

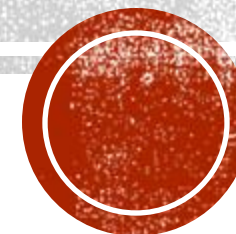


PHARMACOGENETICS & PHARMACOGENOMICS

Dr. Nashwa Aborayah

Associate professor of clinical and experimental pharmacology

Mu'tah University- Faculty of Medicine

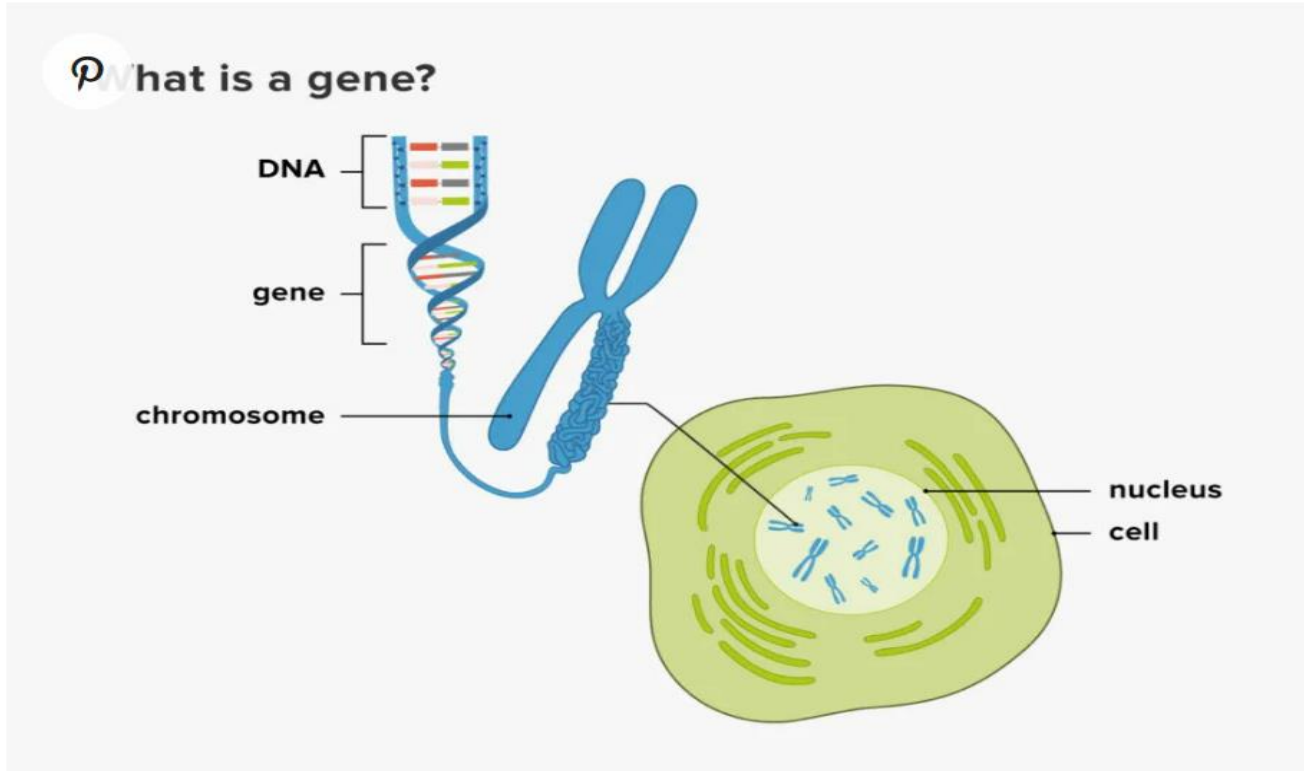


OBJECTIVES

- What is pharmacogenetics (pharmacogenomics)?
- Importance of pharmacogenetics
- Define genetic polymorphism
- Types of genetic polymorphism
- Polymorphism affecting pharmacokinetics
- Polymorphism affecting pharmacodynamics
- polymorphism affecting underlying disease
- Applications of pharmacogenetics
- Personalized medicine



What are genes?



