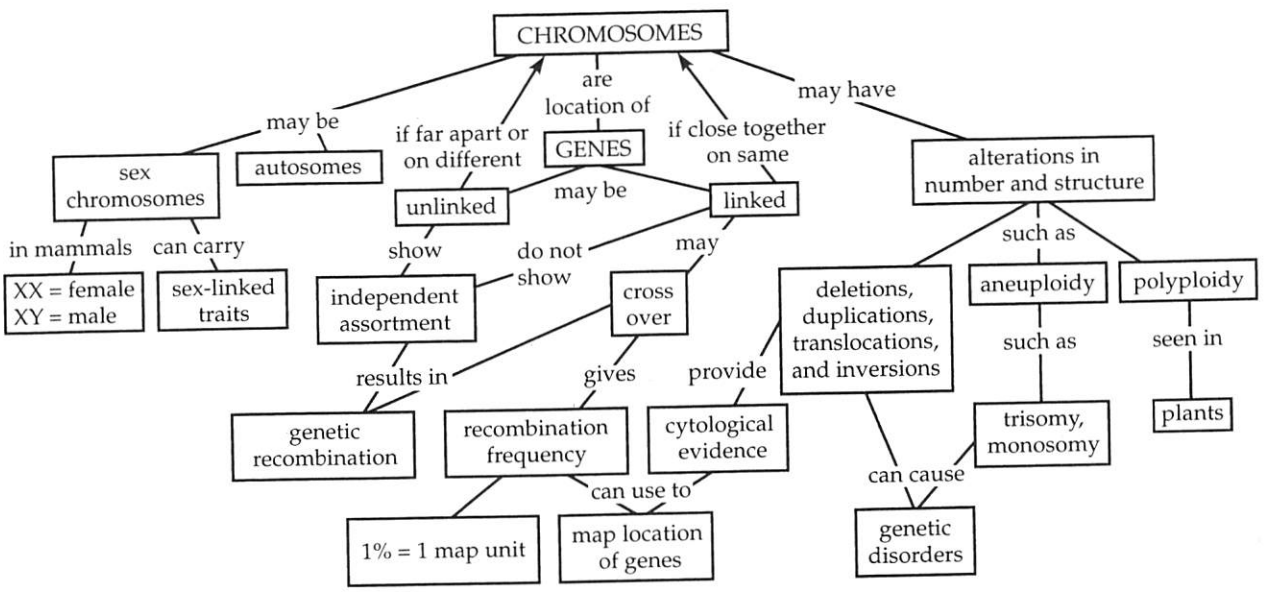
Chapter 12

The Chromosomal Basis of Inheritance

Chapter Focus



Chapter Review

12.1 Mendelian inheritance has its physical basis in the behavior of chromosomes

Mendel's laws, combined with cytological evidence of the process of meiosis, led to the **chromosome theory of inheritance:** Genes occupy specific positions (loci) on chromosomes, and it is the random alignment of pairs of homologous chromosomes at metaphase I and the separation of homologs in anaphase I that result in the independent assortment and segregation of alleles in gamete formation.

Morgan's Experimental Evidence: Scientific Inquiry T. H. Morgan worked with fruit flies, *Drosophila melanogaster*, which are prolific and rapid breeders. Fruit flies have only four pairs of chromosomes; the sex chromosomes occur as XX in female flies and as XY in male flies.

The normal phenotype found most commonly in nature for a character is called the **wild type**, whereas alternative traits, assumed to have arisen as mutations, are called *mutant phenotypes*. A mutant allele is designated with a small letter, the wild-type allele with a superscript +.

Morgan discovered a mutant white-eyed male fly, which he then mated with a wild-type red-eyed female. The F_1 offspring were all red-eyed. In the F_2, however, all female flies were red-eyed, whereas half of the males were red-eyed and half were white-eyed. How did Morgan explain these results? He deduced that the gene for eye color was located on the X chromosome. Males have only one X, so their phenotype is determined by the eye-color allele they inherit from their mother. This association of a specific gene with a chromosome provided evidence for the chromosome theory of inheritance.

FOCUS QUESTION 12.1

Complete the following summary of Morgan's crosses involving the mutant white-eyed fly by filling in the Punnett square and indicating the genotypes and phenotypes of the F_2 generation. (X^w stands for the mutant recessive white allele; X^{w+} for the wild-type red allele.) The Y reminds you that this eye color gene is not present on the Y chromosome.

