

Chapter 15

The Chromosomal Basis of Inheritance

Lecture Outline

Overview

- Today we know that genes—Gregor Mendel’s “hereditary factors”—are located on chromosomes.
- A century ago, the relationship of genes and chromosomes was not so obvious.
- Many biologists were skeptical about Mendel’s laws of segregation and independent assortment until evidence mounted that they had a physical basis in the behavior of chromosomes.

A. Relating Mendelian Inheritance to the Behavior of Chromosomes

1. 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.
 - Using improved microscopy techniques, cytologists worked out the process of mitosis in 1875 and meiosis in the 1890s.
 - 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, Walter Sutton, Theodor Boveri, and others noted these parallels and a **chromosome theory of inheritance** began to take form:
 - Genes occupy specific loci on chromosomes.
 - Chromosomes undergo segregation during meiosis.
 - Chromosomes undergo independent assortment during meiosis.
- The behavior of homologous chromosomes during meiosis can account for the segregation of the alleles at each genetic locus to different gametes.
- The behavior of nonhomologous chromosomes can account for the independent assortment of alleles for two or more genes located on different chromosomes.

2. Morgan traced a gene to a specific chromosome.

- In the early 20th century, Thomas Hunt Morgan was the first geneticist to associate a specific gene with a specific chromosome.
- Like Mendel, Morgan made an insightful choice in his experimental animal. Morgan worked with *Drosophila melanogaster*, a fruit fly 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 called *mutant phenotypes* because they are due to alleles that originate as mutations in the wild-type allele.
 - When Morgan crossed his white-eyed male with a red-eyed female, all the F₁ offspring had red eyes, suggesting that the red allele was dominant to the white allele.
- Crosses between the F₁ offspring produced the classic 3:1 phenotypic ratio in the F₂ offspring.
- Surprisingly, the white-eyed trait appeared only in F₂ males.
 - All the F₂ females and half the F₂ 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, with no corresponding allele present on the Y chromosome.
 - 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. They will be red-eyed if they have a red-eyed allele or white-eyed if they have a white-eyed allele.

3. 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 that tend to be inherited together are called **linked genes**.
- 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 is black (b).
 - The wild-type wing size is normal (vg^+), and the mutant has vestigial wings (vg).
- The mutant alleles are recessive to the wild-type alleles.
- Neither gene is on a sex chromosome.
- Morgan crossed F₁ heterozygous females ($b^+ b vg^+ vg$) 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 are those of the parents.
- Morgan reasoned that body color and wing shape are usually inherited together because the genes for these characters are on the same chromosome.

- The other two phenotypes (gray-vestigial and black-normal) were fewer than expected from independent assortment (but totally unexpected from dependent assortment).
- What led to this **genetic recombination**, the production of offspring with new combinations of traits?

4. *Independent assortment of chromosomes and crossing over produce genetic recombinants.*

- Genetic recombination can result from independent assortment of genes located on nonhomologous chromosomes or from crossing over of genes located on homologous chromosomes.
- Mendel's dihybrid cross experiments produced 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 seed 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 testcross) produces four phenotypes.
 - Half are the **parental types**, with phenotypes that match the original P parents, with either yellow-round seeds or green-wrinkled seeds.
 - Half are **recombinants**, new combinations of parental traits, with yellow-wrinkled or green-round seeds.
- A 50% frequency of recombination is observed for any two genes located on different (nonhomologous) chromosomes.
- The physical basis of recombination between unlinked genes is the random orientation of homologous chromosomes at metaphase I of meiosis, which leads to the independent assortment of alleles.
- The F_1 parent ($YyRr$) produces gametes with four different combinations of alleles: YR , Yr , yR , and yr .
 - The orientation of the tetrad containing the seed-color gene has no bearing on the orientation of the tetrad with 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.
 - If 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 carries the Y and R alleles on the same chromosome, and the other homologous chromosome 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 must occasionally break the physical connection between genes on the same chromosome.

- This process, called **crossing over**, accounts for the recombination of linked genes.
- Crossing over occurs while replicated homologous chromosomes are paired during prophase of meiosis I.
 - One maternal and one paternal chromatid break at corresponding points and then rejoin with each other.
- The occasional production of recombinant gametes during meiosis accounts for the occurrence of recombinant phenotypes in Morgan's testcross.
- The percentage of recombinant offspring, the *recombination frequency*, is related to the distance between linked genes.

