Chapter 9

Human Genetics

9.1 Lesson 9.1: Human Chromosomes and Genes

Lesson Objectives

- What is a genetic disease?
- What is the human genome?
- Discuss the importance of characterizing the human genome.
- Define autosome and sex-chromosome.
- Discuss the importance of SNPs.
- What is a karyotype?
- Define sex-linked and X-inactivation.

Introduction

As has been previously discussed, genetics is the branch of biology that focuses on heredity. The basics of heredity are similar for all organisms that reproduce sexually: the offspring receive one set of genetic material from one parent and the other set from the other parent. But are there aspects of genetics that are specific for us? Let's find out.

A **genetic disease** is a phenotype due to a mutation in a gene or chromosome. Many of these mutations are present at conception and are therefore in every cell of the body. Mutant alleles may be inherited from one or both parents, resulting in a dominant or recessive hereditary disease. Currently, there are over 4,000 known genetic disorders, with many more phenotypes yet to be identified. Theoretically, every human gene, when disrupted due to a mutation, could result in at least one disease-type phenotype. Genetic diseases are typically diagnosed and treated by a **geneticist**, a medical doctor specializing in these disorders, many of which are extremely rare and difficult to diagnose. Individuals and families with genetic diseases, or

suspected genetic diseases, are often counseled by **genetic counselors**, individuals trained in human genetics and counseling. To understand human genetic diseases, you first need to understand human chromosomes and genes.

The Human Genome

What makes each one of us unique? You could argue that the environment plays a role, and it does to some extent. But most would agree that your parents have something to do with your uniqueness. In fact, it is our genes that make each one of us unique – or at least genetically unique. We all have the genes that make us human: the genes for skin and bones, eyes and ears, fingers and toes, and so on. However, we all have different skin colors, different bone sizes, different eye colors and different ear shapes. In fact, even though we have the same genes, the products of these genes work a little differently in most of us. And that is what makes us unique.

The human genome is the genome - all the DNA - of *Homo sapiens*. Humans have about 3 billion bases of information, divided into roughly 20,000 genes, which are spread among non-coding sequences and distributed among 24 distinct chromosomes (22 autosomes plus the X and Y sex chromosomes) (**Figure** 9.1). The **genome** is all of the hereditary information encoded in the DNA, including the genes and non-coding sequences. The Human Genome Project (See the *Biotechnology* chapter) has produced a reference sequence of the human genome. The human genome consists of protein-coding exons, associated introns and regulatory sequences, genes that encode other RNA molecules, and "junk" DNA, regions in which no function as yet been identified.

Chromosomes and Genes

The human genome consists of 24 distinct chromosomes: 22 autosomal chromosomes plus the sex-determining X and Y chromosomes. A chromosome is a threadlike molecule of genes and other DNA located in the nucleus of a cell. Different organisms have different numbers of chromosomes. Human somatic cells have 23 chromosome pairs for a total of 46 chromosomes: two copies of the 22 autosomes (one from each parent), plus an X chromosome from the mother and either an X or Y chromosome from the father (**Figure** 9.2).

There are an estimated 20,000 human protein-coding genes, but many more proteins. Most human genes have multiple exons separated by much larger introns. Regulatory sequences controlling gene expression are associated with exon sequences. The introns are usually excised (removed) during post-transcriptional modification of the mRNA. Human cells make significant use of alternative splicing (see the *Molecular Genetics* chapter) to produce a number of different proteins from a single gene. So even though the human genome is surprisingly similar in size to the genomes of simpler organisms, the human proteome is thought to be much larger. A **proteome** is the complete set of proteins expressed by a

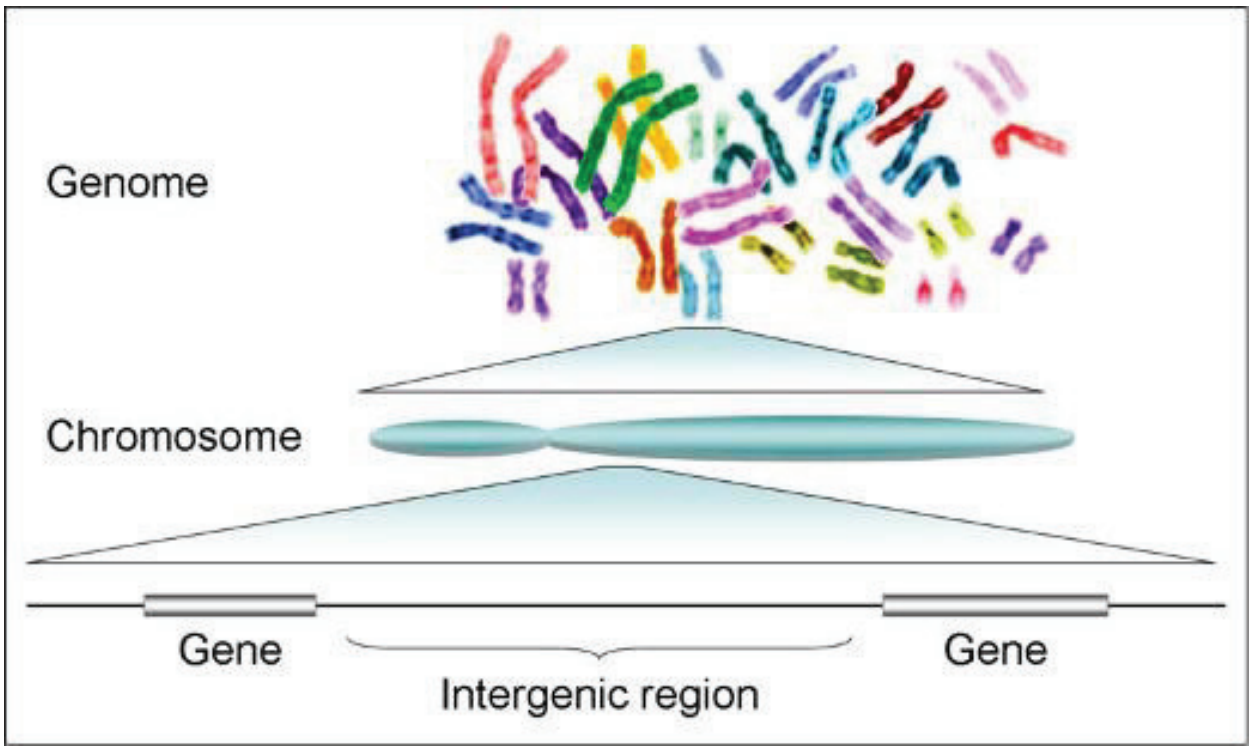

Figure 9.1: The Human Genome is depicted as the stained chromosomes at the top of the figure. The genome consists of chromosomes, which are composed of genes and other regions of DNA between the genes. Notice that there are 23 pairs of chromosomes. (7)

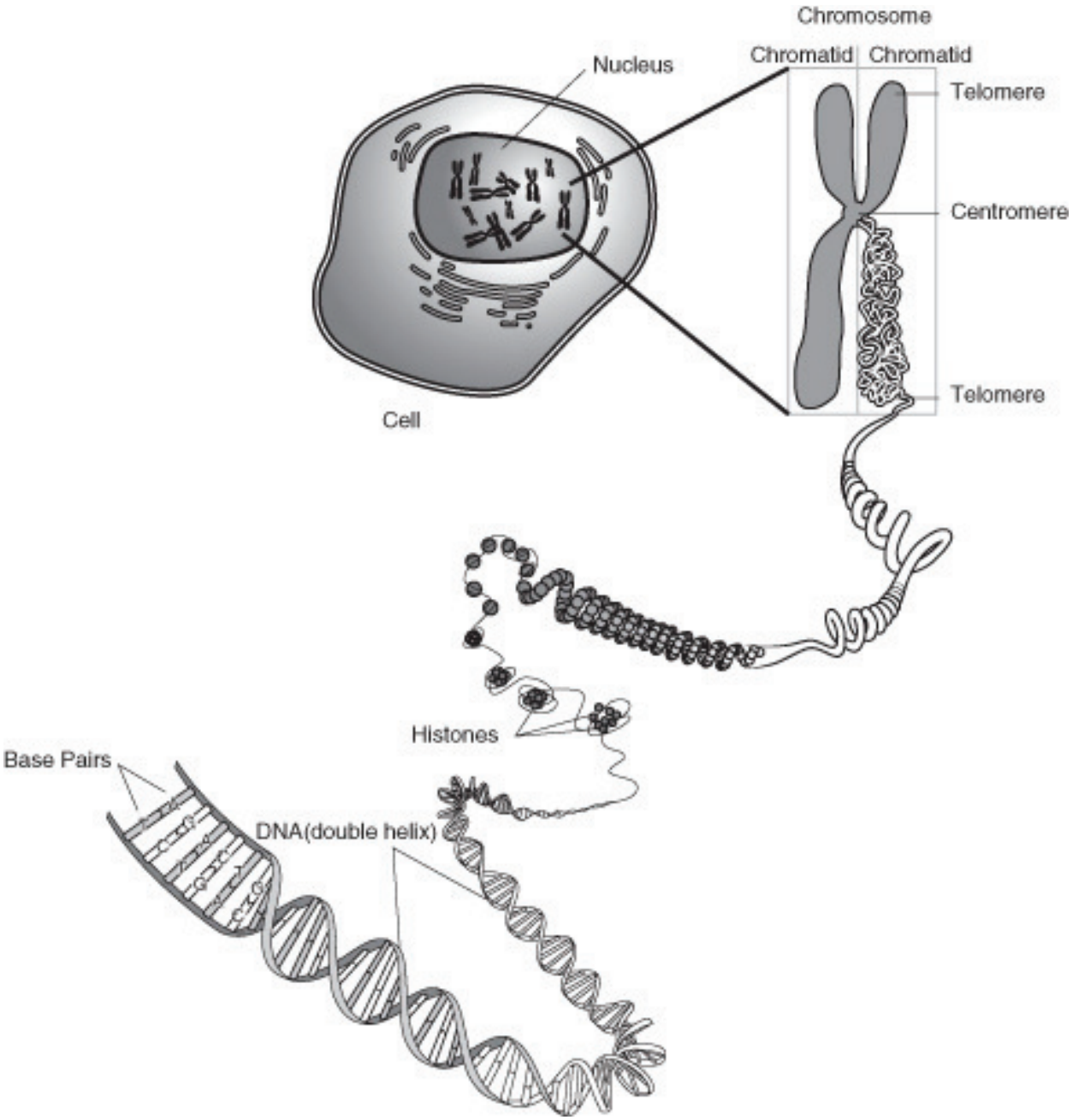

Figure 9.2: The human genome has 23 pairs of chromosomes located in the nucleus of somatic cells. Each chromosome is composed of genes and other DNA wound around histones (proteins) into a tightly coiled molecule. (13)

genome, cell, tissue, or organism.

