Chapter 15

The Chromosomal Basis of Inheritance

Overview: Locating Genes Along Chromosomes

- Today we know that genes—Gregor Mendel's "hereditary factors"—are located on chromosomes.
- A century ago, the relationship between 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.

Concept 15.1 Mendelian inheritance has its physical basis in the behavior of chromosomes

- Around 1902, cytologists and geneticists began to see parallels between the behavior of chromosomes and the behavior of Mendel's proposed hereditary factors.
  - 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 and independent assortment during meiosis.

The behavior of chromosomes during meiosis accounts for Mendel's laws of inheritance.

- 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.
- 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 most commonly observed character phenotype is called the **wild type**.

- Traits that are alternatives to the wild type, such as white eyes in *Drosophila*, are called *mutant phenotypes*.
  - They are due to alleles assumed to have originated as changes, or mutations, in the wild-type allele.
- For a given character in flies, the gene's symbol is chosen from the first mutant discovered.
  - The allele for white eyes in *Drosophila* is symbolized by *w*.
  - A superscript identifies the wild-type (red-eye) allele (w^+).
  - The symbols for human genes are capital letters (for example, *HD* for the allele for Huntington's disease).
- When Morgan crossed his white-eyed male with a red-eyed female, all the F_1 offspring had red eyes, suggesting that the red allele was 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 in only F_2 males.
  - All the F_2 females and half the F_2 males had red eyes.
- Morgan concluded that a fly's eye color was linked to its sex.
- Morgan reasoned that the gene with the white-eyed mutation is on the X chromosome, with no corresponding allele present on the Y chromosome.
  - A female (XX) can have white eyes only when both X chromosomes carry a recessive mutant allele (*w*).
  - Males (XY) have only a single allele. They will have red eyes if they have a red-eyed allele or white eyes if they have a white-eyed allele.
- Morgan's finding of the correlation between a particular trait and an individual's sex provided support for the chromosome theory of inheritance.
  - A specific gene (for eye color) is carried on a specific chromosome (the X chromosome).

Concept 15.2 Sex-linked genes exhibit unique patterns of inheritance

- 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.
- Short segments at either end of the Y chromosome are the only regions that are homologous with the corresponding regions of the X.
  - These homologous regions allow the X and Y chromosomes in males to pair and behave like homologous chromosomes during meiosis in the testes.
- In both testes and ovaries, 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.
- 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).

- Other animals have different methods of sex determination.
  - The X-0 system is found in some insects. Females are XX and 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 humans, the anatomical signs of sex first appear when the embryo is about two months old.
  - Before that, the gonads can develop into either testes or ovaries.

The SRY gene is on the Y chromosome.

- 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 *Y*).
- In individuals with the *SRY* gene, the generic embryonic gonads develop into testes.
  - The *SRY* gene codes for a protein that regulates many other genes, triggering a cascade of biochemical, physiological, and anatomical features.
- In individuals lacking the *SRY* gene, the generic embryonic gonads develop into ovaries.
- In the X-Y system, the Y chromosome is much smaller than the X chromosome.
- Researchers have sequenced the Y chromosome and identified 78 genes coding for about 25 proteins.
  - Half of the genes are expressed only in the testes, and some are required for normal testicular function and the production of normal sperm.

A gene located on either sex chromosome is called a sex-linked gene.

- Genes located on the Y chromosome are called *Y-linked genes.*
  - The Y chromosome is passed along virtually intact from a father to all his sons.
  - Because there are so few Y-linked genes, very few disorders are transferred from father to son on the Y chromosome.
  - A rare example is that in the absence of some of the Y-linked genes, an XY individual is male but does not produce normal sperm.
- The human X chromosome contains approximately 1,100 **X-linked genes**.
  - Because males and females inherit a different number of X chromosomes, the pattern of inheritance of X-linked genes differs from that of genes located on autosomes.
- While most Y-linked genes help determine sex, the X chromosomes have genes for many characters unrelated to sex.
- Human X-linked genes follow the same pattern of inheritance as Morgan's white-eye locus in *Drosophila*.
  - Fathers pass X-linked alleles to all their daughters but none of their sons.
  - Mothers can pass X-linked alleles to both sons and daughters.
- If an X-linked trait is due to a recessive allele, a female will express the phenotype only if she is homozygous for that allele.
  - Heterozygous females are carriers for the recessive trait.
- Because males have only one locus, the terms *homozygous* and *heterozygous* lack meaning for describing their X-linked genes.
  - The term *hemizygous* is used in such cases.

