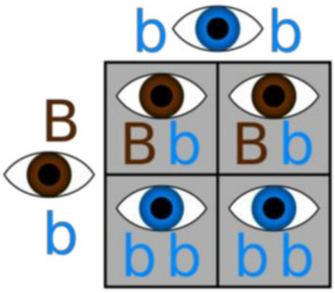
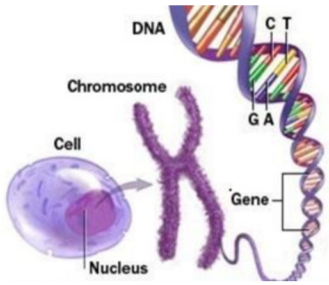
Pharmacogenetics & Pharmacogenomics

High Yield



Concepts:
gene, chromosome, genotype and phenotype

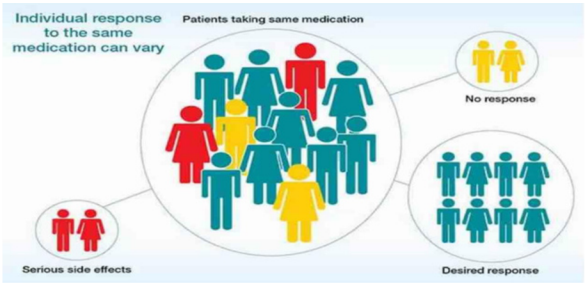


- Genomics – The study of genetic material found in a cell (DNA)
- Pharmacogenomics – is a branch of pharmacology concerned with using DNA data to explain individual variations in drug response.
- Pharmacogenetics– The study or clinical testing of genetic variation affecting individual patients different response to drugs

> Personalized medicine: the tailoring of medical treatment to the specific characteristics of each patient. (right patient, right drug, right dose)

Goal :

- To develop precisely targeted, optimal drug therapy (personalized medicine)
- Minimizing drug related adverse effects



Genetic polymorphism

- Variations in human genome that occurs in 1% of population

Types

1- Single nucleotide polymorphisms(SNPs)

- The most common variation in human DNA
- Each SNP represents a difference in a single DNA building block, called a nucleotide

Example: the substitution of a C for a G in the nucleotide sequence AACGAT, thereby producing the sequence AACCAT

- SNPs in non-coding regions can manifest in a higher risk of cancer
- SNPs in coding regions:
- Silent substitutions do not result in a change of amino acid sequence (silent mutation)
- Non-silent substitutions
- missense– single change in the base results in change in amino acid of protein and its malfunction which leads to disease
- nonsense– mutation in a sequence of DNA that results in a nonsense codon in the transcribed mRNA,

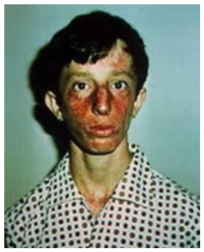
nonfunctional protein product (e.g. Cystic fibrosis mutation in the cystic fibrosis transmembrane conductance(regulator gene)

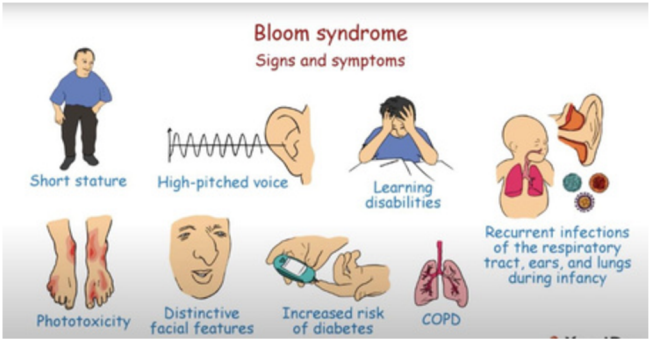
2- Indel (insertion-deletio)

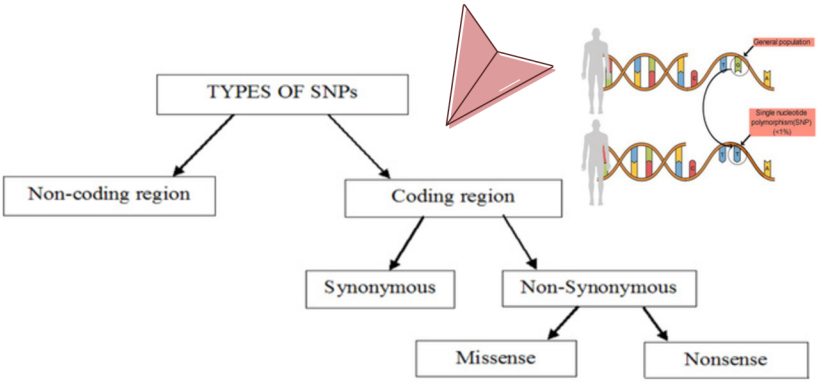
- an insertion or deletion of bases in the genome of an organism

