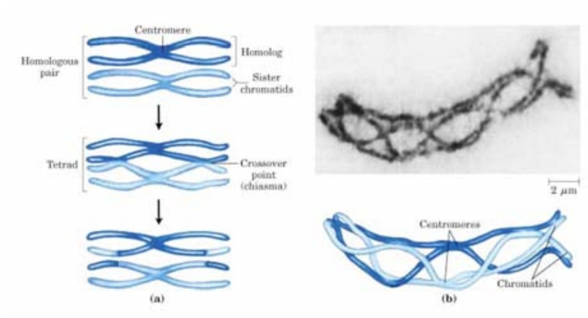


Last lecture….



Last lecture….

- What events happen during Prophase I of meiosis that do not occur in Prophase of mitosis?
  – Synapsis: close pairing of homologs
- What is crossing-over?
  – A precise breakage and reunion event that occurs between two non-sister chromatids



We will look at the genetic implications of recombination later in future lectures

Lecture 2: Introduction to Transmission Genetics

Sometimes referred to as "Classical Genetics"

Text readings: Chapter 1 (all) and Chapter 2 (pp. 31-50).

Note that many of the text problems from Ch. 1 & 2 will be assigned later. You can try them now but I will not cover them now.

Problems from text you CAN do now:

Chapter 1: none

Chapter 2: #4, 5, 6, 8, 9, 14, 16, 17

What is Genetics?

- Experimental science of heredity
- Plant and animal breeders needed a better understanding of inheritance of economically important traits
- Gregor Mendel: discovered principles of heredity
- Today, genes are explained in molecular terms

Transmission Genetics

- Transfer ("transmission") of observable traits from one generation to the next
- Observable "traits" can be physical, chemical, behavioral – this is known as the phenotype
- These "traits" are encoded by genetic information, which we now refer to as the genotype

What is the relationship between genotype and phenotype?

- To what extent do your genes determine your (insert subject here)
  - Behaviour
  - Intelligence
  - Temperament
  - Susceptibility to disease
  - Hopes, dreams, nightmares, habits…….etc?

Is it genetic?

- There is a complex interplay between genes and the environment
- Genes provide potential; environment plays a role in determining how that potential is realized

Molecular basis of genetics

- Genetic material is usually DNA, a double helix of complementary polynucleotides.
- Genes are segments of DNA encoding the amino acid sequence of proteins.
- The DNA of a (eukaryotic) cell is broken up into a series of (usually) linear pieces complexed with proteins – these are the chromosomes.
- In diploid organisms chromosomes come in pairs.
- Hereditary variation is caused by variant forms of genes known as alleles.
- Since alleles are different forms of the same gene, they occupy the same locus (place) on the chromosome.
- Alleles, like chromosomes, come in pairs in each individual (although there may be MANY variant alleles in a population).
- Alleles arise due to changes (mutations) in DNA sequence.

This is a mutant gene

```
>gi|17488858|ref|XM_010627.4| Homo sapiens SRY (sex determining
region Y)-box 13 (SOX13)
GGCATGTGAGCGGGAAGCCTAGGCTGCCAGCCGCGAGGACCGCACGGAGGAGGAG
CAGGAGCGCGGAGCCGCGAGCCCCGAGCCCCGAGCCCGGCGCCTGGCTGAGTAGAT
GTCCATGAGGAGCCCCATCTCTGCCCAGCTGGCCCTGGATGGCGTTGGCACCATGGT
GAACTGCACCATCAAGTCAGAGGAGAAGAAAGAGCCTTGCCACGAGGCCCCCCAGG
GCTCAGCCACTGCCGCTGAACCTCAGCCTGGAGACCCAGCCCGGGCCTCCCAGGAT
AGTGCTGACCCCCAAGCTCCAGCCCAGGGGAATTTCAGGGGCTCCTGGGACTGTAG
CTCTCCAGAGGGTAATGGGTCCCCAGAACCCAAGAGACCAGGAGTGTCGGAGGCTG
CCTCTGGAAGCCAGGAGAAGCTGGACTTCAACCGAAATTTGAAAGAAGTGGTGCCA
GCCATAGAGAAGCTGTTGTCCAGTGACTGGAAGGAGAGGTTTCTAGGAAGGAACTC
TATGGAAGCCAAAGATGTCAAAGGGACCAAGAGAGCCTAGCAGAGAAGGAGCTCC
AGCTTCTGGTCATGATTCACCAGCTGTCCACCCTGCGGGACCAGCTCCTGACAGCCC
ACTCGGAGCAGAAGAACATGGCTGCCATGCTGTTTGAGAAGCAGCAGCAGCAGATG
GAGCTTGCCCGGCAGCAGCAGGAGCAGATTGCAAAGCAGCAGCAGCAGCTGATTCA
GCAGCAGCATAAGATCAACCTCCTTCAGCAGCAGATCCAGCAGGTTAACATGCCTT
ATGTCATGATCCCAGCCTTCCCCCCAAGCCACCAACCTCTGCCTGTCACCCCTGACT
CCCAGCTGGCCTTACCCATTCAGCCCATTCCCTGCAAACCAGTGGAGTATCCGCTGC
AGCTGCTGCACAGCCCCCCTGCCCCAGTGGTGAAGAGGCCTGGGGCCATGGCCACC
CACCACCCCCTGCAGGAGCCCTCCCAGCCCCTGAACCTCACAGCCAAGCCCAAGGC
CCCCGAGCTGCCCAACACCTCCAGCTCCCCAAGCCTGAAGATGAGCAGCTGTGTGCC
CCGCCCCCCCAGCCATGGAGGCCCCACGCGGGACCTGCAGTCCAGC
                              ↓
                              T
```

