SBI3U-C

Chromosomes and Genetic Disorders

Introduction

Cri-du-chat (cat's cry) syndrome is a chromosomal disorder that occurs when a piece of a chromosome is missing. Infants with this disorder often have a high-pitched cry that sounds like a cat's. The disorder is characterized by intellectual disability and delayed development, distinctive facial features, small head size, low birth weight, and weak muscle tone in infancy. Some children with cri-du-chat syndrome are also born with a heart defect. Unfortunately, individuals with cat's cry often die at an early age.

In this lesson, you will learn how genetic traits are inherited on your chromosomes, including sex-linked traits that are inherited on your sex chromosomes. You will learn how mutations occur in genes and chromosomes, and how this can lead to disorders such as hemophilia, Tay-Sachs disease, and cat's cry syndrome. A better understanding of how our chromosomes work is the key to repairing genetic damage and finding cures for these genetic disorders.

Planning Your Study

You may find this time grid helpful in planning when and how you will work through this lesson.

Suggested Timing for This Lesson (hours)	
Chromosomal Theory of Inheritance	1½
What are Genes?	¼
Mutations	1
Human Gene (Allelic) Disorders	½
Key Questions	1

What You Will Learn

After completing this lesson, you will be able to

- describe some genetic disorders caused by chromosomal abnormalities or other genetic mutations in terms of chromosomes affected, physical effects, and treatments
- demonstrate an understanding of concepts, processes, and technologies related to the transmission of hereditary characteristics
- explain the concepts of genotype, phenotype, dominance, incomplete dominance, co-dominance, recessiveness, and sex linkage according to Mendelian laws of inheritance
- use the Punnett square method to solve basic genetics problems involving sex-linked genes

Chromosomal Theory of Inheritance

The chromosomal theory of inheritance states that genes are the units of heredity and that they are found in the chromosomes. It also states that in meiosis, paired chromosomes separate, resulting in each gamete having only one chromosome of the pair (they are haploid); thus, each gamete contains only one allele for each trait, not two as is the case in normal diploid cells.

The development of the chromosomal theory of inheritance has changed medicine forever. Many conditions or diseases are now known to be inherited because of changes in the way the chromosomes segregate during meiosis. It has also been revealed that environmental hazards like pollution, toxins, and radiation can affect human health by damaging chromosomes through mutations. You will learn more about mutations later in the lesson.

There were many scientists who had ideas that led up to the chromosomal theory of inheritance, beginning with the discovery of genes. Through the work of these scientists, we now know that chromsomes are composed of coiled strands of DNA (Figure 7.1).

