Pharmacogenetics & pharmacogenomics

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Objectives

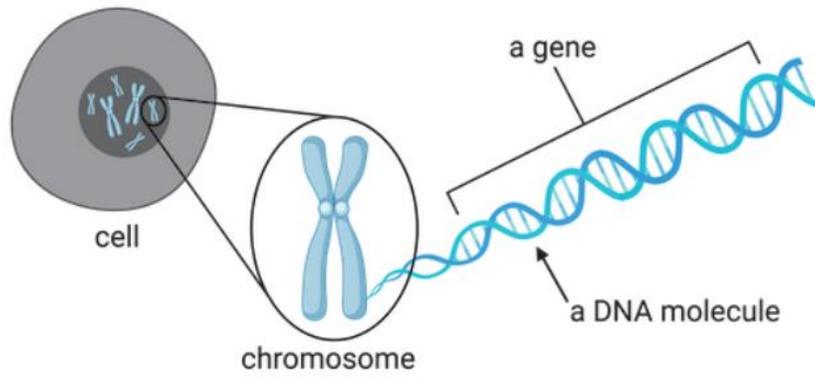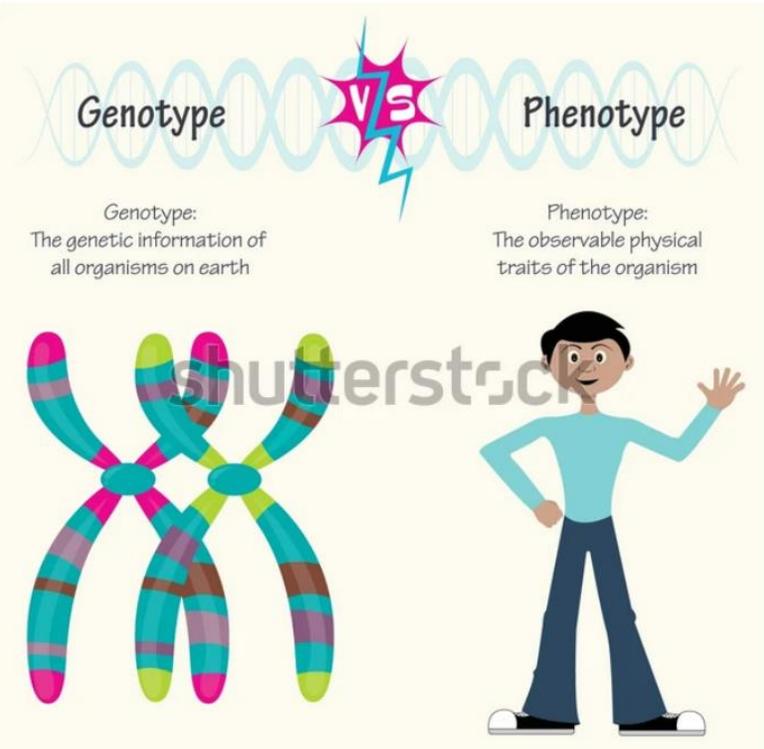- What is pharmacogenetics (pharmacogenomics)?
- Importance of pharmacogenetics
- Define genetic polymorphism
- Types of genetic polymorphism
- Polymorphism affecting pharmacokinetics
- Polymorphism affecting pharmacodynamics
- Polymorphism affecting underlying disease and adverse drug reactions

