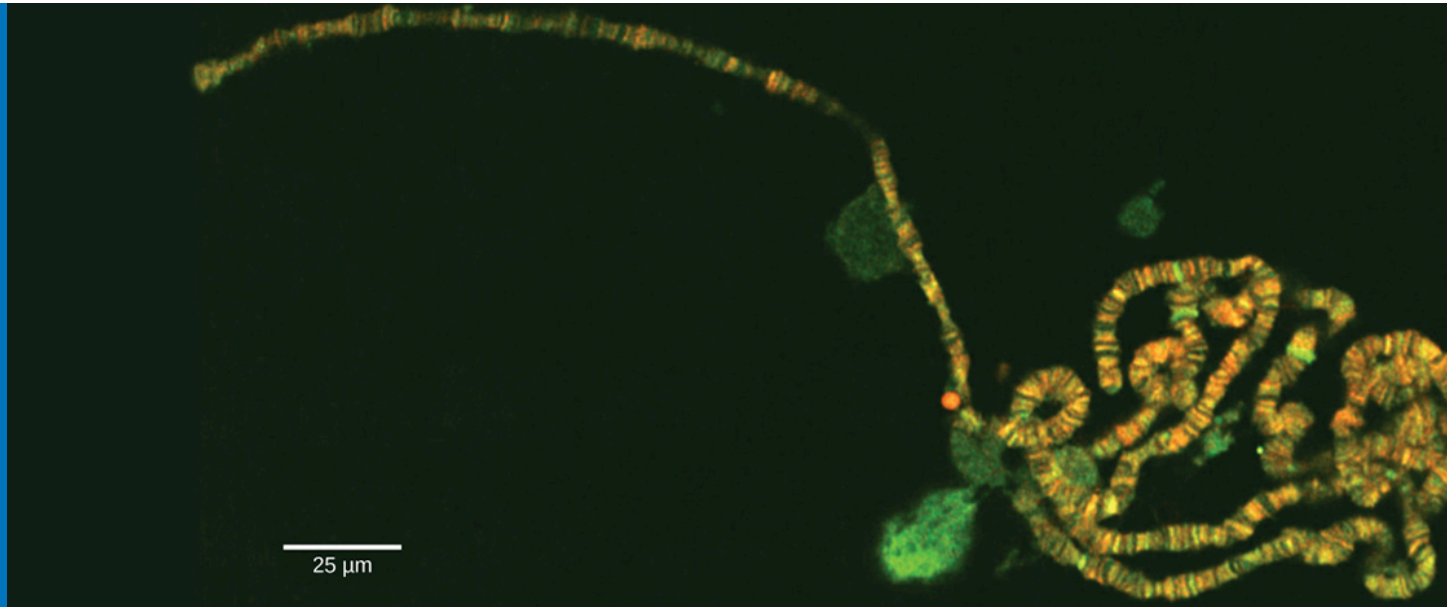# Modern Understandings of Inheritance

Figure 13.1 Chromosomes are threadlike nuclear structures consisting of DNA and proteins that serve as the repositories for genetic information. The chromosomes depicted here were isolated from a fruit fly's salivary gland, stained with dye, and visualized under a microscope. Akin to miniature bar codes, chromosomes absorb different dyes to produce characteristic banding patterns, which allows for their routine identification. (credit: modification of work by "LPLT"/Wikimedia Commons; scale-bar data from Matt Russell)

INTRODUCTION The gene is the physical unit of inheritance, and genes are arranged in a linear order on chromosomes. Chromosome behavior and interaction during meiosis explain, at a cellular level, inheritance patterns that we observe in populations. Genetic disorders involving alterations in chromosome number or structure may have dramatic effects and can prevent a fertilized egg from developing.

Chapter Outline

13.1 Chromosomal Theory and Genetic Linkage

By the end of this section, you will be able to do the following:

- Discuss Sutton's Chromosomal Theory of Inheritance
- Describe genetic linkage
- Explain the process of homologous recombination, or crossing over
- Describe chromosome creation
- Calculate the distances between three genes on a chromosome using a three-point test cross

Long before scientists visualized chromosomes under a microscope, the father of modern genetics, Gregor Mendel, began studying heredity in 1843. With improved microscopic techniques during the late 1800s, cell biologists could stain and visualize subcellular structures with dyes and observe their actions during cell division and meiosis. With each mitotic division, chromosomes replicated, condensed from an amorphous (no constant shape) nuclear mass into distinct X-shaped bodies (pairs of identical sister chromatids), and migrated to separate cellular poles.

Chromosomal Theory of Inheritance

The speculation that chromosomes might be the key to understanding heredity led several scientists to examine Mendel's publications and reevaluate his model in terms of chromosome behavior during mitosis and meiosis. In 1902, Theodor Boveri observed that proper sea urchin embryonic development does not occur unless chromosomes are present. That same year, Walter Sutton observed chromosome separation into daughter cells during meiosis (Figure 13.2). Together, these observations led to the **Chromosomal Theory of Inheritance**, which identified chromosomes as the genetic material responsible for Mendelian inheritance.

(a)   (b)

Figure 13.2 (a) Walter Sutton and (b) Theodor Boveri developed the Chromosomal Theory of Inheritance, which states that chromosomes carry the unit of heredity (genes).

The Chromosomal Theory of Inheritance was consistent with Mendel's laws, which the following observations supported:

- During meiosis, homologous chromosome pairs migrate as discrete structures that are independent of other chromosome pairs.
- Chromosome sorting from each homologous pair into pre-gametes appears to be random.
- Each parent synthesizes gametes that contain only half their chromosomal complement.
- Even though male and female gametes (sperm and egg) differ in size and morphology, they have the same number of chromosomes, suggesting equal genetic contributions from each parent.
- The gametic chromosomes combine during fertilization to produce offspring with the same chromosome number as their parents.

Despite compelling correlations between chromosome behavior during meiosis and Mendel's abstract laws,

scientists proposed the Chromosomal Theory of Inheritance long before there was any direct evidence that chromosomes carried traits. Critics pointed out that individuals had far more independently segregating traits than they had chromosomes. It was only after several years of carrying out crosses with the fruit fly, *Drosophila melanogaster*, that Thomas Hunt Morgan provided experimental evidence to support the Chromosomal Theory of Inheritance.

