Genetic Disorders - Inheritance of Genetic Traits

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Brief History

- First there was Gregor Mendel, a monk who studied inherited characteristics. This was followed by Francis crick and James Watson who unraveled the DNA molecule. This has led us to understanding the human genome sequence.
    - 1866 - Gregor Mendel published the results of his investigations of the inheritance of "factors" in pea plants.
- Rosalind Franklin - 1950's
    - Maurice Wilkins, Rosalind Franklin, Francis H. C. Crick of Britain and James D. Watson of the U.S. Discover chemical structure of DNA, starting a new branch of science--molecular biology. .
- Watson and Crick made a model of the DNA molecule and proved that genes determine heredity
- Arthur Kornberg – 1957 - of the U.S. produced DNA in a test tube.
- Genetic code - 1966
    - The Genetic code was discovered; scientists are now able to predict characteristics by studying DNA.
    - This leads to genetic engineering, genetic counseling.
- Barbara McClintock of the U.S. was awarded the Nobel Prize (1983) for her discovery that genes are able to change position on chromosomes.
- DNA Fingerprinting - late 1980's.
    - An international team of scientists began the project to map the human genome.
    - The first crime conviction based on DNA fingerprinting, in Portland Oregon.
- Gene Therapy - 1990.
    - Gene therapy was used on patients for the first time.
- DNA Testing - 1995
    - DNA testing in forensics cases gains fame in the O.J. Simpson trial
- Cloning Begins - 1997
    - Dolly the sheep - the first adult animal clone.
- Human Genome Project
    - We now have the tools to make the whole world better through science , the science of the human genome.

Mutations

- Gene mutations can be either inherited from a parent or acquired.
- A hereditary mutation is a mistake that is present in the DNA of virtually all body cells.
    - Hereditary mutations are also called *germ line* mutations because the gene change exists in the reproductive cells and can be passed from generation to generation, from parent to newborn.
- Mutations occur all the time in every cell in the body.
    - Each cell, however, has the remarkable ability to recognize mistakes and fix them before it passes them along to its descendants. But a cell's DNA repair mechanisms can fail, or be overwhelmed, or become less efficient with age. Over time, mistakes can accumulate.

General Features of Chromosomal Disorders

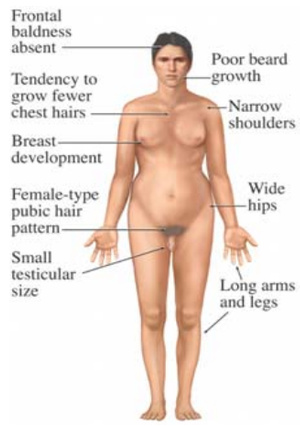
- May be caused by absence (deletion, monosomy), excess (trisomy), or abnormal rearrangements (translocations) of chromosomes.
- In general, loss of chromosomal material produces more severe defects than does gain of chromosomal material.
- Sex chromosomal disorders often produce subtle abnormalities, sometimes not detected at birth.
- Infertility, a common manifestation, cannot be diagnosed until adolescence.

Down's Syndrome or Trisomy 21

- Is the most common of the chromosomal disorders.
- Caused by non-disjunction of the 21st chromosome.
- Maternal age has a strong influence on the incidence of Down syndrome.
    - It occurs in 1 in 1550 live births in women younger than 20 years, in contrast with 1 in 25 live births in women older than 45 years.
- Is a leading cause of severe mental retardation; approximately 80% of those afflicted have an IQ of 25 to 50. Ironically, these severely disadvantaged children may have a gentle, shy manner and may be more easily directed than their more fortunate normal siblings.
- Approximately 40% of the patients have congenital heart disease
    - Most commonly septal defects, and valve malformations
- Children with trisomy 21 have a 10- to 20-fold increased risk of developing acute leukemia.
- Virtually all patients with trisomy 21 older than age 40 develop neuropathologic changes characteristic of Alzheimer disease.
- Patients with Down syndrome demonstrate abnormal immune responses that predispose them to serious infections.
- The diagnostic clinical features of this condition - flat facial profile, oblique palpebral fissures, and epicanthic folds - are usually readily evident at birth.
- Symptoms of Down Syndrome
    - Upward slant to eyes.
    - Small ears that fold over at the top.
    - Small, flattened nose.
    - Small mouth, making tongue appear large.
    - Short neck.
    - Small hands with short fingers.
    - Low muscle tone.
    - Single deep crease across center of palm.
    - Looseness of joints.
    - Small skin folds at the inner corners of the eyes.
    - Excessive space between first and second toe.
    - In addition, down syndrome always involves some degree of mental retardation, from mild to severe. In most cases, the mental retardation is mild to moderate.

