Pharmacology Sheet

Doctors 2022-أثر-MU—Medicine

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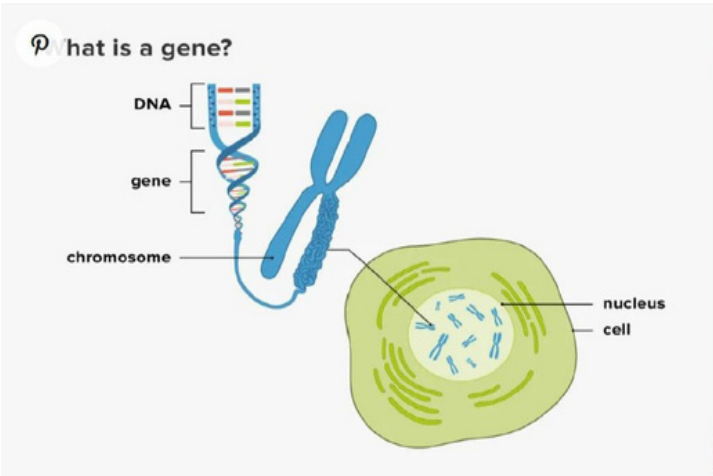
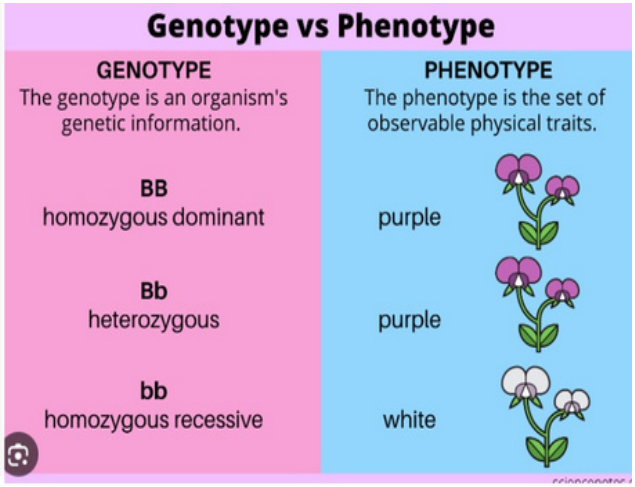
Pharmacogenetics & Pharmacogenomics

Objectives:

- Whatis 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?

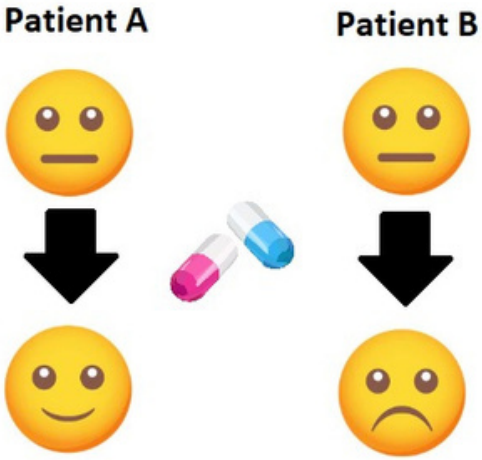




- **Great variability exists among individuals in response to drug therapy** variation of drug response could be attributed to gene variations.
- **It is difficult to predict how effective or safe a medication will be for a particular patient** clinically I can't be sure about drug response.
- **A number of clinical factors are known to influence drug response, including:**
  1. Age liver and kidney functions are declined in elderly and they are not fully developed in young ages.
  2. BodyWeight According to body weight we determine the dosage(dose)of many drugs. Moreover, fat distribution affects drug response.
  3. Renalandhepaticfunction for example in renalfailure the doses of many drugs are decreased and sometimes to half of the original dose due to metabolic problems.
  4. Concomitantdruguse The usage ofmany drugs atthesametime can cause drug interaction as in warfarin when taken with aspirin warfarin effect will be augmented and may even cause toxicity (increased risk of bleeding).

- However, considering these factors alone is often insufficient in predicting the likelihood of drug efficacy or safety for a given patient, as you will see in the next scenario.