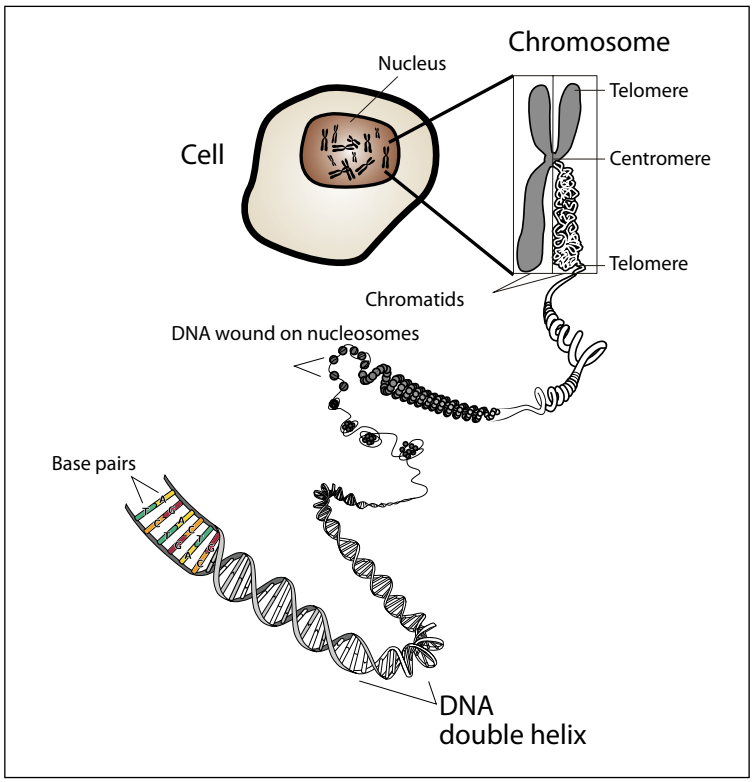

Figure 7.1: Diagram showing how DNA coils around itself to create a chromosome

Source: Wikimedia Commons

Sex-Linked Inheritance

One major discovery that led to the wide acceptance of the chromosomal theory of inheritance was the discovery of traits that occur only on the sex chromosomes—the X and Y chromosomes that determine the offspring's biological sex. The other chromosomes not involved in sex determination are called autosomes.

A female has two X chromosomes (XX); a male has one X and one Y chromosome (XY).

In males, half of the gametes formed would therefore contain the X chromosome, and half would contain the Y chromosome. In females, all the gametes would contain the X chromosome. As a result, the sex of the offspring is determined by the father: 50% of the offspring would have the genotype XX (female) and the other 50% would have XY (male).

Genes that are carried by either sex chromosome are said to be sex-linked. Their phenotypes are called sex-linked traits. If the trait is located on the X chromosome it is called an X-linked trait; if it only occurs on the Y chromosome it is called a Y-linked trait.

How Sex-Linked Traits Are Inherited

Early scientists chose to work on the fruit fly because it reproduces quickly and abundantly, with the females laying up to 100 eggs per day and producing about 500–1000 eggs in a lifetime. Fruit flies also possess easily observable traits, like eye colour and wing shape, that are determined by single genes. Fruit flies have four pairs of chromosomes (three pairs of autosomes, and a single pair of sex chromosomes).

These scientists discovered new phenomena that built on the chromosome theory of heredity. The first finding was sex-linked inheritance, in which homozygous recessive white-eyed flies showed a sex-linked inheritance of eye colour. Cross-breeding hybrid red-eyed flies resulted in all the female offspring having red eyes, whereas half the male offspring had white eyes. The result was an overall phenotypic ratio of 3:1 (red : white) as expected from Mendel's laws, but the ratio varied by sex.

The Punnett squares for the F_1 and F_2 crosses in these experiments are shown below. Dominant and recessive alleles on the X chromosomes are indicated using superscripts.

Let X^R represent red eyes (dominant) on the X chromosome.

Let X^r represent white eyes (recessive) on the X chromosome.

Note: The Y chromosome carries no gene for eye colour.

F_1 Generation

Parents

Red-eyed female (X^RX^R) × white-eyed male (X^rY)

Gametes

X^R X^R × X^r Y

Paternal alleles →

Maternal alleles ↓		X^r	Y
	X^R	X^RX^r	X^RY
	X^R	X^RX^r	X^RY

F_1 genotypes

$2X^RX^r : 2X^RY$

for a ratio of $1X^RX^r : 1X^RY$

F_1 phenotypes

2 red-eyed females : 2 red-eyed males

for a ratio of 1 red-eyed female : 1 red-eyed male

(all offspring are red-eyed)

F_2 Generation

Parents

Red-eyed female (X^RX^r) × red-eyed male (X^RY)

Gametes

X^R X^r × X^R Y

Paternal alleles →

Maternal alleles ↓		X^R	Y
	X^R	X^RX^R	X^RY
	X^r	X^RX^r	X^rY

F_2 genotypes

$1X^RX^R : 1X^RX^r : 1X^RY : 1X^rY$

F_2 phenotypes

2 red eyed-females : 1 red-eyed male : 1 white-eyed male

Thus, the overall ratio of red-eyed offspring to white-eyed is 3:1.

Recommended Activity:

Watch this pencast video, which works through the above example.

Scientists explained these results by proposing that certain genes are carried on the X chromosomes, of which females have two, but males have only one. The female's two X chromosomes can be homozygous (RR or rr) or heterozygous (Rr) for a sex-linked gene like eye colour. Males can carry only one allele for a sex-linked gene (R or r) because the small Y chromosome lacks almost all the genes found on the X chromosome (as is the case for eye colour in fruit flies). Since male fruit flies carry no second copy of the gene, they will express whichever allele is passed on from the maternal gamete.