Linkage

As stated above, our roughly 20,000 genes are located on 24 distinct chromosomes. **Linkage** refers to particular genetic loci, or alleles inherited together, suggesting that they are physically on the same chromosome, and located close together on that chromosome. Two or more loci that are on the same chromosome are physically connected and tend to segregate together during meiosis, unless a cross over event occurs between them. A crossing-over event during prophase I of meiosis is rare between loci that usually segregate together; these loci will usually be close together on the same chromosome. They are, therefore, said to be linked. Alleles for genes on different chromosomes are not linked; they sort independently (independent assortment) of each other during meiosis.

A gene is also said to be linked to a chromosome if it is physically located on that chromosome. For example, a gene (or loci) is said to be linked to the X-chromosome if it is physically located on the X-chromosome chromosome. The physical location of a gene is important when analyzing the inheritance patterns of phenotypes due to that gene. The inheritance patterns of phenotypes may be different if the gene is located on a sex chromosome or an autosome. This will be further discussed in the next lesson.

Linkage Maps

The frequency of recombination refers to the rate of crossing-over (recombination) events between two loci. This frequency can be used to estimate genetic distances between the two loci, and create a **linkage map**. In other words, the frequency can be used to estimate how close or how far apart the two loci are on the chromosome.

In the early 20^{th} century, Thomas Hunt Morgan, working with the fruit fly *Drosophila Melanogaster*, demonstrated that the amount of crossing over between linked genes differs. This led to the idea that the frequency of crossover events would indicate the distance separating genes on a chromosome. Morgan's student, Alfred Sturtevant, developed the first genetic map, also called a linkage map.

Sturtevant proposed that the greater the distance between linked genes, the greater the chance that non-sister chromatids would cross over in the region between the genes during meiosis. By determining the number of recombinants - offspring in which a cross-over event has occured - it is possible to determine the approximate distance between the genes. This distance is called a genetic map unit (m.u.), or a **centimorgan**, and is defined as the distance between genes for which one product of meiosis in 100 products is a recombinant. So, a recombinant frequency of 1% (1 out of 100) is equivalent to 1 m.u. Loci with a recombinant frequency of 10% would be separated by 10 m.u. The recombination frequency will be 50% when two genes are widely separated on the same chromosome or are located on

different chromosomes. This is the natural result of independent assortment. Linked genes have recombination frequencies less than 50%.

Determining recombination frequencies between genes located on the same chromosome allows a linkage map to be developed. Linkage mapping is critical for identifying the location of genes that cause genetic diseases.

Variation

As stated above, even though we essentially all have the same genes, the gene products work a little different in all of us, making us unique. That is, the variation within the human genome results in the uniqueness of our species. In fact, genetically speaking, we are all about 99.9% identical. However, it is this 0.1% variation that results in our physical noticeable differences, as well as traumatic events such as illnesses or congenital deformities. These differences can also be used for societies benefits, such as through forensic DNA analysis (discussed in the *Biotechnology* chapter). Most studies of this genetic variation focus on small differences, know as **SNPs**, or **single nucleotide polymorphisms**, which are substitutions in individual bases along a chromosome. For example, the single base change from the sequence GGATAACGTCA to GGAAAACGTCA would be a SNP. Although not occurring uniformly, in the human genome, it has been estimated that SNPs occur every 1 in 100 to 1 in 1000 bases.

DNA sequences that repeat a number of times are known as **repetitive sequences** or repetitive elements. For example the sequence CACACACACACACA would be a dinucleotide (2 base) repeat, or the sequence GATCGATCGATCGATCGATC would be a tetranucleotide (4 base) repeat. The genomic loci and length of certain types of repetitive sequences are highly variable from person to person, which is the basis of DNA fingerprinting and DNA paternity testing technologies. Longer repetitive elements are also common in the human genome. Examples of repeat polymorphisms are described in **Table** 9.1

Table 9.1: **Repeat Polymorphisms (bp = base pair)**

Dinucleotide	repeats of two bp sequences
Tetranucleotide	repeats of four bp sequences
Microsatellite; Short Tandem Repeats (STRs)	short sequences of 100-200 bp, usually due to repeats of 1-6 bp sequences
Minisatellite	short sequences of 6-10 bp repeats
VNTR: Variable Number of Tandem Repeat	short nucleotide sequence ranging from 14 to 100 nucleotides long, organized into clusters of tandem repeats, usually repeated in the range of between 4 and 40 times per loci

Autosomes and Sex Chromosomes

There are 44 autosomes and 2 sex chromosomes in the human genome, for a total of 46 chromosomes (23 pairs). **Sex chromosomes** specify an organism's genetic sex. Humans can have two different sex chromosomes, one called X and the other Y. Normal females possess two X chromosomes and normal males one X and one Y. An **autosome** is any chromosome other than a sex chromosome. **Figure 3** 9.3 shows a representation of the 24 different human chromosomes. **Figure** 9.4 shows a karyotype of the human genome. A **karyotype** depicts, usually in a photograph, the chromosomal complement of an individual, including the number of chromosomes and any large chromosomal abnormalities. Karyotypes use chromosomes from the metaphase stage of mitosis.

The 22 autosomes are numbered based on size, with the largest chromosome labeled chromosome 1. These 22 chromosomes occur in homologous pairs in a normal diploid cell, with one of each pair inherited from each parent. The sex of an individual is determined by the sex chromosome within the male gamete. Females are homologous, XX, for the sex chromosomes, whereas males are heterozygous, XY. As all individuals inherit an X chromosome from their mother (females can only produce gametes with an X chromosome), it is the sex chromosome that they inherit from their father that determines their sex.

Both autosomal-linked and sex-linked traits and disorders will be discussed later in this chapter.

Sex-Linked Genes

Sex-linked genes are located on either the X or Y chromosome, though it more commonly refers to genes located on the X-chromosome. For that reason, the genetics of **sex-linked** (or **X-linked**) diseases, disorders due to mutations in genes on the X-chromosome, results in a phenotype usually only seen in males. This will be discussed in the next lesson.

In humans, the Y chromosome spans 58 million bases and contains about 78 to 86 genes, which code for only 23 distinct proteins, making the Y chromosome one of the smallest chromosomes. The X chromosome, on the other hand, spans more than 153 million bases and represents about 5% of the total DNA in women's cells, 2.5% in men's cells. The X chromosome contains about 2,000 genes, however few, if any, have anything to do with sex determination. The Y chromosome is the sex-determining chromosome in humans and most other mammals. In mammals, it contains the gene **SRY** (sex-determining region Y), which encodes the testes-determining factor and triggers testis development, thus determining sex. It is the presence or absence of the Y chromosome that determines sex.

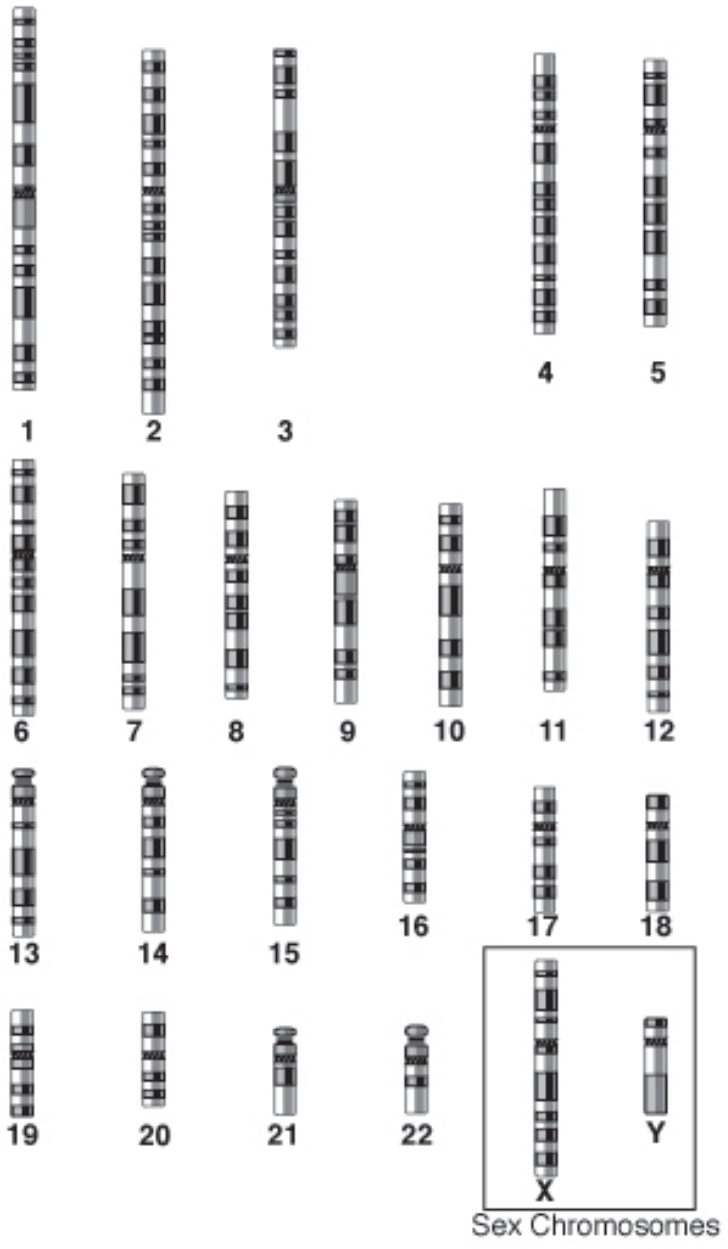

Figure 9.3: The 24 human chromosomes. The autosomes are numbered 1 - 22, based on size, with chromosome 1 being the largest. The X and Y sex chromosomes are shown in the box. (14)