Example:

- causes Bloom syndrome in the Jewish or Japanese population







Pharmacogenomic polymorphism

•Affected genes lead to different phenotypes with modified response and adverse effects to certain drugs:

1- Pharmacokinetic polymorphism
2- Pharmacodynamics polymorphism
3- Polymorphism modifying underlying disease

1 Polymorphisms modifying PKs

• Cytochromes P450 (P450s or CYPs) are a family of enzymes
• Mainly found within the endoplasmic reticulum and mitochondria of liver cell
• They are also found in many other cells of the body
• These membrane-bound proteins are involved in the metabolism of many harmful substrates, such as toxins.
• Of all the different CYP proteins that are present in the human body, 6 of them are involved in the metabolism of 90% of drugs
• The most important are CYP3A4, CYP2C9, CYP2C19 and CYP2D6
• Changes in genes controlling CYP enzymes can make them: more active or less active than normal, or completely inactive

Succinylcholine (scoline) apnea

SCH is rapidly hydrolyzed by butyrylcholinesterase (BCHE, also known as plasma cholinesterase and pseudocholinesterase), which is synthesized in the liver and present in plasma (duration of action: 5 min.)

• Succinylcholine or scoline apnoea, occurs when there are abnormalities in plasma cholinesterase and the body has difficulties in the drug leading to prolonged muscle paralysis and respiratory failure (death)

Rapid and slow acetylators of INH

• The rate of drug acetylation is influenced by genetic factors(hepatic acetyltransferase gene).
• Hepatic acetyltransferase metabolizes INH
• Individuals who are phenotypically slow acetylators are have a higher risk of hepatotoxicity than do rapid acetylators

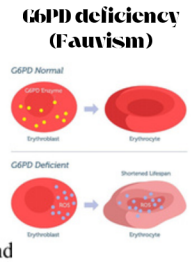
Examples of pharmacokinetic polymorphism

• Clopedogril (anticoagulant, inhibiting platelet aggregation): 85% metabolized by an esterase to inactive metabolite and 15% metabolized by CYP2C19 to active metabolite.
• CYP2C19 poor phenotype: poor anticoagulant action of clopedogril: blood clotting
• Antidepressants: metabolized by: CYP2D6:
• Poor phenotype: increased antidepressant toxicity
• Ultra-rapid phenotype: decreased efficacy

2 Polymorphisms modifying PDs

• Beta-Adrenergic Receptors Gene Polymorphisms alter response to bronchodilators
• Serotonine receptor gene polymorphisms affect response to antidepressant drugs

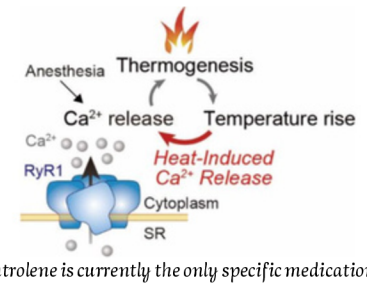
3 Polymorphisms modifying diseases and drug responses



• G6PD deficiency (Fauvism)
• Genetic disorder that causes G6PD deficiency
• More in males
• G6PD protect RBCs against oxidizing agents: antibiotics, antimalarial drugs (chloroquine), aspirin, some anti-cancer medicines and large doses of vitamin C, some foods, particularly fava beans, certain infections
• These agents destroy RBCs causing hemolysis and anemia which can be life-threatening

Malignant hyperthermia (MH)

• MH is a type of severe reaction that occurs in response to particular medications used during general anesthesia (volatile anesthetic agents and succinylcholine) in susceptible individuals.
• Symptoms include muscle rigidity, fever, and tachycardia
• Complications can include muscle breakdown and high blood potassium
• Due to genetic mutations in RYR1 gene
• Ryanodine receptor 1 (RYR1): functions as calcium release channel in the sarcoplasmic reticulum
  • In susceptible individuals, the medications induce the release of stored calcium ions within muscle cells.
  • The resulting increase in calcium concentrations within the cells cause the muscle fibers to contract.
• This generates excessive heat and results in metabolic acidosis



• Dantrolene is currently the only specific medication used for treating a malignant hyperthermia crisis

• **Mechanism of action:**
• Antagonizing the ryanodine receptors, which lessens the excitation-contraction coupling of muscle cells

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إلا ما سعى ♥

Done by :
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