PHENOTYPE

postaxial polydactyly type A1

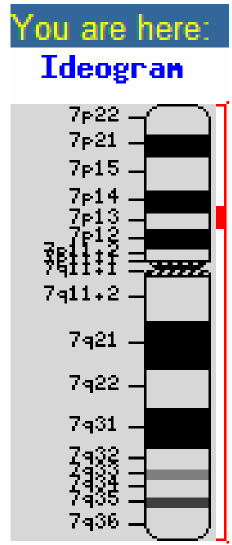
GENOTYPE

GLI3^{-}

GLI-Kruppel family member GLI3

(Greig cephalopolysyndactyly syndrome)

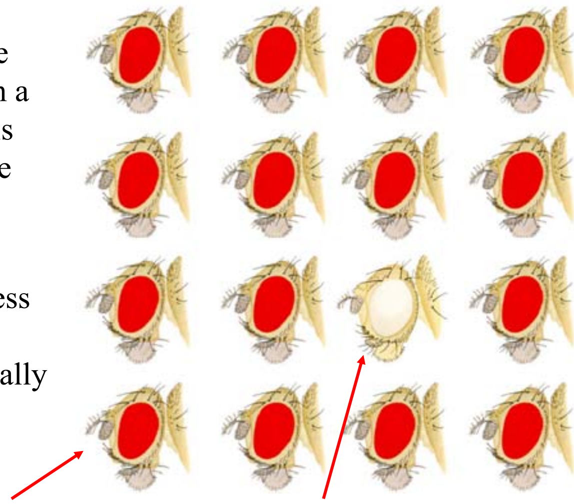
GENE LOCUS



Mutant vs. wild-type (according to Google)

Mutant vs. wild type (according to genetics)

- Wild type alleles are the most common in a population (does this necessarily mean the "best" allele?)
- Mutant alleles are less common in a population (and usually detrimental)



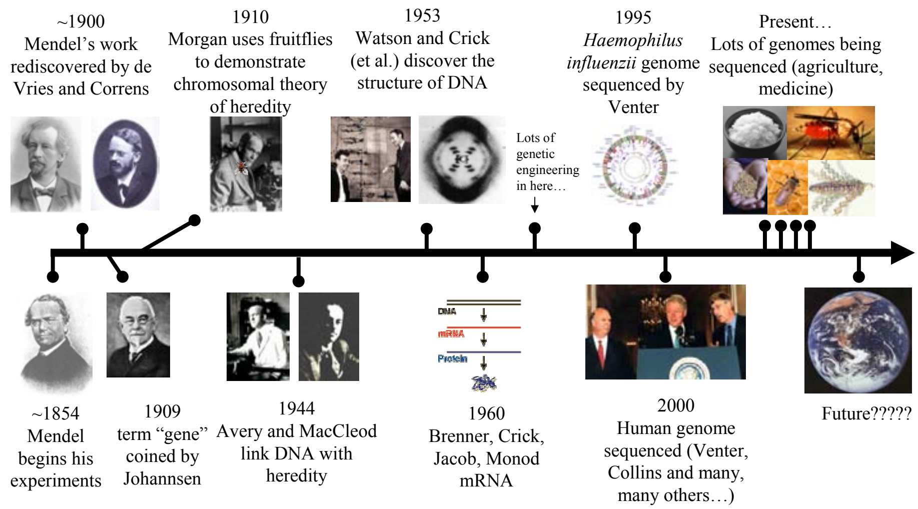
w^+ = "white plus" = wild-type

$w = w^-$ = "white minus" = mutant

Genetic Methods

- Isolation of mutations (natural or induced)
- Analysis of progeny of controlled matings (crosses)
- Genes mapped to positions on chromosomes
- Biochemical analysis of underlying cellular processes
- Microscopic analysis of chromosomes (cytogenetics) and phenotypes
- Direct analysis of DNA
  - genomics: sequencing and annotating genomes
  - bioinformatics: extraction of information from DNA

Mad Romp through History

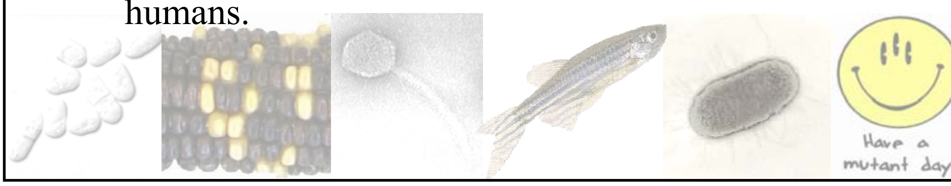


How did Mendel infer the existence of a gene in the 1860's?