Genetic Linkage and Distances

Mendel's work suggested that traits are inherited independently of each other. Morgan identified a 1:1 correspondence between a segregating trait and the X chromosome, suggesting that random chromosome segregation was the physical basis of Mendel's model. This also demonstrated that linked genes disrupt Mendel's predicted outcomes. That each chromosome can carry many linked genes explains how individuals can have many more traits than they have chromosomes. However, researchers in Morgan's laboratory suggested that alleles positioned on the same chromosome were not always inherited together. During meiosis, linked genes somehow became unlinked.

Homologous Recombination

In 1909, Frans Janssen observed chiasmata—the point at which chromatids are in contact with each other and may exchange segments—prior to the first meiosis division. He suggested that alleles become unlinked and chromosomes physically exchange segments. As chromosomes condensed and paired with their homologs, they appeared to interact at distinct points. Janssen suggested that these points corresponded to regions in which chromosome segments exchanged. We now know that the pairing and interaction between homologous chromosomes, or synapsis, does more than simply organize the homologs for migration to separate daughter cells. When synapsed, homologous chromosomes undergo reciprocal physical exchanges at their arms in **homologous recombination**, or more simply, "crossing over."

To better understand the type of experimental results that researchers were obtaining at this time, consider a heterozygous individual that inherited dominant maternal alleles for two genes on the same chromosome (such as *AB*) and two recessive paternal alleles for those same genes (such as *ab*). If the genes are linked, one would expect this individual to produce gametes that are either *AB* or *ab* with a 1:1 ratio. If the genes are unlinked, the individual should produce *AB*, *Ab*, *aB*, and *ab* gametes with equal frequencies, according to the Mendelian concept of independent assortment. Because they correspond to new allele combinations, the genotypes Ab and aB are **nonparental types** that result from homologous recombination during meiosis. **Parental types** are progeny that exhibit the same allelic combination as their parents. Morgan and his colleagues, however, found that when they test crossed such heterozygous individuals to a homozygous recessive parent (*AaBb × aabb*), both parental and nonparental cases occurred. For example, 950 offspring might be recovered that were either *AaBb* or *aabb*, but 50 offspring would also result that were either *Aabb* or *aaBb*. These results suggested that linkage occurred most often, but a significant minority of offspring were the products of recombination.

VISUAL CONNECTION

Inheritance Pattern of Linked and Unlinked Genes

Three hypothetical inheritance patterns for a test cross between a heterozygote and a homozygous recessive individual, based on gene placement, are shown in A through C. The actual experimental results published by Thomas Hunt Morgan in 1912 are shown in D.