- 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.
  - Although males are far more likely to exhibit X-linked recessive disorders than are females, there are females with X-linked disorders.
- For example, color blindness is a mild disorder almost always inherited as an X-linked trait.
  - A color-blind daughter may be born to a color-blind father whose mate is a carrier.
  - The odds of this happening are fairly low.
- Several serious human disorders are X-linked.
- **Duchenne muscular dystrophy** affects one in 3,500 males born in the United States.
  - The disease is characterized by a progressive weakening of the muscles and a loss of coordination. 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.
- **Hemophilia** is an X-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.
  - Bleeding in muscles and joints can be painful and can lead to serious damage.
- In the 1800s, hemophilia was widespread among the royal families of Europe.
  - Queen Victoria of England passed the allele to several of her descendants.
  - Intermarriage with royal family members of other nations, such as Spain and Russia, further spread this X-linked trait.
- People with hemophilia can be treated with intravenous injections of the missing protein.

Although female mammals inherit two X chromosomes, only one X chromosome is active.

- Males and females have the same effective dose (one copy) of genes on the X chromosome.
- During female development, one X chromosome per cell condenses into a compact **Barr body.**
  - Most of the genes on the Barr-body X chromosome are not expressed.
  - The condensed Barr-body chromosome is reactivated in ovarian cells that produce eggs.
- Mary Lyon, a British geneticist, demonstrated that selection of which X chromosome forms the Barr body occurs randomly and independently in each embryonic cells present at the time of X inactivation.
  - As a consequence, females consist of a *mosaic* of two types of cells, some with an active paternal X chromosome and others with an active maternal X chromosome.
  - After an X chromosome is inactivated in a particular cell, all mitotic descendants of that cell will have the same inactive X.
  - If a female is heterozygous for a sex-linked trait, approximately half her cells will express one allele, and the other half will express the alternate allele.
- Similarly, the orange-and-black pattern on tortoiseshell cats is due to patches of cells expressing an orange allele while other patches have a non-orange allele.
- In humans, this mosaic pattern is evident in women who are heterozygous for an X-linked mutation that prevents the development of sweat glands.
  - A heterozygous woman has patches of normal skin and patches of skin lacking sweat glands.

- X inactivation involves modification of the DNA and the histone proteins bound to it by attachment of methyl (—CH_3) groups to one of the nitrogenous bases of DNA nucleotides.
- A particular region of each X chromosome contains several genes involved in the inactivation process.
- The two regions, one on each X chromosome, associate briefly with each other in each cell at an early stage of embryonic development.
- One of the genes called *XIST* (X-inactive specific transcript) becomes active *only* on the Barr-body chromosome.
  - Multiple copies of the RNA product of this gene attach to the X chromosome on which they are made, almost covering it.
  - Interaction of this RNA with the chromosome initiates X inactivation, and the RNA products of other genes nearby on the X chromosome help to regulate the process.

Concept 15.3 Linked genes tend to be inherited together because they are located near each other on the same chromosome

- Each chromosome (except the Y chromosome) has hundreds or thousands of genes.
- Genes located near each other on the same chromosome tend to be inherited together.
  - These genes are called **linked genes**.
- The results of crosses with linked genes differ from those expected according to the law of independent assortment.
- Morgan followed the inheritance of characters for body color and wing size in *Drosophila*.
  - 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 F_1 heterozygous females (b^+bvg^+vg) with homozygous recessive males ($bbvgvg$).
  - According to independent assortment, this should produce four phenotypes in a 1:1:1:1 ratio.
- Morgan observed a large number of wild-type (gray-normal) and double-mutant (black-vestigial) flies among the offspring: the parental phenotypes.
  - The other two phenotypes (gray-vestigial and black-normal) were rarer than expected based on independent assortment.
  - Morgan reasoned that body color and wing shape are usually inherited together because the genes for these characters are on the same chromosome.
- What led to **genetic recombination**, production of offspring with new combinations of traits?

Independent assortment of chromosomes produces genetic recombination of unlinked genes.

- 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 the 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 **recombinant types** or **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*.

Crossing over produces genetic recombination of linked genes.

- Most of the offspring from the *Drosophila* testcross for body color and wing size had parental phenotypes.
  - That suggested that the two genes were on the same chromosome, since the occurrence of parental types with a frequency greater than 50% indicates that the genes are linked.
  - About 17% of offspring, however, were recombinants.
- 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.
  - A set of proteins orchestrates an exchange of corresponding segments of one maternal and one paternal chromatid.
  - The production of recombinant gametes during meiosis accounts for the occurrence of recombinant phenotypes in Morgan's testcross.

