Gregor Mendel (1822-1884)

- In 1857-1865, he grew 28,000 pea plants and recorded 7 traits (also called characters) for each plant:

<table>
<thead>
<tr>
<th>Trait</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dominant</td>
</tr>
<tr>
<td>Seed shape</td>
<td>round (R)</td>
</tr>
<tr>
<td>Seed color</td>
<td>yellow (Y)</td>
</tr>
<tr>
<td>Pod shape</td>
<td>inflated (I)</td>
</tr>
<tr>
<td>Pod color</td>
<td>green (G)</td>
</tr>
<tr>
<td>Flower color</td>
<td>purple (P)</td>
</tr>
<tr>
<td>Flower position</td>
<td>axial (A)</td>
</tr>
<tr>
<td>Height</td>
<td>tall (T)</td>
</tr>
</tbody>
</table>

- He kept track of traits in parents and offspring through many generations over all the years of experiments.
Mendel’s model of inheritance (using modern terminology)

• Each trait is determined by a gene.

• Each gene comes in 2 possible versions, called alleles.

• Each individual has two of each gene. (Cells are diploid.)
Example for height and pea shape

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<tr>
<td></td>
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<td>Seed shape</td>
<td>round (R)</td>
</tr>
<tr>
<td>Height</td>
<td>tall (T)</td>
</tr>
</tbody>
</table>

- An individual may have *genotype* TTRr.
- Two copies of each gene: height TT, shape Rr.
- TT results in a tall plant.
- Rr: when both alleles are present, the *dominant* one wins, so the seed shape is round.
- *Genotype* TTRr gives *phenotype* tall and round.
Terminology

- **Dominant**: If genotype is TT or Tt, plant is tall. **Recessive**: If genotype is tt, plant is short.

The dominant allele is uppercase and the recessive allele is lowercase.

- **Homozygous**: both alleles same (TT or tt). **Heterozygous**: mixed alleles (Tt).

- TT: homozygous dominant
tt: homozygous recessive
Tt: heterozygous dominant
Mendel’s First Law
Law of Segregation

• Half the *gametes* (eggs/sperm) an individual produces have one copy of the gene and half have the other copy. (Gametes are *haploid* – just one copy of each gene.)

  ▪ **An individual with** *Rr*: half their gametes have R and the other half have r.

  ▪ **An individual with** *RR*: half their gametes have the “first” R and half have the “second” R. You can’t tell them apart, so they are all R.
Mendel’s First Law
Law of Segregation

• Individuals inherit one allele of each gene from each parent (one via the sperm, one via the egg).

• Example:
  If egg has genotype TR and sperm has genotype Tr, the offspring has genotype TTRr.
Mendel’s Second Law
Law of Independent Assortment

• Different genes are inherited independently.

• Example for two traits at a time:
  - Female genotype: TtRr
    Egg genotypes: TR, Tr, tR, tr
    each in $\frac{1}{4}$ of the egg cells.
  - Male genotype: TTRr
    Sperm genotypes: TR, Tr
    each in $\frac{1}{2}$ of the sperm cells.
Cross TTRr x TtRr

Punnett Square

- Table showing how genotypes in parents → genotypes in offspring.

<table>
<thead>
<tr>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TR (1/2)</td>
</tr>
<tr>
<td>TR (1/4)</td>
<td>TTRR (1/8)</td>
</tr>
<tr>
<td>Tr (1/4)</td>
<td>TTRr (1/8)</td>
</tr>
<tr>
<td>tR (1/4)</td>
<td>TtRR (1/8)</td>
</tr>
<tr>
<td>tr (1/4)</td>
<td>TtRr (1/8)</td>
</tr>
</tbody>
</table>
**Cross TTRr x TtRr**

**Punnett Square**

- Table showing how genotypes in parents $\rightarrow$ genotypes in offspring.

<table>
<thead>
<tr>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTRR (1/8)</td>
<td>TTRR (1/8)</td>
</tr>
<tr>
<td>TTRR (1/8)</td>
<td>TTRr (1/8)</td>
</tr>
<tr>
<td>TtRR (1/8)</td>
<td>TtRr (1/8)</td>
</tr>
<tr>
<td>TtRr (1/8)</td>
<td>TtRr (1/8)</td>
</tr>
</tbody>
</table>

- Combine equivalent genotypes:
  
  \[ P(TTRr) = \frac{1}{8} + \frac{1}{8} = \frac{1}{4} \]
  \[ P(TtRr) = \frac{1}{8} + \frac{1}{8} = \frac{1}{4}. \]
Cross TTRr x TtRr

**Phenotypes**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTRR (1/8)</td>
<td>Tall &amp; round (3/4)</td>
</tr>
<tr>
<td>TTRr (1/4)</td>
<td></td>
</tr>
<tr>
<td>TtRR (1/8)</td>
<td></td>
</tr>
<tr>
<td>TtRr (1/4)</td>
<td>Tall &amp; wrinkled (1/4)</td>
</tr>
<tr>
<td>TTrr (1/8)</td>
<td></td>
</tr>
<tr>
<td>Trr (1/8)</td>
<td></td>
</tr>
<tr>
<td>Trr (1/8)</td>
<td></td>
</tr>
</tbody>
</table>
Exceptions to Mendel’s Laws