A. Genes on different chromosomes, independently assorted

B. Genes on the same chromosome, no crossover occurs

C. Genes on the same chromosome, crossover occurs 100% of the time

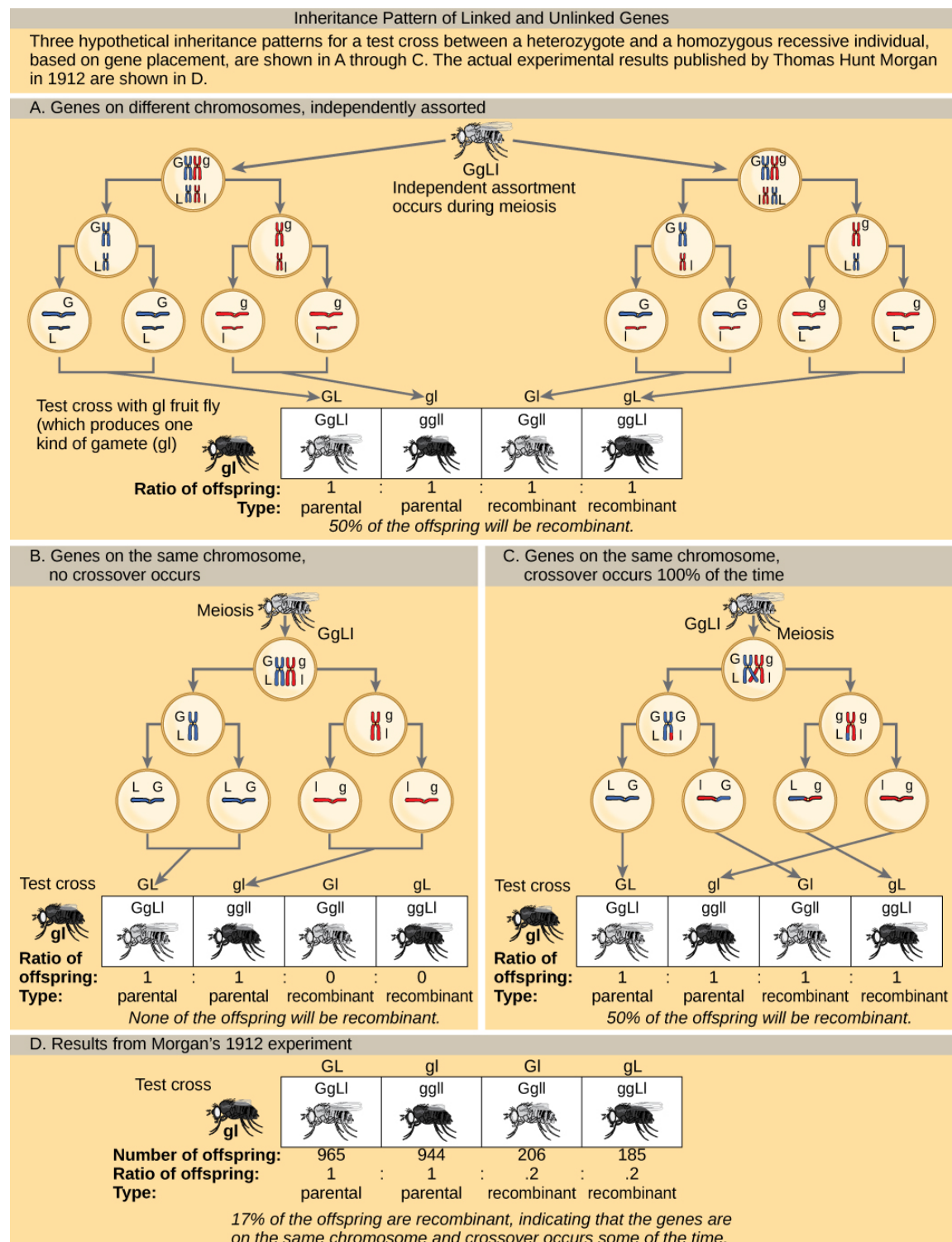D. Results from Morgan's 1912 experiment

Figure 13.3 This figure shows unlinked and linked gene inheritance patterns. In (a), two genes are located on different chromosomes so independent assortment occurs during meiosis. The offspring have an equal chance of being the parental type (inheriting the same combination of traits as the parents) or a nonparental type (inheriting a different combination of traits than the parents). In (b), two genes are very close together on the same chromosome so that no crossing over occurs between them. Therefore, the genes are always inherited together and all the offspring are the parental type. In (c), two genes are far apart on the chromosome such that crossing over occurs during

every meiotic event. The recombination frequency will be the same as if the genes were on separate chromosomes. (d) The actual recombination frequency of fruit fly wing length and body color that Thomas Morgan observed in 1912 was 17 percent. A crossover frequency between 0 percent and 50 percent indicates that the genes are on the same chromosome and crossover sometimes occurs.

In a test cross for two characteristics such as the one here, can the recombinant offspring's predicted frequency be 60 percent? Why or why not?

Genetic Maps

Janssen did not have the technology to demonstrate crossing over so it remained an abstract idea that scientists did not widely believe. Scientists thought chiasmata were a variation on synapsis and could not understand how chromosomes could break and rejoin. Yet, the data were clear that linkage did not always occur. Ultimately, it took a young undergraduate student and an "all-nighter" to mathematically elucidate the linkage and recombination problem.

In 1913, Alfred Sturtevant, a student in Morgan's laboratory, gathered results from researchers in the laboratory, and took them home one night to mull them over. By the next morning, he had created the first "chromosome map," a linear representation of gene order and relative distance on a chromosome (Figure 13.4).

👁 VISUAL CONNECTION

Genetic Map Based on Recombination Frequencies in *Drosophila*		
MUTANT		**WILD TYPE**
Short aristae	0	Long aristae
Black body	48.5	Gray body
Cinnabar eyes	57.5	Red eyes
Vestigial wings	65.5	Normal wings
Brown eyes	104.5	Red eyes
Values in centimorgan (cM) map units; recombination frequency of 0.01 = 1 cM		

Figure 13.4 This genetic map orders *Drosophila* genes on the basis of recombination frequency.

Which of the following statements is true?

a. Recombination of the body color and red/cinnabar eye alleles will occur more frequently than recombination of the alleles for wing length and aristae length.
b. Recombination of the body color and aristae length alleles will occur more frequently than recombination of red/brown eye alleles and the aristae length alleles.
c. Recombination of the gray/black body color and long/short aristae alleles will not occur.
d. Recombination of the red/brown eye and long/short aristae alleles will occur more frequently than recombination of the alleles for wing length and body color.

As Figure 13.4 shows, by using recombination frequency to predict genetic distance, we can infer the relative gene order on chromosome 2. The values represent map distances in centimorgans (cM), which correspond to recombination frequencies (in percent). Therefore, the genes for body color and wing size were 65.5 – 48.5 = 17 cM apart, indicating that the maternal and paternal alleles for these genes recombine in 17 percent of offspring, on average.

To construct a chromosome map, Sturtevant assumed that genes were ordered serially on threadlike chromosomes. He also assumed that the incidence of recombination between two homologous chromosomes could occur with equal likelihood anywhere along the chromosome's length. Operating under these assumptions, Sturtevant postulated that alleles that were far apart on a chromosome were more likely to dissociate during meiosis simply because there was a larger region over which recombination could occur. Conversely, alleles that were close to each other on the chromosome were likely to be inherited

together. The average number of crossovers between two alleles—that is, their **recombination frequency**—correlated with their genetic distance from each other, relative to the locations of other genes on that chromosome. Considering the example cross between *AaBb* and *aabb* above, we could calculate the recombination's frequency as 50/1000 = 0.05. That is, the likelihood of a crossover between genes *A/a* and *B/b* was 0.05, or 5 percent. Such a result would indicate that the genes were definitively linked, but that they were far enough apart for crossovers to occasionally occur. Sturtevant divided his genetic map into map units, or **centimorgans (cM)**, in which a 0,01 recombination frequency corresponds to 1 cM.

By representing alleles in a linear map, Sturtevant suggested that genes can range from linking perfectly (recombination frequency = 0) to unlinking perfectly (recombination frequency = 0.5) when genes are on different chromosomes or genes separate very far apart on the same chromosome. Perfectly unlinked genes correspond to the frequencies Mendel predicted to assort independently in a dihybrid cross. A 0.5 recombination frequency indicates that 50 percent of offspring are recombinants and the other 50 percent are parental types. That is, every type of allele combination is represented with equal frequency. This representation allowed Sturtevant to additively calculate distances between several genes on the same chromosome. However, as the genetic distances approached 0.50, his predictions became less accurate because it was not clear whether the genes were very far apart on the same or on different chromosomes.

In 1931, Barbara McClintock and Harriet Creighton demonstrated the crossover of homologous chromosomes in corn plants. Weeks later, Curt Stern demonstrated microscopically homologous recombination in *Drosophila*. Stern observed several X-linked phenotypes that were associated with a structurally unusual and dissimilar X chromosome pair in which one X was missing a small terminal segment, and the other X was fused to a piece of the Y chromosome. By crossing flies, observing their offspring, and then visualizing the offspring's chromosomes, Stern demonstrated that every time the offspring allele combination deviated from either of the parental combinations, there was a corresponding exchange of an X chromosome segment. Using mutant flies with structurally distinct X chromosomes was the key to observing the products of recombination because DNA sequencing and other molecular tools were not yet available. We now know that homologous chromosomes regularly exchange segments in meiosis by reciprocally breaking and rejoining their DNA at precise locations.

⊘ LINK TO LEARNING

Review Sturtevant's process to create a genetic map on the basis of recombination frequencies here (http://openstax.org/l/gene_crossover) .