Concepts: gene, chromosome, genotype and phenotype
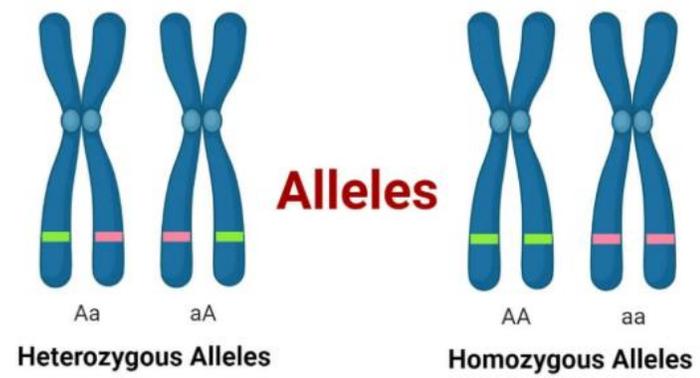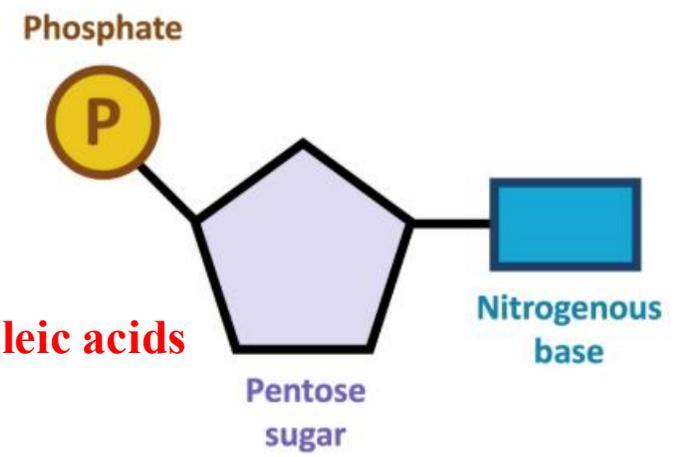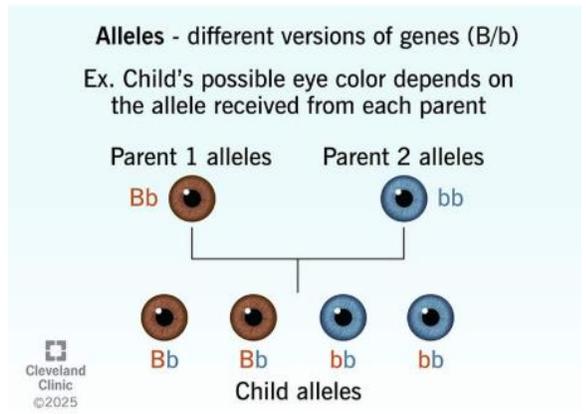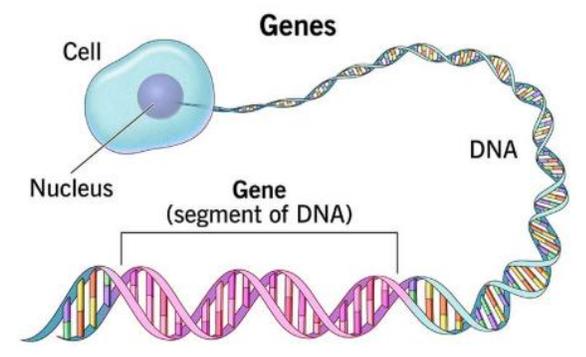
Nucleotide: building block of nucleic acids

Pharmacogenomics & pharmacogenetics

- **Genomics** – The study of genetic material found in a cell (DNA)
- **Pharmacogenetics** focuses on **how a single gene affects a drug's response**: examines **single gene-drug interactions** (monogenic),
- **Pharmacogenomics** is broader, **studying how an entire genome and its interactions influence how a person responds to medications:** considers multiple genes and their complex interactions (**polygenic**)

Example of pharmacogenomics studies

- Polygenic pharmacogenomic research is an emerging field that uses **polygenic risk scores (PRS)** to predict **how an individual will respond to a drug** based on the **cumulative effect of many genetic variants**

- **Beta-blockers**:

- A PRS has been used to **identify heart failure patients** who are more likely to have a **significant survival benefit from beta-blocker treatment** (**personalized medicine**).

Individual response to the same medication can vary

Patients taking same medication
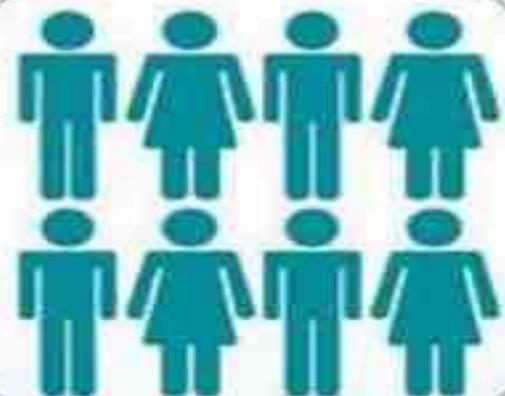
No response

Serious side effects

Desired response

Genetic polymorphism

- Variations in human genome that occurs in **1% of population**
- **Types of genetic polymorphism**:
- 1- Single nucleotide polymorphisms (SNPs): change (substitution) in the **single-nucleotide** of a genome (type of mutation)
- 2- Indel (insertion-deletion)

Types of SNPs

SNPs

SNPs in coding regions

SNPs in non-coding regions:
markers that help scientists locate genes associated with diseases: cancer, schizophrenia

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

Non-sense mutation: in a sequence of DNA that results in a nonsense codon in the transcribed mRNA, nonfunctional protein product (e.g. Cystic fibrosis)

Regulatory region   Coding region

Promoter

TACGCTGATCTGC
AUGCGACUA mRNA
ATGCGACTAGACG

Significance of SNPs in medicine

- **1- Drug response**: Certain SNPs are associated with how a person may respond to specific drugs, which is important for **personalized medicine.**

- **2- Predicting adverse reactions**: SNPs have been linked to adverse reactions like hemolytic anemia.