P Generation			
Phenotype	red-eyed (wild-type) female	×	white-eyed male
Genotype	$X^{w+}X^{w+}$		X^wY

F_1 Generation			
Phenotype	red-eyed female	×	red-eyed male
Genotype	$X^{w+}X^w$		$X^{w+}Y$

F_2 Generation

Eggs \ Sperm		

Genotypes

_____ _____ _____ _____

Phenotypes

_____ _____ _____ _____

12.2 Sex-linked genes exhibit unique patterns of inheritance

The Chromosomal Basis of Sex Sex is a phenotypic character usually determined by sex chromosomes. In humans and other mammals, females, who are XX, produce eggs that each contain an X chromosome. Males, who are XY, produce two kinds of sperm, each with either an X or a Y chromosome.

Whether the gonads of an embryo develop into testes or ovaries depends on the presence or absence of the gene *SRY*, found on the Y chromosome, whose protein product regulates many other genes. Genes located on either sex chromosome are called **sex-linked genes**. The relatively few genes located on the Y chromosome are called *Y-linked genes*. About half of these genes are expressed only in the testis. The term **X-linked genes** refers to the approximately 1,100 genes located on the X chromosome.

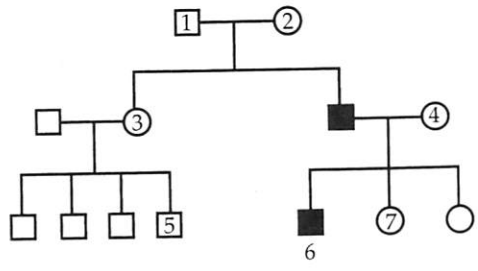
Inheritance of X-Linked Genes X-linked genes code for many characters that are not related to sex. Males inherit X-linked alleles from their mothers; daughters inherit X-linked alleles from both parents. Why are recessive X-linked traits seen more often in males than females? Males are *hemizygous* for X-linked genes—they have only one allele for each gene, and thus a recessive allele is always expressed.

Duchenne muscular dystrophy is an X-linked disorder resulting from the lack of a key muscle protein. **Hemophilia** is an X-linked trait characterized by excessive bleeding due to the absence of one or more blood-clotting proteins.

X Inactivation in Female Mammals Only one of the X chromosomes is fully active in most mammalian female somatic cells. The other X chromosome is contracted into a **Barr body** located inside the nuclear membrane. M. Lyon demonstrated that the selection of which X chromosome is inactivated is a random event occurring independently in embryonic cells. As a result of X inactivation, both males and females have an equal dosage of most X-linked genes. A gene called *XIST* becomes active on the X chromosome that forms the Barr body. Its RNA products appear to trigger DNA methylation and X inactivation.

FOCUS QUESTION 12.2

Two normal color-sighted individuals have two children and seven grandchildren. Fill in the probable genotype of each of the numbered individuals in the following pedigree. *Squares are males, circles are females, and solid symbols represent color blindness. Use the superscript N for the normal allele, and n for the recessive allele for color blindness.*



Genotypes:

1. _____ 5. _____
2. _____ 6. _____
3. _____ 7. _____
4. _____

12.3 Linked genes tend to be inherited together because they are located near each other on the same chromosome

What are **linked genes?** They are genes located near each other on the same chromosome and tend to be inherited together.

How Linkage Affects Inheritance Morgan performed a testcross of F_1 dihybrid wild-type flies with flies that were homozygous recessive for black bodies and vestigial wings. He found that the offspring were not in the predicted 1:1:1:1 phenotypic ratio. Rather, most of the offspring were the same phenotypes as the P generation parents—either wild type (gray, normal wings) or double mutant (black, vestigial). Morgan deduced that these traits were inherited together because their genes were located on the same chromosome.

Genetic recombination results in offspring with combinations of traits that differ from those of either P generation parent.