In other words:

- Both males and females can express X-linked traits, since both inherit X chromosomes.
- A recessive trait located on the X chromosome is more likely to express itself in males than in females, since males have only one X chromosome.
- Only males can express Y-linked traits, since only males have Y chromosomes.

This discovery led to widespread acceptance of the chromosomal theory of inheritance because it showed that traits reside on the chromosome and that they usually occur in pairs, except in the case of sex-linked traits.

Examples of Sex-Linked Traits in Humans

Red-green colour blindness affects 8% of males and 0.04% of females. Colour perception depends on three genes, each producing chemicals sensitive to different parts of the visible light spectrum. The genes for red and green detection are on the X chromosome, while the gene for blue detection is on an autosome. Males inheriting the mutated form of the X chromosome will be red-green colour blind. Females must inherit two copies of the mutated X chromosome to be colour blind, which is why the condition is so much rarer in women.

Hemophilia is a group of diseases in which blood does not clot normally, so that even minor injuries can bleed for days or weeks, sometimes resulting in death. Proteins in the blood, called factors, are involved in clotting. People lacking the normal factor VIII are said to have hemophilia A, the most common form of the disease. Hemophilia is caused by a recessive sex-linked X chromosome disorder, so it mostly affects males. Females rarely get the disease, but can pass on the defective allele to their children. A famous example of this is England's Queen Victoria, who was a carrier for this disease. She passed the allele to one of her sons and two of her daughters, who spread it into the royal families of Europe during the late 1800s. For a while, hemophilia was known as the "royal disease" because so many members of Europe's royal families had it.

Other examples of sex-linked traits in humans include certain types of baldness and the placement of sweat glands.

Support Questions

Be sure to try the Support Questions on your own before looking at the suggested answers provided.

22. Describe the two main principles of the chromosomal theory of inheritance.

Suggested answer

23. If an allele is found on an autosomal chromosome, is it considered to be sex-linked? Explain.

Suggested answer

Solving Genetics Problems for Sex-Linked Traits

You can use Punnett squares to solve genetics problems involving sex-linked traits.

Example

In humans, the allele for normal colour vision is dominant, and the allele for red-green colour blindness is recessive. The characteristic is sex-linked.

Using a Punnett square, show the cross between a heterozygous female and a male with normal vision. State the resulting genotypes and phenotypes as a ratio.

Solution

Let C represent the allele for normal colour vision.

Let c represent the allele for red-green colour blindness.

Parents

Female with normal vision (X^CX^c) × male with normal vision (X^CY)

Gametes

X^C X^c × X^C Y

Paternal alleles →

Maternal alleles ↓		X^C	Y
	X^C	X^CX^C	X^CY
	X^c	X^CX^c	X^cY

F_1 genotypes

$1X^CX^C : 1X^CX^c : 1X^CY : 1X^cY$

F_1 phenotypes

2 normal females : 1 normal male : 1 colour-blind male

Recommended Activity:

Watch this pencast video, which works through the above example.

Support Questions

24. A recessive sex-linked allele (h) located on the X chromosome increases blood- clotting time, causing hemophilia.

a) Using a Punnett square, explain how a son with hemophilia can be born to two normal parents.

b) What genotypes must the parents have in order to produce a daughter with hemophilia?

Suggested answer

25. Using a Punnett square, explain how a woman who is not colour-blind, but whose father is colour-blind, can give birth to a son who is colour-blind.

Suggested answer

What are Genes?

We have called genes the units of heredity, but what exactly is the hereditary material, and how does it work?

DNA is the Genetic Material

The molecule of heredity is called DNA (deoxyribonucleic acid), an acidic polymer that is found in the nucleus of cells. DNA is called a polymer because it is made up of several repeating identical units called nucleotides, which consist of three parts: a nitrogen base, a five-carbon sugar (ribose), and a phosphate group. The structure of a nucleotide is shown in Figure 7.2, below.

