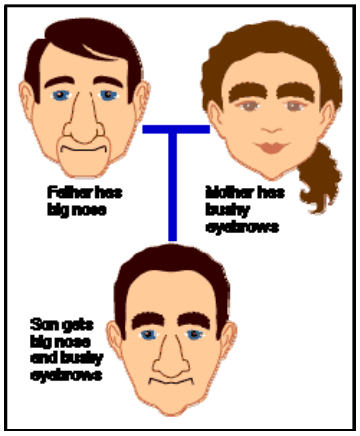
Mutations and Genetic Disorders

Sexual Reproduction as a Source of Genetic Variation

Sexual reproduction can introduce new gene combinations into a population and therefore, is an important source of genetic variation. Siblings, except for identical ones, are not genetically identical to each other, nor are they genetically identical to their parents. This is because there is some **GENETIC SHUFFLING** that occurs first during the creation of egg and sperm and then in the union with of egg with sperm, creating a unique individual with new combinations of genes. For example, a child may have busy eyebrows and a big nose since your mom has genes associated with bushy eyebrows and your father has genes associated with a big nose (see the illustration below). Genetic shuffling can be very important to evolution, since it introduced new combinations of genes into every generation, however, it also can break up "good" combinations of genes as well.



DNA is the hereditary material of all living organisms. A change in the DNA can alter the physiology, looks, and/or the behaviors of an organism.

The Difference between Genes and Alleles

A **GENE** is defined as the specific part of the chromosome that contains the coded information to make a specific polypeptide that influences a particular trait or characteristic in the organism. There are usually two or more ways for a trait to appear. **ALLELES** are the alternate forms of the genes of a given trait.

Example: In pea plants, genes carry information about the color of the seeds. Alleles are the actual color of the seeds – either green (G) or yellow (g).

The Difference between Phenotype and Genotype

PHENOTYPE is defined as the observable physical or biochemical characteristics of an organism. **GENOTYPE** is defined as the genetic makeup of the organism (the way the base pairs are arranged). Mutations change the genotype of the organism. Phenotype changes could lethal (deleterious) or very harmful; mutations could also bring about positive changes that could lead to evolution; mutations may have no effect on the phenotype in any way.

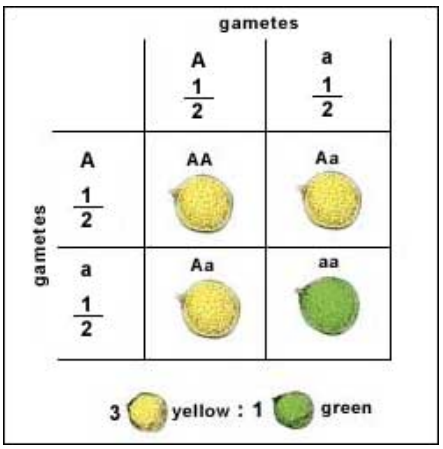
Genotype of a Trait:

In the above example of pea seed color, **seeds can either be green or yellow**.

If **G** is the allele for green color and **g** is the allele for yellow color then there can be three allelic combinations of genes for pea pod color.

Genotypes: *Phenotypes:*

GG	green
Gg	green
Gg	yellow



What is a mutation?

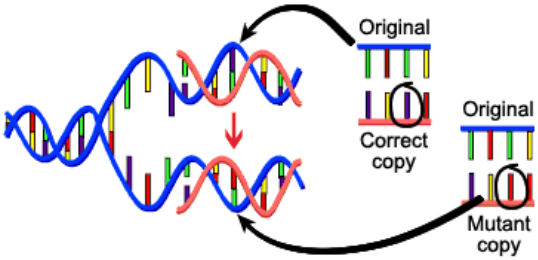
A **MUTATION** is a change in the DNA sequence of bases. Mutations are random and unrelated to how "useful" the change would be for the organism. Mutations can be beneficial, harmful or have no effect on the functioning or appearance of the organism in any way.

Where do mutations occur?

DNA is found in every cell of an organism, so there are many places for mutations to occur. **SOMATIC MUTATIONS** occur in non-reproductive cells (any cell except the sex cells). These mutations can affect the organism but will NOT be passed to its offspring. **GERM LINE MUTATIONS** are mutations that occur in the sex cells (sperm and egg). These mutations can affect the organism and can be passed to its offspring as well. ***Such mutations are another source of change that can lead to evolution.***

Causes of Mutations

DNA Fails to Copy Accurately: Changes occur in the base pairs when DNA copies itself, so that the copy of the DNA is not quite perfect.