- He inferred the existence of a *hereditary factor*
- He didn't *make* the rules, he just helped to *explain* them
- Chose a useful model organism
- Used scientific methodology (large numbers, quantification, reproducibility)
- Developed symbolism to represent abstract hereditary determinants
- Applied the basic rules of probability to explain transmission of phenotypic ratios

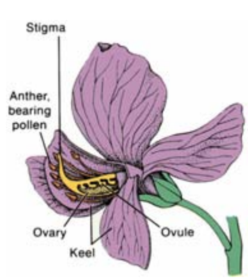
Model Organisms

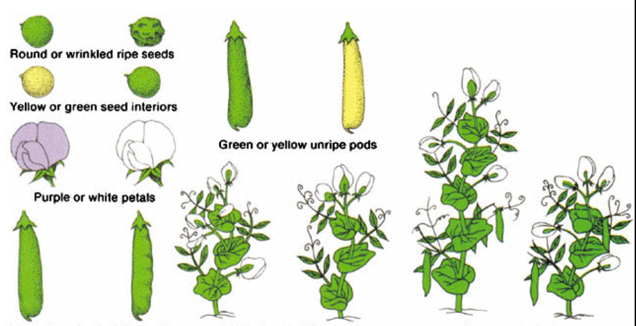
- genetic analysis is carried out on a small number of representative species.
- selected for particular aspects of their life cycle or biological/genetic features that make them especially useful. (short life span, inexpensive, lots of progeny etc.)
- most principles of inheritance and gene and cell function can be extended to other organisms e.g. humans.



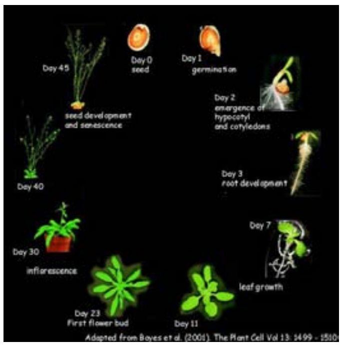
Pea Plant (*Pisum sativum)*

Used for Mendel's classic experiments. Possesses a number of well-defined, true-breeding characteristics





Wall cress (*Arabidopsis thaliana*)



- primary plant model organism for studying molecular genetics.
- Life span can be manipulated by environmental conditions
- Genome sequenced 2000.

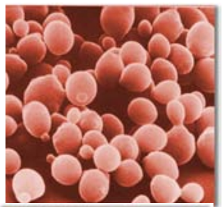
Bacteria (*Escherichia coli*)

E. coli Bacterium

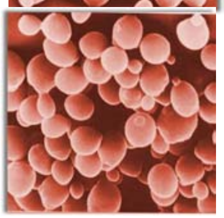
- enormous numbers of cells per unit volume-allows analysis of very rare genetic events.
- simple genome in comparison to eukaryotes.
- Prime organism for recombinant DNA technology
- Genome sequenced 2001

Baker's Yeast (*Saccharomyces cerevisiae*)

"boys"



"girls"



- single celled haploid eukaryote
- can be crossed to produce diploid cell which then undergoes meiosis to reduce chromosome number to haploid.
- very important for genetic analysis of eukaryotic cell cycle.
- Genome sequenced 1996.

Worms (*Caenorhabditis elegans*)

- 3.5 day life cycle (at room temperature); can be easily cultured/maintained on petri plates and fed on bacteria; produce lots of offspring.
- ~1 mm in length; can see internal structures.
- only ~1000 cells in adult; fixed pattern of development, possible to know where each adult cell comes from.
- Genome sequenced 1998.

Fruit Fly (*Drosophila melanogaster*)

- short life cycle 2-3 week length from egg to adult; can be maintained throughout cycle in relatively small bottles or vials.
- produce lots of offspring (progeny).
- complex development; eggs, larvae, pupae and adults.
- lots of genetically determined characters (a lot of pattern).
- Genome sequenced 2000

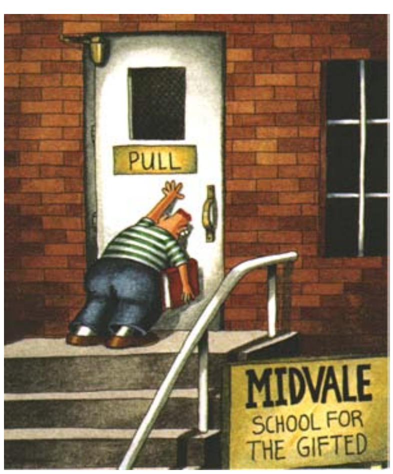
Zebrafish (*Danio rerio*)