5. 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 **genetic map**, an ordered list of the genetic loci along a particular chromosome.
- Sturtevant hypothesized that the frequency of recombinant offspring reflected the distance between genes on a chromosome.
- He assumed that crossing over is a random event, and that the chance of crossing over is approximately equal at all points on a chromosome.
- Sturtevant predicted that *the farther apart two genes are, the higher the probability that a crossover will occur between them, and therefore, the higher the recombination frequency.*
 - The greater the distance between two genes, the more points there are 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 genetic map based on recombination frequencies is called a **linkage map**.
- Sturtevant used the testcross 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 (called a *centimorgan*) 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 reduces the observed number of recombinant offspring.
 - Genes farther 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 its maximum value of 50% and the genes behave as if found on separate chromosomes.
 - In fact, two genes studied by Mendel—for seed color and flower color—are located on the same chromosome but still assort independently.
- Genes located far apart on a chromosome are mapped by adding the recombination frequencies between the distant genes and the 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.
- A linkage map does portray the order of genes along a chromosome, but does not accurately portray the precise location of those genes.
- Combined with other methods like chromosomal banding, geneticists can develop **cytogenetic maps** of chromosomes.
 - These indicate the positions of genes with respect to chromosomal features.
- Recent techniques show the physical distances between gene loci in DNA nucleotides.

B. Sex Chromosomes

1. *The chromosomal basis of sex varies with the organism.*

- Although the anatomical and physiological differences between women and men are numerous, the chromosomal basis of sex is rather simple.
- In humans and other mammals, there are two varieties of sex chromosomes, X and Y.
 - An individual who inherits two X chromosomes usually develops as a female.
 - An individual who inherits an X and a Y chromosome usually develops as a male.
- Other animals have different methods of sex determination.
 - The X-0 system is found in some insects. Females are XX, males are X.
 - In birds, some fishes, and some insects, females are ZW and males are ZZ.
 - In bees and ants, females are diploid and males are haploid.
- In the X-Y system, the Y chromosome is much smaller than the X chromosome.
- Only relatively short segments at either end of the Y chromosome are homologous with the corresponding regions of the X chromosome.
 - The X and Y rarely cross over.
- In both testes (XY) and ovaries (XX), the two sex chromosomes segregate during meiosis, and each gamete receives one.
 - Each ovum receives an X chromosome.
 - Half the sperm cells receive an X chromosome, and half receive a Y chromosome.
- Because of this, each conception has about a fifty-fifty chance of producing a particular sex.
 - If a sperm cell bearing an X chromosome fertilizes an ovum, the resulting zygote is female (XX).
 - If a sperm cell bearing a Y chromosome fertilizes an ovum, the resulting zygote is male (XY).

- In humans, the anatomical signs of sex first appear when the embryo is about two months old.
- In 1990, a British research team identified a gene on the Y chromosome required for the development of testes.
 - They named the gene *SRY* (sex-determining region of the Y chromosome).
- In individuals with the *SRY* gene, the generic embryonic gonads develop into testes.
 - Activity of the *SRY* gene triggers a cascade of biochemical, physiological, and anatomical features because it regulates many other genes.
 - Other genes on the Y chromosome are necessary for the production of functional sperm.
 - In the absence of these genes, an XY individual is male but does not produce normal sperm.
- In individuals lacking the *SRY* gene, the generic embryonic gonads develop into ovaries.

2. Sex-linked genes have unique patterns of inheritance.

- In addition to their role in determining sex, the sex chromosomes, especially the X chromosome, have genes for many characters unrelated to sex.
- A gene located on either sex chromosome is called a **sex-linked gene**.
- In humans, the term refers to a gene on the X chromosome.
- Human sex-linked genes follow the same pattern of inheritance as Morgan's white-eye locus in *Drosophila*.
 - Fathers pass sex-linked alleles to all their daughters but none of their sons.
 - Mothers pass sex-linked alleles to both sons and daughters.
- If a sex-linked trait is due to a recessive allele, a female will express this phenotype only if she is homozygous.
 - Heterozygous females are carriers for the recessive trait.
 - Because males have only one X chromosome (*hemizygous*), any male receiving the recessive allele from his mother will express the recessive trait.
 - The chance of a female inheriting a double dose of the mutant allele is much less than the chance of a male inheriting a single dose.
 - Therefore, males are far more likely to exhibit sex-linked recessive disorders than are females.
- For example, color blindness is a mild disorder inherited as a sex-linked trait.
 - A color-blind daughter may be born to a color-blind father whose mate is a carrier.
 - However, the odds of this are fairly low.
- Several serious human disorders are sex-linked.
- **Duchenne muscular dystrophy** affects one in 3,500 males born in the United States.
 - Affected individuals rarely live past their early 20s.
 - This disorder is due to the absence of an X-linked gene for a key muscle protein called dystrophin.
 - The disease is characterized by a progressive weakening of the muscles and a loss of coordination.
- **Hemophilia** is a sex-linked recessive disorder defined by the absence of one or more proteins required for blood clotting.
 - These proteins normally slow and then stop bleeding.
 - Individuals with hemophilia have prolonged bleeding because a firm clot forms slowly.