Genotype vs Phenotype

GENOTYPE

The genotype is an organism's genetic information.

BB

homozygous dominant

Bb

heterozygous

bb

homozygous recessive

PHENOTYPE

The phenotype is the set of observable physical traits.

purple



purple



white



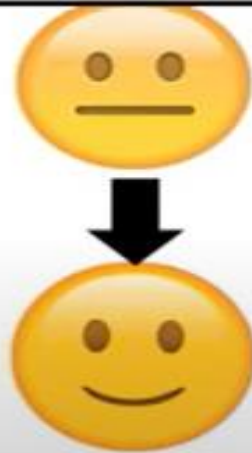
- Great variability exists among individuals in response to drug therapy.
- It is difficult to predict how effective or safe a medication will be for a particular patient.



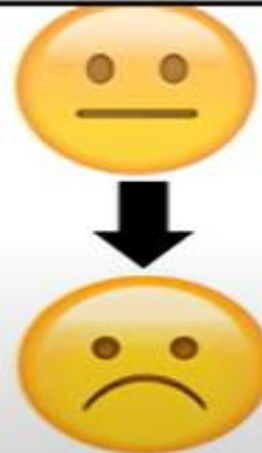
- A number of clinical factors are known to influence drug response, including
 - Age
 - Body weight
 - Renal and hepatic function
 - Concomitant drug use.
- However, considering these factors alone is often insufficient in predicting the likelihood of drug efficacy or safety for a given patient.



Identical antihypertensive therapy in two patients of similar age, sex, race, and with similar medical histories and concomitant drug therapy may produce



adequate blood pressure reduction in one patient



symptomatic hypotension in the other.



Pharmacogenetics

Definitions:

- **Pharmacogenetics** is the study of the genetic basis for variations in drug response.
- **pharmacogenomics** surveying the entire genome to assess multigenic determinants of drug response.



Importance of pharmacogenetics:

Maximize drug efficacy.

Minimize drug toxicity.

Predict patients who will respond to intervention.

Aid in new drug development.



- Genetic variations occur as either rare defects or polymorphisms.

Polymorphisms

- are defined as variations in the genome that occur at a frequency of at least 1% in the human population.



Types of genetic polymorphism:

Single nucleotide polymorphisms (SNPs).

Insertions/deletions (indels).



Types of polymorphism:

1. Single-nucleotide polymorphisms, (SNPs):

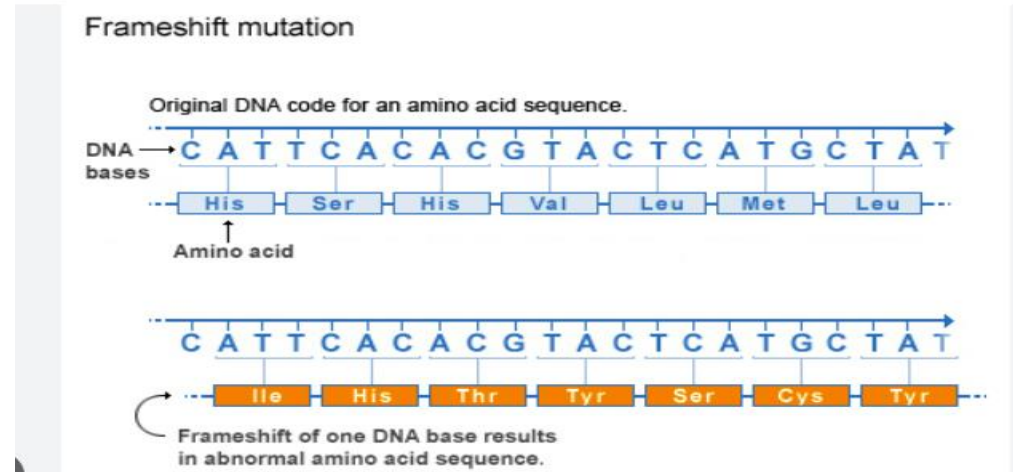
the most common genetic variation in human DNA.