Mendel's Mapped Traits

Homologous recombination is a common genetic process, yet Mendel never observed it. Had he investigated both linked and unlinked genes, it would have been much more difficult for him to create a unified model of his data on the basis of probabilistic calculations. Researchers who have since mapped the seven traits that Mendel investigated onto a pea plant genome's seven chromosomes have confirmed that all the genes he examined are either on separate chromosomes or are sufficiently far apart as to be statistically unlinked. Some have suggested that Mendel was enormously lucky to select only unlinked genes; whereas, others question whether Mendel discarded any data suggesting linkage. In any case, Mendel consistently observed independent assortment because he examined genes that were effectively unlinked.

13.2 Chromosomal Basis of Inherited Disorders

By the end of this section, you will be able to do the following:

- Describe how a karyogram is created
- Explain how nondisjunction leads to disorders in chromosome number
- Compare disorders that aneuploidy causes
- Describe how errors in chromosome structure occur through inversions and translocations

Inherited disorders can arise when chromosomes behave abnormally during meiosis. We can divide chromosome disorders into two categories: abnormalities in chromosome number and chromosomal structural rearrangements. Because even small chromosome segments can span many genes, chromosomal disorders are characteristically dramatic and often fatal.

Chromosome Identification

Chromosome isolation and microscopic observation forms the basis of cytogenetics and is the primary method by which clinicians detect chromosomal abnormalities in humans. A **karyotype** is the number and appearance of chromosomes, and

includes their length, banding pattern, and centromere position. To obtain a view of an individual's karyotype, cytologists photograph the chromosomes and then cut and paste each chromosome into a chart, or **karyogram**. Another name is an ideogram ([Figure 13.5](#)).
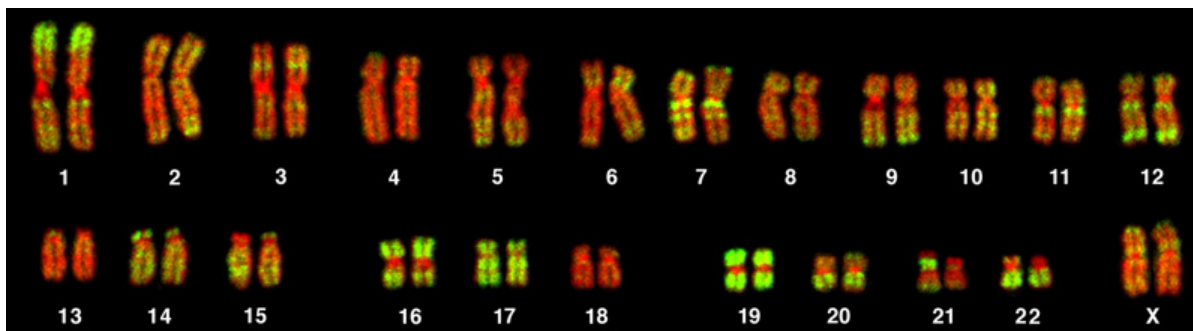

Figure 13.5 This karyotype is of a female human. Notice that homologous chromosomes are the same size, and have the same centromere positions and banding patterns. A human male would have an XY chromosome pair instead of the XX pair. (credit: Andreas Blozer et al)

In a given species, we can identify chromosomes by their number, size, centromere position, and banding pattern. In a human karyotype, **autosomes** or "body chromosomes" (all of the non–sex chromosomes) are generally organized in approximate order of size from largest (chromosome 1) to smallest (chromosome 22). The X and Y chromosomes are not autosomes. However, chromosome 21 is actually shorter than chromosome 22. Researchers discovered this after naming Down syndrome as trisomy 21, reflecting how this disease results from possessing one extra chromosome 21 (three total). Not wanting to change the name of this important disease, scientists retained the numbering of chromosome 21 despite describing it having the shortest set of chromosomes. We may designate the chromosome "arms" projecting from either end of the centromere as short or long, depending on their relative lengths. We abbreviate the short arm p (for "petite"); whereas, we abbreviate the long arm q (because it follows "p" alphabetically). Numbers further subdivide and denote each arm. Using this naming system, we can describe chromosome locations consistently in the scientific literature.

🏛 CAREER CONNECTION

Geneticists Use Karyograms to Identify Chromosomal Aberrations

Although we refer to Mendel as the "father of modern genetics," he performed his experiments with none of the tools that the geneticists of today routinely employ. One such powerful cytological technique is karyotyping, a method in which geneticists can identify traits characterized by chromosomal abnormalities from a single cell. To observe an individual's karyotype, a geneticist first collects a person's cells (like white blood cells) from a blood sample or other tissue. In the laboratory, he or she stimulates the isolated cells to begin actively dividing. The geneticist then applies the chemical colchicine to cells to arrest condensed chromosomes in metaphase. The geneticist then induces swelling in the cells using a hypotonic solution so the chromosomes spread apart. Finally, the geneticist preserves the sample in a fixative and applies it to a slide.

The geneticist then stains chromosomes with one of several dyes to better visualize each chromosome pair's distinct and reproducible banding patterns. Following staining, the geneticist views the chromosomes using bright-field microscopy. A common stain choice is the Giemsa stain. Giemsa staining results in approximately 400–800 bands (of tightly coiled DNA and condensed proteins) arranged along all 23 chromosome pairs. An experienced geneticist can identify each band. In addition to the banding patterns, geneticists further identify chromosomes on the basis of size and centromere location. To obtain the classic depiction of the karyotype in which homologous chromosome pairs align in numerical order from longest to shortest, the geneticist obtains a digital image, identifies each chromosome, and manually arranges the chromosomes into this pattern ([Figure 13.5](#)).

At its most basic, the karyogram may reveal genetic abnormalities in which an individual has too many or too few chromosomes per cell. Examples of this are Down Syndrome, which one identifies by a third copy of chromosome 21, and Turner Syndrome, which has the presence of only one X chromosome in women instead of the normal two characterizes. Geneticists can also identify large DNA deletions or insertions. For instance, geneticists can identify Jacobsen Syndrome—which involves distinctive facial features as well as heart and bleeding defects—by a deletion on chromosome 11. Finally, the karyotype can pinpoint **translocations**, which occur when a segment of genetic material breaks from one chromosome and reattaches to another

chromosome or to a different part of the same chromosome. Translocations are implicated in certain cancers, including chronic myelogenous leukemia.