Environmental Influences: Mutations can also be caused by exposure to certain mutagenic agents, which cause the DNA to break down. When the cell attempts to repair itself, it may not do a perfect job of fixing the DNA so now the cell is left with DNA that is slightly different that the original DNA. Such mutations can often be harmful to the organism. Examples of mutagenic agents include:

- radiation
- x-rays
- ultraviolet radiation
- cosmic rays
- formaldehyde
- cigarette smoke
- pesticides such as Agent Orange

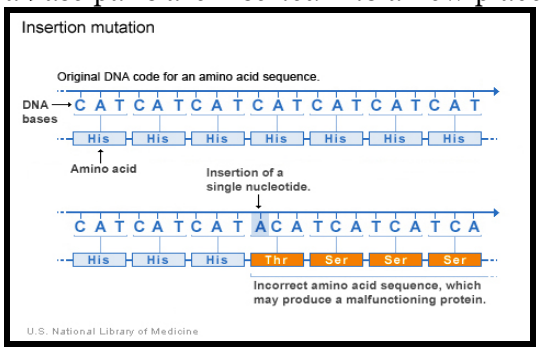
Types of Gene Point Mutations

Substitution: a change in the structure of DNA in which one base is exchanged for another. For instance, in the example below, A was switched to G. The effect of a substitution will depend if the mutation causes a change in the resulting protein that is produced.

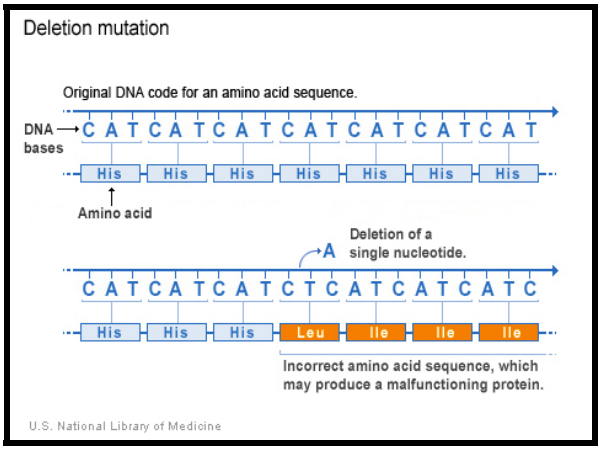
CTGGAG

CTGGGG

Insertion: Mutations where extra base pairs are inserted into a new place in the sequence of the DNA.



Deletion: Mutations where a single base or several bases are deleted from a sequence of DNA as pictured below



Inversion: mutations where there is a reversal in a DNA triplet base pair as seen below.

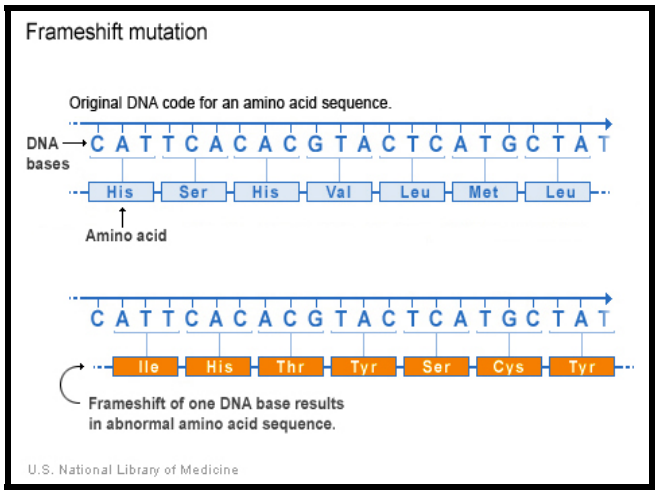
Original DNA: C A T T A G G A T

Inversion: C A T G A T G A T

Frameshift: DNA is divided into triplets that are three bases long. Insertions and deletions can alter a gene that its message is no longer correctly paired. Consider the sentence,
"The fat cat sat". Each word is a DNA base pair triplet. If the first letter is deleted and the sentence paired in triplet form, it doesn't make any sense (see example below). In frameshifts, errors that occur at the DNA level cause the triplets to be paired, read, and translated incorrectly, generating proteins that are often useless.

