

GENETIC IMPLICATIONS

Some Human Genetic Disorders caused by Gene Mutation

1. **Autosomal Recessive disorders** - (read p. 555) one in which the disorder is caused by a recessive allele. Person must have homozygous recessive genotype to have disorder . The allele is carried on autosomes.

Examples:

(A) **Tay Sach's** (p. 555)

symptoms: brains and spinal cords begin to deteriorate by age 8 months. Children are blind, mentally handicapped and have little muscle movement by age one. Most die by age 5.

what causes it: lack an enzyme in the lysosomes of their brain cells so certain lipids cannot be digested in the brain cells. These build up in the lysosomes, causing them to enlarge and destroy the brain cell . (see fig. 16.31, p. 555)

treatment: none available

(B) **PKU** (p. 556)

symptoms: The enzyme that is supposed to convert the amino acid phenylalaline does not work properly so phenylalaline builds up in the brain causing mental handicap within a few months of birth..

What causes the disorder: Person cannot produce the enzyme which digests the amino acid phenylalaline.

Treatment: a diet free of any foods containing phenylalaline for the first 3 years of life until the brain tissue it affects is developed and then follow a diet low in phenylalaline for the rest of their lives. This means eating foods low in protein.

2. **Co- dominant inheritance genetic disorders** - (p. 556) person who has the complete disorder must have two alleles for the disorder. The allele is codominant with the normal allele so carriers have both characteristics.

Example: Sickle Cell Anemia (p. 556)

Symptoms: Sickle - shaped red blood cells. The abnormal shape of the RBC's is because of the abnormal shape of their hemoglobin protein. The improper shape of the RBC's often causes them to block off blood vessels, restricting blood flow to organs. This causes severe pain in these areas. The sickle - shape of the RBC's also causes the RBC's to break apart easily. They cannot be replaced as fast as they break down and this causes **anemia**. Persons have little energy, are in constant pain and may die young.

What causes the disorder: A mutation in the gene responsible for coding to form the protein hemoglobin.

Hemoglobin - a protein in red blood cells responsible for transporting oxygen.

Special Note: Persons heterozygous for this trait (carriers) have **some normal and some abnormal** hemoglobin but are able to lead a normal life. They have an increased risk of heart attack **BUT** they have a resistance to the disease Malaria. Since the disease originated in Africa, this means that persons who were heterozygous had a survival advantage over normal persons.

3. **autosomal dominant genetic disorders** - (p 557) allele causing disorder is dominant to the normal allele. (eg. Huntington's disease, Progeria). **This means that the child of such a person has a 50% chance of inheriting the faulty gene.**

Examples:

(A) **Huntington's Disease (p. 558)**

symptoms: lethal disorder in which the brain progressively deteriorates over a period of about 15 years. Early symptoms are irritability and mild memory loss. Late symptoms are loss

of movement, memory, speech. Often appears after age 35. Most die in their 40's.

Special Note: Doctors can discover if you have the gene for this disorder by doing a test. Many people who develop Huntington's have already had children by this age and may have passed the deadly gene on to their children.

(B) **Progeria** (p. 557)

symptoms: person ages rapidly. Growth fails, producing smaller bodies with larger heads. Lifespan is very short, often only into their late teens and early 20's. Children with Progeria are genetically predisposed to premature, progressive heart disease. As with any person suffering from heart disease, the common events for Progeria children are strokes, high blood pressure, angina, enlarged heart, and heart failure, all conditions associated with aging.

What causes the disorder: not fully known yet.

Special note: the progeria gene has been discovered!!! This research was linked to researching heart disease, the leading cause of death worldwide. *"A better understanding of the causes of this syndrome (Progeria) could lead to better insights into the mechanisms of both development and aging."* - *National Institute of Aging Associate Director Dr. Huber Warner*

4. incomplete dominance genetic disorders - (p. 558) normal allele and abnormal allele show incomplete dominance.