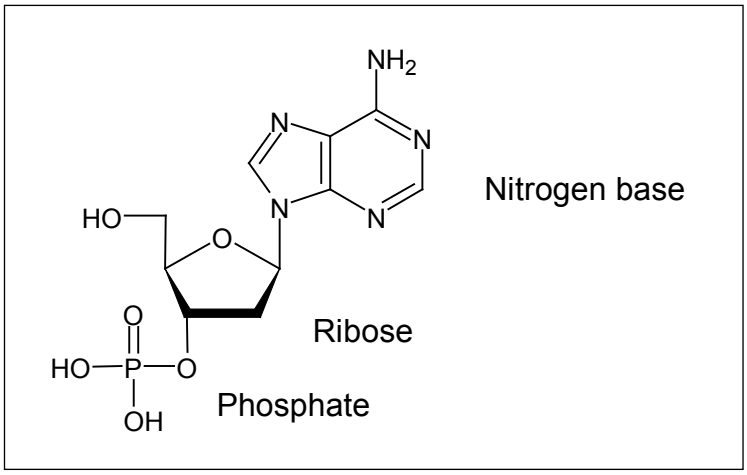

Figure 7.2: DNA nucleotide

The structure of DNA is a double helix that resembles a twisted ladder. Sugar and phosphate molecules make up the sides of the ladder, and the rungs are the nitrogen bases, as shown in Figure 7.3, below.

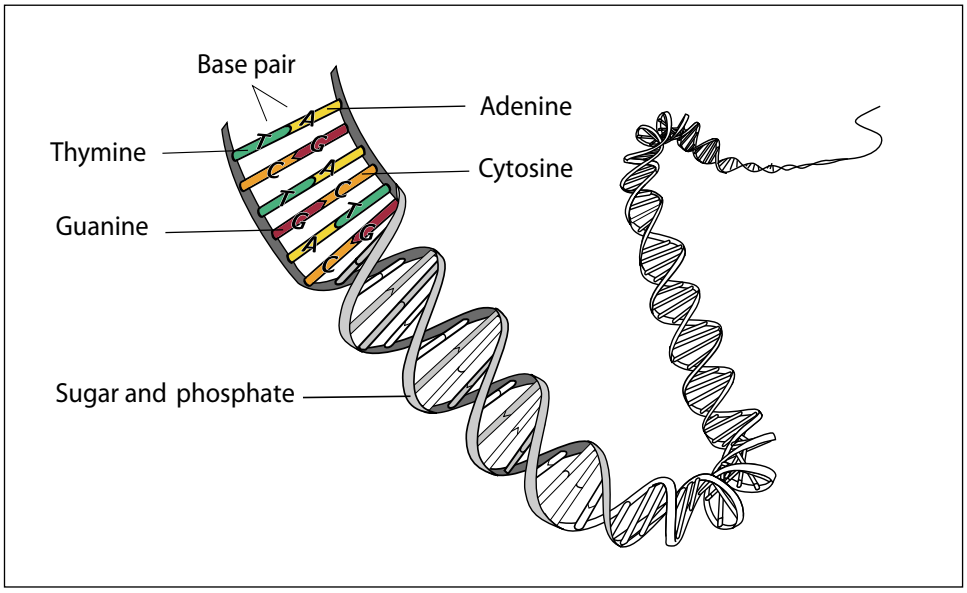

Figure 7.3: Structure of DNA molecule

The information in DNA is stored as a sequence of four nitrogen bases: adenine (A), guanine (G), cytosine (C), and thymine (T) (Figure 7.4).

