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 1900, cytologists and geneticists began to see parallels between the behavior of chromosomes and the behavior of Mendel’s factors.
* Using improved microscopy techniques, cytologists worked out the process of mitosis in 1875 and meiosis in the 1890s.
* Chromosomes and genes are both present in pairs in diploid cells.
* Homologous chromosomes separate and alleles segregate during meiosis.
* Fertilization restores the paired condition for both chromosomes and genes.
* Around 1902, Walter Sutton, Theodor Boveri, and others noted these parallels, and a **chromosome theory of inheritance** began to take form:
* Genes occupy specific loci on chromosomes.
* Chromosomes undergo segregation during meiosis.
* Chromosomes undergo independent assortment during meiosis.
* The behavior of homologous chromosomes during meiosis can account for the segregation of the alleles at each genetic locus to different gametes.
* The behavior of nonhomologous chromosomes can account for the independent assortment of alleles for two or more genes located on different chromosomes.
* In the early 20th century, Thomas Hunt Morgan was the first geneticist to associate a specific gene with a specific chromosome.
* Like Mendel, Morgan made an insightful choice in his experimental animal. Morgan worked with *Drosophila melanogaster*, a fruit fly that eats fungi on fruit.
* Fruit flies are prolific breeders and have a generation time of two weeks.
* Fruit flies have three pairs of autosomes and a pair of sex chromosomes (XX in females, XY in males).
* Morgan spent a year looking for variant individuals among the flies he was breeding.
* He discovered a single male fly with white eyes instead of the usual red.
* The normal character phenotype is called the **wild type**.
* 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).
* Alternative traits are called *mutant phenotypes* because they are due to alleles that originate as mutations in the wild-type allele.
* When Morgan crossed his white-eyed male with a red-eyed female, all the F1 offspring had red eyes, suggesting that the red allele was dominant to the white allele.
* Crosses between the F1 offspring produced the classic 3:1 phenotypic ratio in the F2 offspring.
* Surprisingly, the white-eyed trait appeared in only F2 males.
* All the F2 females and half the F2 males had red eyes.
* Morgan concluded that a fly’s eye color was linked to its sex.
* Morgan deduced that the gene with the white-eyed mutation is on the X chromosome, with no corresponding allele present on the Y chromosome.
* Females (XX) may have two red-eyed alleles and have red eyes or may be heterozygous and have red eyes.
* Males (XY) have only a single allele. They will 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 (XY) and ovaries (XX), the two sex chromosomes segregate during meiosis, and each gamete receives one.
* Each ovum receives an X chromosome.
* Half the sperm cells receive an X chromosome, and half receive a Y chromosome.
* Therefore, 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.
* In 1990, a British research team identified a gene on the Y chromosome required for the development of testes.
* They named the gene *SRY* (sex-determining region of the Y chromosome).
* In individuals with the *SRY* gene, the generic embryonic gonads develop into testes.
* 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.
* Some genes on the Y chromosome are necessary for the production of functional sperm.
* In the absence of these genes, an XY individual is male but does not produce normal sperm.
* In addition to their role in determining sex, the sex chromosomes, especially the X chromosome, have genes for many characters unrelated to sex.
* A gene located on either sex chromosome is called a **sex-linked gene.**
* In humans, the term *sex-linked gene* refers to a gene on the X chromosome.
* Human sex-linked genes follow the same pattern of inheritance as Morgan’s white-eye locus in *Drosophila*.
* Fathers pass sex-linked alleles to all their daughters but none of their sons.
* Mothers pass sex-linked alleles to both sons and daughters.
* If a sex-linked trait is due to a recessive allele, a female will express this phenotype only if she is homozygous.
* Heterozygous females are carriers for the recessive trait.
* Because males have only one X chromosome *(hemizygous),* any male who receives the recessive allele from his mother will express the recessive trait.
* The chance of a female inheriting a double dose of the mutant allele is much less than the chance of a male inheriting a single dose.
* Therefore, males are far more likely to exhibit sex-linked recessive disorders than are females.
* For example, color blindness is a mild disorder inherited as a sex-linked trait.
* A color-blind daughter may be born to a color-blind father whose mate is a carrier.
* The odds of this happening are fairly low.
* Several serious human disorders are sex-linked.
* **Duchenne muscular dystrophy** affects one in 3,500 males born in the United States.
* Affected individuals rarely live past their early 20s.
* This disorder is due to the absence of an X-linked gene for a key muscle protein called dystrophin.
* The disease is characterized by a progressive weakening of the muscles and a loss of coordination.
* **Hemophilia** is a sex-linked recessive disorder defined by the absence of one or more proteins required for blood clotting.
* These proteins normally slow and then stop bleeding.
* Individuals with hemophilia have prolonged bleeding because a firm clot forms slowly.
* Bleeding in muscles and joints can be painful and can lead to serious damage.
* Today, 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.
* Therefore, 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 object called a **Barr body.**
* Most of the genes on the Barr-body chromosome are not expressed.
* The condensed Barr-body chromosome is reactivated in ovarian cells that produce ova.
* Mary Lyon, a British geneticist, demonstrated that selection of which X chromosome will form the Barr body occurs randomly and independently in embryonic cells 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 other 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 that lacks sweat glands.
* 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.
* X inactivation involves modification of the DNA by the attachment of methyl (—CH3) groups to one of the nitrogenous bases on the X chromosome that will become the Barr body.
* Researchers have discovered a gene called *XIST* (X-inactive specific transcript).
* This gene is active *only* on the Barr-body chromosome and produces multiple copies of an RNA molecule that attach to the X chromosome on which they were made.
* This initiates X inactivation.
* The mechanism that connects *XIST* RNA and DNA methylation is unknown.
* What determines which of the two X chromosomes has an active *XIST* gene is also unknown.

