

## Chapter 15

# The Chromosomal Basis of Inheritance

### *Lecture Outline*

#### 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 20<sup>th</sup> 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.
  - Inter-marriage 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 ( $-\text{CH}_3$ ) 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 ( $bbvvgg$ ).
  - 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 than 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 male births.
  - 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<sub>3</sub>) 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.