Mendel's Laws
Haldane's Mapping Formula

Math 186 / Math 283

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Prof. Tesler

Gregor Mendel (1822-1884)

- In 1857-1865, he grew 28000 pea plants and recorded 7 *traits* (also called *characters*) for each plant:

Trait	Phenotype	
	Dominant	*Recessive*
Seed shape	round (R)	wrinkled (r)
Seed color	yellow (Y)	green (y)
Pod shape	inflated (I)	constricted (i)
Pod color	green (G)	yellow (g)
Flower color	purple (P)	white (p)
Flower position	axial (A)	terminal (a)
Height	tall (T)	short (t)

- 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

Trait	Phenotype	
	Dominant	*Recessive*
Seed shape	round (R)	wrinkled (r)
Height	tall (T)	short (t)

- 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 ¼ of the egg cells.
  - *Male genotype:* TTRr
    Sperm genotypes: TR, Tr
    each in ½ of the sperm cells.

Cross TTRr x TtRr
Punnett Square

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

		Male	
		TR (1/2)	**Tr (1/2)**
Female	**TR (1/4)**	TTRR (1/8)	TTRr (1/8)
	Tr (1/4)	TTRr (1/8)	TTrr (1/8)
	tR (1/4)	TtRR (1/8)	TtRr (1/8)
	tr (1/4)	TtRr (1/8)	Ttrr (1/8)

Cross TTRr x TtRr
Punnett Square

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

		Male	
		TR (1/2)	**Tr (1/2)**
Female	**TR (1/4)**	TTRR (1/8)	TTRr (1/8)
	Tr (1/4)	TTRr (1/8)	TTrr (1/8)
	tR (1/4)	TtRR (1/8)	TtRr (1/8)
	tr (1/4)	TtRr (1/8)	Ttrr (1/8)

- Combine equivalent genotypes:

  P(TTRr)= 1/8 + 1/8 = 1/4

  P(TtRr) = 1/8 + 1/8 = 1/4.

Cross TTRr x TtRr
Phenotypes

Genotype	*Phenotype*
TTRR (1/8) TTRr (1/4) TtRR (1/8) TtRr (1/4)	Tall & round (3/4)
TTrr (1/8) Ttrr (1/8)	Tall & wrinkled (1/4)

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:

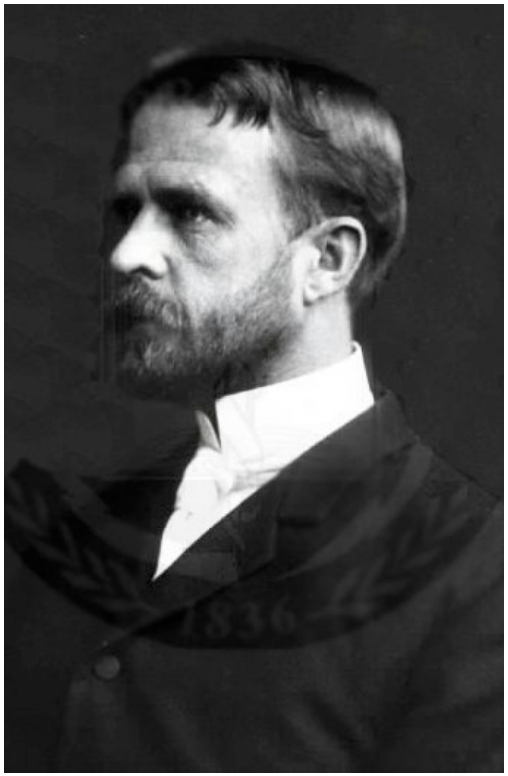
- Genes come in chromosomes. The law of independent assortment is only for genes on different chromosomes.
- Sex chromosomes pair XX (female mammals), XY (male mammals), breaking the 2 of each gene rule.
- Some genes have more than 2 alleles.
  Some traits are determined by combinations of multiple genes.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