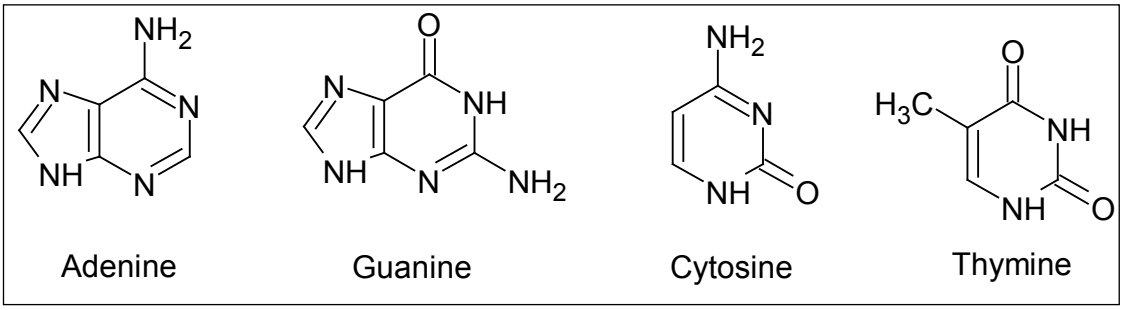

Figure 7.4: Nitrogen bases found in DNA

Adenine and guanine are purines (double-ring structure), while cytosine and thymine are pyrimidines (single-ring structure). The nitrogen bases can be joined together into pairs using hydrogen bonds between a purine and pyrimidine. Because of the way they are structured, adenine only pairs up with thymine, and guanine only pairs up with cytosine. This is referred to as complementary base pairing.

The DNA in your cells consists of about 3 billion base pairs. The order, or sequence, of these bases stores the information required for building and maintaining you. This is similar to the way letters of the alphabet appear in a certain order to form words and sentences. The "words" in the DNA code are three base pairs long and are called codons. Genes are made up of thousands of codons, and each codon codes for an amino acid. The chain of amino acids produced from a gene makes a unique protein.

Mutations

Mutations are changes in the DNA sequence, caused by radiation, viruses, and certain chemicals like those found in tobacco and other environmental contaminants. Mutations occur during meiosis or DNA replication.

One look around a room tells you that each person is unique and, therefore, their DNA is also unique. However, the similarity in human DNA from one individual to another is about 99%, so the differences among us are due to very small changes in the sequence.

How Mutations Occur

The DNA in your cells will experience some change during the course of your life. These changes may occur in a number of ways.

Every time a cell divides, its entire DNA is copied, so that each of the two resulting cells has a full set of DNA. Sometimes, simple copying errors are introduced when this happens. Other changes are introduced as a result of DNA damage through environmental agents including sunlight, cigarette smoke, and radiation. Our cells have built-in mechanisms that catch and repair most of the changes that occur during DNA replication or as a result of environmental damage. As we age, however, our DNA repair does not work as effectively, and we accumulate changes in our DNA. These mutations from environmental agents can cause diseases such as cancer.

Mutations that occur in the DNA of cells, such as in skin cells as a result of sun exposure, are not hereditary. But mutations can also occur in the DNA of gametic cells (sperm and eggs), and these mutations can be passed from parent to child (hereditary mutations). If a child inherits a mutation from their parents, the DNA in every cell in their body will have this mutation. Hereditary mutations are what cause diseases such as hemophilia and Huntington's disease to run in families.

Gene Mutations

Gene mutations can occur either in body cells or in gametes. They can occur during the DNA replication process or during crossing-over in meiosis. Gene mutations usually involve small changes in the base pair sequence that affect a single gene. Cystic fibrosis, Huntington's disease, sickle-cell anemia, hemophilia, and Duchenne muscular dystrophy are a few disorders that are caused by gene mutations. There are five types of gene mutations.

1. Point Mutation

A point mutation is a simple change in one base (or point) of the gene sequence. Note the one-letter change in the DNA strand shown below.

Original	ATG GGA TTA CGC
Point Mutation	ATG GGA TT**T** CGC

For example, sickle-cell disease (a disease where the red blood cells do not form properly) results from a point mutation. The nitrogen base A is replaced by T at the 17th nucleotide of the gene for hemoglobin. This changes the DNA codon GAG (for the amino acid glutamic acid) to GTG (for the amino acid valine). Thus, the 6th amino acid in the chain becomes valine instead of glutamic acid. This single substitution causes the red blood cells to not form properly.

2. Frame-shift Mutation

In a frame-shift mutation, one or more bases are inserted or deleted. But because our cells read DNA in three-letter codons, adding or removing one letter changes the order in each subsequent codon. This type of mutation can make the DNA meaningless, and often results in a shortened protein.