New combinations of alleles provide variation for natural selection.

- Recombinant chromosomes resulting from crossing over bring alleles together in new combinations.
  - The subsequent events of meiosis distribute to gametes the recombinant chromosomes in a multitude of combinations.
  - Random fertilization increases further the number of variant allele combinations.
- This genetic variation provides the raw material on which natural selection works.
  - If the traits conferred by particular combinations of alleles are better suited for a given environment, organisms possessing those genotypes will leave more offspring, ensuring the continuation of their genetic complement.
- Ultimately, the interplay between environment and genotype will determine which genetic combinations persist over time.

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

- One of Morgan's students, Alfred Sturtevant, used the 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 percentage of recombinant offspring, the *recombination frequency*, depends on 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 positions 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 positions of three fruit fly genes: body color (*b*), wing size (*vg*), and eye color (*cn*).
  - Cinnabar (*cn*), one of many *Drosophila* genes affecting eye color, results in a bright red eye.
  - 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 as **map units**.
  - One map unit is equivalent to a 1% recombination frequency.
- 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.
- At least two of the genes studied by Mendel are located on the same chromosome but still assort independently.
  - Such genes are *physically connected* because they are on the same chromosome, but *genetically unlinked* because they sort 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 *linkage groups*, one for each chromosome.
- A linkage map provides an approximate 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.
- By combining linkage maps with other methods like chromosomal banding, geneticists can develop **cytogenetic maps** of chromosomes.
  - These maps indicate the positions of genes with respect to chromosomal features.
- Ultimate maps show the physical distances between gene loci in DNA nucleotides.

Concept 15.4 Alterations of chromosome number or structure cause some genetic disorders

- Physical and chemical disturbances, as well as errors during meiosis, can damage chromosomes in major ways or alter their number in a cell.

- Major chromosomal damage in humans and other mammals often leads to miscarriage.
  - Individuals born with these types of genetic defects commonly exhibit various developmental disorders.
- Plants tolerate genetic defects better than animals.

Nondisjunction leads to abnormal chromosome number.

- **Nondisjunction** may occur if members of a pair of homologous chromosomes do not separate properly during meiosis I or sister chromatids fail to separate during meiosis II.
  - As a consequence of nondisjunction, one gamete receives two of the same type of chromosome, and another gamete receives no copy.
- Offspring resulting from the fertilization of a normal gamete with one produced by nondisjunction have an abnormal number of a particular chromosome, a condition known as **aneuploidy**.
  - **Trisomic** cells have three copies of a particular chromosome type and have $2n + 1$ chromosomes.
  - **Monosomic** cells have only one copy of a particular chromosome type and have $2n - 1$ chromosomes.
- If the organism survives, aneuploidy typically leads to a distinct phenotype.
- Aneuploidy can also occur during mitosis. If this happens early in development, the aneuploid condition is passed along by mitosis to a large number of cells.
  - This is likely to have a substantial effect on the organism.
- Organisms with more than two complete sets of chromosomes are **polyploid**.
- The terms *triploidy* ($3n$) and *tetraploidy* ($4n$) indicate three or four chromosomal sets, respectively.
  - Triploidy may occur when a normal gamete fertilizes a diploid gamete produced by nondisjunction of all its chromosomes.
  - If a $2n$ zygote fails to divide after replicating its chromosomes, a *tetraploid* ($4n$) embryo results from subsequent successful cycles of mitosis.
- The spontaneous origin of polyploid individuals plays an important role in the evolution of plants.
  - Many crop plants are polyploid. Bananas are triploid, wheat is hexaploid ($6n$), and strawberries octoploid ($8n$).
- Polyploid animal species are less common, although there are fish and amphibian polyploid species.
- Polyploids are more nearly normal in phenotype than aneuploids.
  - One extra or missing chromosome apparently upsets the genetic balance during development more than does an entire extra set of chromosomes.

Breakage of a chromosome can lead to four types of changes in chromosome structure.

- A **deletion** occurs when a chromosomal fragment is lost. The chromosome is missing certain genes.
- A **duplication** occurs when a fragment becomes attached as an extra segment to a sister chromatid.
  - Alternatively, a detached fragment may attach to a nonsister chromatid of a homologous chromosome.

- In this case, the duplicated segments will not be identical if the homologs carry different alleles.