During Mendel's lifetime, inheritance was an abstract concept that one could only infer by performing crosses and observing the traits that offspring expressed. By observing a karyogram, today's geneticists can actually visualize an individual's chromosomal composition to confirm or predict genetic abnormalities in offspring, even before birth.

Chromosome Number Disorders

Of all of the chromosomal disorders, chromosome number abnormalities are the most obviously identifiable from a karyogram. Chromosome number disorders include duplicating or losing entire chromosomes, as well as changes in the number of complete sets of chromosomes. They are caused by **nondisjunction**, which occurs when homologous chromosome pairs or sister chromatids fail to separate during meiosis. Misaligned or incomplete synapsis, or a spindle apparatus dysfunction that facilitates chromosome migration, can cause nondisjunction. The risk of nondisjunction occurring increases with the parents' age.

Nondisjunction can occur during either meiosis I or II, with differing results (Figure 13.6). If homologous chromosomes fail to separate during meiosis I, the result is two gametes that lack that particular chromosome and two gametes with two chromosome copies. If sister chromatids fail to separate during meiosis II, the result is one gamete that lacks that chromosome, two normal gametes with one chromosome copy, and one gamete with two chromosome copies.
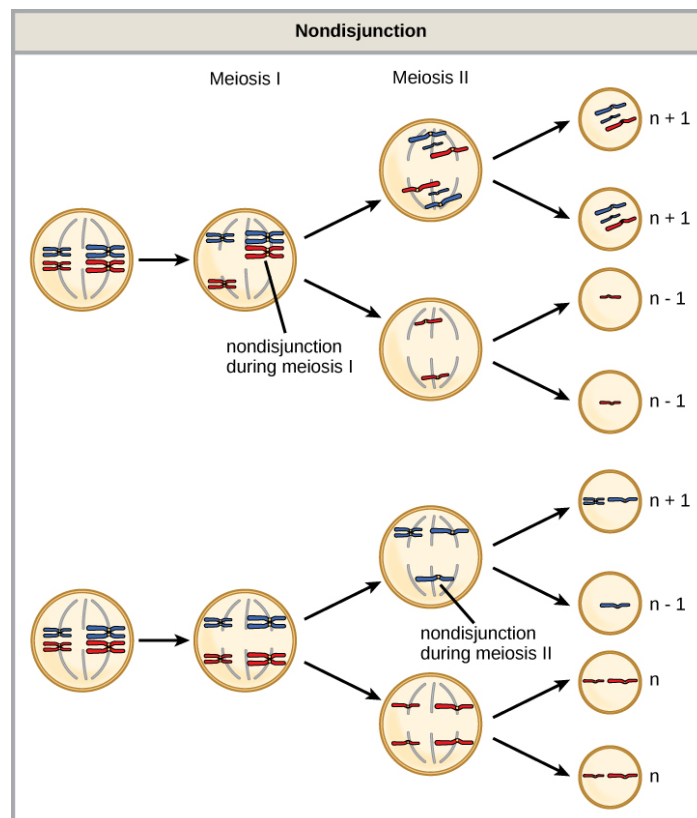
👁 VISUAL CONNECTION

Figure 13.6 Nondisjunction occurs when homologous chromosomes or sister chromatids fail to separate during meiosis, resulting in an abnormal chromosome number. Nondisjunction may occur during meiosis I or meiosis II.

Which of the following statements about nondisjunction is true?

   a.   Nondisjunction only results in gametes with n+1 or n−1 chromosomes.

b.   Nondisjunction occurring during meiosis II results in 50 percent normal gametes.
c.   Nondisjunction during meiosis I results in 50 percent normal gametes.
d.   Nondisjunction always results in four different kinds of gametes.

Aneuploidy

Scientists call an individual with the appropriate number of chromosomes for their species **euploid**. In humans, euploidy corresponds to 22 pairs of autosomes and one pair of sex chromosomes. An individual with an error in chromosome number is described as **aneuploid**, a term that includes **monosomy** (losing one chromosome) or **trisomy** (gaining an extraneous chromosome). Monosomic human zygotes missing any one copy of an autosome invariably fail to develop to birth because they lack essential genes. This underscores the importance of "gene dosage" in humans. Most autosomal trisomies also fail to develop to birth; however, duplications of some smaller chromosomes (13, 15, 18, 21, or 22) can result in offspring that survive for several weeks to many years. Trisomic individuals suffer from a different type of genetic imbalance: an excess in gene dose. Individuals with an extra chromosome may synthesize an abundance of the gene products, which that chromosome encodes. This extra dose (150 percent) of specific genes can lead to a number of functional challenges and often precludes development. The most common trisomy among viable births is that of chromosome 21, which corresponds to Down Syndrome. Short stature and stunted digits, facial distinctions that include a broad skull and large tongue, and significant developmental delays characterize individuals with this inherited disorder. We can correlate the incidence of Down syndrome with maternal age. Older women are more likely to become pregnant with fetuses carrying the trisomy 21 genotype (Figure 13.7).
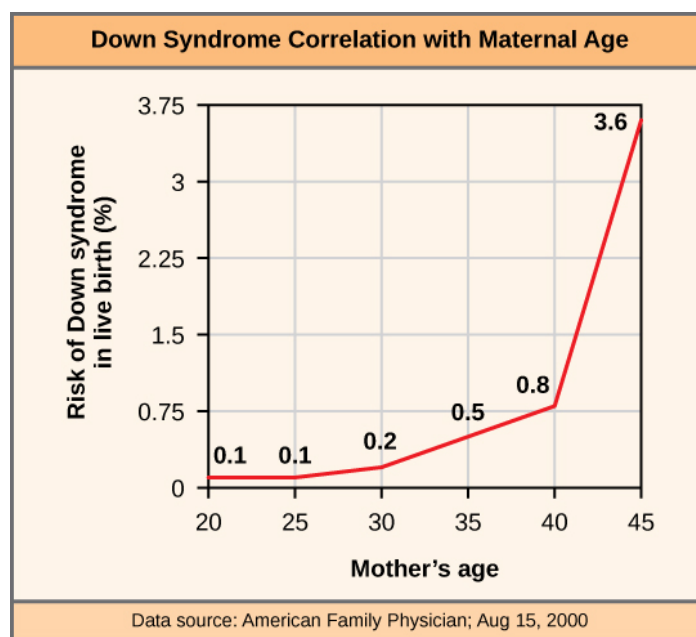

Figure 13.7 The incidence of having a fetus with trisomy 21 increases dramatically with maternal age.