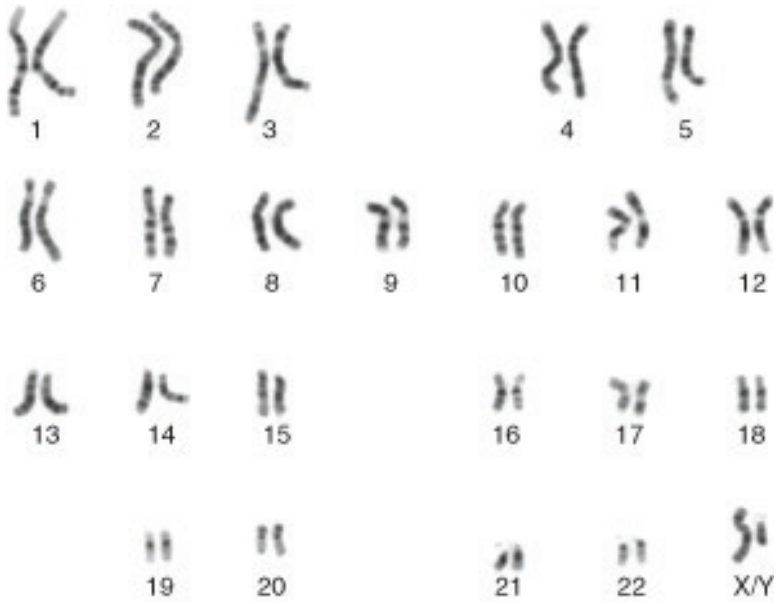

Figure 9.4: A karyotype of the human genome. Is this from a male or female? (12)

X-Inactivation

Early in embryonic development in females, one of the two X chromosomes is randomly inactivated in nearly all somatic cells. This process, called **X-inactivation**, ensures that females, like males, have only one functional copy of the X chromosome in each cell. X-inactivation creates a Barr body, named after their discover, Murray Barr. The Barr body chromosome is generally considered to be inactive, however there are a small number of genes that remain active and are expressed.

Lesson Summary

- A genetic disease is a phenotype due to a mutation in a gene or chromosome.
- Many of these mutations are present at conception, and are therefore in every cell of the body.
- Mutant alleles may be inherited from one of both parents, resulting in a dominant or recessive hereditary disease.
- Currently there are over 4,000 known genetic disorders, with many more phenotypes yet identified.
- The genome refers to all the DNA of a particular species.
- The human genome consists of 24 distinct chromosomes: 22 autosomal chromosomes, plus the sex-determining X and Y chromosomes.
- Linkage refers to particular genetic loci or alleles inherited together, suggesting that they are physically on the same chromosome, and located close together on that chro-

mosome.
- The variation within the human genome results in the uniqueness of our species.
- There are 44 autosomes and 2 sex chromosomes in the human genome, for a total of 46 chromosomes.
- Sex chromosomes specify an organism's genetic sex. Humans have two different sex chromosomes, one called X and the other Y.
- Sex-linked genes are located on either the X or Y chromosome, though it more commonly refers to genes located on the X-chromosome.
- Early in embryonic development in females, one of the two X chromosomes is randomly inactivated in nearly all somatic cells. This process is called X-inactivation.

Review Questions

1. What is a genetic disease?
2. Discuss the main difference between autosomal and sex-linked.
3. Why is variation within the human genome important?
4. Why is it more common for males to have X-linked disorders?
5. Describe how a mutation can lead to a genetic disease.
6. Discuss how a new mutation can become a new dominant allele.
7. How are autosomal traits usually inherited? Give examples of traits.
8. How are genetic diseases usually inherited? Are there exceptions? Research examples.

Further Reading / Supplemental Links

- The National Human Genome research Institute:
- http://www.genome.gov
- The Dolan DNA Learning Center:
- http://www.dnalc.org/home_alternate.html
- DNA Interactive:
- http://www.dnai.org/
- A Science Odyssey: DNA Workshop:
- http://www.pbs.org/wgbh/aso/tryit/dna/
- Kimball's Biology Pages:
- http://users.rcn.com/jkimball.ma.ultranet/BiologyPages
- http://en.wikipedia.org

Vocabulary

autosome Any chromosome other than a sex chromosome.

Barr body The inactive X-chromosome in females.

chromosome A threadlike molecule of genes and other DNA wound around histone proteins; located in the nucleus of a cell.

genetic counselor An individual trained in human genetics and counseling.

genetic disease A phenotype due to a mutation in a gene or chromosome.

geneticist A medical doctor specializing in genetic disorders.

genetics The branch of biology that focuses on heredity.

genome All of the hereditary information encoded in the DNA, including the genes and non-coding sequences.

karyotype Depicts, usually in a photograph, the chromosomal complement of an individual, including the number of chromosomes and any large chromosomal abnormalities.

linkage Refers to particular genetic loci or alleles inherited together, suggesting that they are physically on the same chromosome, and located close together on that chromosome.

microsatellite Short sequences of 100-200 bp, usually due to repeats of 1-6 bp sequences; also known as a STR (Short Tandem Repeat) polymorphism.

minisatellite Short sequence polymorphisms of 6-10 bp repeats.

proteome The complete set of proteins expressed by a genome, cell, tissue, or organism.

repetitive sequences DNA sequences that repeat a number of times; also known as repetitive elements.

sex chromosomes Specify an organism's genetic sex; in humans, the X and Y chromosomes.

sex-linked disease A disorder due to a mutation in a gene on the X-chromosome; also called X-linked disorder.

SNPs Single Nucleotide Polymorphisms; substitutions in individual bases along a gene or chromosome.

SRY Sex-determining region Y; gene which encodes the testes-determining factor and triggers testis development, thus determining sex; located on the Y chromosome.

VNTR Variable Number of Tandem Repeat; short nucleotide sequence ranging from 14 to 100 nucleotides long, organized into clusters of tandem repeats, usually repeated in the range between 4 and 40 times per loci.

X-inactivation The random inactivation of one X-chromosome in females; occurs early in embryonic development.

Points to Consider

- How are traits inherited? How about the inheritance of genetic disorders? Are inheritance patterns of traits and disorders similar?
- Could simple Mendelian inheritance account for such complex traits with vast phenotypic variation such as height or skin color? What do you think?

9.2 Lesson 9.2: Human Inheritance

Lesson Objectives

- Describe the difference between a genetic trait and a genetic disease/disorder.
- Define the various modes of inheritance, focusing on the differences between autosomal and sex-linked.
- Gives examples of dominant and recessive genetic disorders.
- Discuss the inheritance of sex-linked traits.
- Discuss complex inheritance patterns.
- Define codominant alleles and give examples.
- Define incomplete dominance.
- Give examples of multiple allele traits.
- Discuss how a trisomy condition may be detected.
- What is Down syndrome?
- List some examples of phenotypes due to abnormal numbers of sex chromosomes.
- Discuss the importance of gene therapy.
- Describe the most common method of gene therapy.

Introduction

What is a genetic trait? Is a genetic disease a trait? The answer to these questions may be debated, but a genetic trait is a characteristic of you encoded in your DNA. Could you say

that a genetic disease is encoded in your DNA? Well, by definition, yes you can.

How are traits inherited? Do different traits have different patterns of inheritance? Is it as simple as a one allele – one phenotype relationship? Or is it more complex? Is there a difference if the gene is located on an autosome or a sex chromosome? Can there be traits due to multiple genes? The answer to all of the above questions is a resounding 'sometimes.' Sometimes it is as simple as a one allele – one phenotype relationship, sometimes it is more complex. Sometimes there is a difference depending on the location of the gene. Sometimes traits can be due to multiple genes. Human genetics is an exciting aspect of biology and medicine; an aspect of biology that is extremely important to our health and well being.

Autosomal and Sex-Linked Traits: Mutations and Genetic Disorders

Autosomal vs. sex-linked. In terms of genetics, is the location of a gene or trait an important piece of information? Does it make a difference if the gene is located on a sex chromosome or an autosome? It might. Remember from lesson 9.1 that sex chromosomes determine an organism's sex, so the autosomes are the other chromosomes. Autosomal-linked traits are due to genes on the **autosomes**; **sex-linked traits** are due to genes located on the **sex chromosomes**.

What is the difference between a trait and a genetic disorder? Could a disorder be considered a trait? We tend to think of traits as hair color or skin color and disorders as something that is bad for you. But in terms of genetics, a genetic disorder is a trait. Both may be due to your genes.

Simple Dominant Heredity

How are traits due to genes on autosomes inherited? Autosomal traits due to the effects of one gene are usually inherited in a simple Mendelian pattern. That is, they can be either dominant or recessive. In humans, whereas many genetic disorders are inherited in a recessive manner, simple dominant inheritance accounts for many of a person's physical characteristics, such as chin, earlobe, hairline and thumb shape. For example, having earlobes that are attached to the head is a recessive trait, whereas heterozygous and homozygous dominant individuals have freely hanging earlobes. If you have a cleft chin, a pointed frontal hairline (called a widow's peak), or a hitchhiker's thumb, you have inherited the dominant allele for each characteristic from at least one of your parents. Other dominant traits include the presence of hair on the middle section of your fingers, thick lips, and almond-shaped eyes. A widow's peak and earlobe shape are displayed in **Figure** 9.5 and **Figure** 9.6.

Figure 9.5: A young woman with a widow's peak, due to a dominant allele. (6)

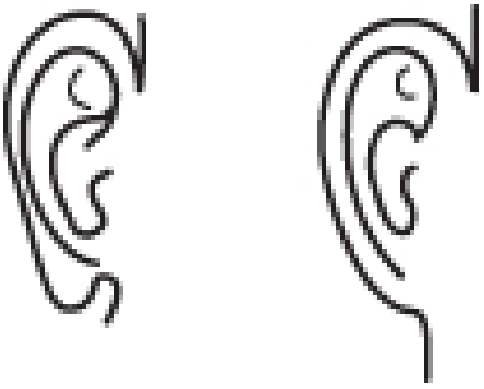

Figure 9.6: A diagram showing free (left) and attached (right) earlobes. Attached earlobes is a recessive trait. (1)

Mutations and Genetic Disorders

Mutations, changes in the DNA or RNA sequence, can have significant phenotypic effects or no effects. We have previously discussed various types of mutations. Now, let's discuss the outcomes of some of those mutations. As mentioned at the beginning of this chapter, a genetic disorder is a condition caused by abnormalities, such as mutations, in your genes or chromosomes. Genetic disorders are usually present from conception. These disorders include chromosomal abnormalities, in which the individual has too few or too many chromosomes or chromosomes with large alterations, or diseases due to a mutation in a specific gene. These defective genes are usually inherited from the parents, hence the term hereditary disease or genetic disorder. Genetic disorders can be inherited in a dominant or recessive manner (**Figure** 9.7 and **Figure** 9.8). Recessive disorders require the inheritance of a defective gene from each parent. The parents are usually unaffected and are healthy carriers of the defective gene.