Original	ATG GGA TTA CGC
Frame Shift	TGG GAT TAC GC (first 'A' has been deleted)

Notice how every codon after the deletion has changed. In this way, even small changes can produce large effects in the gene. Insertions or deletions that occur in multiples of three will not cause frame-shift mutations, but will still change the final protein coded for by the gene.

3. Deletion

Mutations that result in missing DNA are called deletions. These can be small, such as the removal of just one nucleotide or codon, or longer deletions that affect a large number of genes on the chromosome. Deletions can cause frame-shift mutations.

Original	ATG GGA TTA CGC
Deletion	ATG GGA CGC (entire 'TTA' codon missing)

Because the deletion here was three letters long, a whole codon was deleted, which does not produce a frame-shift mutation. However, the resulting protein will be missing one amino acid in the chain, which could have serious consequences for the structure or function of the protein.

If the deletion involves a large number of base pairs, or even large sections of a chromosome, the consequences can be severe. Cri-du-chat syndrome is the result of a missing part of chromosome 5.

4. Insertion

Mutations that result in the addition of extra DNA are called insertions. Insertions can also cause frame-shift mutations, and generally result in a nonfunctional protein. In the example shown below, the insertion added three letters (CCG).

Original	ATG GGA TTA CGC
Insertion	ATG GGA CCG TTA CGC

Because the insertion was three letters long, it did not result in a frame-shift mutation. However, the added amino acid created by the inserted codon alters the final protein.

Several disorders in humans are caused by the inheritance of genes that have undergone insertions of a string of three or four nucleotides repeated over and over. For example, a location on the human X chromosome contains a sequence of bases in which the triplet CGG is repeated many times (CGGCGGCGGCGG…). The number of CGGs may be as few as 5 or as many as 100 without producing a harmful phenotype. However, these longer repetitions have

a tendency to grow longer still from one generation to the next, sometimes reaching as many as 4000 repetitions. Eventually, this causes a constriction in the X chromosome, which makes it quite fragile. Males who inherit such a chromosome (only from their mothers, of course) exhibit a number of harmful phenotypic effects including mental disability.

5. Inversion

In an inversion mutation, the order of an entire section of DNA gets reversed because a section of DNA has been cut out and re-inserted upside down. A small inversion may involve only a few bases within a gene, while longer inversions involve large regions of a chromosome containing several genes. In the example shown below, an entire section (the two middle codons, 'GGA TTA') has been reversed.

Original	ATG GGA TTA CGC
Insertion	ATG ATT AGG CGC

Chromosomal Mutations

Mutations can happen at the level of the chromosome in addition to the gene. Like gene mutations, these can cause changes in the structure or function of the proteins coded for by the genes. However, in the case of chromosome mutations, the changes may affect more than one gene.

Mutations can also occur to change the number of chromosomes in a cell. These mutations are the result of nondisjunction, an error that occurs during meiosis which makes homologous chromosomes fail to segregate, producing gametes with too many or too few chromosomes (aneuploidy). This can result in disorders such as Down syndrome and Klinefelter syndrome.

How do you count the number of chromosomes in a cell? Normally, this is very difficult because most of the time chromosomes are not very distinct within the nucleus. However, during meiosis and cell division, the chromosomes form distinct homologous pairs that can be easily seen under a microscope, making it easier to identify and count them.

Karyotype Charts

A karyotype is a chart of the chromosome makeup of a cell. They are useful for determining whether or not the chromosomes are normal in number and structure. Karyotypes are made by photographing the nucleus of a cell undergoing division and cutting out the chromosomes and arranging them in homologous pairs. Figure 7.5, below, depicts a karyotype for a human male. There are 23 pairs of chromosomes made up of 22 autosomes (numbered 1 to 22) and 1 pair of sex chromosomes (XY).