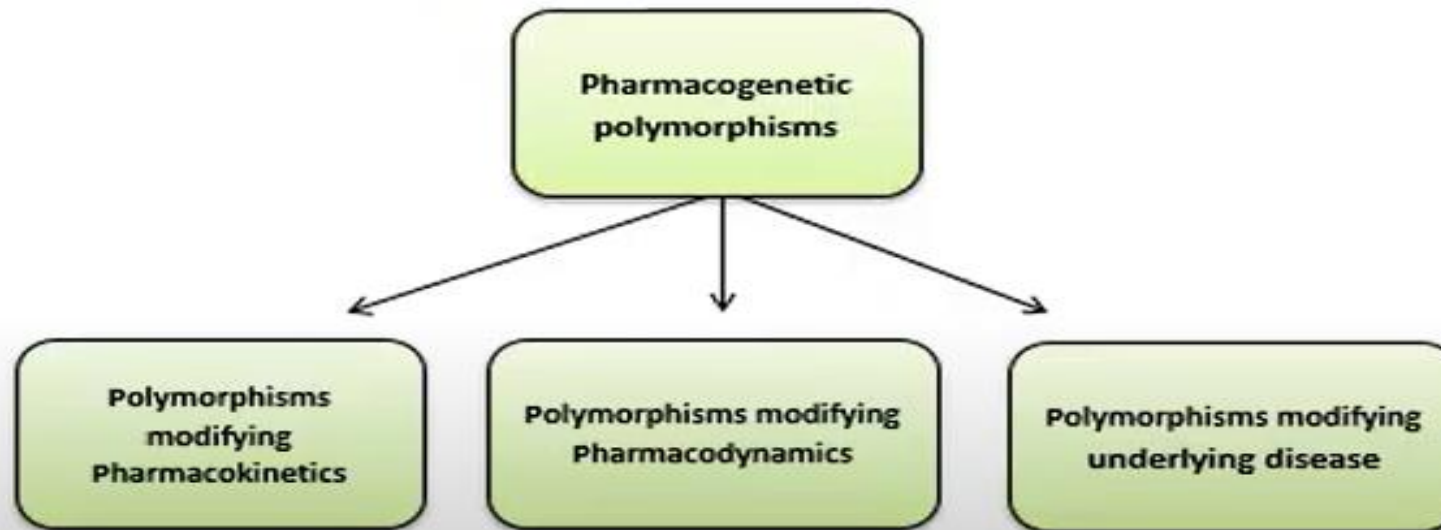
- **Single nucleotide polymorphisms (SNPs):**
- The term single nucleotide polymorphisms (SNPs) means single base pair substitution.
- **Types:**
 - **Missense SNPs** result in a nucleotide substitution that changes the amino acid codon e.g. (proline (CCG) to glutamine (CAG) which could change protein structure, stability or substrate affinity.
 - **Sense SNPs(silent)** don't change the amino acid codon.



- *Insertion-deletion polymorphisms* (indels):
= **Frame shift mutation**
- In which a nucleotide or nucleotide sequence is either added to or deleted from a DNA sequence.