- An **inversion** occurs when a chromosomal fragment reattaches to the original chromosome, but in the reverse orientation.
- In **translocation,** a chromosomal fragment joins a nonhomologous chromosome.
- Deletions and duplications are especially likely to occur during meiosis.
  - Homologous chromatids may break and rejoin at incorrect places during crossing over, so that one chromatid loses more genes than it receives.
  - The products of such an unequal crossover are one chromosome with a deletion and one chromosome with a duplication.
- A diploid embryo that is homozygous for a large deletion or a male with a large deletion to its single X chromosome is usually missing many essential genes.
  - This is usually lethal.
- Duplications and translocations are typically harmful.
- Reciprocal translocations or inversions can alter phenotype because a gene's expression is influenced by its location among neighboring genes.

Human disorders are due to chromosome alterations.

- Several serious human disorders are due to alterations of chromosome number and structure.
- Although the frequency of aneuploid zygotes may be quite high in humans, most of these alterations are so disastrous to development that affected embryos are spontaneously aborted long before birth.
- Certain aneuploid conditions upset the genetic balance less than others, making survival to birth and beyond possible.
  - Surviving individuals have a set of symptoms—a *syndrome*—characteristic of the type of aneuploidy.
  - Genetic disorders caused by aneuploidy can be diagnosed before birth by fetal testing.
- One aneuploid condition, **Down syndrome,** is due to three copies of chromosome 21, or *trisomy 21*.
  - Trisomy 21 affects one in 700 children born in the United States.
- Although chromosome 21 is the smallest human chromosome, trisomy 21 severely alters an individual's phenotype in specific ways.
  - Individuals with Down syndrome have characteristic facial features, short stature, correctable heart defects, and developmental delays.
  - They are susceptible to respiratory infection, mental retardation, and have an increased risk of developing leukemia and Alzheimer's disease.
  - All males and half of females with Down syndrome are sexually underdeveloped and sterile.
- Most cases of Down syndrome result from nondisjunction during gamete production in one parent.
- The frequency of Down syndrome increases with the age of the mother.
  - Trisomy 21 may be linked to some age-dependent abnormality in a meiosis I checkpoint that normally delays anaphase until all the kinetochores are attached to the spindle.

- Trisomies of other chromosomes also increase in incidence with maternal age, but it is rare for infants with these autosomal trisomies to survive for long.
- Prenatal screening for trisomies in the embryo is now offered to all pregnant women.
  - In 2008, the Prenatally and Postnatally Diagnosed Conditions Awareness Act was signed into law in the United States.
  - This law stipulates that medical practitioners give accurate information about any prenatal or postnatal diagnosis received by parents and that they connect parents with appropriate support services.
- Nondisjunction of sex chromosomes produces a variety of aneuploid conditions in humans, upsetting the genetic balance less severely that autosomal aneuploidy.
  - This may be because the Y chromosome contains relatively few genes and because extra copies of the X chromosome become inactivated as Barr bodies in somatic cells.
- An XXY male has *Klinefelter syndrome*, which occurs once in every 500 to 1,000 live malebirths.
  - These individuals have male sex organs but abnormally small testes and are sterile.
  - Although the extra X is inactivated, some breast enlargement and other female characteristics are common.
  - Affected individuals may have subnormal intelligence.
- Males with an extra Y chromosome (XYY) tend to be somewhat taller than average.
- Trisomy X (XXX), which occurs once in every 1,000 births live female births, produces healthy females.
- Monosomy X, or *Turner syndrome* (X0), occurs once in every 2,500 births live female births.
  - This is the only known viable monosomy in humans.
  - X0 individuals are phenotypically female but are sterile because their sex organs do not mature.
  - When given estrogen replacement therapy, girls with Turner syndrome develop secondary sex characteristics.
  - Most have normal intelligence.
- Deletions, even in a heterozygous state, can cause severe problems.
- One syndrome, *cri du chat*, results from a specific deletion in chromosome 5.
  - These individuals are mentally retarded, have small heads with unusual facial features, and have a cry like the mewing of a distressed cat.
  - This syndrome is fatal in infancy or early childhood.
- Chromosomal translocations have been implicated in certain cancers, including *chronic myelogenous leukemia (CML).*
  - CML occurs when a large fragment of chromosome 22 switches places with a small fragment from the tip of chromosome 9.
  - The resulting short and easily recognized chromosome 22 is called the *Philadelphia chromosome*.
  - The exchange causes cancer by activating a gene that leads to uncontrolled cell cycle progression.

Concept 15.5 Some inheritance patterns are exceptions to the standard Mendelian inheritance

The phenotypic effects of some mammalian genes depend on whether they are inherited from the mother or the father.