⊘ LINK TO LEARNING

Visualize adding a chromosome that leads to Down syndrome in this video simulation (http://openstax.org/l/down_syndrome) .

Polyploidy

We call an individual with more than the correct number of chromosome sets (two for diploid species) **polyploid**. For instance, fertilizing an abnormal diploid egg with a normal haploid sperm would yield a triploid zygote. Polyploid animals are extremely rare, with only a few examples among the flatworms, crustaceans, amphibians, fish, and lizards. Polyploid animals are sterile because meiosis cannot proceed normally and instead produces mostly aneuploid daughter cells that cannot yield viable zygotes. Rarely, polyploid animals can reproduce asexually by haplodiploidy, in which an unfertilized egg divides mitotically to produce offspring. In contrast, polyploidy is very common in the plant kingdom, and polyploid plants tend to be larger and more robust than euploids of their species (Figure 13.8).

Figure 13.8 As with many polyploid plants, this triploid orange daylily (*Hemerocallis fulva*) is particularly large and robust, and grows flowers with triple the number of petals of its diploid counterparts. (credit: Steve Karg)

Sex Chromosome Nondisjunction in Humans

Humans display dramatic deleterious effects with autosomal trisomies and monosomies. Therefore, it may seem counterintuitive that human females and males can function normally, despite carrying different numbers of the X chromosome. Rather than a gain or loss of autosomes, variations in the number of sex chromosomes occur with relatively mild effects. In part, this happens because of the molecular process **X inactivation**. Early in development, when female mammalian embryos consist of just a few thousand cells (relative to trillions in the newborn), one X chromosome in each cell inactivates by tightly condensing into a quiescent (dormant) structure, or a Barr body. The chance that an X chromosome (maternally or paternally derived) inactivates in each cell is random, but once this occurs, all cells derived from that one will have the same inactive X chromosome or Barr body. By this process, females compensate for their double genetic dose of X chromosome. In so-called "tortoiseshell" cats, we observe embryonic X inactivation as color variegation (Figure 13.9). Females that are heterozygous for an X-linked coat color gene will express one of two different coat colors over different regions of their body, corresponding to whichever X chromosome inactivates in that region's embryonic cell progenitor.

Figure 13.9 In cats, the gene for coat color is located on the X chromosome. In female cats' embryonic development, one of the two X chromosomes randomly inactivates in each cell, resulting in a tortoiseshell pattern if the cat has two different alleles for coat color. Male cats, having only one X chromosome, never exhibit a tortoiseshell coat color. (credit: Michael Bodega)

An individual carrying an abnormal number of X chromosomes will inactivate all but one X chromosome in each of her cells. However, even inactivated X chromosomes continue to express a few genes, and X chromosomes must reactivate for the proper maturation of female ovaries. As a result, X-chromosomal abnormalities typically occur with mild mental and physical defects, as well as sterility. If the X chromosome is absent altogether, the individual will not develop in utero.

Scientists have identified and characterized several errors in sex chromosome number. Individuals with three X chromosomes, triplo-X, are phenotypically female but express developmental delays and reduced fertility. The XXY genotype, corresponding to one type of Klinefelter syndrome, corresponds to phenotypically male individuals with small testes, enlarged breasts, and reduced body hair. More complex types of Klinefelter syndrome exist in which the individual has as many as five X chromosomes. In all types, every X chromosome except one undergoes inactivation to compensate for the excess genetic dosage. We see this as several Barr bodies in each cell nucleus. Turner syndrome, characterized as an X0 genotype (i.e., only a single sex chromosome), corresponds to a phenotypically female individual with short stature, webbed skin in the neck region, hearing and cardiac impairments, and sterility.

Duplications and Deletions

In addition to losing or gaining an entire chromosome, a chromosomal segment may duplicate or lose itself. Duplications and deletions often produce offspring that survive but exhibit physical and mental abnormalities. Duplicated chromosomal segments may fuse to existing chromosomes or may be free in the nucleus. Cri-du-chat (from the French for "cry of the cat") is a syndrome that occurs with nervous system abnormalities and identifiable physical features that result from a deletion of most 5p (the small arm of chromosome 5) (Figure 13.10). Infants with this genotype emit a characteristic high-pitched cry on which the disorder's name is based.

Figure 13.10 This figure shows an individual with cri-du-chat syndrome at two, four, nine, and 12 years of age. (credit: Paola Cerruti Mainardi)

Chromosomal Structural Rearrangements

Cytologists have characterized numerous structural rearrangements in chromosomes, but chromosome inversions and translocations are the most common. We can identify both during meiosis by the adaptive pairing of rearranged chromosomes with their former homologs to maintain appropriate gene alignment. If the genes on two homologs are not oriented correctly, a recombination event could result in losing genes from one chromosome and gaining genes on the other. This would produce aneuploid gametes.

Chromosome Inversions

A **chromosome inversion** is the detachment, 180° rotation, and reinsertion of part of a chromosome. Inversions may occur in nature as a result of mechanical shear, or from transposable elements' action (special DNA sequences capable of facilitating rearranging chromosome segments with the help of enzymes that cut and paste DNA sequences). Unless they disrupt a gene sequence, inversions only change gene orientation and are likely to have more mild effects than aneuploid errors. However, altered gene orientation can result in functional changes because regulators of gene expression could move out of position with respect to their targets, causing aberrant levels of gene products.