- Identical antihypertensive therapy in two patients of similar: age, sex, race and with similar medical histories and concomitant drug therapy (all possible varying factors are constant) may produce:
  - Adequate blood pressure reduction in one patient (patient A).
  - Symptomatic hypotension in the other (patient B).
  - Different responses despite the similar conditions mostly due to difference in genetics.



Pharmacogenetics:

Definitions:

- Simply put: how an individual's genes affect drug response.
- 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:

- Study of genes affecting drug response
- Maximize drug efficacy.
- Minimize drug toxicity.
- Predict patients who will respond to intervention and whom will be
- safe Aid in new drug developments

❖ Genetic variations occur as either rare defects (around 1%) or polymorphisms.

Polymorphisms:

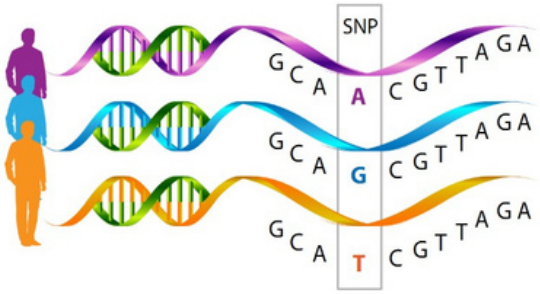
- Are defined as variations in the genome that occur at a frequency of at least 1% in the human population.

Types of genetic polymorphism:

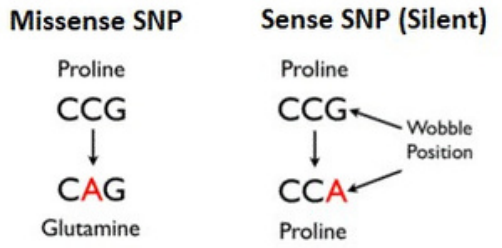
A. Single nucleotide polymorphisms (SNPs).

B. **Insertions/ deletions (indels).**

A. Single Nucleotide Polymorphisms (SNPs):



- **Change a nucleotide in a strand of DNA which leads to change in sequence and change in the code of a specific amino acid.**
- **The most common genetic variation in human DNA.**
- **The term singe nucleotide polymorphisms (SNPs) means single base pair substitution.**
- **Types:**
  1. MissenseSNPs: **resultinanucleotide substitution that changes the amino acid codon e.g. Proline (CCG) to glutamine (CAG) which could change protein structure, stability or substrate affinity.**
  2. SenseSNPs(silent): **don'tchangethe amino acid codon.**



B. Insertion- deletion polymorphisms (indels):

- **= Frame shift mutation**
- **The most common genetic variation in human DNA.**
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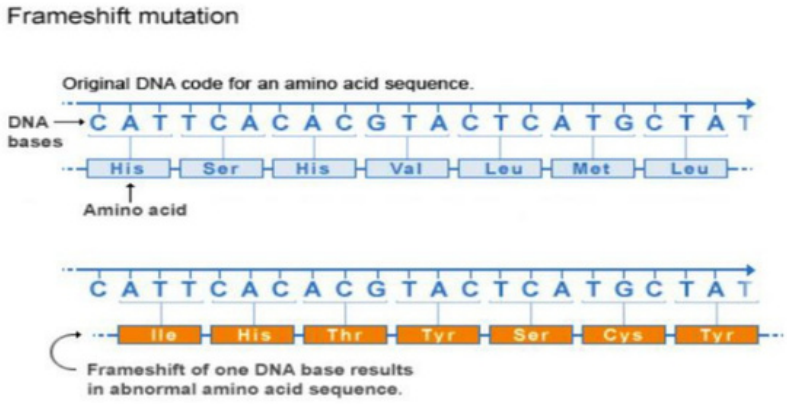
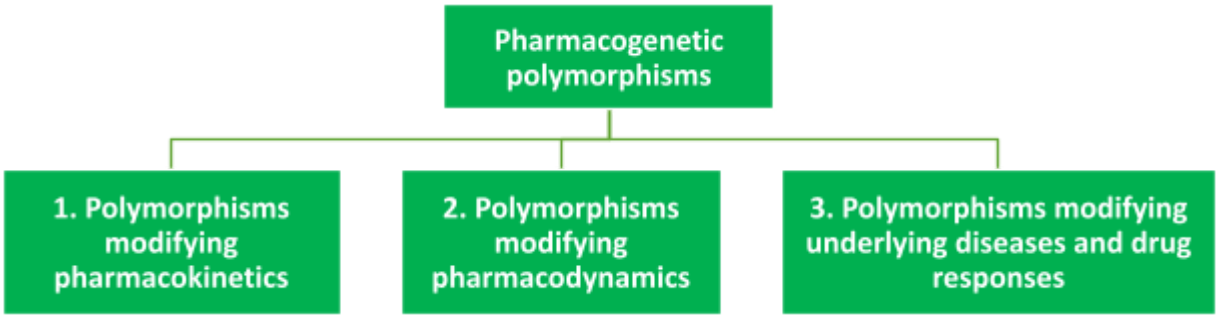