Multiple alleles: ABO gene

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

Genotype	*Phenotype*
AA or Ai	blood type A
BB or Bi	blood type B
AB	blood type AB
ii	blood type O

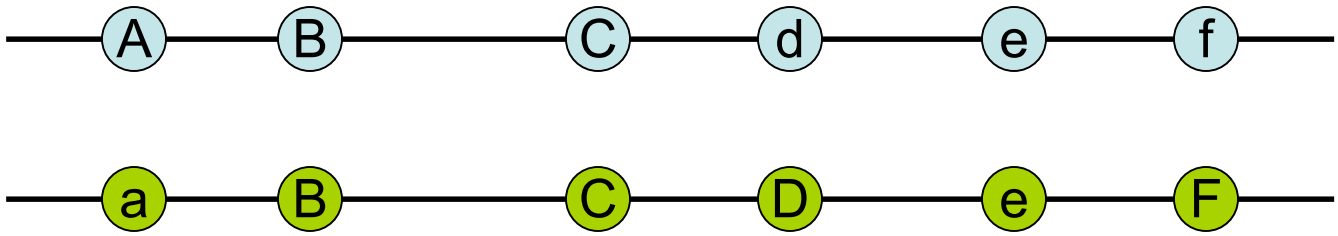
Thomas Morgan (1866-1945)



- 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

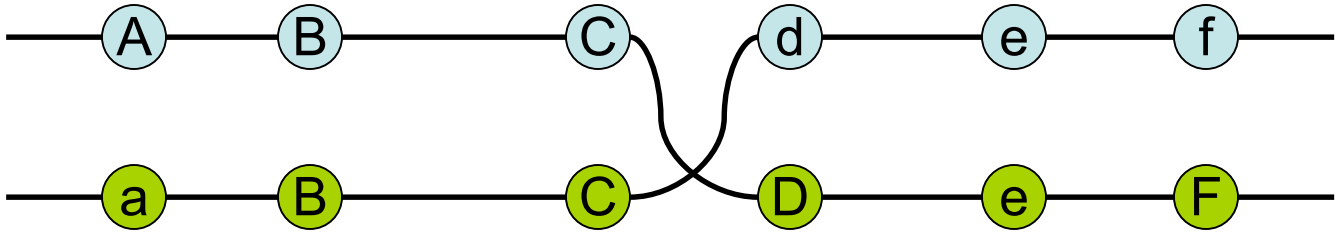
- When gametes are formed in *meiosis*, the two copies of each chromosome may be mixed together via *crossovers*.
- **Mother's two copies of chromosome 1:**



- 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:

DF	Df	dF	df
.49	.01	.01	.49

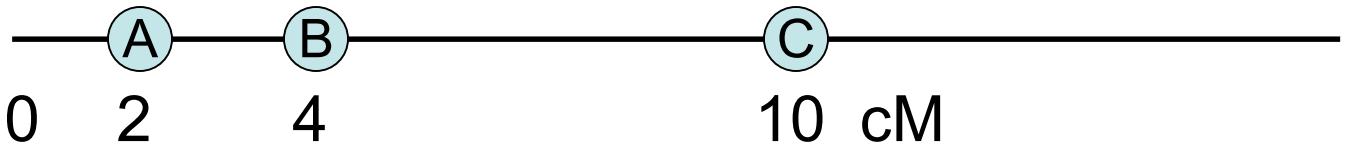
  instead of all being 1/4.
- The two recombination probabilities are equal (.01) and the two nonrecombination probabilities are equal (.49).
- The *recombination rate* is r=.01+.01=.02=2% instead of 50%.

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.