- For most genes, a specific allele has the same effect whether it is inherited from the mother or the father.
- For a few dozen mammalian traits, phenotype varies depending on which parent passed along the alleles for those traits.
- Variation in phenotype depending on whether an allele is inherited from the male or female parent is called **genomic imprinting**.
  - Most of the genes involved are on autosomes.
- Genomic imprinting occurs during gamete formation and results in the silencing of a particular allele of certain genes. Imprinted genes are not expressed.
- Because genes are imprinted differently in sperm and ova, a zygote expresses only one allele of an imprinted gene, inherited from either the female or the male parent.
  - The imprint genes are transmitted to all body cells during development.
- In each generation, old imprints are "erased" in gamete-producing cells, and the chromosomes of the developing gametes are newly imprinted according to the sex of the individual forming the gametes.
- Patterns of imprinting are characteristic of a given species.
- The mouse gene for insulin-like growth factor 2 (*Igf2*) is required for normal prenatal growth.
  - Only the paternal allele is expressed.
- Evidence that the *Igf2* allele is imprinted came from crosses between wild-type mice and dwarf mice homozygous for a recessive mutation in the *Igf2* gene.
  - The phenotypes of heterozygous offspring differ, depending on whether the mutant allele comes from the mother or the father.
  - The *Igf2* allele is imprinted in eggs, turning off expression of the imprinted allele.
  - In sperm, the *Igf2* allele is not imprinted and functions normally.
- In many cases, the genomic imprint consists of methyl (—CH_3) groups that are added to the cytosine nucleotides of one of the alleles.
- The hypothesis that methylation directly silences an allele is consistent with the evidence that heavily methylated genes are usually inactive.
- For a few genes, methylation has been shown to *activate* expression of the allele.
  - This is the case for the *Igf2* gene: Methylation of certain cytosines on the paternal chromosome leads to expression of the paternal *Igf2* allele.
- This inconsistency was explained when researchers found that DNA methylation operates indirectly by recruiting enzymes that modify DNA-associated proteins (histones), leading to condensation of the local DNA.
  - Depending on the original function of the condensed DNA in regulating allele expression, the result is either silencing or activation of a given allele.
- Most known imprinted genes are critical for embryonic development.
- In experiments with mice, embryos engineered to inherit both copies of certain chromosomes from the same parent die before birth, whether their lone parent is male or female.
- In 2004, scientists in Japan combined the genetic material from two eggs in a zygote, while allowing expression of the *Igf2* gene from only one of the egg nuclei.

- The zygote developed into a healthy mouse.

- Normal development requires that embryonic cells have one active copy of certain genes.
- Aberrant imprinting is associated with abnormal development and certain cancers.

Extranuclear genes exhibit a non-Mendelian pattern of inheritance.

- Not all of a eukaryote cell's genes are located on nuclear chromosomes or in the nucleus.
- *Extranuclear* or *cytoplasmic genes* are found in mitochondria and chloroplasts.
  - These organelles reproduce themselves and transmit their genes to daughter organelles.
  - Organelle genes do not display Mendelian inheritance.
- Karl Correns first observed cytoplasmic genes in plants in 1909, when he studied the inheritance of patches of yellow or white on the leaves of an otherwise green plant.
  - This variegation is due to mutations in plastid genes that control pigmentation.
- In most plants, a zygote receives all of its plastids from the egg cytoplasm.
  - As a result, the maternal parent determines the coloration of the offspring's leaves.
- An egg may contain plastids with different alleles for a pigmentation gene.
  - As the zygote develops, plastids containing wild-type or mutant pigmentation genes are distributed randomly to daughter cells.
  - The pattern of leaf coloration exhibited by a plant depends on the ratio of wild-type to mutant plastids in its various tissues.
- Because a zygote inherits all its mitochondria from the ovum, all mitochondrial genes in most animals and plants demonstrate maternal inheritance.
- Several rare human disorders are produced by mutations to mitochondrial DNA.
  - These disorders primarily affect the ATP supply by producing defects in the electron transport chain or ATP synthase.
- Tissues that require large energy supplies (the nervous system and muscles) may suffer energy deprivation from these defects.
  - For example, a person with *mitochondrial myopathy* suffers weakness, intolerance of exercise, and muscle deterioration.
- Another mitochondrial disorder is *Leber's hereditary optic neuropathy,* which can produce sudden blindness in young adults.
  - The four mutations that have been found thus far to cause this disorder affect oxidative phosphorylation during cellular respiration, clearly a crucial function for the cell.
- Other mitochondrial mutations may contribute to diabetes, heart disease, and other diseases of aging, such as Alzheimer's disease.
  - Over a lifetime, new mutations gradually accumulate in mitochondrial DNA.
  - Some researchers think that these mutations play a role in the normal aging process.