Genetic Recombination and Linkage Let's first look at the recombination of genes that are not linked. Consider a cross between a dihybrid heterozygote and a doubly recessive homozygote. The dihybrid parent will produce four types of gametes; the homozygous parent only one type. Of the four types of offspring that will be produced, one-half will be **parental types** and have phenotypes like one or the other of the parental (P) generation (both dominant traits or both recessive traits). The other half of the offspring, called **recombinant types (recombinants)**, will have new combinations of the two traits. This 50% frequency of recombination is observed when two genes are located on different chromosomes, and it results from the random alignment of pairs of homologous chromosomes at metaphase I and the resulting independent assortment of the two unlinked genes.

FOCUS QUESTION 12.3

In a testcross between a heterozygote tall, purple-flowered pea plant and a dwarf, white-flowered plant,

a. what are the phenotypes of offspring that are parental types?

b. what are the phenotypes of offspring that are recombinants?

Linked genes, on the other hand, do not assort independently, and one would not expect to see recombination of parental traits in the offspring. Recombination of linked genes does occur, however, due to **crossing over**, the reciprocal trade between nonsister (a maternal and a paternal) chromatids of paired homologous chromosomes during prophase of meiosis I.

Recombinant chromosomes produced by crossing over, independent assortment, and random fertilization all contribute to the generation of new assortments of alleles, providing an abundance of genetic variation on which natural selection can work.

FOCUS QUESTION 12.4

With unlinked genes, an equal number of parental and recombinant offspring are produced. With linked genes, are more or fewer parentals than recombinants produced? Explain your answer.

Mapping the Distance Between Genes Using Recombination Data: Scientific Inquiry A **genetic map** is an ordered list of genes on a chromosome. The percentage of recombinant offspring produced in a genetic cross is called the *recombination frequency*. A. H. Sturtevant suggested that recombination frequencies reflect the relative distance between genes; for genes that are farther apart, the probability that crossing over will occur between them is greater than for genes that are closer together. Sturtevant used recombination data to create a **linkage map**, in which one **map unit** is defined as equal to a 1% recombination frequency.

The sequence of genes on a chromosome can be determined by finding the recombination frequency between different pairs of genes. Linkage cannot be determined if genes are so far apart that crossovers between them are almost certain. They would then have the 50% recombination frequency typical of unlinked genes. Such genes are *physically linked* but *genetically unlinked*. Distant genes on the same chromosome may be mapped by adding the recombination frequencies between them and intermediate genes.

Sturtevant and his colleagues found that the genes for the various known mutations of *Drosophila* clustered into four groups of linked genes, providing additional evidence that genes are located on chromosomes—in this case, on the four *Drosophila* chromosomes.

The frequency of crossing over may vary along the length of a chromosome, and a linkage map provides the sequence but not the exact location of genes on chromosomes. **Cytogenetic maps** locate gene loci in reference

to visible chromosomal features. Physical maps provide the number of DNA nucleotides between genes.

FOCUS QUESTION 12.5

The following recombination frequencies have been determined for several gene pairs. Create a linkage map for these genes, showing the map unit distance between loci.

j, k: 12% *j, m:* 9% *k l:* 6% *l, m:* 15%

12.4 Alterations of chromosome number or structure cause some genetic disorders

Abnormal Chromosome Number **Nondisjunction** occurs when a pair of homologous chromosomes does not separate properly in meiosis I, or when sister chromatids do not separate in meiosis II. As a result, a gamete may receive either two copies or no copies of that chromosome. A zygote formed with one of these aberrant gametes has a chromosomal alteration known as **aneuploidy**, a nontypical number of a chromosome. The zygote will be either **trisomic** for that chromosome (chromosome number is $2n + 1$) or **monosomic** ($2n - 1$). Aneuploid organisms that survive usually have a set of symptoms caused by the abnormal dosage of genes. A mitotic nondisjunction early in embryonic development is also likely to be harmful.

Polyploidy is a chromosomal alteration in which an organism has more than two complete chromosomal sets, as in *triploidy* ($3n$) or *tetraploidy* ($4n$). Polyploidy is common in the plant kingdom and has played an important role in the evolution of plants.

FOCUS QUESTION 12.6

a. What is the difference between an organism with a trisomy and a triploid organism?

b. Which of these two organisms is likely to exhibit the more deleterious effects as a result of its chromosomal anomaly?