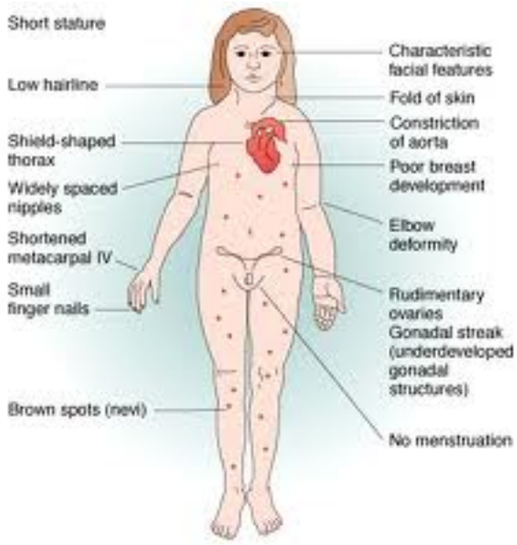
Kleinfelter's Syndrome

- Is best defined as male hypogonadism that develops when there are at least two X chromosomes and one or more Y chromosomes.
- The Sperm containing both X and Y combines with an egg containing the X, results in a male child. The egg may contribute the extra X chromosome.
- Males with some development of breast tissue normally seen in females.
- Little body hair is present, and such person are typically tall, have small testes.
- Infertility results from absent sperm.
- Evidence of mental retardation may or may not be present



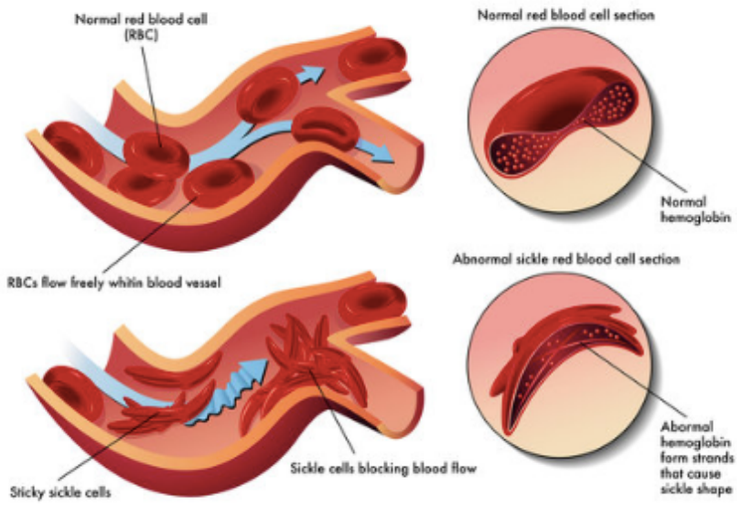
Turner's Syndrome

- Characterized by hypogonadism in females.
- The entire X chromosome is found to be missing in 57% of patients, resulting in a underdeveloped ovaries, short stature.
- Bull neck, and broad chest.
- Individuals are sterile, and lack expected secondary sexual characteristics.
- Mental retardation typically not evident.



Sickle Cell Anemia

- An inherited, chronic disease in which the red blood cells, normally disc-shaped, become crescent shaped. into a sickle shape.
- The cells die early, leaving a shortage of healthy red blood cells (sickle cell anemia), and can block blood flow causing pain (sickle cell crisis).
- As a result, they function abnormally and cause small blood clots.
- These clots give rise to recurrent painful episodes called "sickle cell pain crises".
- Treatments include medications, blood transfusions, and rarely a bone-marrow transplant.