These laws are true for the genes Mendel observed, but exceptions to these laws in more experiments lead to many discoveries, including:

- Genes come in chromosomes. The law of independent assortment is only for genes on different chromosomes.
- Sex chromosomes pair XX (female mammals), XY (male mammals), breaking the 2 of each gene rule.
- Some genes have more than 2 alleles. Some traits are determined by combinations of multiple genes.
- Dominant / recessive rules can be more complex.
Multiple alleles: ABO gene

• Human ABO gene determines blood type.
• Alleles A, B, i.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA or Ai</td>
<td>blood type A</td>
</tr>
<tr>
<td>BB or Bi</td>
<td>blood type B</td>
</tr>
<tr>
<td>AB</td>
<td>blood type AB</td>
</tr>
<tr>
<td>ii</td>
<td>blood type O</td>
</tr>
</tbody>
</table>
Thomas Morgan (1866-1945)

- Morgan studied *Drosophila melanogaster* (fruit flies).
- He found traits that did not combine in the predicted proportions. He called them *linked genes*.
- This lead him to discover chromosomes (1908).
- He won the Nobel Prize in Physiology or Medicine 1933 for this. The first U.S. born scientist to win a Nobel Prize. The first Nobel prize in genetics.
Linked genes

• When gametes are formed in *meiosis*, the two copies of each chromosome may be mixed together via *crossovers*.

• **Mother’s two copies of chromosome 1:**

  ![Diagram of linked genes]

• Mother’s autosomal (non-sex) cells are diploid: they have one copy of both.
Linked genes

• When gametes are formed in *meiosis*, the two copies of each chromosome may be mixed together via *crossovers*.

• **Crossover produces two eggs:**

• Each egg has one of each chromosome. Each meiosis is different, though.
Probabilities for linked genes

- Genes on the same chromosome do not sort independently.
- Closer genes have a higher probability of staying together. Example numbers:

<table>
<thead>
<tr>
<th>DF</th>
<th>Df</th>
<th>dF</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>.49</td>
<td>.01</td>
<td>.01</td>
<td>.49</td>
</tr>
</tbody>
</table>

instead of all being 1/4.

- The two recombination probabilities are equal (.01) and the two nonrecombination probabilities are equal (.49).
- The *recombination rate* is r=.01+.01=.02=2% instead of 50%.
Mapping genes

• We will make a scale along the chromosome in units called centi-Morgans (abbreviated cM) or Morgans (abbreviated M).

• The unit Morgan is defined so that crossovers occur at an average rate 1 per Morgan (M) or .01 per centi-Morgan (cM).

• If the recombination rate is exactly \( r = 2\% \), then D and F are approximately 2 centi-Morgans apart (2 cM) on the scale.

• We’ll work out the exact formula.
Crossover probabilities

- If there is an even number of crossovers between two sites, they wind up on the same gamete. The net effect is no recombination.
- If there is an odd number of crossovers between sites, they recombine.

- $AB = \text{event "recombination between A & B"} = \text{"odd # of crossovers between A & B"}$
- $P(AB) = r_{AB}$
- Make analogous definitions for AC, BC.
Recombination rates aren’t additive

• Assume crossovers between A & B are independent of crossovers between B & C.*

• \[ P(AC) = P(AB \cap BC^c) + P(AB^c \cap BC) \]
  \[ = P(AB)P(BC^c) + P(AB^c)P(BC) \]

• \[ r_{AC} = r_{AB}(1 - r_{BC}) + (1 - r_{AB})r_{BC} \]
  \[ = r_{AB} + r_{BC} - 2r_{AB}r_{BC} \]

*Note: There is a phenomenon called crossover interference, which prevents crossovers from occurring too close to each other. There are more complicated formulas for that.
Haldane’s Mapping Function

- $r =$ recombination rate, on a scale from 0 to $\frac{1}{2}$.
- $d =$ distance in Morgans (1 M = 100 cM).

\[
 r = \frac{1}{2} \left( 1 - e^{-2d} \right)
\]

\[
 d = -\frac{1}{2} \ln(1 - 2r)
\]

- $r$ is often on a scale from 0% to 50%, and $d$ is often in centi-Morgans. **They need to be converted to the other scales to use those formulas.**
Haldane’s Mapping Function

• What is the distance if the recombination rate is 2%?

• $r = 2\% = .02$

\[
d = -\frac{1}{2} \ln(1 - 2(.02)) \\
= -\frac{1}{2} \ln(.96) = 0.02041 \text{ M}
\]

so $d = 2.041$ cM.

• For small values,

\[
r (0 \text{ to } \frac{1}{2}\text{ scale}) \approx d \text{ (in Morgans)}
\]

\[
r (\% \text{ scale}) \approx d \text{ (in centi-Morgans)}
\]
Mouse linkage map

- Distance between Pdk2 and D11Moh3:
  \[ d = 55.65 - 55.50 = 0.15 \text{ cM} \]
  \[ = 0.0015 \text{ M} \]
  (use the absolute value)

- Recombination rate
  \[ r = \frac{1}{2} \left(1 - e^{-2(0.0015)}\right) \]
  \[ = 0.001497 \]
  \[ = 0.1497\% \]

Mouse chr. 11: 55.50-55.70 cM.
Linkage map obtained from Mouse Genome Database (MGD),
http://www.informatics.jax.org