Alterations of Chromosome Structure Chromosome breakage can result in chromosome fragments that are lost, called **deletion;** that join to a sister chromatid (or a nonsister chromatid), called **duplication;** that rejoin the original chromosome in the reverse orientation, called **inversion;** or that join a nonhomologous chromosome, called **translocation**. An unequal crossover can result in a deletion and duplication in nonsister chromatids, caused by unequal exchange between chromatids.

FOCUS QUESTION 12.7

Two nonhomologous chromosomes have gene orders, respectively, of *A-B-C-D-E-F-G-H-I-J* and *M-N-O-P-Q-R-S-T*. What types of chromosome alterations would have occurred if daughter cells were found to have a gene sequence of *A-B-C-O-P-Q-G-J-I-H* on the first chromosome?

Human Disorders Due to Chromosomal Alterations The frequency of aneuploid zygotes may be fairly high in humans, but development is usually so disrupted that embryos spontaneously abort. Some genetic disorders, expressed as *syndromes* of characteristic traits, are the result of aneuploidy.

Down syndrome, caused by trisomy of chromosome 21, results in characteristic facial features, short stature, correctable heart defects, and developmental delays. The incidence of Down syndrome increases for older mothers.

XXY males exhibit *Klinefelter syndrome*, a condition in which the individual has abnormally small testes, is sterile, and may have subnormal intelligence. Males with an extra Y chromosome do not exhibit any well-defined syndrome.

Trisomy X results in females who are healthy and distinguishable only by karyotype, although they are slightly taller than average and at risk of learning disabilities. Monosomy X individuals (X0) exhibit *Turner syndrome* and are phenotypically female, sterile individuals with usually normal intelligence.

Structural alterations of chromosomes, such as deletions or translocations, may be associated with specific human disorders, such as *cri du chat* syndrome and *chronic myelogenous leukemia* (*CML*). The reciprocal

translocation involved in CML produces a short, recognizable *Philadelphia chromosome.*

FOCUS QUESTION 12.8

Why do most sex chromosome aneuploidies have less deleterious effects than do autosomal aneuploidies?

Word Roots

aneu- = without (*aneuploidy:* a chromosomal aberration in which one or more chromosomes are present in extra copies or are deficient in number)

cyto- = cell (*cytogenetic map:* a map of a chromosome that locates genes with respect to chromosomal features distinguishable in a microscope)

hemo- = blood (*hemophilia:* a human genetic disease that is caused by an X-linked recessive allele and characterized by excessive bleeding following injury)

mono- = one (*monosomic:* referring to a diploid cell that has only one copy of a particular chromosome instead of the normal two)

non- = not; **dis-** = separate (*nondisjunction:* an error in meiosis or mitosis in which members of a pair of homologous chromosomes or a pair of sister chromatids fail to separate properly from each other)

poly- = many (*polyploidy:* a chromosomal alteration in which the organism possesses more than two complete chromosome sets; result of an accident of cell division)

re- = again; **com-** = together; **bin-** = two at a time (*recombinant:* an offspring whose phenotype differs from that of the true-breeding P generation parents; also refers to the phenotype itself)

trans- = across (*translocation:* an aberration in chromosome structure resulting from attachment of a chromosomal fragment to a nonhomologous chromosome)

tri- = three; **soma-** = body (*trisomic:* referring to a diploid cell that has three copies of a particular chromosome)

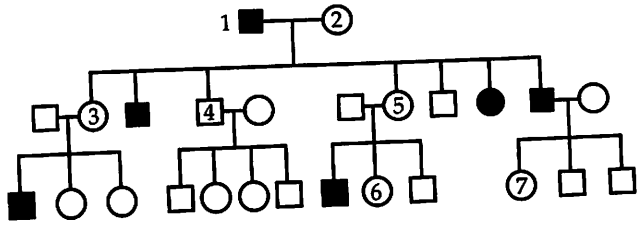
Structure Your Knowledge

1. Mendel's law of independent assortment applies to genes that are on different chromosomes. However, at least two of the genes Mendel studied were actually located on the same chromosome. Explain why genes located more than 50 map units apart behave as though they are not linked. How can one determine whether these genes are linked, and what the relative distance is between them?
2. You have found a new mutant phenotype in fruit flies that you suspect is recessive and X-linked. What is the single, best cross you could make to confirm your predictions?
3. Various human disorders or syndromes are related to chromosomal abnormalities. What explanation can you give for the adverse phenotypic effects associated with these chromosomal alterations?