- **3- Drug discovery and development**: Companies use genetic information from drug trials to identify **patients who are more likely to respond positively,** making the development of new drugs faster and more cost-effective.

- **4- Understanding disease**

Indel (insertion-deletion)

• **Random removal or addition** of **nucleotides** from a **DNA sequence** (**insertion or deletion of bases**)

• This can be enough to **stop a gene from functioning**

• **Mechanism**: Indels occur when DNA is broken and "sloppily" repaired by the cell in a process called **non-homologous end joining (NHEJ).**

• **Example**:

• **Bloom syndrome** in the **Jewish** or **Japanese population**.

• A rare, inherited disorder characterized by **growth deficiency**, a **sun-sensitive skin rash,** and a **high risk of developing various cancers early in life**.
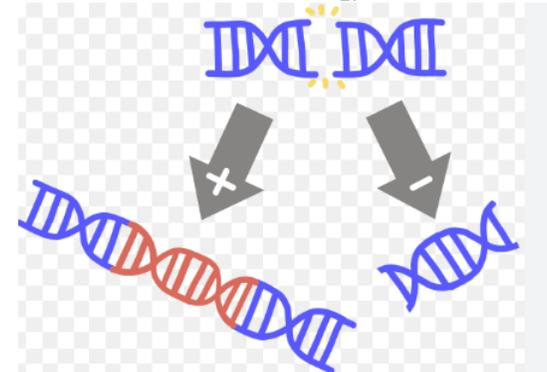
Pharmacogenomic polymorphism

•**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

Genetic polymorphism affecting drugs
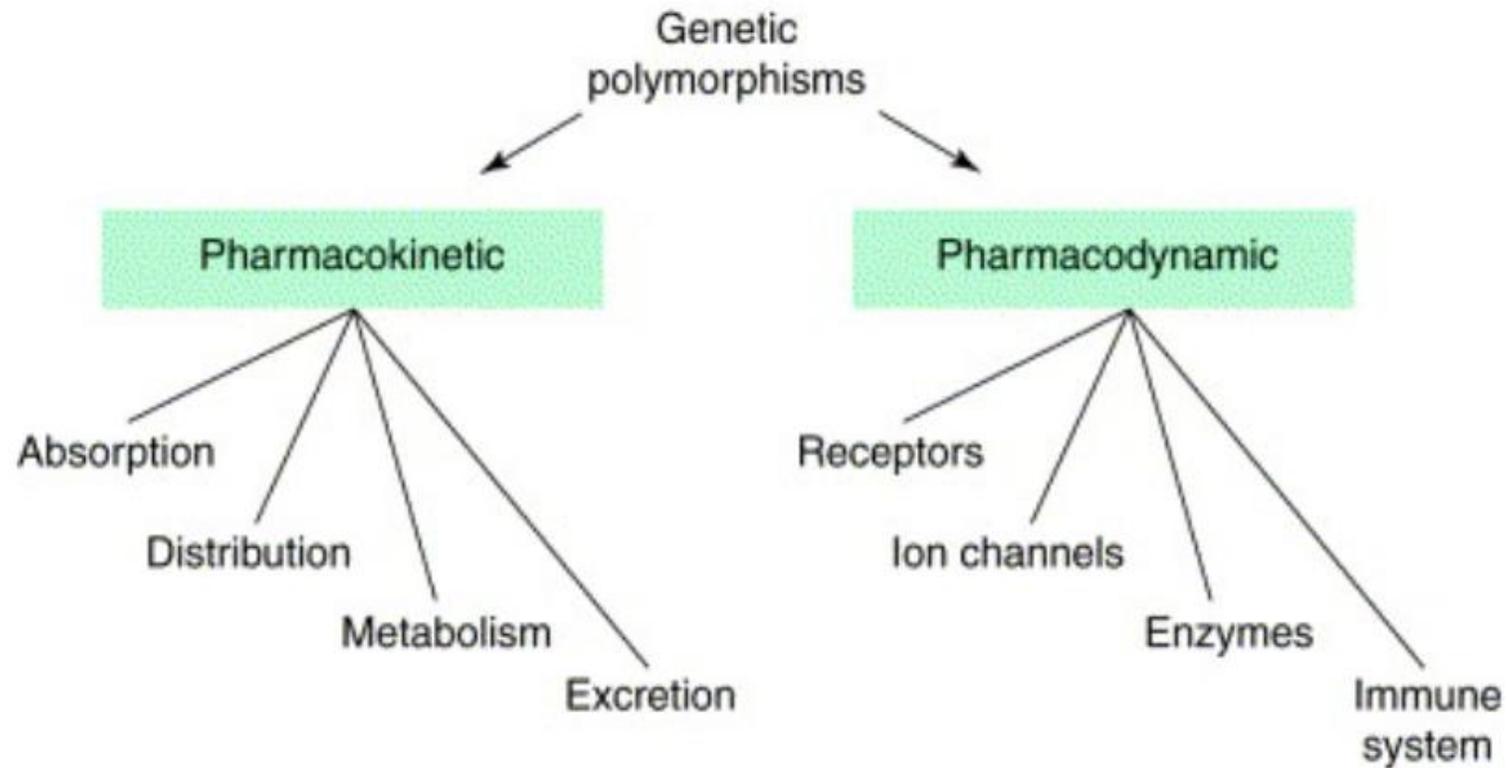
Polymorphisms modifying PKs