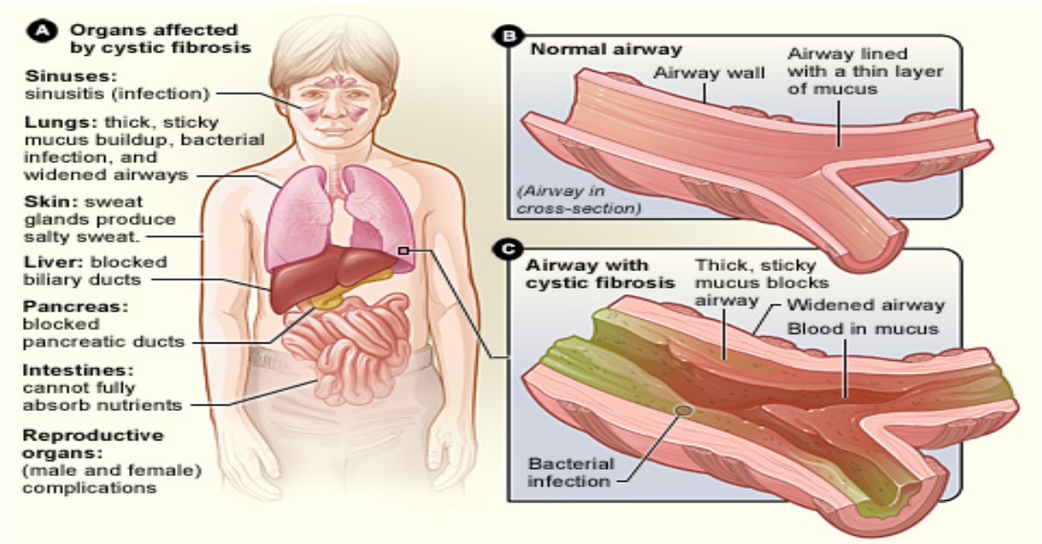


Cystic Fibrosis (CF)

- Inherited disease that causes thick, sticky mucus to build up in the lungs and digestive tract
- The most common type of chronic lung disease in children and young adults
  - 1 in every 3,300 – most children and teenagers
- Cardiopulmonary complications constitute the most common cause of death
- S & S
  - Pneumonitis, bronchiectasis, lung abscesses, pancreatic insufficiency
  - Chronic cough and sputum production
  - Persistent chest radiograph abnormalities (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
  - Airway obstruction manifested by wheezing and air trapping
  - Bronchiectasis and right-sided heart failure are long-term sequelae
  - Gastrointestinal abnormalities of meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
  - Liver disease, including cirrhosis, is increasing in frequency due to improved survival.

Cystic Fibrosis (CF) - continued

- Diagnosis
    - Established by the sweat electrolyte test
    - The principal defect is of chloride ion transport, resulting in high salt concentrations in sweat and in viscous luminal secretions in respiratory and gastrointestinal tracts.



Tay-Sachs Disease

- Tay-Sachs disease is a rare disorder passed from parents to child.
- In the most common form, a baby about 6 months old will begin to show symptoms.
- As the disease progresses, the child's body loses function, leading to blindness, deafness, paralysis and death usually before 2-3 years old.
- That happens because a fatty substance in the child's brain builds up to toxic levels and affects the child's nerve cells.
- There is no cure for Tay-Sachs disease.
- The disease is rare in the general population.
- In Ashkenazi Jews, French Canadians of southeastern Quebec, the Old Order Amish of Pennsylvania, and the Cajuns of southern Louisiana, the condition is more common.
- Approximately 1 in 3,600 Ashkenazi Jews at birth are affected.
    - About 1 in every 27 members of the Ashkenazi Jewish population carries the Tay-Sachs gene.

Muscular Dystrophy

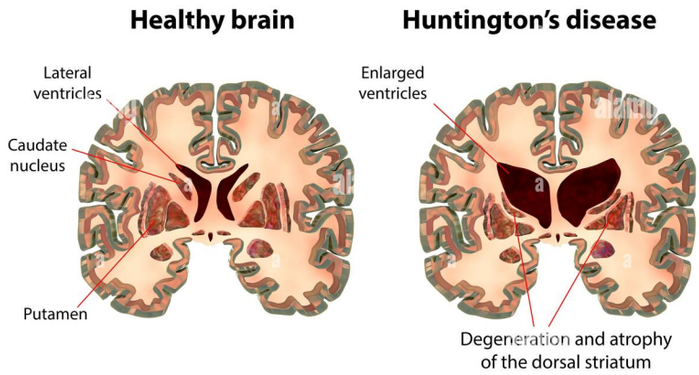
- Muscular dystrophy is a disease in which the muscles of the body get weaker and weaker and slowly stop working because of a lack of a certain protein
- Can be passed on by one or both parents, depending on the form of Muscular Dystrophy
    - Females will typically be carriers with males affected. Sons of carrier mothers have a 50% chance of inheriting the defective gene
    - Daughters of mother carriers have a 50% chance of being carriers
- Causes proximal muscle weakness
- Usually affects young boys with weakness of pelvic and shoulder muscles
- The affected muscles are large and bulky, but very weak because the muscle cells do not contract properly