Example:

FH (high bad cholesterol (LDL) that "runs" in families)

symptoms: persons with two genes for FH have 6 times the normal levels of cholesterol. Heterozygous persons have about twice the normal levels. This can lead to atherosclerosis and heart attack. Homozygous individuals with both FH genes can have heart attack by age 2. Heterozygous individuals by age 35.

What causes the disorder: the normal gene codes for making cell membrane receptor proteins which accept cholesterol. The

faulty gene (FH) does not make the receptors correctly, therefore the person's cells cannot take cholesterol out of the blood.

5. X - Linked recessive inheritance genetic disorders (p. 558 - 559)

-- recessive, abnormal allele carried on the X chromosome but not on the male Y. Recall: **more common in males** - do you remember why?

(eg. Muscular Dystrophy, Hemophilia, Colour Blindness). The sons of carrier females each have a 50% chance of having the disease, and the daughters each have a 50% chance of being carriers.

Examples:

(A.) Duchenne Muscular Dystrophy

Symptoms: Symptoms usually appear before age 6 and may appear as early as infancy. Deterioration of the muscles; physical weakness which leads to eventual paralysis and death by early late teens. Survival beyond age 25 is rare.

What causes the disorder: an abnormal gene for making dystrophin (a protein in the muscles)

Treatment: none available.

Special note: the gene causing the disorder has been located and may lead to a treatment or cure in the future.

(B) Hemophilia

What causes the disorder: Hemophilia is a disorder in which one or more of the plasma proteins needed to form a clot is missing or reduced.

Symptoms: When a person with hemophilia is injured, he (or, occasionally, she) does not bleed harder or faster than normal, but will have prolonged bleeding because he cannot make a firm clot. Small cuts on the skin are usually not a problem, but bleeding in any deeper

area can be prolonged. Some bleeding episodes occur as a result of injury, but many occur seemingly without cause.

(C) **red - green colour - blindness** (p. 558)

symptoms: Person cannot distinguish between shades of red and green.

what causes it: recessive allele on the X chromosome which does not allow a person to detect color in this range.

Pedigree Charts

-see pp.544, 558, 560 -562

-a diagram that illustrates the genetic relationships between a group or related individuals. It can be used to determine if a trait is autosomal dominant, autosomal recessive or sex - linked. Researchers look for patterns in the inheritance pattern.

-squares represent males, circles females. Shading is used to represent those who are recessive or dominant for a trait. Half - shading may indicate a person is a carrier.

-see **fig. 16.17, p. 544.** This shows shading keys examples.

-see **p. 560.- pedigree of Queen Victoria's Royal family** following the inheritance of hemophilia. This shows the inheritance of a sex - linked disorder.

-do "The Case of the Caped Murderer", p. 561.

-do # 9, 10, 11, 12 on p. 562.

-do pedigree worksheets

-do extra examples of Public exam problems or lab from old 3201 course.

Genetic Engineering

genetic engineering - the use of recombinant DNA and cloning techniques to manipulate the genes of organisms.

Genetic Counselling

genetic counsellor - study the medical histories of couples and their families and help parents - to - be by advising them of the frequencies of genetic disorders within affected families and helping them determine the probable risk of having a child with a disorder.

-used by persons who have knowledge of genetic disorders in their family tree.

Methods of Detecting Genetic Disorders (pp. 607 - 608)

1. **Amniocentesis**- a needle is inserted into the amniotic sac and amniotic fluid is withdrawn. Allows karyotype to detect any chromosomal disorders. (monosomy, trisomy, etc.)
- can't be done until 14 weeks after pregnant
2. **CVS** - (chorionic villi sampling) fetal cells are removed from the chorion membrane. allows karyotype to detect chromosomal disorders.
- can be done as early as 9 weeks.
3. **fetoscopy** - an endoscope is surgically inserted into the abdomen and the fetus is viewed for visible abnormalities .
4. **genetic markers** -

genetic marker - a known sequence of nucleotides on DNA that is always found close to a gene that causes a disorder or is a sequence of DNA nucleotides that is actually part of the faulty gene.

- We now know genetic markers for several genetic disorders. Finding a genetic marker present can diagnose a genetic disease in a fetus.