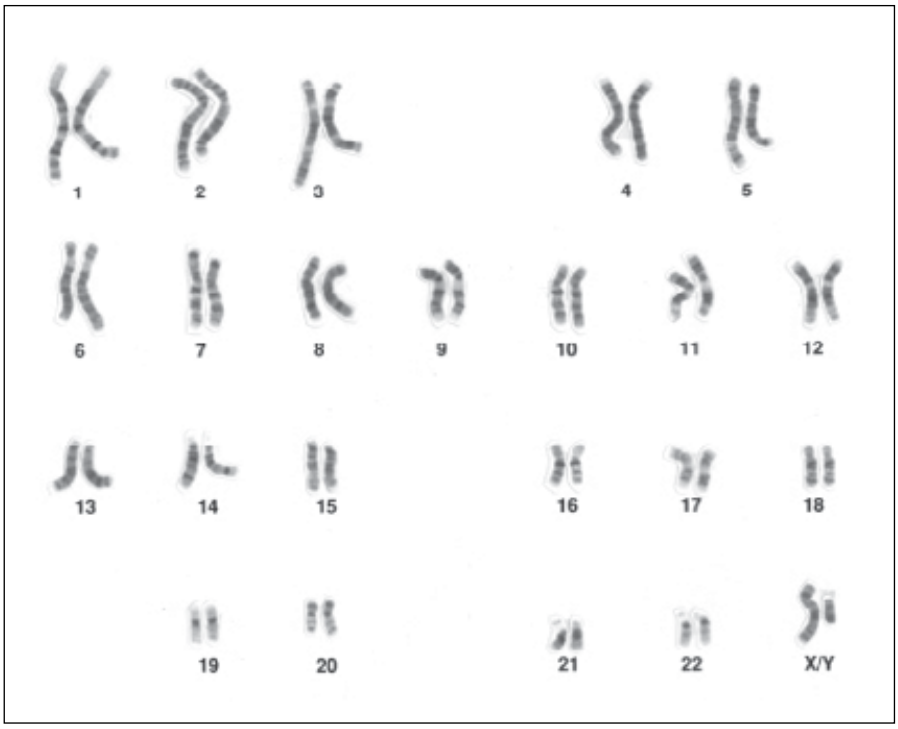

Figure 7.5: Karyotype for a human male

Source: Wikipedia

To make a karyotype, a small sample of tissue is mixed with a solution that stimulates mitosis. Another solution is added during metaphase that stops mitosis. Mitosis is halted during metaphase because the chromosomes are most dense. The metaphase cells are placed onto a slide and then stained, so that distinctive bands appear. A photograph is taken and enlarged and then the homologous chromosomes are paired up. The pairs are aligned at their centromeres in decreasing size order, with the sex chromosomes appearing last.

Support Questions

26. Briefly summarize the types of gene mutations you learned about in this section.

Suggested answer

Human Gene (Allelic) Disorders

In 1905, the first genetic disorder was described in humans. It was brachydactyly, which results in a shortness of the fingers and toes. Today, more than 3500 genetic disorders are known. In the following sections, you will learn about some of the more common autosomal disorders and the conditions they can cause.

Recessive disorders

Recessive traits are those that are expressed only when two copies of the recessive allele are present in the individual. There are several conditions and diseases associated with the expression of recessive traits. These conditions are rare because the alleles are rare, so being homozygous for these alleles is even rarer.

Albinism

Albinos are characterized by the lack of pigmentation in their skin, hair, and eyes. The brown pigment melanin cannot be made by albinos. This pigment is what gives your skin colour, and the number of melanin-producing cells determines how dark or light your skin colour is. Albinism is an autosomal recessive (aa) trait. If both parents are heterozygous with normal pigmentation (Aa), then one out of four of their children could be albinos (aa).

Phenylketonuria (PKU)

PKU is caused by an autosomal recessive trait whose sufferers lack the ability to synthesize an enzyme to convert the amino acid phenylalanine into tyrosine. Individuals who are homozygous for the recessive allele have a build-up of phenylalanine and abnormal breakdown products in the urine and blood. The breakdown products can be harmful to brain development and lead to intellectual disabilities after birth. One in 15 000 infants are born with this problem. Genetic testing for PKU homozygotes in newborns is now routinely done in developed countries and the condition can be treated fairly easily.