How can you, or a geneticist, determine the inheritance pattern of a phenotype? A **pedigree**, which is essentially a representation of genetic inheritance, is helpful. A pedigree is a chart, much like a family tree, which shows all of the known individuals within a family with a particular phenotype (**Table** 9.2). Pedigrees have been discussed in the chapter titled *Mendelian Genetics*. Examples of autosomally inherited disorders include cystic fibrosis, Tay-Sachs disease, phenylketonuria, and achondroplasia.

Table 9.2: **Autosomal and Sex-linked Inheritance Patterns**

Inheritance Pattern	Description	Example
Autosomal Dominant	Only one mutated allele is needed for a person to be affected by an **autosomal dominant disorder**. Each affected person usually has one affected parent. There is a 50% chance that a child will inherit the mutated gene.	Huntingtons disease, Achondroplasia, Neurofibromatosis 1, Marfan Syndrome, Hereditary nonpolyposis colorectal cancer
Autosomal Recessive	Both copies of the gene must be mutated for a person to be affected by an **autosomal recessive disorder**. An affected person usually has unaffected parents who each carry a single copy of the mutated gene (and are referred to as carriers).	Cystic fibrosis, Sickle cell anemia, Tay-Sachs disease, Spinal muscular atrophy

Table 9.2: (continued)

Inheritance Pattern	Description	Example
X-linked Dominant	**X-linked dominant disorders** are caused by mutations in genes on the X chromosome. Only a few disorders have this inheritance pattern.	
X-linked Recessive	**X-linked recessive disorders** are also caused by mutations in genes on the X chromosome. Males are more frequently affected than females. The sons of a man with an X-linked recessive disorder will not be affected, and his daughters will carry one copy of the mutated gene. A woman who carries an X-linked recessive disorder has a 50% chance of having sons who are affected and a 50% chance of having daughters who carry one copy of the mutated gene.	Hemophilia A, Duchenne muscular dystrophy, Color blindness
Y-Linked	**Y-linked disorders** are caused by mutations on the Y chromosome. Only males can get them, and all of the sons of an affected father are affected. Y-linked disorders only cause infertility, and may be circumvented with the help of some fertility treatments.	Male Infertility

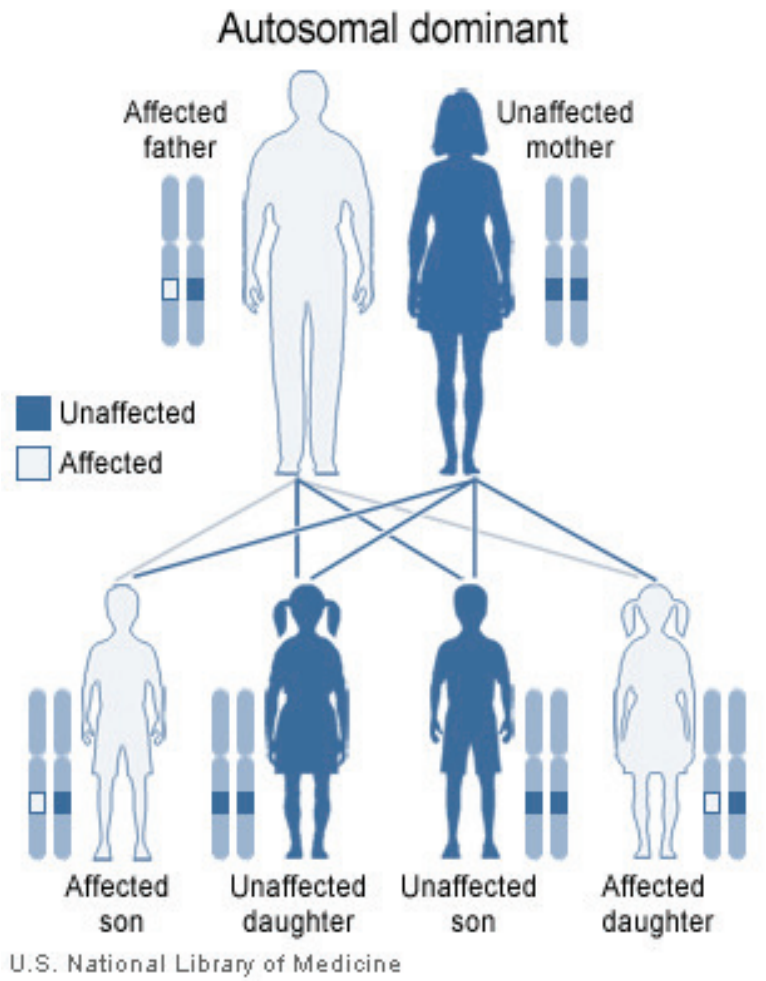

Figure 9.7: Autosomal Dominant Inheritance. Only one "affected" allele is necessary to result in the "affected" phenotype. For a genetic disease inherited in this manner, only one mutant allele is necessary to result in the phenotype. Achondroplasia (discussed later) is an example of a dominant disorder. Both homozygous and heterozygous individuals will show the phenotype. (11)

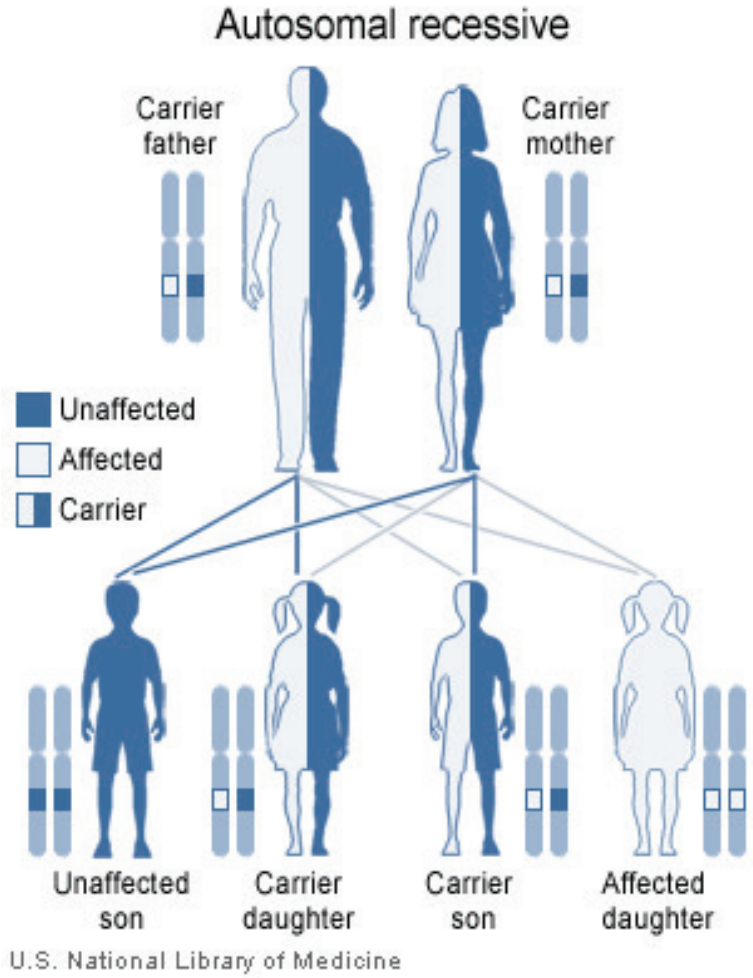

Figure 9.8: Autosomal Recessive inheritance. For a genetic disease inherited in this manner, two mutant alleles are necessary to result in the phenotype. Tay-Sachs Disease (discussed later) is an example of a recessive disorder. Notice that both parents are unaffected carriers of the mutant allele. These unaffected carriers allow the allele to be maintained in the gene pool - the complete set of a population's genes. Even if the allele is lethal in the homozygous recessive condition, the allele will be maintained through heterozygous individuals. (2)

Cystic Fibrosis

Cystic fibrosis (CF) is a recessive inheritable disorder caused by a mutation in a gene called the cystic fibrosis transmembrane conductance regulator (CFTR). The product of this gene is a chloride ion channel important in creating sweat, digestive juices, and mucus. Although most people without CF have two working copies of the CFTR gene, only one is needed to prevent cystic fibrosis. CF develops when individuals have a mutation in both copies of the gene, such that neither gene product works normally. CF is one of the most common life shortening diseases. Diagnosis is usually made in childhood. In the United States, approximately 1 in 3,900 children is born with CF (**Figure** 9.9). One in 22 people of European descent are carriers of a mutated CFTR gene. CF mainly affects the lungs and digestive system, causing difficulty breathing due to thick mucus production, progressive disability, and for some individuals, premature death.

Individuals can be diagnosed prior to birth by genetic testing. Because development of CF in the fetus requires each parent to pass on a mutated copy of the CFTR gene and because CF testing is expensive, testing is often initially performed on just one parent. If that parent is found to be a carrier of a CFTR gene mutation, the other parent is then tested to calculate the risk that their children will have CF. CF can result from more than a thousand different mutations; currently it is not possible to test for each one. As new DNA testing methodologies are developed, testing for more mutations will become more common and less expensive. Testing analyzes DNA for the most common mutations, such as a deletion of amino acid 508 (phenylalenine, also known as ΔF508). If a family has a known uncommon mutation, specific screening for that mutation can be performed. However, it must be noted that because there may be other not yet identified mutations that result in CF, and as not all known mutations are found on current tests, a negative screen does not guarantee that a child will not have CF.