- **Cytochromes P450 (P450s or CYPs)** are a family of enzymes

- Mainly found within the **endoplasmic reticulum and mitochondria of liver cells.**

- 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 and drugs.**

- 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 CYP**3A4**, CYP**2C9**, CYP**2C19** and CYP**2D6**.

- **Changes in genes controlling CYP enzymes** can make them: **more active** or **less active** than normal, or **completely inactive**

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 (thrombosis)
- **Codeine:**
- Genetic polymorphism in the **CYP2D6** enzyme affect how a person metabolizes codeine into its active form (morphine).
- **Fast metabolizers: excessive side effects**
- while **poor metabolizers: in**adequate pain relief.

Succinylcholine (scoline) apnea

- **Definition**: prolonged paralysis of the respiratory muscles that can occur after a patient receives the **muscle relaxant succinylcholine**

- **Cause**: **deficiency in the enzyme pseudocholinesterase** (also known as butyrylcholinesterase). (duration of action: 5 min.)

- This deficiency can be **hereditary** or **acquired** through conditions like **liver disease or pregnancy**.

- When this happens, the body cannot break down the drug as quickly as usual, and the **muscle paralysis can last for hours instead of minutes**.

- **Treatment:**

- 1- **Mechanical ventilation** until the drug is metabolized and breathing can resume

- 2- Keeping the patient **sedated and comfortable**.

- 3- **Fresh blood transfusion**

Rapid and slow acetylators of INH

- **The rate of drug acetylation** is influenced by genetic factors (**hepatic acetyltransferase gene**).

- **Hepatic acetyltransferase** metabolizes **INH (isoniazid)**

- **Genetic variation in the activity of N-acetyltransferase: resulting in two types**: **slow acetylators**, **who have decreased or absent enzyme activity, and** **fast acetylators**, **who possess normal or increased enzyme activity.**

- Individuals who are **phenotypically slow acetylators** are have a **higher risk of hepatotoxicity** than do rapid acetylators.

Polymorphisms modifying PDs

- **Beta-Adrenergic Receptors** Gene Polymorphisms alter response to **bronchodilators (tachyphylaxis to salbutamol)**

- **HER2-positive breast cancer:**

- **Genetic testing for the HER2 receptor is used to see if a patient's tumor has high levels of it.**

- **If it does, drugs like trastuzumab (Herceptin) can be used to target and kill the cancer cells.**

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Polymorphisms modifying PDs

- **Abacavir (antiviral drug):**
- A genetic test for the **HLA-B*5701 gene** is used before prescribing the **HIV drug abacavir** to identify patients at a high risk of a potentially fatal hypersensitivity reaction.