Hemophilia

- Hemophilia is the oldest known hereditary bleeding disorder.
    - The New Testament of the Bible mentioned a woman who had hemorrhaged for 12 years, before touching the hem of Jesus' garment, when she was healed.
- Hemophilia is sometimes referred to as "the royal disease" because it affected the royal families of England, Germany, Russia and Spain in the 19th and 20th centuries.
    - Queen Victoria of England is believed to have been the carrier of hemophilia B, or factor IX deficiency. She passed the trait on to three of her nine children.
- A medical condition in which the ability of the blood to clot is severely reduced, causing the sufferer to bleed severely from even a slight injury.
- The condition is typically caused by a hereditary lack of a coagulation factor, most often factor VIII.
- There are about 20,000 hemophilia patients in the United States.
- One can bleed to death with small cuts.
- The severity of hemophilia is related to the amount of the clotting factor in the blood. About 70% of hemophilia patients have less than one percent of the normal amount and, thus, have severe hemophilia.

Huntington's Disease

- Huntington's disease (HD) is an inherited, degenerative brain disorder which results in an eventual loss of both mental and physical control.
- The disease is also known as Huntington's chorea.
- Chorea means "dance-like movements" and refers to the uncontrolled motions often associated with the disease.
- Most people with Huntington's disease develop signs and symptoms in their 40s or 50s, but the onset of disease may be earlier or later in life.
- When disease onset begins before age 20, the condition is called juvenile Huntington's disease.
- Earlier onset often results in a somewhat different presentation of symptoms and faster disease progression.



Phenylketonuria or PKU

- People with PKU cannot consume any product that contains aspartame.
- PKU is a metabolic disorder that results when the PKU gene is inherited from both parents.
- Caused by a deficiency of an enzyme which is necessary for proper metabolism of an amino acid called phenylalanine.
    - Phenylalanine is an essential amino acid and is found in nearly all foods which contain protein, dairy products, nuts, beans, tofu… etc.
- A low protein diet must be followed.
- Brain damage can result if the diet is not followed causing mental retardation…and mousy or musty body odor (phenylacetic acid is in sweat).
- Phenylalanine-free diet

ALS - Amyotrophic Lateral Sclerosis, or Lou Gehrig's Disease

- The disease strikes people between the ages of 40 and 70, and as many as 30,000 Americans have the disease at any given time.
- This mutation is believed to make a defective protein that is toxic to motor nerve cells.
- A common first symptom is a painless weakness in a hand, foot, arm or leg, other early symptoms include speech swallowing or walking difficulty.

Diabetes

- Disease in which the body does not produce or properly use insulin.
    - Insulin is a hormone that is needed to convert sugar, starches, and other food into energy needed for daily life.
- Genetic mutation can lead to Type 1 Diabetes.
    - If you are a man with type 1 Diabetes, the odds of your child developing diabetes are 1 in 17**.**
    - If you are a woman with type 1 diabetes and your child was born before you were 25, your child's risk is 1 in 25.
    - If your child was born after you turned 25, your child's risk is 1 in 100.
    - Your child's risk is doubled if you developed diabetes before age 11.
    - If both you and your partner have type 1 diabetes, the risk is between 1 in 4 to 1 in 10.
- Type 1 reveals itself in childhood an is referred to as Juvenile Onset Diabetes.
- Type 2 is referred to as adult onset diabetes is related to lifestyle.
- 3 classic symptoms – Polydipsia, Polyuria, Polyphagia
- Warning signs
    - Blurry vision from time to time
    - Unusual fatigue or drowsiness
    - Unexplained weight loss
    - Diabetes is the leading cause of kidney failure, blindness, and amputation in adults, and can also lead to heart disease.

Color Blindness

- The genes that can give you red-green color blindness are passed down on the X chromosome.
    - Since it's passed down on the X chromosome, red-green color blindness is more common in men.
    - 1/10 males have, 1/100 females have.
- Individuals are unable to distinguish shades of red-green.

Albinism

- Patients are unable to produce skin or eye pigments, and are light-sensitive.
- The cause of albinism is a defect in one of several genes that produce or distribute melanin, the pigment that gives skin, eyes, and hair their coloring.
- The defect may result in the absence of melanin production or a reduced amount of melanin production.
- The incidence rate in most populations is 1 in 40,000 births.
- The incidence rate in the USA is 1 in 17,000 births. Approximately 1 in 18,000 current cases in the USA.