Genetics Problems

Again, one of the best ways to learn genetics is to do problems.

1. The following pedigree traces the inheritance of a genetic trait.



   a. What type of inheritance does this trait show?
   b. Choose an appropriate allele labeling system, and give the predicted genotype for the following individuals:

   1. _____ 5. _____
   2. _____ 6. _____
   3. _____ 7. _____
   4. _____

   c. What is the probability that a child of individual # 6 and a phenotypically normal male will have this trait?

2. Use the following recombination frequencies to determine the order of the genes on the chromosome.

   a, c: 10% a, d: 30% b, c: 24% b, d: 16%

3. In guinea pigs, black (*B*) is dominant to brown (*b*), and solid color (*S*) is dominant to spotted (*s*). A heterozygous black, solid-colored pig is mated with a brown, spotted pig. The offspring from several litters are as follows: black solid: 16; black spotted: 5; brown solid: 5; and brown spotted: 14. Are these genes linked or unlinked? If they are linked, how many map units are they apart?

4. A woman is a carrier for an X-linked lethal allele that causes an embryo with the allele to spontaneously abort. She has nine children. How many of these children do you expect to be boys?

5. A dominant sex-linked allele *B* produces white bars on black chickens, as seen in the Barred Plymouth Rock breed. A clutch of chicks has equal numbers of black and barred chicks. (Remember that sex is determined by the Z-W system in birds: ZZ are males, ZW are females.)
   a. If only the females are found to be black, what were the genotypes of the parents?
   b. If males and females are evenly represented in the black and barred chicks, what were the genotypes of the parents?

Test Your Knowledge

MULTIPLE CHOICE: *Choose the one best answer.*

1. Which of the following statements is part of the chromosome theory of inheritance?
   a. Genes are located on chromosomes.
   b. Homologous chromosomes and their associated genes undergo segregation during meiosis.
   c. Chromosomes and their associated genes undergo independent assortment in gamete formation.
   d. Mendel's laws of inheritance relate to the behavior of chromosomes in meiosis.
   e. all of the above

2. A wild type is
   a. the phenotype found most commonly in nature.
   b. the dominant allele.
   c. designated by a small letter if it is recessive or a capital letter if it is dominant.
   d. a trait found on the X chromosome.
   e. your basic party animal.

3. Sex-linked traits
   a. are carried on an autosome but expressed only in males.
   b. are coded for by genes located on a sex chromosome.
   c. are found in only one sex, depending on the sex-determination system of the species.
   d. are always inherited from the mother in mammals and fruit flies.
   e. depend on whether the gene was inherited from the mother or the father.

4. In which of the following structures would you expect to find a Barr body?
   a. an egg
   b. a sperm
   c. a liver cell of a man
   d. a liver cell of a woman
   e. a mitochondrion

5. A cross of a wild-type red-eyed female *Drosophila* with a violet-eyed male produces all red-eyed offspring. If the gene is X-linked, which of the following should the reciprocal cross (violet-eyed female × red-eyed male) produce? (Assume that the red allele is dominant to the violet allele.)
   a. all violet-eyed flies
   b. 3 red-eyed flies to 1 violet-eyed fly
   c. a 1:1 ratio of red and violet eyes in both males and females
   d. red-eyed females and violet-eyed males
   e. all red-eyed flies

6. Linkage and cytogenetic maps for the same chromosome
   a. are both based on mutant phenotypes and recombination data.
   b. may have different orders of genes.
   c. have both the same order of genes and intergenic distances.
   d. have the same order of genes but different intergenic distances.
   e. are created using chromosomal abnormalities.

7. A 1:1:1:1 ratio of offspring from a dihybrid testcross indicates that
   a. the genes are linked.
   b. the dominant organism was homozygous.
   c. crossing over has occurred.
   d. the genes are 25 map units apart.
   e. the genes are not linked or are more than 50 map units apart.