- Live about 5 years, produces 300-500 eggs per spawning
- Complex vertebrate model
- Transparent embryos – can study developmental genetics
- Genome sequencing in progress
- (can buy engineered fluorescent versions from pet shops…)

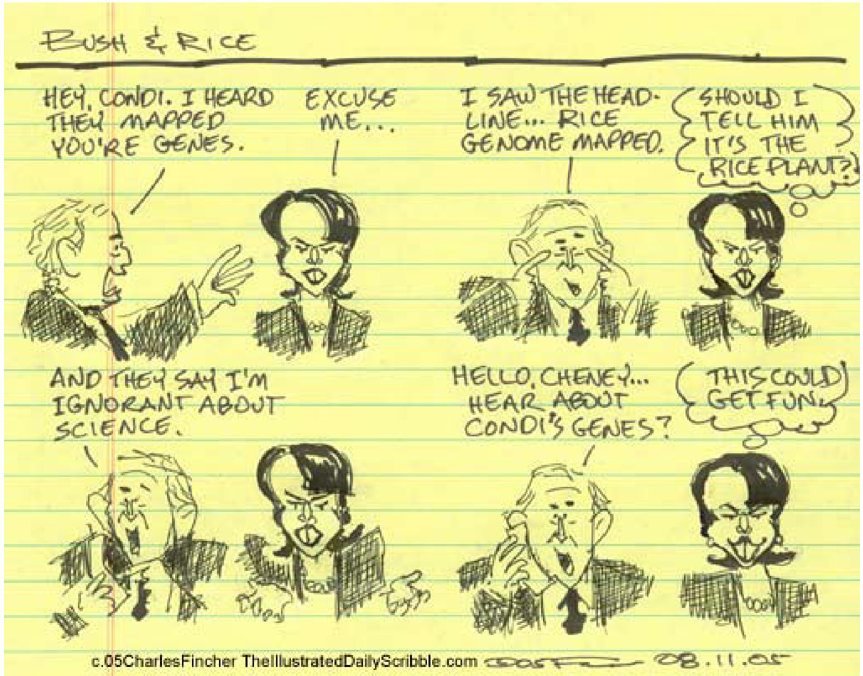
Mouse (*Mus musculus*)

- mammal, model for human diseases.
- Good genetics, BUT much longer life cycle (live 2-3 years, but breed pretty fast!)
- very costly to rear.
- Cute.
- Genome sequenced 2002.

Human (*Homo sapiens*)



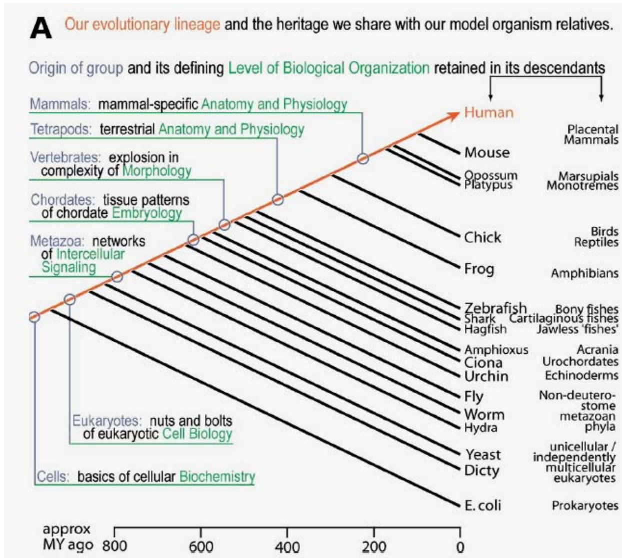
- very long generation time.
- not enough offspring for analysis
- humans insist on choosing their own mates
- only analysis possible is through the use of pedigrees
  - i.e. trace backwards using genealogies.
- NOT a good model organism.
- Genome sequenced 2000



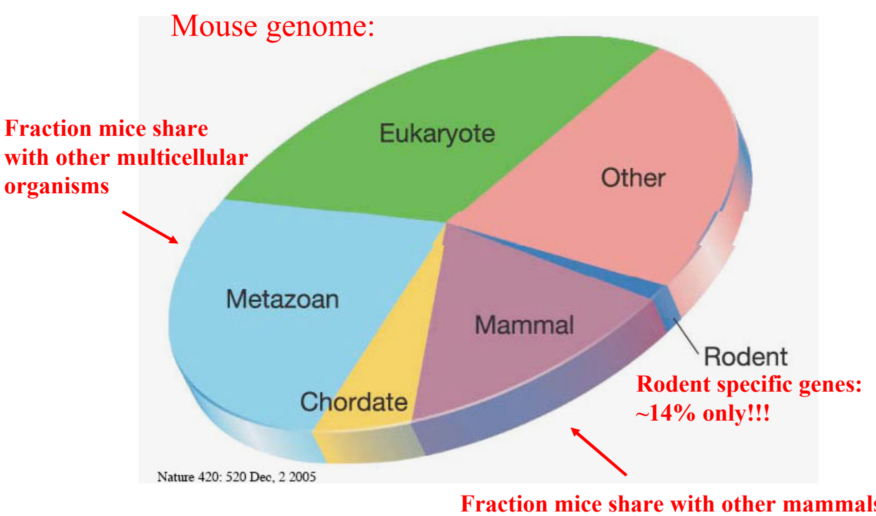
Summary of criteria for model

- Can be raised easily in the lab
- Can produce large numbers of progeny through controlled matings
  - *Why are large numbers important?*
- Short generation time
- Phenotypic variants readily available
- Extension to other organisms

How can flies or mice or plants tell me *anything* about myself???