❖ **Affected genes lead to different phenotypes with modified therapeutic and adverse response to certain drugs.**



1. Polymorphisms modifying pharmacokinetics:

- **We will only focus on metabolism**

- Cytochrome P450 (P/4/50 to read it) enzymes a system of enzymes (not only one) that metabolizes drugs.
- CYP2C9, CYP2C19 and CYP2D6, are responsible for approximately 70% of drug metabolism in the body.

Antidepressants or Antipsychotics: (Scenario A)	Antidepressants or Antipsychotics: (Scenario B)
When give to pateints with deficient CYP2D6 (the one responsible for metabolizing a group of CNS related drugs).	When give to pateints with ultra-rapid phenotype
The result will be Increased toxicity (because it can't be metabolized) --> caused by polymorphism.	The result will be decreased efficacy (because it will be metabolized rapidly --> it can't be absorbed well) --> caused by polymorphism.
To avoid this we decrease the given dose.	To avoid this we increase the given dose.

- ***Cytochrome P450 Enzymes:***

-Poor phenotype of CYP2C19 (responsible for metabolizing a group of drugs such those used in peptic ulcer treatment) is more common in Chinese and Japanese populations (The enzyme is weak in them the drug will stay in their bodies for longer times in high concentrations the drug will have increased effects).

-Several Proton Pump Inhibitors (PPIs) including esomeprazole and lansoprazole are metabolized by CYP2C19. (those two drugs do not produce high toxicity. They have high therapeutic window no problems in cases of larger than needed doses).

-In Chinese and Japanese populations upon exposure to the drug a greater effect and a higher probability if ulcer cure than other individuals (they take less than the usual 8 weeks course needed by other patients).

- ***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.
- CYP2C9deficiency causes toxicity manifested in bleeding.

- *The next part is important*
- ***Succinylcholine Apnea:***
- Succinylcholine is a drug used in surgeries – with a duration of 5 minutes- to cause skeletal muscle relaxation IN SPECIFIC CASES it may cause paralysis of respiratory muscles, or apnea.
- Occurs when a patient has been given the muscle relaxant succinylcholine, but does not have pseudocholinesterase, the enzyme that metabolizes it (it is found in plasmanotliver) prolongeddepressionofrespiratorymuscles.
- To solve this problem a fresh blood transfusion (it contains the enzyme) should be administered to the patient.

- ***Fast acetylators and slow acetylators of Isoniazid:***
- The N- acetyl transferase enzyme (metabolizes Isoniazid, a drug used in tuberculosis [TB] treatment) is controlled by two genes, which are responsible for clinically significant two different phenotypes:
  1. Slowacetylators peripheralneuropathy(toxicityiscausedbyaccumulationof the drug, generally more accumulation than fast acetylators).
  2. Fastacetylators hepatotoxicity(uponliveraccumulation).

2. Polymorphisms modifying pharmacodynamics:

- Beta adrenergic receptor (located in bronchi and responsible for bronchodilation) polymorphisms alter the response to bronchodilators.
- Polymorphisms in HMG- CoA reductase (the target enzyme for many lipid lowering drugs) affect the degree of lipid lowering following statins (lipid lowering drugs with a suffix of -statins).
- Serotonin (enzyme) receptor polymorphisms affect the responsiveness to antidepressants (when a patient has depression, one way of treatment is to give drugs that will increase serotonin level in brain).