Tay-Scahs Disease

Tay-Sachs disease is a genetic disorder that is fatal in its most common variant, known as Infantile Tay-Sachs disease. Tay-Sachs is an autosomal recessive disorder, requiring the inheritance of a defective gene from each parent. The disease results from the accumulation of harmful quantities of fat in the nerve cells of the brain. Tay-Sachs results from mutations in the HEXA gene located on chromosome 15, which encodes the alpha-subunit of the lysosomal enzyme beta-N-acetylhexosaminidase A, which normally breaks down the fat. More than 90 mutations, including substitutions, insertions, deletions, splice site mutations, and other more complex patterns have been characterized in this gene, and new mutations are still being reported. Each of these mutations alters the protein product, inhibiting the function of the enzyme.

Tay-Sachs disease is a rare disease. Unaffected carriers of a Tay-Sachs allele may not know they have the allele. Other autosomal disorders such as cystic fibrosis and sickle cell anemia

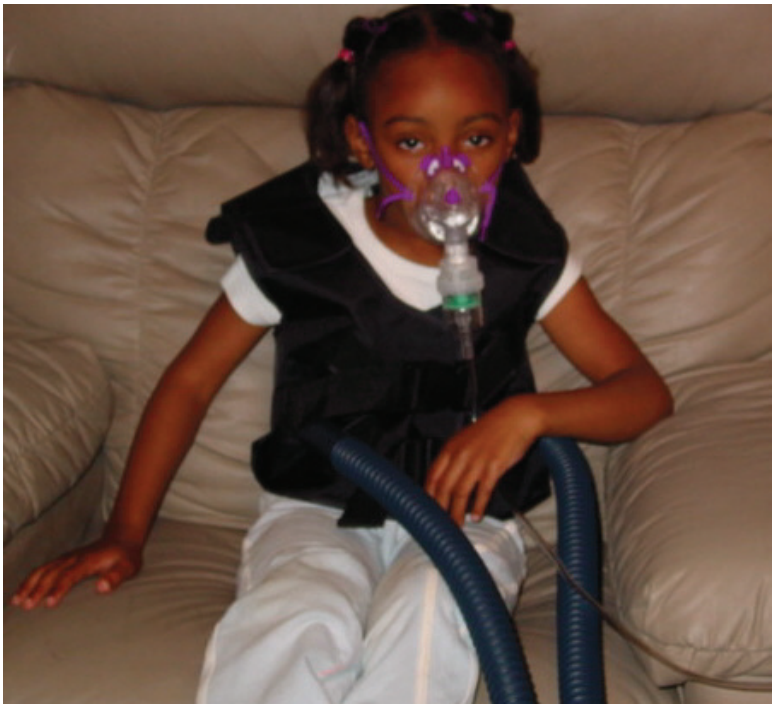

Figure 9.9: A young cystic fibrosis patient undergoing breathing treatment. Cystic fibrosis is a recessively inherited genetic disorder. (5)

are far more common. The importance of Tay-Sachs lies in the fact that an inexpensive enzyme assay test was developed. The automation of this analysis has provided one of the first "mass screening" tools in medical genetics. Two unaffected carriers can have a child homozygous for a Tay-Sachs allele, resulting, currently, in a lethal phenotype. Tay-Sachs alleles are maintained in a population through these unknowing heterozygous carriers.

The analysis and screening for Tay-Sachs has became a research and public health model for understanding and preventing all autosomal genetic disorders. Another genetic disease that is easily analyzed in phenylketonuria.

Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive genetic disorder characterized the inability to metabolize the amino acid phenylalanine. PKU is due to a deficiency in the enzyme phenylalanine hydroxylase (PAH). When PAH is deficient, phenylalanine accumulates and is converted into phenylketones, which can be detected in the urine. Left untreated, this condition can cause problems with brain development, leading to progressive mental retardation and seizures. However, PKU can be treated with a specific diet, one low in phenylalanine. A diet low in phenylalanine and high in tyrosine can bring about a nearly total cure.

The incidence of PKU is about 1 in 15,000 live births. In the United States PKU is screened at birth as part of a national biochemical screening program, for every baby born in a hospital. Babies born at home may not be screened. If PKU is diagnosed early enough, an affected newborn can grow up with normal brain development, but only by eating a special diet low in phenylalanine for the rest of his or her life. In essence, this is a protein-free diet. This requires severely restricting or eliminating foods high in protein content (containing phenylalanine), such as breast milk, meat, chicken, fish, nuts, cheese and other dairy products. Starchy foods such as potatoes, bread, pasta, and corn must also be monitored. Many diet foods and diet soft drinks that contain the sweetener aspartame must also be avoided, as aspartame consists of two amino acids: phenylalanine and aspartic acid. Supplementary infant formulas are used in these patients to provide the amino acids and other necessary nutrients that would otherwise be lacking in their diet. Since phenylalanine is required for the synthesis of many proteins, it is necessary to have some of this amino acid, but levels must be strictly controlled. In addition, tyrosine, which is normally derived from phenylalanine, must also be supplemented.

Achondroplasia

Whereas cystic fibrosis, Tay-Sachs, and phenylketonuria are all autosomal recessive disorders, **achondroplasia** is an autosomal dominant disorder. Achondroplasia is the most common cause of dwarfism. Achondroplasia is a result of an autosomal dominant mutation in the fibroblast growth factor receptor gene 3 (FGFR3), which causes an abnormality of cartilage formation. FGFR3 normally has a negative regulatory effect on bone growth. In achondroplasia, the mutated form of the receptor is constitutively active (constantly "turned on") and this leads to severely shortened bones. Individuals with achondroplasia are heterozygous for the mutation (one mutant copy, one normal copy). Homozygous for the achondroplasia mutation is lethal prior to birth or shortly after birth.

For autosomal dominant disorders, a person with the disorder has a 50% chance of passing on the gene to their offspring. For achondroplasia, this means there will be a 50% chance that each child will have achondroplasia. Since two copies are fatal, if two people with achondroplasia have a child, there is a 25% chance of the child dying shortly after birth, a 50% chance the child will have achondroplasia, and a 25% chance the child will have a normal phenotype. However, in 3 out of 4 cases, people with achondroplasia are born to parents who don't have the condition. This is the result of a new mutation. New achondroplasis mutations are associated with increasing paternal age (over 35 years). Studies have demonstrated that new gene mutations are exclusively inherited from the father and occur during spermatogenesis. More than 98% of achondroplasia is caused by a G to A point mutation at nucleotide 1138 of the FGFR3 gene, which causes a glycine to arginine substitution. This makes this particular nucleotide one of the most, if not the most, mutable base in the human genome.

There are three other syndromes with a genetic basis similar to achondroplasia: hypochon-

droplasia, thanatophoric dysplasia, and SADDAN Dysplasia (severe achondroplasia, developmental delay, acanthosis nigricans (a skin condition)). Each of these disorders is also caused by a mutation in the *FGFR3* gene. Each of the conditions results in a distinct difference in the degree of severity of the phenotype, with hypochondroplasia having the mildest phenotype. Other genes in which mutations cause a phenotypic spectrum of disease include the collagen genes among others.

Sex-Linked Traits

Traits controlled by genes located on the sex chromosomes (X and Y) are called sex-linked traits (**Figure** 9.10). Remember, females have two X chromosomes and males have a X and a Y chromosome. Therefore, any recessive allele on the X chromosome of a male will not be masked by a dominant allele. X-linked traits include the hemophilia and color blindness. Hemophilia is the name of a family of hereditary genetic illnesses that impair the body's ability to control coagulation. Color Blindness, or color vision deficiency, in humans is the inability to perceive differences between some or all colors that other people can distinguish.

Hemophilia is a group of diseases in which blood does not clot normally. Factors in blood are involved in clotting. Hemophiliacs lacking the normal Factor VIII are said to have Hemophilia A, the most common form. England's Queen Victoria was a carrier for this disease. The allele was passed to two of her daughters and one son. Since royal families in Europe commonly intermarried, the allele spread, and may have contributed to the downfall of the Russian monarchy.

Genetic red-green color blindness affects men much more often than women, because the genes for the red and green color receptors are located on the X chromosome. Females are red-green color blind only if both of their X chromosomes carry the defective gene, whereas males are color blind if their single X chromosome carries the defective gene. As males have only the one X-chromosome, the gene for red-green color blindness is transmitted from a color blind male to all his daughters, who are usually heterozygous carriers and therefore unaffected. Subsequently, this carrier woman has a fifty percent chance of passing on a X chromosome with a defective gene to each of her male offspring. The sons of an affected male will not inherit the trait from him, since they receive his Y chromosome and not his X chromosome. Should an affected male have children with a carrier or colorblind woman, their daughters may be colorblind by inheriting a X chromosome with the mutant gene from each parent.

Muscular dystrophy is a term encompassing a variety of muscle wasting diseases. The most common type, **Duchenne Muscular Dystrophy** (DMD), affects cardiac and skeletal muscle, as well as some mental functions. DMD is an X-linked recessive disorder occurring in 1 in 3,500 newborns. Most affected individuals die before their 20th birthday.

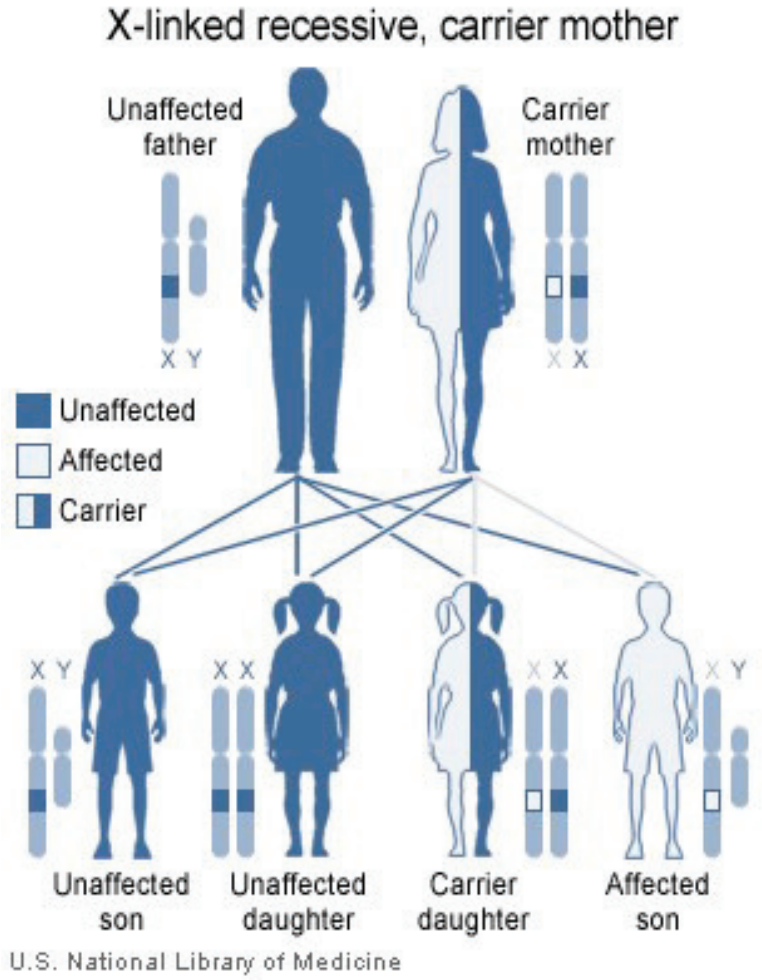

Figure 9.10: X-linked recessive inheritance. As boys have only one X-chromosome, if they inherit the mutant allele from their mother, they will possess the phenotype that results from that allele. (4)

Complex Traits

So far we have discussed traits inherited in a simple Mendelian pattern. Either the trait is dominate or recessive. The trait is affected by only one gene. But this is not the case for many genes; rarely is inheritance that simple. More complex patterns of inheritance are common. These were introduced in the chapter titled *Mendelian Genetics*.