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

* Each chromosome has hundreds or thousands of genes.
* Genes located on the same chromosome that tend to be inherited together are called **linked genes.**
* The results of crosses with linked genes differ from those expected according to the law of independent assortment.
* Morgan observed this linkage and its deviations when he 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 F1 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.
* Surprisingly, Morgan observed a large number of wild-type (gray-normal) and double-mutant (black-vestigial) flies among the offspring.
* These phenotypes are those of the parents.
* Morgan reasoned that body color and wing shape are usually inherited together because the genes for these characters are on the same chromosome.
* The other two phenotypes (gray-vestigial and black-normal) were rarer than expected based on independent assortment (but totally unexpected from dependent assortment).
* What led to this **genetic recombination,** the production of offspring with new combinations of traits?

Independent assortment of chromosomes produces genetic recombination of unlinked genes.

* Genetic recombination can result from independent assortment of genes located on nonhomologous chromosomes.
* Mendel’s dihybrid cross experiments produced offspring that had a combination of traits that did not match either parent in the P generation.
* If the P generation consists of a yellow-round seed parent (*YYRR*) crossed with a green-wrinkled seed parent (*yyrr*), all the F1 plants have yellow-round seeds (*YyRr*).
* A cross between an F1 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 F1 parent (*YyRr*) produces gametes with four different combinations of alleles: *YR*, *Yr*, *yR*, and *yr*.
* The orientation of the tetrad containing the seed-color gene has no bearing on the orientation of the tetrad with the seed-shape gene.

Crossing over produces genetic recombination of linked genes.

* In contrast, linked genes, genes located on the same chromosome, tend to move together through meiosis and fertilization.
* Under normal Mendelian genetic rules, we would not expect linked genes to recombine into assortments of alleles not found in the parents.
* The results of Morgan’s testcross for body color and wing shape did not conform to either independent assortment or complete linkage.
* Under independent assortment, the testcross should produce a 1:1:1:1 phenotypic ratio.
* Under complete linkage, we should expect to see a 1:1:0:0 ratio, with only parental phenotypes among the offspring.
* Most of the offspring had parental phenotypes, suggesting linkage between the genes.
* However, a small percentage of the flies were recombinants, suggesting incomplete linkage.
* Morgan proposed that some mechanism must occasionally break the physical connection between genes on the same chromosome.
* This process, called **crossing over,** accounts for the recombination of linked genes.
* Crossing over occurs while replicated homologous chromosomes are paired during prophase of meiosis I.
* One maternal and one paternal chromatid break at corresponding points and then rejoin with each other.
* The occasional production of recombinant gametes during meiosis accounts for the occurrence of recombinant phenotypes in Morgan’s testcross.
* The percentage of recombinant offspring, the *recombination frequency,* is related to the distance between linked genes.