How can flies or mice or plants tell me *anything* about myself???

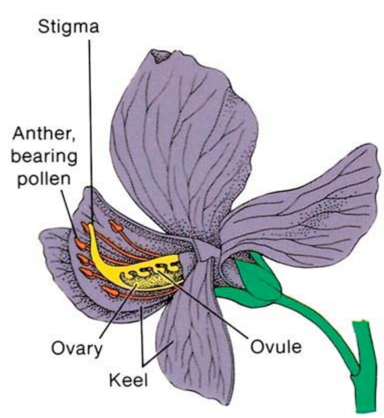


So, model organisms are useful. Why did Mendel choose peas?

"Brother Mendel! We grow tired of peas!"
Cartoon by J. Chase.

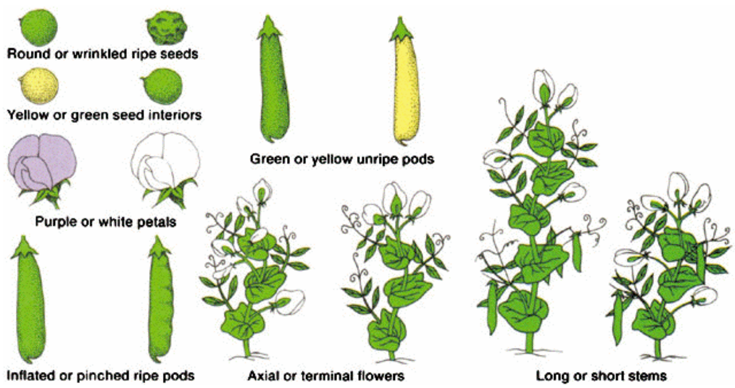
So, model organisms are useful. Why did Mendel choose peas?

- All the usual reasons (easily available, cheap, easy to propagate etc)
- Reproduction of the pea can be artificially manipulated
- Pea plants will self pollinate (=self =self fertilize) unless the anthers of the flower are removed by the experimenter before they release pollen
- Mendel could thus artificially cross-pollinate two different pea plants (controlled breeding)
- Also, he had many different varieties of plants available to him



Easy to score true-breeding traits

For each trait, he selected lines exhibiting one of two alternative variations or forms. For example, for the trait of flower color, each of Mendel's lines were true-breeding for either purple flowers or white flowers. These are alternative phenotypes. A gene is defined by specific phenotypic differences.



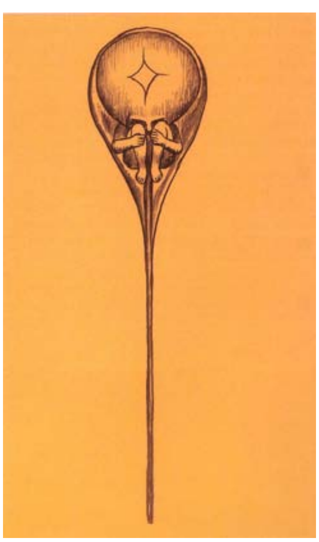
What does true breeding mean?

- Before starting his experiments, Mendel tested his lines for two years to ensure they were *true-breeding*.
- Truebreeding line: a pure line, when selfed or cross-pollinated within the same breeding line, will only give rise to progeny identical to the parents.
- This important step demonstrated that the outcome of selfing (or crossing within) the various strains was predictable and consistent.
- Therefore, deviations following cross-pollination between different strains would be scientifically significant.

Classical definition of a gene

- In classical genetic methodology, the existence of a gene controlling a trait is inferred from phenotypic variation between individual organisms or groups of organisms.
- The inheritance pattern of a specific trait can only be studied if phenotypic differences (mutant alleles) in the trait are available.

What questions did Mendel ask?



- Do males and females contribute equally to the appearance of their offspring?
- Are parental traits irreversibly blended in the offspring?
- Are there basic rules, which can be described mathematically, for the transmission of hereditary elements from one generation to another?

Versuche

über

Pflanzen-Hybriden,

von

Gregor Mendel.

(Separatabdruck aus dem IV. Bande der Verhandlungen des naturforschenden Vereines.)

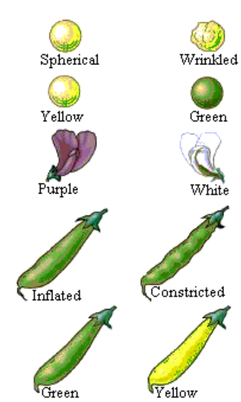
Im Verlage des Vereines.