Mendel's pea plants showed complete dominance of one allele over the other. The offspring always completely looked like one of the parents – there was never any phenotype "in between" the two parents. The heterozygous individuals were indistinguishable from the homozygous dominant individuals. Is it possible for both alleles to be dominant, or neither to be completely dominant? The answer to both of these questions is yes.

Codominance

Codominance is when two alleles are both expressed in the heterozygous individual; that is, they both affect the phenotype in separate and distinguishable ways (**Figure** 9.11). The A, B alleles of the ABO blood group system are a classic example, and these have been discussed in the chapter titled *Mendelian Genetics.* The A and B alleles are codominant with each other. When a person has both an A and a B allele, the person has type AB blood. When two persons with AB blood type have children, the children can be type A, type B, or type AB. There is a 1A:2AB:1B phenotype ratio instead of the 3:1 phenotype ratio found when one allele is dominant and the other is recessive.

Incomplete Dominance

Incomplete dominance is seen in heterozygous individuals with an intermediate phenotype. For example, if Mendel had ever observed a medium stem length plant when a tall and short plant were crossed, that would have suggested incomplete dominance. In incomplete dominant situations, the phenotype expression is dependent on the dosage of the genes. Two copies of the gene result in full expression, while only one copy produces partial expression and an intermediate phenotype.

Multiple-Allele Traits

Traits controlled by more than two alleles have multiple alleles. Theoretically, any base change will result in a new allele. In fact, within the human population, it may be safe to say that most human genes have more than 2 alleles. Whereas, we think of base changes, or mutations, as resulting in a new phenotype or disease, many base changes result in alleles that do not cause significant change in phenotypes. This is common in collagen genes, for example. The best characterized example of multiple alleles in humans is the ABO blood

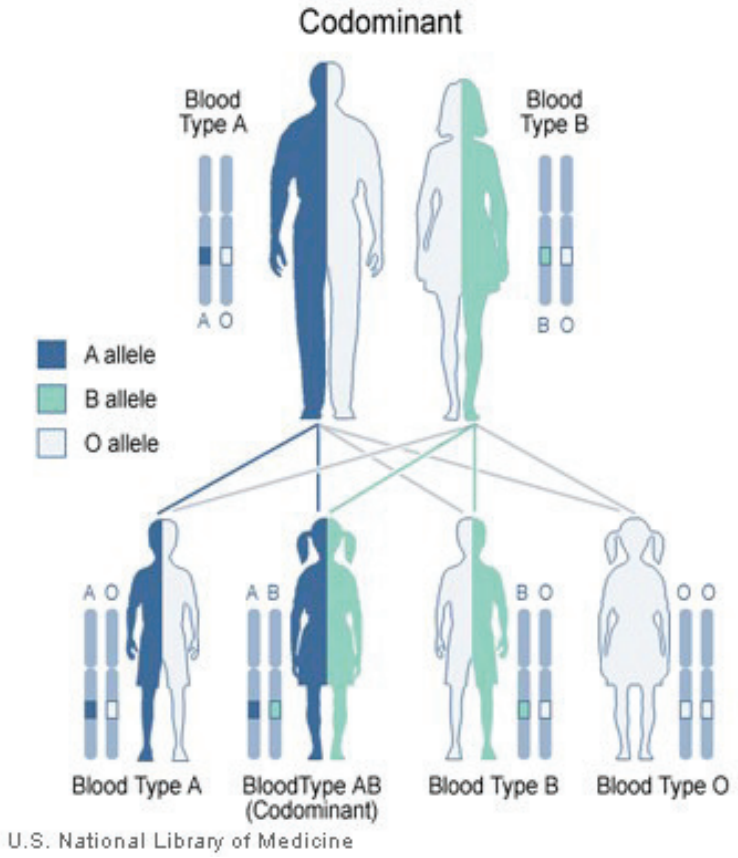

Figure 9.11: Codominant Inheritance. The A and B alleles are codominant. An AB heterozygous individual has type AB blood. (9)

groups, discussed in the chapter titled *Mendelian Genetics*.

It is easiest to consider situations where each gene affects only one phenotypic characteristic. However, other situations where genes have other effects are common. As mentioned above, multiple alleles resulting in multiple phenotypes are not uncommon.

Pleiotropy

Many genes have multiple phenotypic effects, a property called **pleiotropy**. Thus, a new mutation in the gene will affect all the phenotypes/traits associated with the gene simultaneously. For example, the symptoms associated with sickle-cell disease are due to pleiotropic alleles. Another example is the collagen genes mentioned above. As you will learn later, many bones develop from a cartilage template. This cartilage template is made out of many proteins, with type II collagen, the predominant protein in the cartilage. The gene for this collagen, COL2A1, when mutated, not only affects the skeletal system, but due to its pleiotropic nature, it may also affect a person's eyes and hearing.

Epistasis

Epistasis is when a gene at one location (locus) alters the phenotypic expression of a gene at another locus. This is seen in the inheritance of coat color in mice. Epistasis takes place when the action of one gene is modified by one or several other genes, which are sometimes called modifier genes. The gene whose phenotype is expressed is said to be epistatic, while the phenotype altered or suppressed is said to be hypostatic.

Polygenic Traits

Polygenic traits are due to the actions of more than one gene and often, their interaction with the environment. These usually result in a measurable range in phenotype, such as height, eye color or skin color. These are known as multifactoral or quantitative characteristics. Polygenic inheritance results in an additive effect of the genes on a single phenotype.

Skin color is a polygenic trait and obviously demonstrates quantitative characteristics. A number of genes factor into determining a person's natural skin color, so modifying only one of those genes changes the color only slightly. It is currently thought that at least three separately inherited genes contribute to skin pigmentation. Let's call these three genes A, B, and C. A, B, and C are incompletely dominant to a, b, and c, with A, B, and C each contributing a "unit of darkness" to the phenotype. Therefore an AABBCC individual is very dark, darker than an AaBbCc individual, and much darker than a aabbcc individual. A person may have as many as 6 "dark units" to as few as no "dark units," and any combination in between. This will result in a phenotypic spectrum of color gradation.

Many disorders with genetic components are polygenic, including autism, certain cancers, diabetes and numerous others. Most phenotypic characteristics are the result of the interaction of multiple genes. The environment plays a significant role in many of these phenotypes. But what happens when multiple genes are either missing or duplicated?

Changes in Chromosome Number

So far we have focused on traits due to one gene or several genes. But what about many genes? What would happen if an entire chromosome were missing or duplicated? What if a human had only 45 chromosomes? Or 47? This real possibility is usually due to mistakes during meiosis; the chromosomes do not fully separate from each other during sperm or egg formation. Specifically, **nondisjunction** is the failure of replicated chromosomes to separate during anaphase II. If a zygote forms from a gamete lacking a chromosome, a viable embryo cannot be produced. Most human abnormal chromosome numbers result in the death of the developing embryo, often before a woman even realizes she is pregnant. Occasionally, a zygote with an extra chromosome can become a viable embryo and develop.

Trisomy is a state where humans have an extra autosome. That is, they have three of a particular chromosome instead of two. For example, trisomy 18 results from an extra chromosome 18, resulting in 47 total chromosomes. To identify the chromosome number (including an abnormal number), a sample of cells is removed from an individual or developing fetus. Metaphase chromosomes are photographed and a karyotype is produced. A karyotype will display any abnormalities in chromosome number or large chromosomal rearrangements. Trisomy 8, 9, 12, 13, 16, 18, and 21 have been identified in humans. Trisomy 16 is the most common trisomy in humans, occurring in more than 1% of pregnancies. This condition, however, usually results in spontaneous miscarriage in the first trimester. The most common trisomy in viable births is **Trisomy 21**.

Trisomy 21: Down Syndrome

One of the most common chromosome abnormalities is Down syndrome, due to nondisjunction of chromosome 21 resulting in an extra complete chromosome 21, or part of chromosome 21 (**Figure** 9.13). Down syndrome is the only autosomal trisomy where an affected individual may survive to adulthood. Individuals with Down syndrome often have some degree of mental retardation, some impairment of physical growth, and a specific facial appearance. With proper assistance, individuals with Down syndrome can become successful, contributing members of society (**Figure** 9.14). The incidence of Down syndrome increases with maternal age.