The fat cat sat

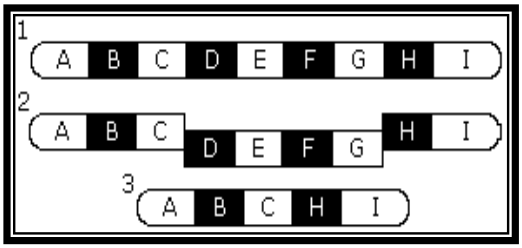
hef atc ats at



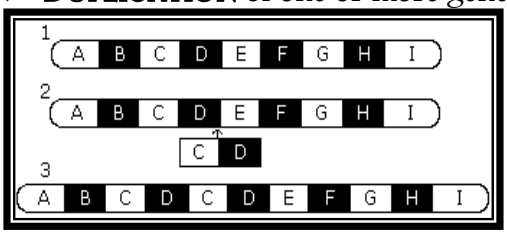
Chromosome Mutations

Mutations can also occur in the structure and/or number of chromosomes found in each cell. These mutations may change the locations of genes on chromosomes and even the number of copies of some genes.

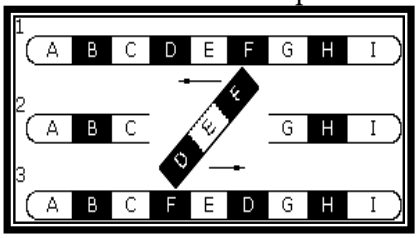
- **DELETION** of a section of a chromosome



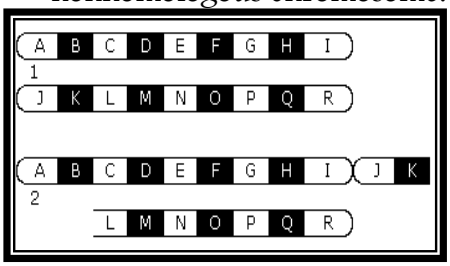
- **DUPLICATION** of one or more genes on a chromosome



- **INVERSION** of a sequence of genes



- **TRANSLOCATION** where one of two homologous chromosomes breaks off and attaches to nonhomologous chromosome.



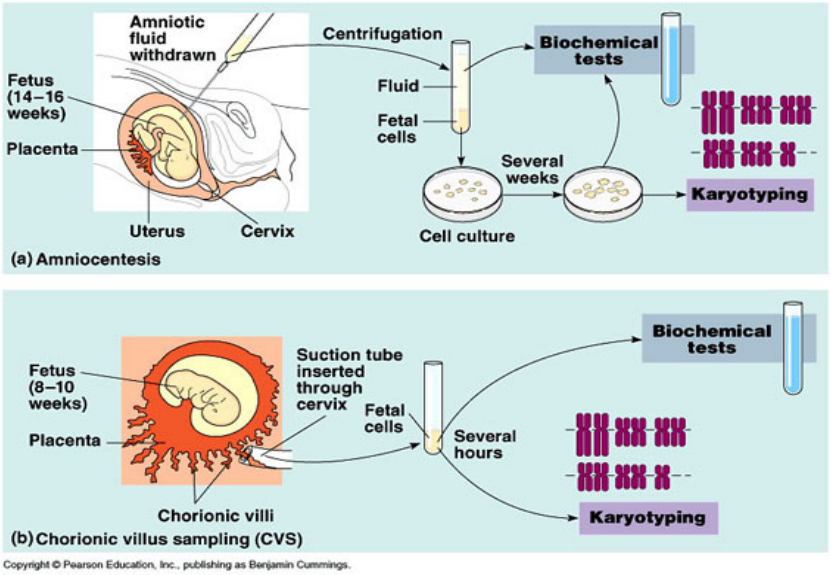
Diagnostic Testing of Genetic Disorders

Chorionic Villi Testing

- Used to diagnose certain birth defects early in the first trimester (Tay Sachs, Down's Syndrome)
- A small bit of placental tissue is gently suctioned into a syringe. Since placental tissue is formed from embryonic tissue, it is genetically identical to the fetus and can be analyzed for potentially dangerous birth defects.
- The incidence of miscarriage is a bit higher when compared to amniocentesis.