Brünn, 1866.

Aus Georg Gastl's Buchdruckerei, Postgasse Nr. 446.

Simplicity of Mendel’s design

- Mendel’s characters (short vs tall, round vs wrinkled etc) each controlled by a single gene (“hereditary factor”)
- This is excellent for understanding the basic mechanics of genetics, but life is more complex, and most traits are controlled by many genes. (We will get to that later…)



Bei diesen beiden Versuchen erhält man gewöhnlich aus jeder Hülse beiderlei Samen. Bei gut ausgebildeten Hülsen, welche durchschnittlich 6 bis 9 Samen enthielten, kam es öfters vor, dass sämmtliche Samen rund (Versuch 1) oder sämmtliche gelb (Versuch 2) waren; hingegen wurden mehr als 5 kantige oder 5 grüne in einer Hülse niemals beobachtet. Es scheint keinen Unterschied zu machen, ob die Hülse sich früher oder später an der Hybride entwickelt, ob sie der Hauptaxe oder einer Nebenaxe angehört. An einigen wenigen Pflanzen kamen in den zuerst gebildeten Hülsen nur einzelne Samen zur Entwicklung, und diese besassen dann ausschliesslich das eine der beiden Merkmale; in den später gebildeten Hülsen blieb jedoch das Verhältniss normal. So wie in einzelnen Hülsen, ebenso variirt die Vertheilung der Merkmale auch bei einzelnen Pflanzen. Zur Veranschaulichung mögen die ersten 10 Glieder aus beiden Versuchsreihen dienen:

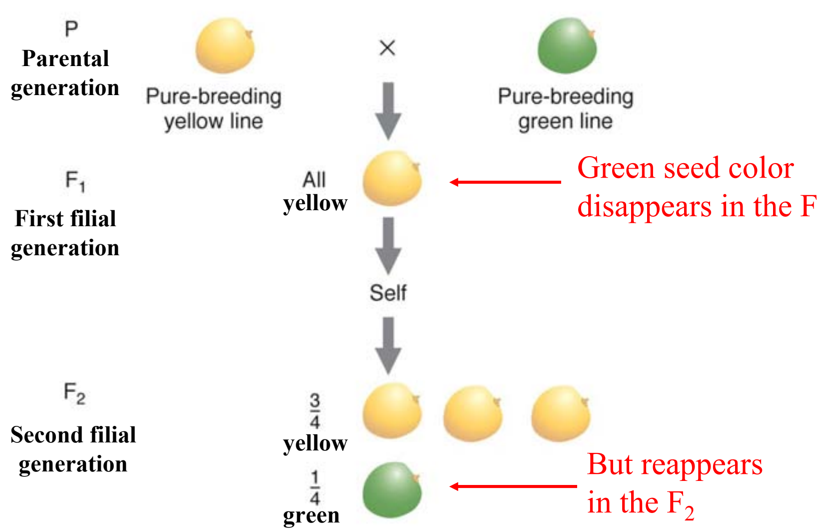
	1. Versuch.		2. Versuch.	
	Gestalt der Samen.		Färbung des Albumens.	
Pflanze	rund	kantig	gelb	grün
1	45	12	25	11
2	27	8	32	7
3	24	7	14	5
4	19	10	70	27
5	32	11	24	13
6	26	6	20	6
7	88	24	32	13
8	22	10	44	9
9	28	6	50	14
10	25	7	44	18

Als Extreme in der Vertheilung der beiden Samen-Merkmale an einer Pflanze wurden beobachtet bei dem 1. Versuche 43 runde und nur 2 kantige, ferner 14 runde und 15 kantige Samen. Bei dem 2. Versuche 32 gelbe und nur 1 grüner Same, aber auch 20 gelbe und 19 grüne.

Diese beiden Versuche sind wichtig für die Feststellung der mittleren Verhältnisszahlen, weil sie bei einer geringeren Anzahl von Versuchspflanzen sehr bedeutende Durchschnitte möglich machen. Bei der Abzählung der Samen wird jedoch, namentlich beim 2. Versuche, einige

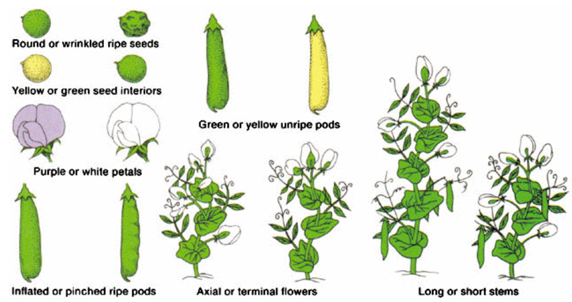
What did Mendel observe

when he crossed two true-breeding lines that differed in a single trait?