3. Polymorphisms Modifying Diseases and Drug Responses:

● Some genes may be involved in an underlying disease this disease will not be seen until you take the drug.

1. ***Acute Intermittent Porphyria:***

● Hepatic microsomal enzyme inducers as barbiturates(drug sused to cause various effects from mild sedation to general anesthesia) can precipitate acute attacks in susceptible individuals.

● Barbiturates induce amino levulinic acid(ALA)synthase enzyme increases porphyrin synthesis and production in patients with a genetic defect (if the patient has defects in the enzymes included in the sequence of hemoglobin formation the enzyme levels will be lower than normal the formation process of Heme stops at porphyrin precursor stage accumulation of porphyrin the disease will manifest as fits with a triad of symptoms: 1. Abdominal pain, 2. CNS defect and 3. peripheral neuropathy).

2. ***Polymorphismsin ion channels:***

● Heart is full on ionic channels

● When a patient takes a drug that affect the action potential of heart the polymorphism in ion channels that a patient has will appear.

● Affect risk of cardiac arrhythmias, accentuatedinthe presence of a drug prolonging QT interval (macrolide antibiotics, antihistamines) those two classes of drugs affect QT interval cardiac arrhythmia.

- ***Then extpartis important***

3. Glucose-6-phosphatede hydrogenase(G6PD) deficiency:

● well-knownasfavism.

● Oxidation of red blood cells(RBCs)leads to rupture.G6PD prevents RBCs oxidation no rupture and vice versa (G6PD deficiency oxidation of RBCs rupture).

● People with G6PD deficiency should avoid medicines that contain aspirin(ASA, acetyl salicylic acid) and anti-malarias (chloroquine, pamaquine, primaquine, quinidineandquinine). those drugs oxidizeRBCs the risk of RBCs oxidation will be higher in cases of G6PD deficiency.

● If an oxidizing agent was administered vomiting and red urine upon examination they will have hemolysis and severe anemia. This scenario is more likely to happen to children.

4. ***MalignantHyperthermia:***

- **Mutation of the Ryanodine receptor, located on sarcoplasmic reticulum mediate the release of calciumions increases intracellular calcium Increased muscle contraction.**
- **Triggered by exposure to certain drugs e.g. Halothane this drug exposes the mutation the drug goes to the sarcoplasmic reticulum opens calcium channels tooutside muscles contraction a majorsymptom ofmalignant hyper thermia.**
- **Moreover, malignant hyperthermia might also be suspected whenever a person during a surgery experiences a very high body temperature that did not respond to IV aspirin.**
- **Dantrolene drug is the only cure of malignant hyperthermia.**

Applications of Pharmacogenetics:

1. **Cancer therapy:**
- **By studying pharmacogenetics, it can be easy to identify which patients are most likely to respond to certain anti-cancer drugs.**
2. **Cystic fibrosis.**
3. **Diabetes mellitus.**

Personalized Medicine:

- **Means individualizations of drug therapy according to genomic information.**

References:

Lippincott's Illustrated Review
Pharmacology, 5th edition
Lippincott Williams & Wilkins

Katzung *by Anthony Trevor, Bertram Katzung, and Susan Masters .*
last edition McGraw Hill,
Rang & Dale's Pharmacology: *by Humphrey P. Rang ; James M.*
Ritter ; Rod Flower Churchill Livingstone; 6 edition

نُؤمِنُ بنَصر يُحَرّرُ النُّفوسَ إن أخلَصَت، ويَفتَحُ الأبواب إن جاهَدَت، كُلّ عظيم لا بُدّ لَهُ مِن ثَمَن! لا بُدَّ للمُراد مِن مُقابل! قَد تُعِدُّ للفَتح ولا تَراه، قَد تَبني البَيتَ ولا تَسكُنُه، المُهم أن تَعمَل دونَ انتِظار، أن تَغرِس وإنْ لَم ترَ الثَّمَر، وهذا مَقامُ صِدقٍ بَليغ!

ـ قصي عاصم العسيلي.