Mendelian inheritance has its physical basis in the behavior of chromosomes during sexual life cycles

- Around 1900, cytologists and geneticists began to see parallels between the behavior of chromosomes and the behavior of Mendel's factors (genes).
    - Chromosomes and genes are both present in pairs in diploid cells.
    - Homologous chromosomes separate and alleles segregate during meiosis.
    - Fertilization restores the paired condition for both chromosomes and genes.
- Around 1902, a **chromosome theory of inheritance** began to take form.

Morgan traced a gene to a specific chromosome

- Thomas Hunt Morgan was the first to associate a specific gene with a specific chromosome in the early 20th century.
- Like Mendel, Morgan made an insightful choice as an experimental animal, *Drosophila melanogaster*, a fruit fly species that eats fungi on fruit.
    - Fruit flies are prolific breeders and have a generation time of two weeks.
    - Fruit flies have three pairs of autosomes and a pair of sex chromosomes (XX in females, XY in males).
- Morgan spent a year looking for variant individuals among the flies he was breeding.
    - He discovered a single male fly with white eyes instead of the usual red.
- The normal character phenotype is the **wild type**.
- Alternative traits are *mutant phenotypes*.

- When Morgan crossed his white-eyed male with a red-eyed female, all the F_1 offspring had red eyes,
  - The red allele appeared dominant to the white allele.
- Crosses between the F_1 offspring produced the classic 3:1 phenotypic ratio in the F_2 offspring.
- Surprisingly, the white-eyed trait appeared only in males.
  - All the females and half the males had red eyes.
- Morgan concluded that a fly's eye color was linked to its sex.
- Morgan deduced that the gene with the white-eyed mutation is on the X chromosome alone, a sex-linked gene.
  - Females (XX) may have two red-eyed alleles and have red eyes or may be heterozygous and have red eyes.
  - Males (XY) have only a single allele and will be red eyed if they have a red-eyed allele or white-eyed if they have a white-eyed allele.

Linked genes tend to be inherited together because they are located on the same chromosome

- Each chromosome has hundreds or thousands of genes.
- Genes located on the same chromosome, **linked genes**, tend to be inherited together because the chromosome is passed along as a unit.
- Results of crosses with linked genes deviate from those expected according to independent assortment.
- Morgan observed this linkage and its deviations when he followed the inheritance of characters for body color and wing size.
  - The wild-type body color is gray (b^+) and the mutant black (b).
  - The wild-type wing size is normal (vg^+) and the mutant has vestigial wings (vg).
- Morgan crossed F_1 heterozygous females (b^+bvg^+vg) with homozygous recessive males (bbvgvg).
- According to independent assortment, this should produce 4 phenotypes in a 1:1:1:1 ratio.
- Surprisingly, Morgan observed a large number of wild-type (gray-normal) and double-mutant (black-vestigial) flies among the offspring.
  - These phenotypes correspond to those of the parents.

- Morgan reasoned that body color and wing shape are usually inherited together because their genes are on the same chromosome.

- The other two phenotypes (gray-vestigial and black-normal) were fewer than expected from independent assortment (and totally unexpected from dependent assortment).

- These new phenotypic variations must be the result of crossing over.

Independent assortment of chromosomes and crossing over produce genetic recombinants

- The production of offspring with new combinations of traits inherited from two parents is **genetic recombination**.
- Genetic recombination can result from independent assortment of genes located on non homologous chromosomes ***<u>or</u>*** from crossing over of genes located on homologous chromosomes.
- Mendel's dihybrid cross experiments produced some offspring that had a combination of traits that did not match either parent in the P generation.
    - If the P generation consists of a yellow-round parent (YYRR) crossed with a green-wrinkled seed parent (yyrr), all F_1 plants have yellow-round seeds (YyRr).
    - A cross between an F_1 plant and a homozygous recessive plant (a test-cross) produces four phenotypes.
    - Half are **parental types**, with phenotypes that match the original P parents, either with yellow-round seeds or green-wrinkled seeds.
    - Half are **recombinants**, new combination of parental traits, with yellow-wrinkled or green-round seeds.
- A 50% frequency of recombination is observed for any two genes located on different (non homologous) chromosomes.
- The physical basis of recombination between unlinked genes is the random orientation of homologous chromosomes at metaphase 1.
    - The F_1 parent (YyRr) can produce gametes with four different combinations of alleles.
        - These include YR, Yr, yR, and yr.
        - The orientation of the tetrad containing the seed color gene has no bearing on the orientation of the tetrad containing the seed shape gene.
- In contrast, linked genes, genes located on the same chromosome, tend to move together through meiosis and fertilization.
- Under normal Mendelian genetic rules, we would not expect linked genes to recombine into assortments of alleles not found in the parents.
    - <u>If</u> the seed color and seed coat genes were linked, we would expect the F_1 offspring to produce only two types of gametes, YR and yr when the tetrads separate.
    - One homologous chromosome from a P generation parent carries the Y and R alleles on the same chromosome and the other homologous chromosome from the other P parent carries the y and r alleles.