-Genetic markers are found using a **genetic probe**.

genetic probe - This is a radioactive piece of DNA that has the complimentary sequence to the DNA marker

-DNA extracted from the fetus is prepared by forcing it to unzip. It is then mixed in a solution with the complimentary genetic probe. If the probe binds to the genetic maker site, then the fetus has that disorder. The radioactivity lets the scientists track the DNA.

Methods of Treating Genetic Disorders. (pp. 609 - 612)

1. **screening and prevention** - routine screening procedures at birth using special biochemical procedures can detect disorders such as PKU early enough so that treatment may be possible.
2. **Surgery** - reconstructive surgery may be possible to repair heart defects, cleft palates, etc.
3. **environmental control** - minimize the effects of the symptoms by not exposing the person with the genetic disorder to things in the environment that worsen

their condition. e.g. persons with albinism must limit their exposure to light because they do not produce any skin pigment melanin. A lactose intolerant person avoids dairy products, etc. A child with PKU avoids all foods that can harm him/her.

4. **gene therapy** - is a medical procedure in which normal or modified genes are transferred into the defective cells of a person. In theory, the normal genes will allow the cells to function normally again and properly produce the polypeptide that they cannot. Viruses are used to deliver the genes to the cells. A virus is modified to carry the good gene. The virus is then allowed to infect the “target “ cells. Because of the way viruses reproduce , the gene would become part of the cells DNA and hopefully function properly.

see fig 18.5, p. 610.

- p. 610 - read the case of the 30 year old Quebec woman who received gene therapy in 1992 and made genetic history therapy

To date, gene therapy has not produced any cure for genetic disorders however breakthroughs are just around the corner.

Some Techniques Used in Genetic Engineering (pp. 613 - 618)

1. **restriction enzymes** - these enzymes recognize a specific, short sequence of nucleotides on a strand of DNA and cut the strand at a particular point in that sequence. The same enzyme will cut a strand of DNA the same way each time. The smaller fragments they leave behind are called **restriction fragments**. This is why they are called “DNA scissors”.

Most restriction enzymes produce a staggered cuts that leaves a few unpaired nucleotides remaining on a single strand at each end of the restriction fragment. (see fig. 18.8, p. 614). These unpaired ends are called “**sticky ends**”.

2. **recombinant DNA** - segments of DNA from two different species that are joined in the lab to form a single molecule of DNA. This is done with the aid of restriction enzymes (DNA scissors) . The resulting restriction fragments’ will have stick ends. They are then mixed together, causing the DNA from the two species to form complimentary bonds and combine.

3. **DNA amplification** - the process of generating a large sample of a target DNA sequence from a single gene or DNA sequence.

DNA can be amplified in 2 ways:

- (i) Cloning using a bacterial vector (p. 614)

Plasmid - small loops of DNA found in bacteria that are separate from the main chromosome.

cloning vector - a molecule that replicates foreign DNA within a cell.

see fig. 18.9, p. 615.

Plasmids can be transferred from one bacteria to another during sexual conjugation. Scientists can use this mechanism as a tool to introduce produce large numbers of duplicate sequences of DNA. The plasmid is used as a cloning vector. First, they separate the DNA sequence its chromosome and then splice it into a plasmid. This process relies on the use of restriction enzymes. The target DNA sequence is cut by a restriction enzyme and produces sticky ends. The same restriction enzyme is then used to cut the bacterial plasmid DNA. Secondly, they insert this plasmid, with its recombinant DNA, into a bacteria. Each time this bacteria reproduces, the DNA sequence will be reproduced as well.

- (ii) **polymerase chain reaction (PCR)**

An almost entirely automated method of replicating DNA that allows researchers to target and amplify (copy over and over) a very specific sequence within a DNA sample.

- see fig. 18.10, p. 615

- relies on the action of specially developed heat resistant DNA polymerase enzyme.