# Polymorphisms modifying diseases and drug responses

- **G6PD deficiency (Fauvism)**
- Genetic disorder that causes **G6PD deficiency**
- **More in males**
- **G6PD function:**
- Protecting RBCs against oxidizing agents:
- **antibiotics**
- **antimalarial drugs** (chloroquine)
- **anti-cancer drugs**
- **Aspirin**
- **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.**

G6PD deficiency (Fauvism)
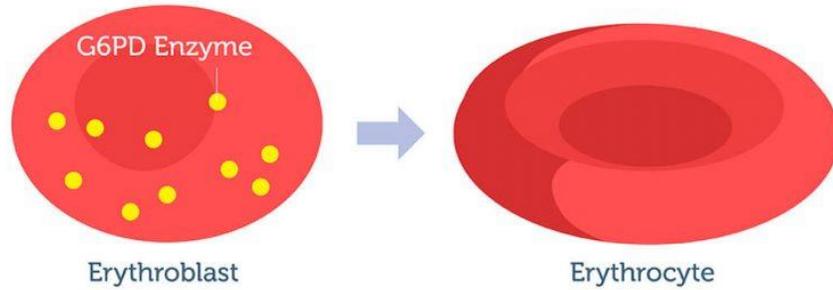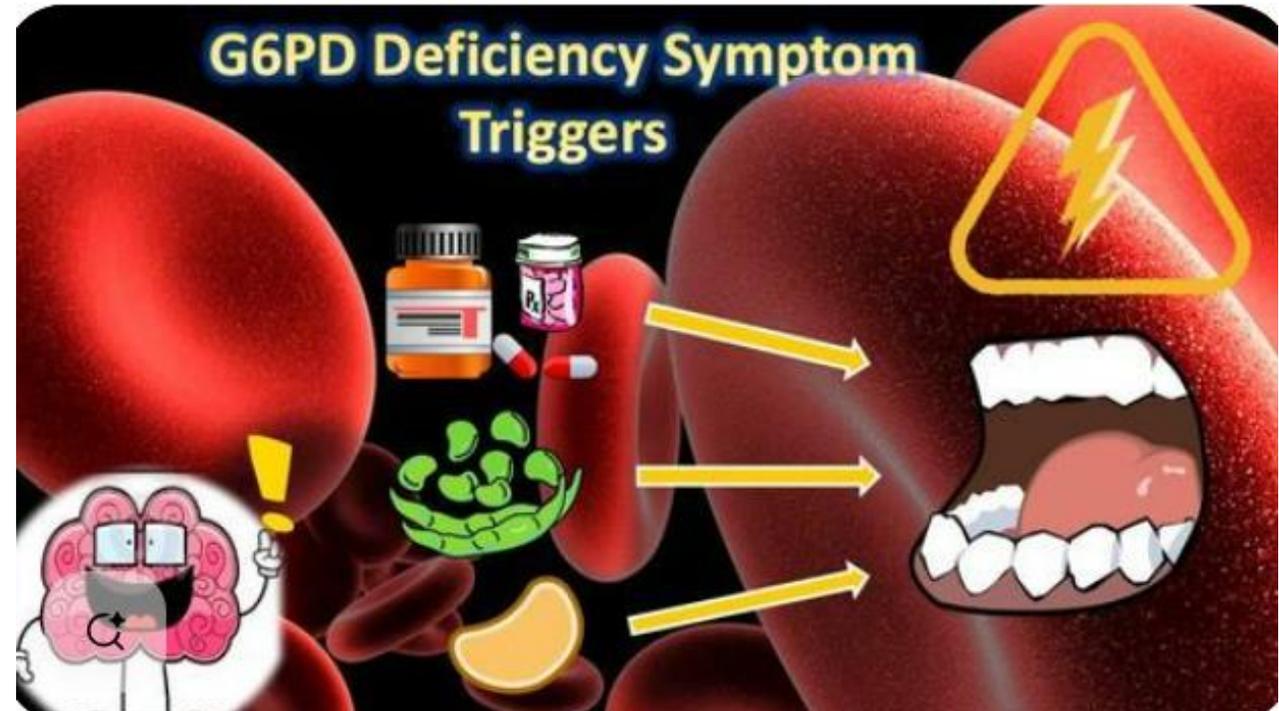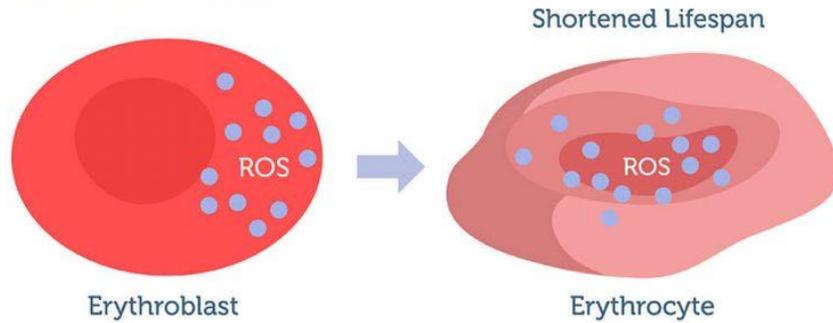
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Thank you