Amniocentesis

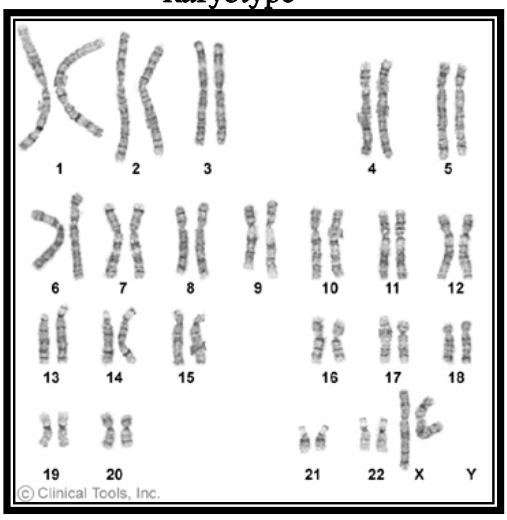
- A hollow needle is inserted through the mother's abdomen into the amniotic sac in order to draw some fluid for analysis
- By examining the amniotic fluid, chromosome abnormalities, neural tube defects, and genetic disorders can be detected.
- Generally performed during the 14th -20th week of pregnancy.
- Risks of miscarriage are relatively low – 2%-3%



Karyotyping

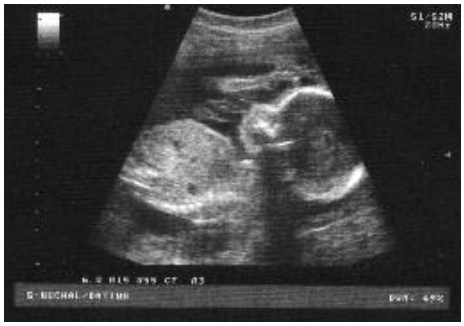
- Enlarged picture of homologous chromosomes in a cell.
- Chromosomes are examined for abnormalities.
- Sex of fetus can also be determined.

Karyotype



Obstetric Sonogram

- The examination can be performed transabdominally, usually with a full bladder to achieve better visualization, or transvaginally with a special vaginal transducer.
- Having a full bladder for the transabdominal portion of the exam is helpful because sound travels through fluid, which helps to better visualize the uterus, which lies posteriorly to the bladder.



- The procedure is painless, noninvasive, and safe.

Fetus at 22 weeks

Cystic Fibrosis (CF)

- CF is a severe, genetically inherited, life-threatening disease that causes mucus build up in the lungs and gastrointestinal tract.
- In particular, the presence of mucus in the lungs can make breathing for the CF patient very difficult.
- The thick mucus also promotes bacterial infection, causing inflammation of the airways that can lead to lung damage.
- Mucus build-up in the digestive tract and pancreas prevents enzymes to get to the small intestine, so proper digestion can occur.
- CF occurs in about 1 out of every 2,500 births among Caucasian children, with a far lower incidence rate among Asian and Black children.
- It is caused by a mutation to a gene on Chromosome 7.
- This gene, called cystic fibrosis transmembrane conductance regulator (**CFTR**), codes for a protein that enable the transport of chloride ions out of cells.
- People with cystic fibrosis have two mutant genes (one from each parent) that do not make the proper protein to permit the movement of chloride ions across the cell membrane.
- There are now more than 500 different mutations of the CFTR gene that are known to cause CF.

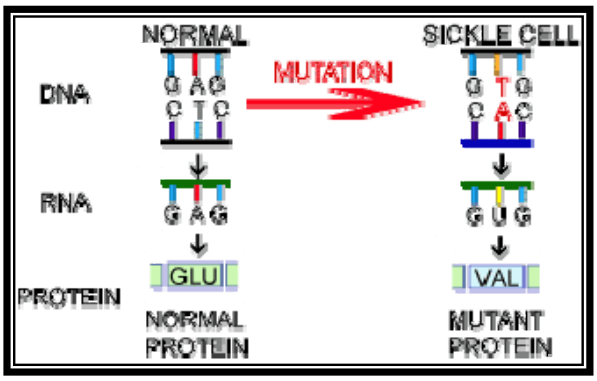
- **Diagnosis:** genetic carrier test, newborn screening, sweat test
- **Treatment:** keeping lungs and digestive system free of mucus, antibiotic therapy