Steps:

1. sample DNA is placed in a solution along with free nucleotides and primers.
2. solution is heated to split base pairs; helix opens up

3. solution is cooled
 4. heat resistant polymerase is added and DNA replication begins; takes one minute to finish
 5. mixture is reheated and the cycle repeats itself.
4. **Gel electrophoresis** - a process used to separate molecules according to their mass and electrical charge. This process allows fragments of DNA to be separated so that they can be compared.

- see fig 18.11, p. 617

Steps:

1. DNA is applied to one end of a gel
2. electrical current is passed through the gel
3. ends of gel become polarized
4. DNA has a negative charge so it drifts towards the gel's positive end
5. the smaller fragments move more quickly, causing the fragments to eventually separate into a pattern of bands called a **DNA fingerprint**.

DNA fingerprint - pattern of bands formed by using gel electrophoresis on DNA fragments.

DNA fingerprints are analysed to solve crimes. In order to get enough DNA to work with, DNA amplification is often necessary. This involves the use of restriction enzymes, bacterial vector cloning and polymerase chain reaction.. Then, electrophoresis does the rest to catch the bad guy!

do thinking lab, p. 616.

5. **DNA sequencing** -the process of determining the sequence of nucleotides in a DNA fragment.

-replicated DNA is synthesized in a series of small fragments rather than on one strand. Uses a modified polymerase chain reaction.

-nucleotide that ends each fragment is tagged with a radioactive or fluorescent marker.

-when fragments are run on an electrophoresis gel, can identify the base each fragment ends with

-once all strands are analysed, the information is pieced together and the whole sequence can be determined.

The Human Genome Project (p. 618)

- completed in 2001
- combined work of thousands of researchers from thousands of labs around the world.

- has determined the complete nucleotide sequence of human chromosomes.

- gives us a better understanding of genes and what they do.

Discovered 3 very Important details:

- (1) 99.9% of all human DNA is identical. (differences in individuals result from variations in fewer than 1000 nucleotides in each individual's genome)

- (2) human genome **only contains 35,000 genes** (not the expected 100,000!!!)

- (3) human body produces over 100,000 proteins, so this means that , on average, each gene can synthesize 3 proteins.

Risks and Benefits to Society of Applying the Knowledge of the HGP

- see text p. 619.

Risks:

1. privacy -eg. could companies get access to your genetic profile and use it against you in hiring (eg. you have a genetic disease)?

2. financial - eg. could a company that has worked on a gene associated with breast cancer prevent others from using this information?

3. ethical - eg. companies can benefit from genetic information gathered from populations of people - but who really owns this information? Newfoundland has a unique gene pool with a strong founder's effect - our gene pool has remained relatively unchanged for some time and has a high incidence of several genetic disorders. This is a valuable resource for companies doing genetic research. see p. 620
 - anger at companies who have sold this info. without permission
 - anger at companies who have not shared the wealth with NL

Benefits:

1. knowledge of the chances of a person getting sick in the future; if they carry a disorder.
2. analysis, prevention and treatment of diseases.

GMO's and GMF's.

GMF's - genetically modified foods.

E.G.

1. corn and canola - ½ production contains recombinant DNA
eg. herbicide resistant corn has been developed by implanting a bacterial gene into corn that provides resistance to herbicides, which are sprayed to kill weeds, but the corn won't be hurt.
2. golden rice - was genetically engineered to produce higher amounts of vitamin A and iron to help malnourished people in developing countries where the incidence of disorders linked to vitamin A and iron deficiencies is high.
3. transgenic salmon - the fish are genetically engineered to grow to harvest size much faster than normal salmon do.

GMO's - genetically modified microorganisms

Examples of GMO's:

1. genetically engineered bacteria which have the cattle gene for growth hormone spliced into them. The hormone is produced cheaply this way. Cattle in the USA today have increased milk production due to the growth hormone somatotrophin given to them
2. insulin producing bacteria - in 1982 human insulin was produced by genetically engineered strain of bacteria into which they spiced the human gene for producing insulin. Today, all insulin for diabetes treatment is

produced by these bacteria.