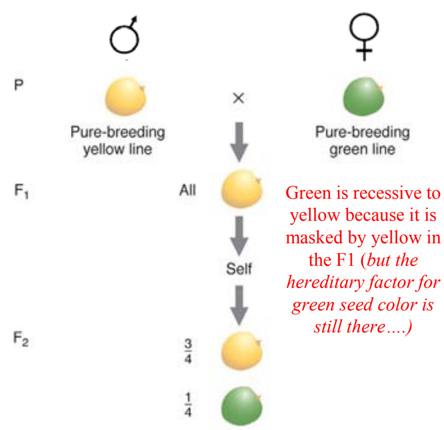
This 3:1 ratio appeared reproducibly for many of his traits

Parental phenotype	F_1	F_2	F_2 ratio
1. Round × wrinkled seeds	All round	5474 round; 1850 wrinkled	2.96 : 1
2. Yellow × green seeds	All yellow	6022 yellow; 2001 green	3.01 : 1
3. Purple × white petals	All purple	705 purple; 224 white	3.15 : 1
4. Inflated × pinched pods	All inflated	882 inflated; 299 pinched	2.95 : 1
5. Green × yellow pods	All green	428 green; 152 yellow	2.82 : 1
6. Axial × terminal flowers	All axial	651 axial; 207 terminal	3.14 : 1
7. Long × short stems	All long	787 long; 277 short	2.84 : 1



Mendel's observations

- Mendel designated the trait that appeared in the F1 as dominant, and the trait that returned as a minority in the F2 as recessive.
- Recessive traits are *masked* by dominant traits in the F1…
- …but the traits remain distinct – *there is no blending of inherited traits*
- Results from reciprocal crosses (pollen from green on stigma of yellow or *vice versa*) were the same, *so both parents contribute equally to the outcome of a cross*



This same pattern of inheritance holds (F1 all dominant phenotypes, F2 characterized by a 3:1 ratio of dominant: recessive phenotypes) regardless of which sex donated pollen in the P generation

Mendel's conclusions

- Mendel proposed that the hereditary determinants for each trait are discrete and do not become blended together in the F1, *but maintain their integrity from generation to generation*.

- Mendel also proposed that, for each trait examined, the pea plant contains two copies of the hereditary determinant (gene) controlling the trait, *one copy coming from each parent*.

Terminology and nomenclature

- Mendel developed a simple symbolism to describe his genotypes.
- Each hereditary factor was given a letter designation, and the dominant trait was capitalized while the recessive trait was lowercase.
  - So the trait for yellow seed color was *Y* for the dominant, *y* for the recessive (green). *Note: this symbolism has not stuck!*
- Now we call a hereditary factor a gene, and the different forms are dominant and recessive alleles.
- Genotypes with identical alleles (*Y/Y* or *y/y*) are homozygous, and genotypes with different alleles (*Y/y*) are heterozygous.
- The slash (/) shows that the alleles form *a pair* (think about where they might physically reside).

Mendel's principle of equal segregation

- Mendel proposed that during gamete formation in the F1, the paired *Y/y* alleles would separate into different gamete cells and that about 1/2 of the gametes would carry the dominant *Y* allele and 1/2 would carry the recessive *y* allele.
- This would be true for both the male and female gametes

Mendel and probability

- Mendel assumed that the male and female gamete cell would combine at random, so, a given *Y* or *y* male gamete would have an equal chance of fertilizing an *Y*-bearing or an *y*-bearing ovule.
- First element of chance: the chance that a gamete is *Y* vs. *y*.
- Second element of chance: the random (with respect to genotype) combination of male gametes with female gametes.
- Therefore, we can the rules of probability to make predictions about the genotypic and phenotypic composition of the F2 progeny.

Rules of probability

- A probability is a measure of the likelihood or chance, that an event will have a particular outcome.
- A probability is usually expressed as a fraction between 0 and 1.
- 1: the event is certain to occur
- 0: the event is certain not to happen
- In all other cases the chance that a particular event will occur increases as the probability approaches 1

The product (*both/and*) rule

- The probability of two independent events both occurring is the product of each of their respective probabilities.
- To use the product rule, the events must be independent: the occurrence of one event cannot affect in any way the probability of the other event occurring
- This rule can apply to multiple independent events

What is the chance that an F2 progeny shows the recessive phenotype?

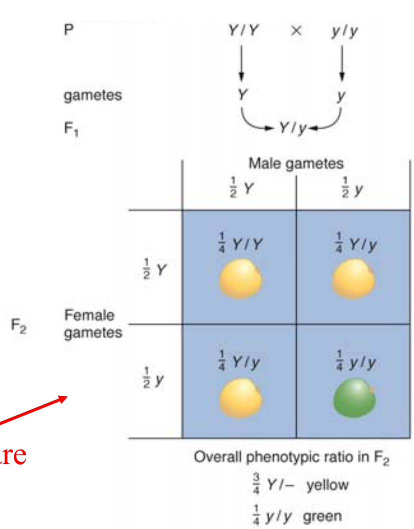
- According to the product (both-and) rule of probability, the probability that a given zygote (that's the cell that results from fertilization) received an *y* allele from both the male and females gametes is 1/2 X 1/2 or 1/4

F1 → *Y/y* X *Y/y*

gametes → ½ *Y* ½ *y* ½ *Y* ½ *y*

Probability F2 is homozygous recessive → ½ *y* x ½ *y* = ¼ *y/y*

What is the chance that an F2 progeny shows the recessive phenotype?