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 frequency of recombinant offspring reflects 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, the recombination frequency, as **map units.**
* One map unit (called a *centimorgan*) is equivalent to a 1% recombination frequency.
* You may notice that the three recombination frequencies in our mapping example are not quite additive: 9% (*b*-*cn*) + 9.5% (*cn*-*vg*) > 17% (*b*-*vg*). This results from multiple crossing-over events.
* A second crossing over “cancels out” the first and reduces the observed number of recombinant offspring.
* Genes father apart (for example, *b*-*vg*) are more likely to experience multiple crossing-over events.
* Some genes on a chromosome are so far apart that a crossover between them is virtually certain.
* In this case, the frequency of recombination reaches its maximum value of 50% and the genes behave as if found on separate chromosomes.
* In fact, two genes studied by Mendel—for seed color and flower color—are located on the same chromosome but still assort independently.
* Such genes are *physically linked*, because they are on the same chromosome, but *genetically unlinked*, because they sort independently on each other.
* Genes located far apart on a chromosome are mapped by adding the recombination frequencies between the distant genes and the intervening genes.
* Sturtevant and his colleagues were able to map the linear positions of genes in *Drosophila* into four groups, one for each chromosome.
* A linkage map provides an imperfect picture of a chromosome.
* Map units indicate relative distance and order, not precise locations of genes.
* The frequency of crossing over is not actually uniform over the length of a chromosome.
* 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.
* Recent techniques 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 can damage chromosomes in major ways.
* Errors during meiosis can alter the number of chromosomes in a cell.
* Plants tolerate genetic defects to a greater extent than do animals.
* **Nondisjunction** occurs when problems with the meiotic spindle cause errors in daughter cells.
* Nondisjunction may occur if tetrad chromosomes do not separate properly during meiosis I.
* Alternatively, sister chromatids may 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 chromosome number, a condition known as **aneuploidy.**
* **Trisomic** cells have three copies of a particular chromosome type and have 2*n* + 1 total chromosomes.
* **Monosomic** cells have only one copy of a particular chromosome type and have 2*n* − 1 chromosomes.
* If the organism survives, aneuploidy typically leads to a distinct phenotype.
* Aneuploidy can also occur during failures of the mitotic spindle.
* 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.**
* Polyploidy may occur when a normal gamete fertilizes another gamete in which there has been nondisjunction of all its chromosomes.
* The resulting zygote is *triploid* (3*n*).
* Alternatively, if a 2*n* zygote fails to divide after replicating its chromosomes, a *tetraploid* (4*n*) embryo results from subsequent successful cycles of mitosis.
* Polyploidy is relatively common among plants and much less common among animals, although it is known to occur in fishes and amphibians.
* The spontaneous origin of polyploid individuals plays an important role in the evolution of plants.
* Many crop plants are polyploid. For example, bananas are triploid and wheat is hexaploid (6*n*)*.*
* Recently, researchers in Chile identified a new rodent species that may be tetraploid.
* 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 chromosome fragment lacking a centromere is lost during cell division.
  + - This chromosome will be 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 a *nonreciprocal* 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 translocation or inversion 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 the embryos are spontaneously aborted long before birth.
* Severe developmental problems result from an imbalance among gene products.
* Certain aneuploid conditions upset the balance less, 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, heart defects, susceptibility to respiratory infection, mental retardation, and increased risk of developing leukemia and Alzheimer’s disease.
* Most 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.
* Nondisjunction of sex chromosomes produces a variety of aneuploid conditions in humans.
* This aneuploidy upsets 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’s syndrome*, which occurs once in every 2,000 live 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 have normal intelligence.
* Males with an extra Y chromosome (XYY) tend to be somewhat taller than average.
* Trisomy X (XXX), which occurs once in every 2,000 live births, produces healthy females.
* Monosomy X, or *Turner syndrome* (X0), occurs once in every 5,000 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.
* Structural alterations of chromosomes can also cause human disorders.
* 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 between nonhomologous chromosomes are also associated with human disorders.
* 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, easily recognized chromosome 22 is called the *Philadelphia chromosome.*

**Concept 15.5 Some inheritance patterns are exceptions to the standard chromosome theory.**

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

* For most genes, it is a reasonable assumption that a specific allele will have 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.
* The genes involved are not necessarily sex-linked and may or may not lie on the X chromosome.
* Variation in phenotype depending on whether an allele is inherited from the male or female parent is called **genomic imprinting.**
* Genomic imprinting occurs during the formation of gametes and results in the silencing of certain genes.
* Imprinted genes are not expressed.
* Because different genes are imprinted in sperm and ova, some genes in a zygote are maternally imprinted and others are paternally imprinted.
* These maternal and paternal imprints are transmitted to all body cells during development.
* For a maternally imprinted gene, only the paternal allele is expressed.
* For a paternally imprinted gene, only the maternal allele is expressed.
* Patterns of imprinting are characteristic of a given species.
* The gene for insulin-like growth factor 2 (*Igf2*) was one of the first imprinted genes to be identified.
* Although the growth factor is required for normal prenatal growth, only the paternal allele is expressed.
* Evidence that the *Igf2* allele is imprinted initially 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 (—CH3) 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.
* Other mechanisms may lead to silencing of imprinted genes.
* For a few genes, however, methylation has been shown to *activate* expression of the allele.
* This is the case for the *Igf2* gene: Methylation of certain DNA nucleotides on the paternal chromosome leads to expression of the paternal *Igf2* allele.
* Most of the 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.
* 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 even in the nucleus.
* *Extranuclear* or *cytoplasmic genes* are found in small circles of DNA in mitochondria and chloroplasts.
* These organelles reproduce themselves and transmit their genes to daughter organelles.
* Their cytoplasmic genes do not display Mendelian inheritance because they are not distributed to offspring according to the same rules that direct the distribution of nuclear chromosomes during meiosis.
* 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.
* Correns determined that this variegation was 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.
* 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 affect primarily 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.