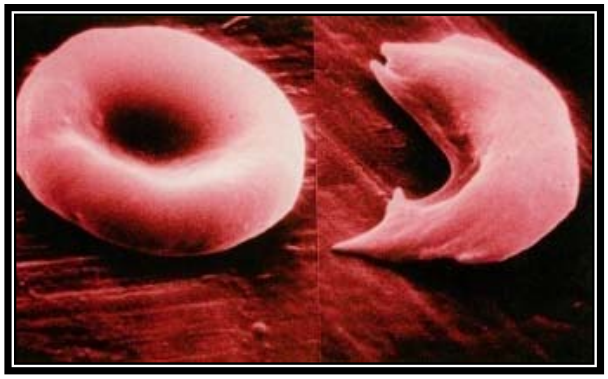
Cycstic Fibrosis-mutation region							
normal sequence:	att	atc	atc	ttt	ggt	gtt	tcc
mutated sequence:	att	atc	***	ttt	ggt	gtt	tcc

Sickle Cell Anemia

- One serious illness that results from a simple base substitution is **sickle-cell anemia,** a genetically inherited disease most commonly associated with people of African American descent.
- People with sickle cell anemia are very tired, lack energy due to an insufficient amount of oxygen in their cells to carry on aerobic respiration to release needed energy for metabolic processes
- They are often in severe pain from the abnormally shaped red blood cells as they move through the capillaries.
- This disease is caused by a mutated version of the gene that helps to make hemoglobin, the red respiratory pigment that carries oxygen on the red blood cells.
- People with two copies of this gene have the disease; those with one copy of the gene do not have the disease but can pass the gene onto their children.
- **Diagnosis**: blood test
- **Treatment:** Blood transfusions, pain management

There are effects at the DNA level. There are effects at the protein level.





Normal Cell Sickle Cell

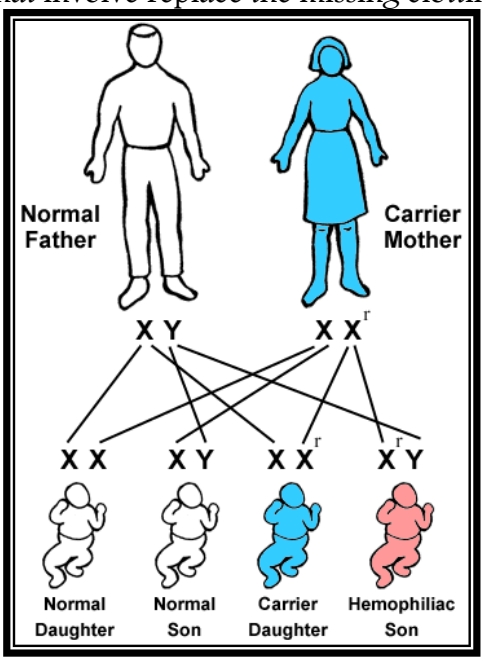
Albinism

- Inherited condition that is recessive (must have a gene from each parent.)
- All people with albinism have vision problems.
- Most have blue eyes, but some individuals have red or violet eyes.
- Pigmentation is weak or non-existent, leaving individuals with very pale skin, white hair and eyelashes.
- Individuals with albinism are very sensitive to light and with little melanin, must wear sun block to prevent severe burning in the sun.

- **Diagnosis:** vision test, amniocentesis
- **Treatment:** watch sun exposure, use screen with at least SPF 20 at all times

Hemophilia

- Caused by a defect in a gene that makes clotting factors for the blood.
- The blood had difficulty clotting; even small cuts can be life threatening.
- Some symptoms include chronic bleeding gums, bleeding into joints, urine and stool. Afflicted individuals often have frequent bruising, particularly in children.
- This is a sex-linked trait, meaning it is carried on the mother's X chromosome
- Since is a sex-linked trait, males only need one X chromosome to have the disease, females need to X chromosomes with the afflicted gene to have hemophilia.
- **Diagnosis:** Blood test to determine the damage to clotting factors
- **Treatment:** Therapies that involve replace the missing clotting factor(s).