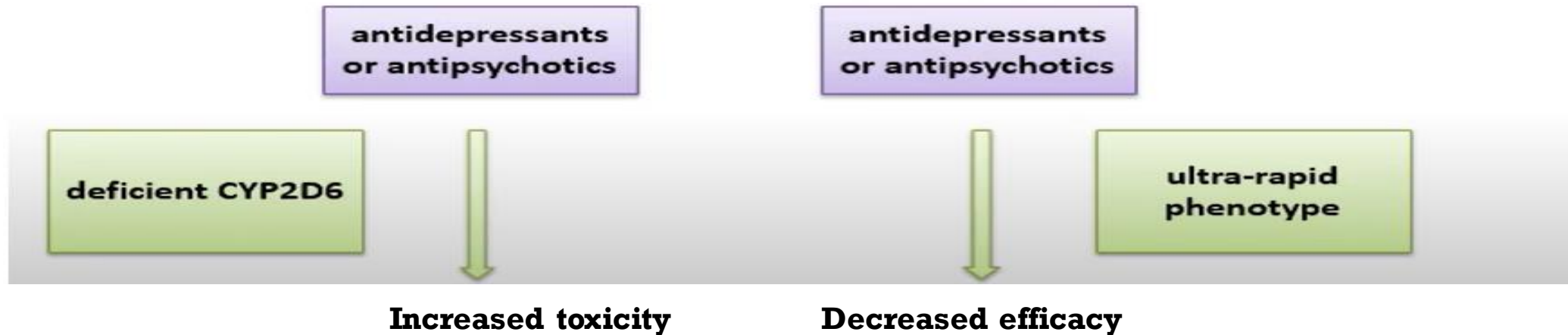


Affected genes lead to different phenotypes with modified therapeutic and adverse response to certain drugs.



Polymorphisms modifying Pharmacokinetics

- **Cytochrome P450 enzymes**
- CYP2C9, CYP2C19, and CYP2D6, are responsible for approximately 70% of drug metabolism in the body.



Cytochrome P450 enzymes

- Poor phenotype of **CYP2C19** is more common in **Chinese and Japanese** populations.
- Several **proton pump inhibitors**, including omeprazole and lansoprazole, are metabolised by CYP2C19.
- On exposure to the drug → a greater effect and a higher probability of ulcer cure than other individuals.



Cytochrome P450 enzymes

- The anticoagulant **warfarin** is catabolized by **CYP2C9**.
- **Deficient** polymorphisms in **CYP2C9** are common → lower warfarin clearance, lower dose requirements and a higher risk of bleeding complications.



- **Succinylcholine apnea:**
- Occurs when a patient has been given the muscle relaxant succinylcholine, but does not have pseudocholinesterase, the enzymes that metabolize it → prolonged depression of respiratory muscles.



- **Fast acetylators and slow acetylators of Isoniazid:**
- The N-acetyl transferase enzyme controlled by two genes, are responsible for clinically significant two different phenotypes.
- **Slow acetylators → peripheral neuropathy.**
- **Fast acetylators → hepatotoxicity.**



Polymorphisms modifying Pharmacodynamics:

- **Beta adrenergic receptor polymorphisms** alter the response to bronchodilators.
- **Polymorphisms in HMG-COA reductase** affect the degree of lipid lowering following statins.
- **Serotonin receptor polymorphisms** affect the responsiveness to antidepressants.



3-Polymorphism-Modifying Diseases and Drug Responses:

Some genes may be involved in an underlying disease.

1- Acute intermittent porphyria:

- Hepatic microsomal enzyme inducers as barbiturates can precipitate acute attacks in susceptible individuals.
- Barbiturates induce aminolevulinic acid (ALA) synthase enzyme \uparrow porphyrin synthesis and production in patients with a genetic defect.



2- Polymorphisms in ion channels:

- affect risk of cardiac arrhythmias, accentuated in the presence of a drug prolonging QT interval (macrolide antibiotics, antihistamines).



3- Glucose-6-phosphate dehydrogenase (G6PD) deficiency

- People with **G6PD** deficiency should avoid medicines that contain aspirin (salicylic acid).
Antimalarials: chloroquine, pamaquine, primaquine, quinidine and quinine.



4- Malignant Hyperthermia:

- Mutation of the **Ryanodine receptor**, located on sarcoplasmic reticulum mediate the release of calcium ions $\square \uparrow$ intracellular calcium thus, muscle contraction.
- Triggered by exposure to certain drugs e.g. Halothane.



Applications of pharmacogenetics:

- **Cancer therapy:**

- By studying pharmacogenetics it can be easy to identify which patients are most likely to respond to certain anticancer drug.

- **Cystic fibrosis**

- **Diabetes mellitus**



Personalized medicine

- means individualizations of drug therapy according to genomic information.



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Thank you