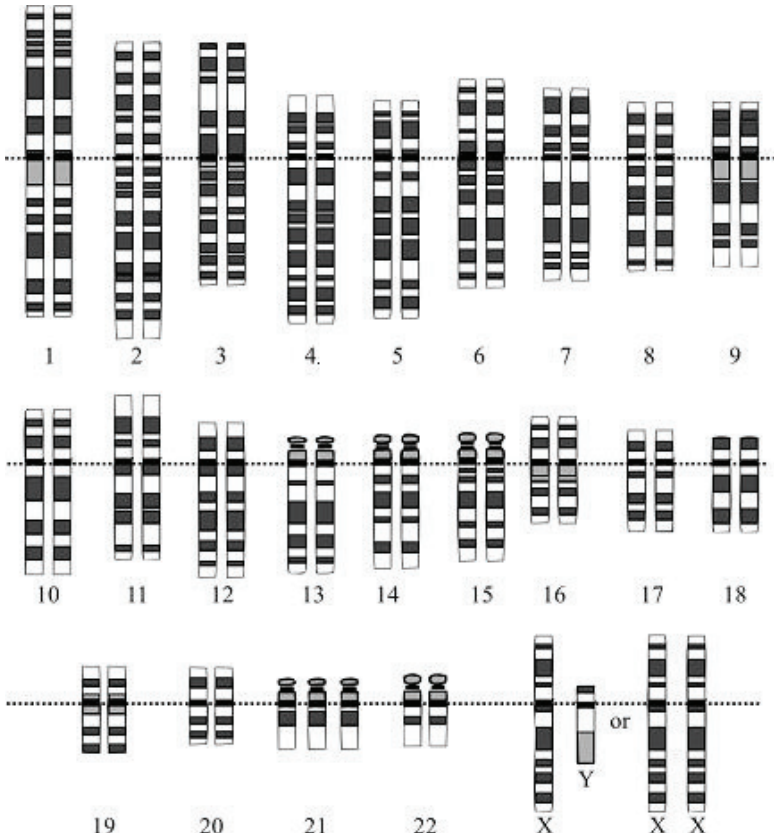

Figure 9.12: Trisomy 21 (Down Syndrome) Karyotype. Note the extra chromosome 21. (3)

Figure 9.13: Child with Down syndrome, exhibiting characteristic facial appearance. (8)

Figure 9.14: Boy with Down Syndrome assembling a bookcase. (10)

Abnormal Numbers of Sex Chromosomes

What about when a person has more than 2 Y chromosomes, or more than 2 X chromosomes? Or a female with only one X chromosome? Sex-chromosome abnormalities may be caused by nondisjunction of one or more sex chromosomes. Many conditions are known in which there are an abnormal number of sex chromosomes. An X chromosome may be missing (XO), or there may be an extra one (XXX or XXY). There may also be an extra Y chromosome (XYY). Any combination of X and Y chromosomes, as long as there is a Y chromosome, will produce a male (up to XXXXY). These individuals can lead relatively normal lives, but they cannot have children. They may also have some degree of mental retardation. These syndromes include Klinefelter's syndrome, Turner syndrome and trisomy X.

Klinefelter's syndrome is caused by the presence of one or more extra copies of the X chromosome in a male's cells. Extra genetic material from the X chromosome interferes with male sexual development, preventing the testicles from functioning normally and reducing the levels of testosterone. Triple X syndrome (**trisomy X**) results from an extra copy of the X chromosome in each of a female's cells. Females with trisomy X have a lower IQ than their siblings. Turner syndrome results when each of a female's cells has one normal X chromosome and the other sex chromosome is missing or altered. The missing genetic material affects development and causes the characteristic features of the condition, including short stature and infertility.

Diagnosis and Treatment of Genetic Disorders

If someone has a rare genetic disease in her family, can she still have a baby? Is she predisposed to pass that phenotype along to her child? These are questions for a professional trained in human genetics. A geneticist and **genetic counselor** are usually involved in the diagnosis and treatment of human genetic disorders. Families with a genetic disease are referred to a genetic counselor, especially when they wish to determine a baby's likelihood of inheriting a genetic disease.

Individuals or their families at risk of inheriting a genetic disorder have many questions. What exactly is a genetic disorder? How does a person get it? Can it be passed onto the next generation? Can it be treated? What are the symptoms? Do the symptoms get worse with age? These and many more questions are where a genetic specialist, such as a genetic counselor can help. **Genetic counseling** is the process by which individuals or their families who are at risk of an inherited disorder, are counseled on many different aspects of the disorder. Genetic counseling may be necessary at any time throughout life, from before pregnancy to adulthood. Before pregnancy, genetic counseling would be appropriate for at risk individuals who are planning a family, such as when one or both individuals are either carriers or have a certain genetic trait. During pregnancy, genetic counseling is necessary for couples if the woman will be over 35 years of age at the time of delivery, if prenatal testing is recommended for any reason, or if an abnormality is noted on an ultrasound or other test. After birth, genetic counseling is appropriate if a birth defect is detected. During childhood, genetic counseling is appropriate if the child manifests any signs of developmental delay or a genetic syndrome, and in adulthood, genetic counseling is appropriate if signs of an adult onset genetic disorder is detected. During genetic counseling, individuals are advised of the consequences and nature of the disorder, the probability of developing or transmitting the disorder, and the options open to them in management and family planning in order to make appropriate decisions. In terms of the actual diagnosis of the disease, molecular analysis may be necessary; this will be discussed in the chapter titled Biotechnology.

Prenatal Diagnosis

"Is it possible to test the developing baby for potential genetic problems? Do you need to remove some of the baby's DNA? How do you do that?" These questions are appropriate for a geneticist. Sometimes, to make sure the baby is developing properly, prenatal diagnosis is necessary. **Prenatal diagnosis** refers to the diagnosis of a disease or condition before the baby is born. The reason for prenatal diagnosis is to detect birth defects such as neural tube defects, chromosome abnormalities, genetic diseases and other conditions. It can also be used to determine the sex of the unborn baby, though this can usually be determined by an ultrasonography (ultrasound).

Diagnostic prenatal testing can be by invasive methods or non-invasive methods. Non-invasive methods are much less risky to the patient. Non-invasive methods can only evaluate

the risk of a condition and cannot actually determine if the fetus has a condition. Non-invasive techniques include examinations of the mother's womb through ultrasonography and analysis of maternal serum. If an abnormality is indicated by a non-invasive procedure, a more invasive technique may be employed to gather more information. **Amniocentesis** and **chorionic villus sampling** (CVS) are invasive procedures. These involve probes or needles that are inserted into the placenta. Amniocentesis can be done from about 14 weeks up to about 20 weeks of the pregnancy and CVS can be done earlier, between 9.5 and 12.5 weeks, but is slightly more risky to the unborn child.

During Amniocentesis a small amount of amniotic fluid, which contains fetal tissues, is extracted from the amnion or amniotic sac surrounding a developing fetus, and the fetal DNA is examined for genetic abnormalities. Amniocentesis is not performed for every pregnancy, but is generally done when an increased risk of genetic defects in the fetus is indicated, by mother's age (over 35 years is common), family history of genetic defects, or other factors.

Chorionic villus sampling (CVS) involves removing a sample of the chorionic villus (placental tissue) and testing it. It is generally carried out only on pregnant women over the age of 35 and those whose offspring have a higher risk of Down syndrome and other chromosomal conditions. The advantage of CVS is that it can be carried out 10-12 weeks after the last period, earlier than amniocentesis.

DNA from the developing baby may be isolated from either an amniocentesis or CVS. A karyotype may be created from fetal chromosomes following either procedure, or a specific mutation may be analyzed. The analysis of specific mutations will be discussed in the chapter titled Biotechnology.

Gene Therapy

So, how do you treat genetic disorders? If medically possible, each manifestation can be treated separately. But is there a way to use genetics to treat the root cause of the disease – that is, to fix the mistake in the DNA?

Gene therapy is the insertion of a new gene into an individual's cells and tissues to treat a disease, replacing a mutant disease-causing allele with a normal, non-mutant allele. Although the technology is still in its early stages of development, it has been used with some success.

There are a number of mechanisms used to replace or repair a defective gene in gene therapy.

- A normal gene may be inserted into a nonspecific location within the genome to replace a nonfunctional gene. This approach is most common.
- An abnormal gene could be replaced by a normal gene through homologous recombination.
- The abnormal gene could be repaired through selective reverse mutation, which returns the gene to its normal, non-mutant state.

- The regulation (the degree to which a gene is turned on or off) of a particular gene could be altered.

As stated above, the most common gene therapy approach is to replace a disease-causing allele with a normal allele. To deliver the new allele to the appropriate cells, a carrier, called a vector, must be used. Currently, the most common type of vectors are viruses that have been genetically altered to carry normal human DNA, and not to result in any phenotypes associated with the virus. As viruses have evolved a robust method of delivering their viral genes to human cells, scientists have tried to develop (and are continuing to develop) methods to take advantage of this process, and have these vectors insert human DNA into target cells. Scientists have manipulated the viral genome to remove disease-causing genes and insert therapeutic human genes (**Figure** 9.15). For obvious reasons, this is currently a field of intense biomedical research.

A patient's target cells, such as liver or lung cells are infected with the genetically altered virus. The vector then unloads its genetic material containing the therapeutic human gene into the target cell. The generation of a functional protein product from the therapeutic gene should restore the target cell to a normally functioning phenotype. To date, this process has had limited success, but who can say what will happen in the future.

Severe Combined Immunodeficiency

Severe Combined Immunodeficiency, or SCID, is a heritable immunodeficiency - a genetic disorder that cripples the immune system. It is also known as the 'bubble boy' disease, named after David Vetter, SCID's most famous patient who lived for over 12 years in a sterilized environment, just like living inside a "bubble." SCID affects about 1 in 100,000 live births. These babies, if untreated, usually die within one year due to severe, recurrent infections. Treatment options have improved considerably and include bone marrow transplants and gene therapy. Children no longer have to live inside a bubble as did David Vetter, who was placed inside his sterile bubble about 10 seconds after birth. He died 15 days after he left his sterile environment, due to an undetected virus in the bone marrow transplant. David was one of the first bone marrow recipients.

More recently gene therapy has proved successful in treating SCID. Insertion of the correct gene into cells of the immune system should correct the problem. Trials started in 1990, and in 1999, the first SCID patients were detected with functional immune systems. Due to some complications these trials had to be stopped, but these issues seem to have been resolved. Gene therapy in individuals with SCID have been human genetics only gene therapy success stories. Since 1999, gene therapy has restored the immune systems of at least seventeen children with the disorder. This raises great hope for other genetic disorders. In your lifetime, it is definitely possible that many genetic disorders may be "cured" by gene therapy. As was mentioned earlier, no one can say what will happen in the future, and no one knows what lies ahead.