Punnett square

(This is Mr. Punnett)

The sum (either-or) rule

- The probability of either one of two mutually exclusive events occurring is the sum of their respective probabilities
- In other words we are determining the probability of one event OR another event (either-or rule)
- This rule applies to multiple events

What is the chance that an F2 progeny shows the dominant phenotype?

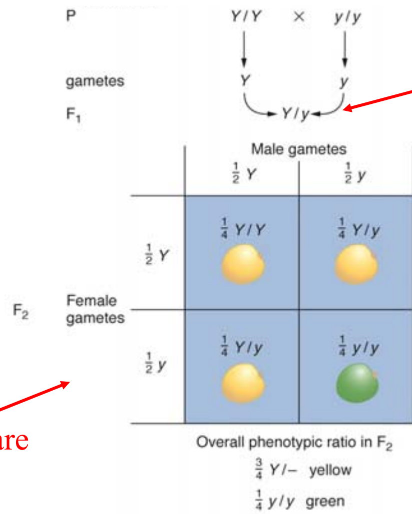
- To show a dominant phenotype, the genotype of the F2 can be either *Y/Y* or *Y/y*.

- The probability of a dominant phenotype

  = (1/2)(1/2) + 2(1/2)(1/2) =3/4

  (*Y/Y*) (*Y/y*)

What is the chance that an F2 progeny shows the dominant phenotype?



Monohybrid

Punnett square

(This is Mr. Punnett)

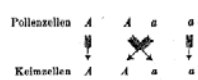
How does this translate to large numbers of progeny?

- Large numbers of progeny represent many independent fertilization events.
- The probabilities of dominant and recessive phenotypes translate into fractions of progeny.
- 3/4 of the F2 progeny should show the dominant phenotype and 1/4 the recessive for the single gene under study.
- This is Mendel's famous 3:1 ratio.

How did Mendel know that the dominant F2's consisted of two different genotypes?

- Self the F2 and examine the F3
- The recessive phenotype should breed true
- But now there are two classes of dominant phenotypes.
- One class breeds true.
- The other class recapitulates the 3:1 ratio.

Fraction of F2	Phenotype of F2	Phenotype of F3	Genotype of F3
1/4	dominant	ALL dominant	*Y/Y*
1/2	dominant	¾ dominant ¼ recessive	*Y/y*
1/4	recessive	ALL recessive	*y/y*



Das Ergebniss der Befruchtung lässt sich dadurch anschaulich machen, dass die Bezeichnungen für die verbundenen Keim- und Pollenzellen in Bruchform angesetzt werden, und zwar für die Pollenzellen über, für die Keimzellen unter dem Striche. Man erhält in dem vorliegenden Falle:

$$\frac{A}{A} + \frac{A}{a} + \frac{a}{A} + \frac{a}{a}$$

Bei dem ersten und vierten Gliede sind Keim- und Pollenzellen gleichartig, daher müssen die Producte ihrer Verbindung constant sein, nämlich A und a; bei dem zweiten und dritten hingegen erfolgt abermals eine Vereinigung der beiden differirenden Stamm-Merkmale, daher auch die aus diesen Befruchtungen hervorgehenden Formen mit der Hybride, von welcher sie abstammen, ganz identisch sind. Es findet demnach eine wiederholte Hybridisirung statt. Daraus erklärt sich die auffallende Erscheinung, dass die Hybriden im Stande sind, nebst den beiden Stammformen auch Nachkommen zu erzeugen, die ihnen selbst gleich sind; $\frac{A}{a}$ und $\frac{a}{A}$ geben beide dieselbe Verbindung Aa, da es, wie schon früher angeführt wurde, für den Erfolg der Befruchtung keinen Unterschied macht, welches von den beiden Merkmalen der Pollen- oder Keimzelle angehört. Es ist daher

$$\frac{A}{A} + \frac{A}{a} + \frac{a}{A} + \frac{a}{a} = A + 2Aa + a.$$

So gestaltet sich der mittlere Verlauf bei der Selbstbefruchtung der Hybriden, wenn in denselben zwei differirende Merkmale vereinigt sind. In einzelnen Blüthen und an einzelnen Pflanzen kann jedoch das Verhältniss, in welchem die Formen der Reihe gebildet werden, nicht unbedeutende Störungen erleiden. Abgesehen davon, dass die Anzahl, in welcher beiderlei Keimzellen im Fruchtknoten vorkommen, nur im Durchschnitte als gleich angenommen werden kann, bleibt es ganz dem Zufalle überlassen, welche von den beiden Pollenarten an jeder einzelnen Keimzelle die Befruchtung vollzieht. Deshalb müs-