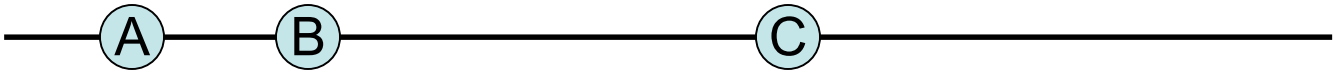
Crossover probabilities



- 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 = event "recombination between A & B"
  = "odd # of crossovers between A & B"
- P(AB) = r_{AB}
- Make analagous 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 ½ .
- *d* = distance in Morgans (1 M = 100 cM).

$$r = \tfrac{1}{2}(1 - e^{-2d})$$

$$d = -\tfrac{1}{2}\ln(1 - 2r)$$

- *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

$$d = -\tfrac{1}{2}\ln(1-2(.02))$$
$$= -\tfrac{1}{2}\ln(.96) = 0.02041 \text{ M}$$

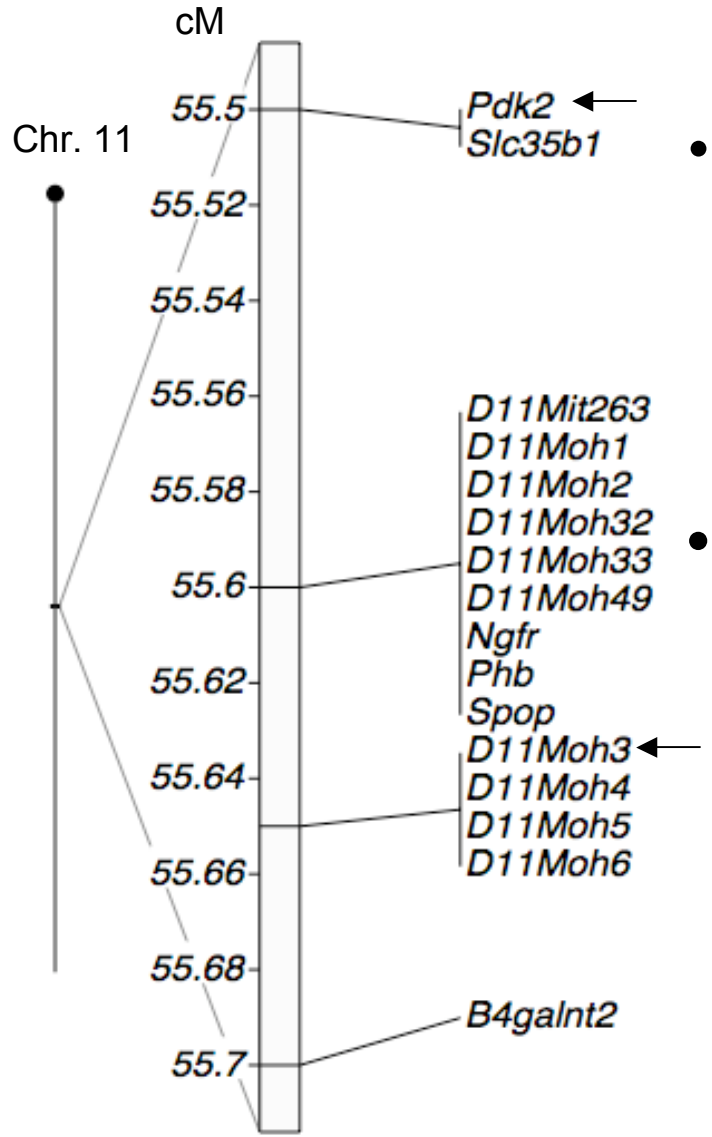
so d = 2.041 cM.

- For small values,

r (0 to ½ scale) ≈ d (in Morgans)

r (% scale) ≈ d (in centi-Morgans)

Mouse linkage map



- Distance between Pdk2 and D11Moh3:

  d= 55.65 - 55.50 = 0.15 cM
  = 0.0015 M

  (use the absolute value)

- Recombination rate

$$r = \frac{1}{2}(1 - e^{-2(0.0015)})$$
$$= 0.001497$$
$$= 0.1497\%$$

Mouse chr. 11: 55.50-55.70 cM.
Linkage map obtained from Mouse Genome Database (MGD), The Jackson Laboratory, Bar Harbor, Maine. Feb. 17, 2008.
http://www.informatics.jax.org