8. Genes *A* and *B* are linked and 12 map units apart. A heterozygous individual, whose parents were *AAbb* and *aaBB*, would be expected to produce gametes in which of the following frequencies?
   a. 44% *AB* 6% *Ab* 6% *aB* 44% *ab*
   b. 6% *AB* 44% *Ab* 44% *aB* 6% *ab*
   c. 12% *AB* 38% *Ab* 38% *aB* 12% *ab*
   d. 6% *AB* 6% *Ab* 44% *aB* 44% *ab*
   e. 38% *AB* 12% *Ab* 12% *aB* 38% *ab*

9. Which of the following chromosomal alterations does not alter genic balance but may affect gene expression and thus phenotype?
   a. deletion
   b. inversion
   c. duplication
   d. nonidentical duplication
   e. nondisjunction

10. A female tortoiseshell cat is heterozygous for the gene that determines black or orange coat color, which is located on the X chromosome. A male tortoiseshell cat
    a. cannot occur.
    b. is hemizygous at this locus.
    c. must have resulted from a nondisjunction and has a Barr body in each of his cells.
    d. must have two alleles for coat color in each of his cells, one from his father and one from his mother.
    e. would be hermaphroditic.

11. When we say that a few of the genes for Mendel's pea characters were physically linked but genetically unlinked, we mean that
    a. the genes are on the same chromosome, but they are more than 50 map units apart.
    b. the genes assort independently even though the chromosomes they are on travel to the metaphase plate together.
    c. their alleles segregate in anaphase I, and each gamete receives a single allele for all of these genes.
    d. dihybrid crosses with these genes produce more than 50% recombinant offspring even though they are on the same chromosome.
    e. Mendel could not determine that the genes were on the same chromosome because he did not perform crosses with these gene pairs.

12. Two true-breeding *Drosophila* are crossed: a normal-winged, red-eyed female and a miniature-winged, vermilion-eyed male. The F_1s all have normal wings and red eyes. When F_1 offspring are crossed with miniature-winged, vermilion-eyed flies, the following offspring resulted:

    233 normal wing, red eye
    247 miniature wing, vermilion eye
    7 normal wing, vermilion eye
    13 miniature wing, red eye

    From these results, you could conclude that the alleles for miniature wings and vermilion eyes are
    a. both X-linked and dominant.
    b. located on autosomes and dominant.
    c. recessive, and that these genes are located 4 map units apart.
    d. recessive, and that these genes are located 20 map units apart.
    e. recessive, and that the deviation from the expected 9:3:3:1 ratio is due to epistasis.

13. Which of the following statements is *not* true about genetic recombination?
    a. Recombination of linked genes occurs by crossing over.
    b. Recombination of unlinked genes occurs by independent assortment of chromosomes.
    c. Genetic recombination results in offspring with combinations of traits that differ from the phenotypes of both parents.
    d. Recombinant offspring outnumber parental type offspring when two genes are 50 map units apart on a chromosome.
    e. The number of recombinant offspring is proportional to the distance between two gene loci on a chromosome.

14. Suppose that alleles for an X-linked character for wing shape in flies show incomplete dominance. The X^+ allele codes for pointed wings, the X^r for round wings, and X^+X^r individuals have oval wings. In a cross between an oval-winged female and a round-winged male, the following offspring were observed: oval-winged females, round-winged females, pointed-winged males, and round-winged males. A rare pointed-winged female was noted. Cytological study revealed that she had two X chromosomes. Which of the following events could account for this unusual offspring?
    a. a crossover between the two X chromosomes
    b. a crossover between the X and Y chromosomes
    c. a nondisjunction in meiosis II between two X^+ chromatids
    d. a nondisjunction between the X and Y chromosomes, producing some sperm with no sex chromosome
    e. Both **c** and **d** together could produce an X^+X^+ female when an XX egg was fertilized by a sperm in which there was no sex chromosome.

15. Some girls who fail to undergo puberty are found to have Swyer syndrome, a condition in which they are externally female but have an XY genotype. Which of the following statements may explain the origin of this syndrome?
    a. A mutation in the *XIST* gene, which codes for RNA molecules that coat the X chromosome and initiate X-inactivation, must have occurred.
    b. A nondisjunction in the egg from the mother resulted in both sex chromosomes coming from the father.
    c. These individuals are actually XXY; the second X is not seen because it is condensed into a Barr body. They have small testes and are sterile but otherwise appear female.
    d. A mutation or deletion of the *SRY* gene on the Y chromosome prevented development of testes and production of the male sex hormones required for a male phenotype.
    e. A translocation of part of an X chromosome to the Y chromosome resulted in a double dose of female-determining genes.