An inversion can be **pericentric** and include the centromere, or **paracentric** and occur outside the centromere (Figure 13.11). A pericentric inversion that is asymmetric about the centromere can change the chromosome arms' relative lengths, making these inversions easily identifiable.
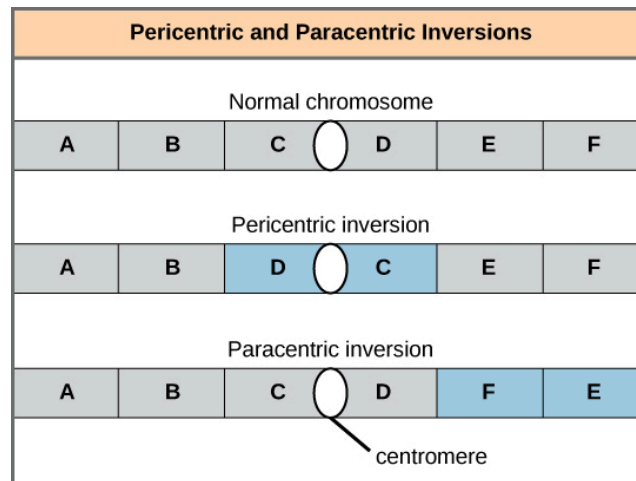

Figure 13.11 Pericentric inversions include the centromere, and paracentric inversions do not. A pericentric inversion can change the chromosome arms' relative lengths. A paracentric inversion cannot.

When one homologous chromosome undergoes an inversion but the other does not, the individual is an inversion heterozygote. To maintain point-for-point synapsis during meiosis, one homolog must form a loop, and the other homolog must mold around it. Although this topology can ensure that the genes correctly align, it also forces the homologs to stretch and can occur with imprecise synapsis regions (Figure 13.12).
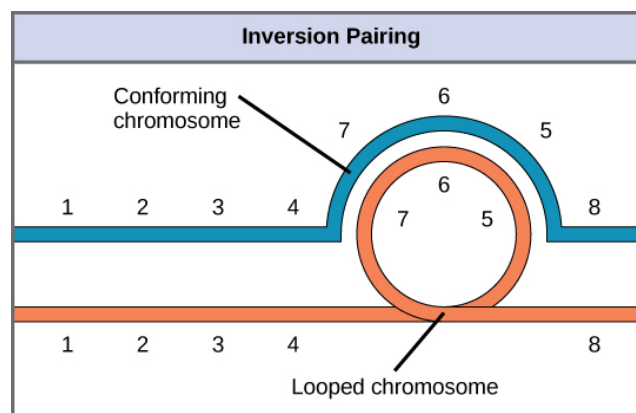

Figure 13.12 When one chromosome undergoes an inversion but the other does not, one chromosome must form an inverted loop to retain point-for-point interaction during synapsis. This inversion pairing is essential to maintaining gene alignment during meiosis and to allow for recombination.

EVOLUTION CONNECTION

The Chromosome 18 Inversion

Not all chromosomes' structural rearrangements produce nonviable, impaired, or infertile individuals. In rare instances, such a change can result in new species evolving. In fact, a pericentric inversion in chromosome 18 appears to have contributed to human evolution. This inversion is not present in our closest genetic relatives, the chimpanzees. Humans and chimpanzees differ cytogenetically by pericentric inversions on several chromosomes and by the fusion of two separate chromosomes in chimpanzees that correspond to chromosome two in humans.

Scientists believe the pericentric chromosome 18 inversion occurred in early humans following their divergence from a common ancestor with chimpanzees approximately five million years ago. Researchers characterizing this inversion have suggested that approximately 19,000 nucleotide bases were duplicated on 18p, and the duplicated region inverted and reinserted on chromosome 18 of an ancestral human.

A comparison of human and chimpanzee genes in the region of this inversion indicates that two genes—*ROCK1* and *USP14*—that are adjacent on chimpanzee chromosome 17 (which corresponds to human chromosome 18) are more distantly positioned on human chromosome 18. This suggests that one of the inversion breakpoints occurred between these two genes. Interestingly, humans and chimpanzees express *USP14* at distinct levels in specific cell types, including cortical cells and fibroblasts. Perhaps the chromosome 18 inversion in an ancestral human repositioned specific genes and reset their expression levels in a useful way. Because both *ROCK1* and *USP14* encode cellular enzymes, a change in their expression could alter cellular function. We do not know how this inversion contributed to hominid evolution, but it appears to be a significant factor in the divergence of humans from other primates.[1]

Translocations

A **translocation** occurs when a chromosome segment dissociates and reattaches to a different, nonhomologous chromosome. Translocations can be benign or have devastating effects depending on how the positions of genes are altered with respect to regulatory sequences. Notably, specific translocations have occurred with several cancers and with schizophrenia. Reciprocal translocations result from exchanging chromosome segments between two nonhomologous chromosomes such that there is no genetic information gain or loss (Figure 13.13).
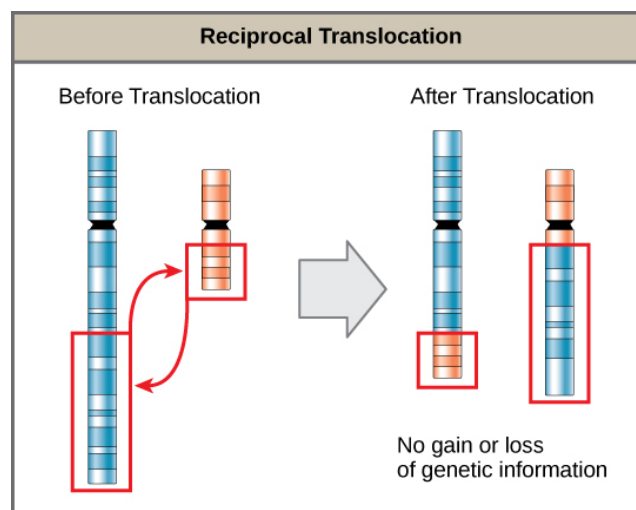

Figure 13.13 A reciprocal translocation occurs when a DNA segment transfers from one chromosome to another, nonhomologous chromosome. (credit: modification of work by National Human Genome Research/USA)

1Violaine Goidts et al., "Segmental duplication associated with the human-specific inversion of chromosome 18: a further example of the impact of segmental duplications on karyotype and genome evolution in primates," *Human Genetics*. 115 (2004):116-122