Phenylketonuria (PKU)

- Recessive disorder (need a defective gene from each parent)
- Abnormal gene does not allow the body to use (metabolize) the essential amino acid, phenylalanine.
- As a result, phenylalanine accumulates in the brain and other body tissue, causing irreversible brain damage and other neurological problems.
- **Diagnosis:** must occur in the first days of life via a blood test to avoid permanent brain damage.
- **Treatment:** a lifetime maintenance of a diet low in phenylalanine consumption

Tay-Sachs Disorder

- Recessive disorder, more common among individual of eastern European Jewish origin
- Due to a faulty gene, a fatty substance accumulates around nerve cells, particularly those of the brain.
- The destructive process begins early in pregnancy although symptoms are often not apparent until the child is a few months old.

- The afflicted child will continue a downward decline and eventually become blind, low mental function, paralyzed, and unresponsive to the external environment.
- By the age of 5, most Tay-Sachs children die.
- Diagnosis: genetic screening of parents prior to pregnancy to determine if either one is a carrier; chorionic villi testing to determine if mother is carrying a Tay-Sachs baby

Down's Syndrome (Trisomy 21)

- Chromosomal disorder, occurs as a result of the nondisjunction of the 21st chromosome, so all cells have 2n+1 (47) chromosomes in all cells of the body.
- Down's syndrome children look similar. They are shorter in stature and stocky, have short fingers and toes, sometimes with webbing. Their faces have a slant to the eyes and tend to be flatter in appearance. They are most often limited in intelligence.
- They may suffer from hear disorders, dementia, hearing problems, and digestive diseases.
- **Diagnosis**: amniocentesis, karyotype
- **Treatment:** early intervention to maximize child's mental and physical abilities.

Turner Syndrome

- Chromosomal disorder due to a missing X chromosome.
- Turner syndrome females have only one X chromosome.
- They generally are shorter in stature, have premature ovary failure, heart diseases, and kidney disorders
- **Diagnosis:** amniocentesis, karyotype
- **Treatment:** growth hormones, estrogen treatment

Questions:

1. Identify 2 sources of mutations.
2. Explain the meaning of genetic shuffling.
3. Define the meaning of somatic and "germ-line". (you may have to look this up!)
4. What is a mutation?
5. Describe the difference between somatic and "germ line" mutations.
6. Differentiate between phenotype and genotype
7. When creating new cells, DNA must copy itself to preserve the genetic code. Describe what can occur if DNA fails to copy itself correctly?
8. Identify 7 environmental sources of mutations.
9. Where must mutations occur to be passed on to one's offspring?
10. What is a gene point mutation?
11. Explain what happens in the following gene point mutations:
    a. Substitution
    b. Insertion
    c. Deletion
    d. Inversion
    e. Frameshift
12. Answer the following questions with respect to sickle cell anemia:
    a. What is hemoglobin?
    b. How are RBCs affected by the sickle cell mutation?
    c. Describe the symptoms of sickle cell anemia.
13. Answer the following questions with respect to cystic fibrosis:
    a. Is this a dominant or recessive disease (think back to your middle school genetics)
    b. Describe the symptoms of this disease
    c. Where does the mutation occur (be specific).
    d. Describe the biological effect of the mutation on the cells.

14. What are chromosome mutations?
15. Describe what happens during the following chromosome mutations:
    a. Deletion
    b. Duplication
    c. Inversion
    d. Translocation
16. Compare chorionic villi testing with amniocentesis (you can make a chart if you like).
17. What is a karyotype?
18. What is an obstetric sonogram and why is it used?
19. Describe the genetic disorder of cystic fibrosis. In your answer include the following:
    a. Describe the symptoms
    b. Gene that is afflicted
    c. Recessive or dominant disease
    d. What the mutation changes in the cell
    e. Diagnosis
    f. Treatment
20. Describe the genetic disorder sickle cell anemia. In your answer include the following:
    a. Describe the symptoms
    b. Recessive or dominant disease
    c. What the mutation changes in the cell
    d. Diagnosis
    e. Treatment
21. Describe the genetic disorders of albinism, Hemophilia, PKU, Tay Sachs Disorder, Down's Syndrome and Turner's Syndrome. In your answer include the following:
    a. Describe the symptoms
    b. Recessive or dominant disease
    c. What the mutation changes in the cell
    d. Diagnosis
    e. Treatment