Tay-Sachs Disease

Tay-Sachs disease is caused by an autosomal recessive trait resulting in degeneration of the nervous system. Symptoms show up after birth. Children who are homozygous recessive for this allele rarely survive past five years of age. Sufferers lack the ability to make an enzyme which breaks down a certain type of lipid. This lipid accumulates in brain cells, eventually killing the brain cells. Although rare in the general population (1 in 300 000 births), until recently, it was higher among Jews of eastern and central European descent (1 in 3600 births).

Sickle-cell Anemia

Sickle-cell anemia is caused by an autosomal recessive trait resulting in red blood cells that are abnormal in shape (they are crescent-shaped, like the curved blade of a sickle). Nine percent of African-Americans are heterozygous, while 0.2% are homozygous recessive. The recessive allele causes a single amino acid substitution in the beta chains of hemoglobin. When oxygen concentration is low, sickling (malformation) of cells occurs. Heterozygotes make enough "good" beta-chain hemoglobin that they do not suffer as long as oxygen concentrations remain high, such as at sea level. Heterozygotes also appear to be more resistant to malaria, a disease common in Africa and other tropical areas. This may explain why the recessive allele causing sickle-cell anemia is still present in the human population. If there were no benefit to the allele, then it is expected that natural selection would have removed it a long time ago.

Dominant Disorders

Autosomal dominant disorders are rare, although they are (by definition) more commonly expressed.

Achondroplasia Dwarfism

Achondroplasia dwarfism is caused by an autosomal dominant trait that affects cartilage formation. This results in the individual being much shorter than average. It occurs even though those individuals who show it usually have reduced fertility. No one is sure why the alleles that cause this condition persist in the population; they may provide an evolutionary advantage in other ways not yet understood.

Huntington's Disease

Also referred to as Woody Guthrie's disease, after the folk singer who died of it in the 1960s, Huntington's disease is caused by an autosomal dominant trait resulting in progressive destruction of brain cells. If a parent has the disease, 50% of the children will have it (unless that parent was homozygous dominant, in which case all children would have the disease). It usually does not appear until after age 30, although some instances of early onset are reported among individuals in their twenties. The late appearance of the disease is a concern, since individuals may not know they are affected prior to starting a family and passing the gene on to their children.

Polydactyly

Polydactyly is the result of an autosomal dominant trait that produces a sixth digit. In modern times, the extra finger was often cut off at birth, so many individuals did not know they carried this trait. Anne Boleyn, one of the wives of Henry VIII of England, is said to have had an extra finger.

Support Questions

27. Describe one example of an autosomal recessive disorder and an autosomal dominant disorder.

Suggested answer

28. Use the Internet to research information on the genetic disorder cystic fibrosis and answer the following three questions.

a) Is the disease the result of a recessive or dominant trait?

b) Describe three symptoms of the disease.

c) Natural selection usually removes alleles from a population that cause early death. Why do you think the mutated allele causing cystic fibrosis is still present in the human population?

Suggested answer

Key Questions

Now work on your Key Questions in the online submission tool. You may continue to work at this task over several sessions, but be sure to save your work each time. When you have answered all the unit's Key Questions, submit your work to the ILC.

(18 marks)

21. In humans, the recessive allele that causes a form of red-green colour blindness (c) is found on the X chromosome.

a) Determine the genotypes and phenotypes of the F_1 generation from a colour-blind father and a mother who is homozygous for normal colour vision. **(4 marks)**

b) Determine the genotypes and phenotypes of the F_1 generation from a father who has normal colour vision and a mother who is heterozygous for colour vision. **(4 marks)**

c) Draw the possible Punnett squares to determine the genotypes of parents that could produce a daughter who is colour-blind. **(4 marks)**

22. Hypophosphatemia is a dominant genetic disorder caused by a deficiency of phosphates in the blood. Assuming the other parent is free of the disorder, males with the disorder will pass it on to all their daughters but not their sons. Females with the disorder will pass it on to approximately half of their children.

a) Is this pattern of inheritance autosomal or sex-linked? Explain. **(2 marks)**

b) Draw Punnett squares to show the inheritance pattern of the disorder in each of the two scenarios. **(4 marks)**

Now go on to Lesson 6. Send your answers to the Key Questions to the ILC when you have completed Unit 2 (Lessons 5 to 8).