KEY TERMS

aneuploid   individual with an error in chromosome number; includes chromosome segment deletions and duplications

autosome   any of the non-sex chromosomes

centimorgan (cM)   (also, map unit) relative distance that corresponds to a 0,01 recombination frequency

Chromosomal Theory of Inheritance   theory proposing that chromosomes are the genes' vehicles and that their behavior during meiosis is the physical basis of the inheritance patterns that Mendel observed

chromosome inversion   detachment, 180° rotation, and chromosome arm reinsertion

euploid   individual with the appropriate number of chromosomes for their species

homologous recombination   process by which homologous chromosomes undergo reciprocal physical exchanges at their arms, also crossing over

karyogram   a karyotype's photographic image

karyotype   an individual's chromosome number and appearance; includes the size, banding patterns, and centromere position

monosomy   otherwise diploid genotype in which one chromosome is missing

nondisjunction   failure of synapsed homologs to completely separate and migrate to separate poles during the meiosis' first cell division

nonparental (recombinant) type   progeny resulting from homologous recombination that exhibits a different allele combination compared with its parents

paracentric   inversion that occurs outside the centromere

parental types   progeny that exhibits the same allelic combination as its parents

pericentric   inversion that involves the centromere

polyploid   individual with an incorrect number of chromosome sets

recombination frequency   average number of crossovers between two alleles; observed as the number of nonparental types in a progeny's population

translocation   process by which one chromosome segment dissociates and reattaches to a different, nonhomologous chromosome

trisomy   otherwise diploid genotype in which one entire chromosome duplicates

X inactivation   condensing X chromosomes into Barr bodies during embryonic development in females to compensate for the double genetic dose

CHAPTER SUMMARY

13.1 Chromosomal Theory and Genetic Linkage

Sutton and Boveri's Chromosomal Theory of Inheritance states that chromosomes are the vehicles of genetic heredity. Neither Mendelian genetics nor gene linkage is perfectly accurate. Instead, chromosome behavior involves segregation, independent assortment, and occasionally, linkage. Sturtevant devised a method to assess recombination frequency and infer linked genes' relative positions and distances on a chromosome on the basis of the average number of crossovers in the intervening region between the genes. Sturtevant correctly presumed that genes are arranged in serial order on chromosomes and that recombination between homologs can occur anywhere on a chromosome with equal likelihood. Whereas linkage causes alleles on the same chromosome to be inherited together, homologous recombination biases alleles toward an independent inheritance pattern.

13.2 Chromosomal Basis of Inherited Disorders

The number, size, shape, and banding pattern of chromosomes make them easily identifiable in a karyogram and allows for the assessment of many chromosomal abnormalities. Disorders in chromosome number, or aneuploidies, are typically lethal to the embryo, although a few trisomic genotypes are viable. Because of X inactivation, aberrations in sex chromosomes typically have milder phenotypic effects. Aneuploidies also include instances in which a chromosome's segments duplicate or delete themselves. Inversion or translocation also may rearrange chromosome structures. Both of these aberrations can result in problematic phenotypic effects. Because they force chromosomes to assume unnatural topologies during meiosis, inversions and translocations often occur with reduced fertility because of the likelihood of nondisjunction.

VISUAL CONNECTION QUESTIONS

1. Figure 13.3 In a test cross for two characteristics such as the one shown here, can the predicted frequency of recombinant offspring be 60 percent? Why or why not?

2. Figure 13.4 Which of the following statements is true?
   a. Recombination of the body color and red/cinnabar eye alleles will occur more frequently than recombination of the alleles for wing length and aristae length.
   b. Recombination of the body color and aristae length alleles will occur more frequently than recombination of red/brown eye alleles and the aristae length alleles.
   c. Recombination of the gray/black body color and long/short aristae alleles will not occur.
   d. Recombination of the red/brown eye and long/short aristae alleles will occur more frequently than recombination of the alleles for wing length and body color.

3. Figure 13.6 Which of the following statements about nondisjunction is true?
   a. Nondisjunction only results in gametes with n+1 or n−1 chromosomes.
   b. Nondisjunction occurring during meiosis II results in 50 percent normal gametes.
   c. Nondisjunction during meiosis I results in 50 percent normal gametes.
   d. Nondisjunction always results in four different kinds of gametes.

REVIEW QUESTIONS

4. X-linked recessive traits in humans (or in *Drosophila*) are observed _____.
   a. in more males than females
   b. in more females than males
   c. in males and females equally
   d. in different distributions depending on the trait

5. The first suggestion that chromosomes may physically exchange segments came from the microscopic identification of _____.
   a. synapsis
   b. sister chromatids
   c. chiasmata
   d. alleles

6. Which recombination frequency corresponds to independent assortment and the absence of linkage?
   a. 0
   b. 0.25
   c. 0.50
   d. 0.75

7. Which recombination frequency corresponds to perfect linkage and violates the law of independent assortment?
   a. 0
   b. 0.25
   c. 0.50
   d. 0.75

8. Which of the following codes describes position 12 on the long arm of chromosome 13?
   a. 13p12
   b. 13q12
   c. 12p13
   d. 12q13

9. In agriculture, polyploid crops (like coffee, strawberries, or bananas) tend to produce _____.
   a. more uniformity
   b. more variety
   c. larger yields
   d. smaller yields

10. Assume a pericentric inversion occurred in one of two homologs prior to meiosis. The other homolog remains normal. During meiosis, what structure—if any—would these homologs assume in order to pair accurately along their lengths?
    a. V formation
    b. cruciform
    c. loop
    d. pairing would not be possible

11. The genotype XXY corresponds to
    a. Klinefelter syndrome
    b. Turner syndrome
    c. Triplo-X
    d. Jacob syndrome

12. Abnormalities in the number of X chromosomes tends to have milder phenotypic effects than the same abnormalities in autosomes because of _____.
    a. deletions
    b. nonhomologous recombination
    c. synapsis
    d. X inactivation

13. By definition, a pericentric inversion includes the _____.
    a. centromere
    b. chiasma
    c. telomere
    d. synapse

CRITICAL THINKING QUESTIONS

14. Explain how the Chromosomal Theory of Inheritance helped to advance our understanding of genetics.

15. Using diagrams, illustrate how nondisjunction can result in an aneuploid zygote.