4. PCB eating bacteria - PCB's are dangerous and toxic compounds used in industry which can bioamplify in food chains. Scientists are experimenting with a bacteria designed to break PCB's down into harmless compounds in the soil.
5. oil eating bacteria - have been genetically engineered to help clean up oil spills. The hardest places to clean up are beaches where oil has come ashore. These bacteria can live in this environment and break down the oil.

DO: Have students identify and explain the major risks associated with GMO's and GMF's. Include: (a) environmental threats (b) health effects (c) social and economic issues (ref pp. 625 - 626)

Cloning (pp.627 - 629)

Cloning - the process used to make a genetically identical copy of an organism or part of an organism that has the same genetic make-up as the parent organism (ie making a clone)

Clone - a genetically identical copy of an organism or part of an organism that has the same genetic make-up as the parent organism.

- Genetically identical organisms, i.e. clones, have the same genotype (have identical traits)
- lab techniques are used to clone animals.
- Dolly the sheep was the first mammal cloned in 1997
- **Important: look at cloning process on p. 629, figure 18.22**

To produce Dolly, researchers first had to find a way to stop the cell cycle and "reverse" the process of differentiation. They wanted to restore the ability to differentiate to an undifferentiated cell.

process steps use to produce Dolly:

1. Unfertilized eggs are harvested; their nuclei are removed
2. Udder cells from a donor and their cell division chemically stopped
3. Udder cell nuclei transplanted into collected egg cells
4. Electric current is used to stimulate the egg cells to start division
5. Some eggs produce embryos.
6. Embryos are implanted into a surrogate mother sheep
7. One embryo survives to produce a clone, genetically identical to the genotype of the animal which donated the udder cells.

DO: Have students identify the benefits and risks (pros and cons) of cloning: Ref pp. 628 - 632. Students do a list of these.

- human cloning; therapeutic and reproductive
 - pros
 - **therapeutic cloning** - culturing of human cells for medical purposes. Would allow us to grow perfectly matched tissues/organs to replace damaged/diseased ones.
 - cons:
 - destruction of human embryos to get cells necessary
 - **reproductive cloning** - the production of a cloned human. Many moral, ethical and legal issues concerning this.
- **transgenic animals** - genetically engineered animals; produced by moving DNA from one organism to another to produce a new combination to achieve desired traits.
 - pros:**
 - more productivity and profit. Eg. Transgenic salmon are cold tolerant, grow faster and larger
 - cons:**
 - consumer safety; will consumption have long term effects?
 - safety of the biodiversity/gene pool of the natural salmon stock. Escaped transgenic salmon could breed with wild salmon and alter the gene pool. Already there is evidence that this would be a disaster. Transgenic fish could outcompete the wild stocks, altering nature and food chains.

DO: Have students identify and explain the following science - based careers related to the field of biotechnology:

(A) cytogeneticist (B) medical geneticist (C) genetic engineer

Cytogeneticists - are experts in studying chromosomes from samples of human blood, tissue, bone marrow or other bodily fluids, which is very important in diagnosing genetic diseases. The majority of the Clinical Cytogeneticists work revolves around three main categories:

1. Analysis of Genetic Material

The genetic material can be used in samples from, for example, newborn babies with abnormalities and their parents, patients who are infertile or whose secondary sexual development has failed or couple with reproductive difficulties.

2. Prenatal Diagnosis - Cells are examined for possible abnormalities in the foetus.

Medical Geneticists - evaluate, diagnose and treats genetic diseases - preparing and reviewing case histories and clinical records, and interviewing patients or parents to obtain clinical and family histories and constructs pedigrees. They examine patients, determine the need for laboratory or other testing, and interpret pedigrees, examination findings and test results.

Genetic Engineer - uses technologies to change the genetic makeup of cells to produce specific characteristics in organisms (eg. Splicing the human gene for producing insulin into bacteria so we have a cheap, fast source of producing insulin for diabetes).

Review: questions:

DO p. 633 # 1 - 5, 9 - 14

DO p. 634 # 16, 19, 21, 23, 27, 28