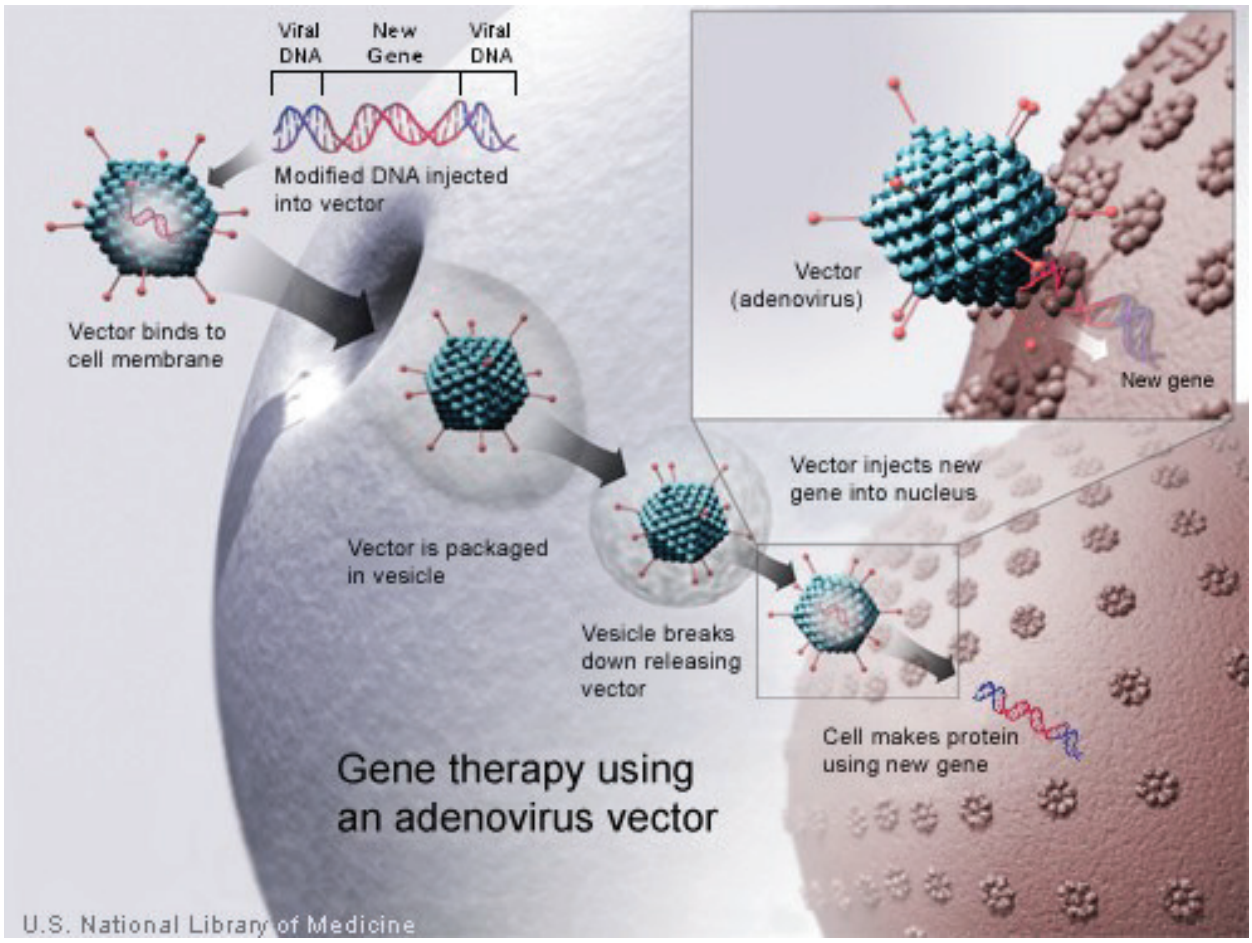

Figure 9.15: Gene Therapy using a viral vector. The new gene is inserted into the viral genome, the virus binds to the cell membrane and enters the cell by endocytosis. The viral genome, containing the new gene is injected into the cell nucleus, where the viral DNA is transcribed, starting the process of protein synthesis. (15)

Lesson Summary

- In humans, whereas many genetic disorders are inherited in a recessive manner, simple dominant inheritance accounts for many of a person's physical characteristics.
- Genetic diseases may also be dominantly inherited, such as with achondroplasia.
- Genetic diseases may be due to specific mutations within a gene or to large chromosomal abnormalities.
- Traits controlled by genes located on the sex chromosomes (X and Y) are called sex-linked traits.
- Any recessive allele on the X chromosome of a male will not be masked by a dominant allele.
- Codominance is when two alleles are both expressed in the heterozygous individual.
- Incomplete dominance is seen in heterozygous individuals with an intermediate phenotype.
- Traits controlled by more than two alleles have multiple alleles.
- Many genes have multiple phenotypic effects, a property called pleiotropy.
- Epistasis is when a gene at one location (locus) alters the phenotypic expression of a gene at another locus.
- Polygenic traits are due to the actions of more than one gene and often, their interaction with the environment.
- Trisomy is a state where humans have an extra autosome; they have three of a particular chromosome instead of two.
- The most common trisomy in viable births is Trisomy 21 (Down Syndrome).
- Prenatal diagnosis refers to the diagnosis of a disease or condition before the baby is born.
- Amniocentesis and choronic villus sampling are invasive methods involved in prenatal diagnosis.
- Gene therapy is the insertion of a new gene into an individual's cells and tissues to treat a disease, replacing a mutant disease-causing allele with a normal, non-mutant allele.

Review Questions

1. What is a genetic disease?
2. Discuss the main difference between autosomal and sex-linked.
3. Why is variation within the human genome important?
4. Why is it more common for males to have X-linked disorders?
5. Describe how a mutation can lead to a genetic disease.
6. Discuss how a new mutation can become a new dominant allele.
7. How are autosomal traits usually inherited? Give examples of traits.
8. How are genetic diseases usually inherited? Are there exceptions? Give examples.
9. Discuss the difference between codominance and incomplete dominance. Give exam-

ples.

10. What is meant by trisomy? **(Beginning)** How can trisomy phenotypes be detected?
11. What is the most common viable trisomy disorder?
12. List conditions involving an abnormal number of sex chromosomes.
13. Why is genetic counseling important?
14. What is gene therapy?
15. Describe the most common approach to gene therapy.

Further Reading / Supplemental Links

- The National Human Genome research Institute:
- http://www.genome.gov
- The Dolan DNA Learning Center:
- http://www.dnalc.org/home_alternate.html
- DNA Interactive:
- http://www.dnai.org/
- A Science Odyssey: DNA Workshop:
- http://www.pbs.org/wgbh/aso/tryit/dna/
- Kimball's Biology Pages:
- http://users.rcn.com/jkimball.ma.ultranet/BiologyPages
- http://en.wikipedia.org

Vocabulary

achondroplasia An autosomal dominant disorder; the most common cause of dwarfism.

amniocentesis A prenatal diagnostic procedure in which a small amount of amniotic fluid, which contains fetal tissues, is extracted from the amnion or amniotic sac surrounding a developing fetus, so that the fetal DNA is examined for genetic abnormalities.

autosomal dominant disorder A disorder in which only one mutated allele is needed for a person to be affected.

autosomal recessive disorder A disorder in which both copies of the gene must be mutated for a person to be affected.

autosome Any chromosome other than a sex chromosome.

chorionic villus sampling (CVS) A prenatal diagnostic procedure which involves removing a sample of the chorionic villus (placental tissue) and testing it.

codominance When two alleles are both expressed in the heterozygous individual; both alleles affect the phenotype in separate and distinguishable ways.

cystic fibrosis (CF) A recessive inheritable disorder caused by a mutation in a gene called the cystic fibrosis transmembrane conductance regulator (CFTR).

Duchenne muscular dystrophy (DMD) The most common type of muscular dystrophy; an X-linked recessive disorder.

epistasis When a gene at one location (locus) alters the phenotypic expression of a gene at another locus.

gene therapy The insertion of a new gene into an individual's cells and tissues to treat a disease, replacing a mutant disease-causing allele with a normal, non-mutant allele.

genetic counseling The process by which individuals or their families who are at risk of an inherited disorder are counseled on many different aspects of the disorder.

genetic counselor An individual trained in human genetics and counseling.

hemophilia A group of diseases in which blood does not clot normally.

incomplete dominance Occurs in heterozygous individuals with an intermediate phenotype; neither allele is dominant over the other.

Klinefelter's syndrome Caused by the presence of one or more extra copies of the X chromosome in a male's cells.

multiple allele traits Traits controlled by more than two alleles.

muscular dystrophy A term encompassing a variety of muscle wasting diseases.

mutation A change in the nucleotide sequence of DNA or RNA.

nondisjunction The failure of replicated chromosomes to separate during anaphase II of meiosis.

pedigree A chart which shows all of the known individuals within a family with a particular phenotype; a representation of genetic inheritance.

Phenylketonuria (PKU) An autosomal recessive genetic disorder characterized the inability to metabolize the amino acid phenylalanine.

pleiotropy Having multiple phenotypic effects.

polygenic traits Traits that are due to the actions of more than one gene and often, their interaction with the environment.

prenatal diagnosis The diagnosis of a disease or condition in a developing baby; done before the baby is born.

Severe Combined Immunodeficiency (SCID) A heritable immunodeficiency; a genetic disorder that cripples the immune system.

sex chromosomes Specify an organism's genetic sex; in humans, the X and Y chromosomes.

sex-linked traits Traits controlled by genes located on the sex chromosomes (X and Y).

Tay-Sachs disease An autosomal recessive genetic disorder that is fatal in early childhood; results from the accumulation of harmful quantities of fat in the nerve cells of the brain.

trisomy A state where humans have an extra autosome, having 47 chromosomes instead of 46. For example, trisomy 16 results in a third chromosome 16.

trisomy 21 Down syndrome; individuals often have some degree of mental retardation, some impairment of physical growth, and a specific facial appearance.

trisomy X Triple X syndrome; results from an extra copy of the X chromosome in each of a female's cells.

X-linked disorder A disorder caused by a mutation in a gene on the X chromosome; may be dominant or recessive, though the majority of X-linked disorders are recessive.

Y-linked disorder A disorder caused by a mutation in a gene on the Y chromosome; only affects males.

Points to Consider

In this chapter, we discussed human genetics as involved in human health. In the next chapter, we will discuss biotechnology. With gene therapy, we can see how biotechnology will play a significant role in society's future.

- Can you speculate on the role of biotechnology in our future?
- What other roles for biotechnology do you envision?
- Why is biotechnology important?

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