- The results of Morgan's testcross for body color and wing shape did not conform to either independent assortment or complete linkage.
  - Under independent assortment the testcross should produce a 1:1:1:1 phenotypic ratio.
  - If completely linked, we should expect to see a 1:1:0:0 ratio with only parental phenotypes among offspring.
- Most of the offspring had parental phenotypes, suggesting linkage between the genes.
- However, 17% of the flies were recombinants, suggesting incomplete linkage.
- Morgan proposed that some mechanism occasionally exchanged segments between homologous chromosomes.
  - This switched alleles between homologous chromosomes.
- The actual mechanism, crossing over during prophase I, results in the production of more types of gametes than one would predict by Mendelian rules alone.
- The occasional production of recombinant gametes during prophase I accounts for the occurrence of recombinant phenotypes in Morgan's testcross.

Geneticists can use recombination data to map a chromosome's genetic loci

- One of Morgan's students, Alfred Sturtevant, used crossing over of linked genes to develop a method for constructing a **chromosome map**.
- This map is an ordered list of the genetic loci along a particular chromosome.
- Sturtevant hypothesized that the frequency of recombinant offspring reflected the distances between genes on a chromosome.
- The farther apart two genes are, the higher the probability that a crossover will occur between them and therefore a higher recombination frequency.
  - The greater the distance between two genes, the more points between them where crossing over can occur.
- Sturtevant used recombination frequencies from fruit fly crosses to map the relative position of genes along chromosomes, a **linkage map**.
- Sturtevant used the test cross design to map the relative position of three fruit fly genes, body color (b), wing size (vg), and eye color (cn).
  - The recombination frequency between cn and b is 9%.
  - The recombination frequency between cn and vg is 9.5%.
  - The recombination frequency between b and vg is 17%.
  - The only possible arrangement of these three genes places the eye color gene between the other two.

- Sturtevant expressed the distance between genes, the recombination frequency, as **map units**.
  - One map unit is equivalent to a 1% recombination frequency.
- You may notice that the three recombination frequencies in our mapping example are not quite additive: 9% (b-cn) + 9.5% (cn-vg) > 17% (b-vg).
- This results from multiple crossing over events.
  - A second crossing over "cancels out" the first and reduced the observed number of recombinant offspring.
  - Genes father apart (for example, b-vg) are more likely to experience multiple crossing over events.
- Some genes on a chromosome are so far apart that a crossover between them is virtually certain.
- In this case, the frequency of recombination reaches is its maximum value of 50% and the genes act as if found on separate chromosomes and are inherited independently.
  - In fact, several genes studies by Mendel are located on the same chromosome.
    - For example, seed color and flower color are far enough apart that linkage is not observed.
    - Plant height and pod shape should show linkage, but Mendel never reported results of this cross.
- Genes located far apart on a chromosome are mapped by adding the recombination frequencies between the distant genes and intervening genes.
- Sturtevant and his colleagues were able to map the linear positions of genes in *Drosophila* into four groups, one for each chromosome.
- A linkage map provides an imperfect picture of a chromosome.
- Map units indicate relative distance and order, not precise locations of genes.
  - The frequency of crossing over is not actually uniform over the length of a chromosome.
- Combined with other methods like chromosomal banding, geneticists can develop **cytological maps**.
  - These indicated the positions of genes with respect to chromosomal features.
- More recent techniques show the absolute distances between gene loci in DNA nucleotides