Pharmacogenetics and pharmacogenomics lec-11

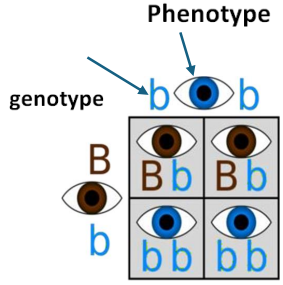
Genomics:study of genetic material found in a cell

- 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 "Using genomic data"

- Goal: personalized medicine

Personalized medicine: the tailoring of medical treatment to the specific characteristics of each patient. الدوا المناسب للشخص المناسب

Genetic polymorphism 1% '1gene=multiple phenotypes"	**SNPs (Single Nucleotide Polymorphisms) m/c**	**Indels (Insertions/Deletions)**
Definition	Single base substitution in DNA sequence.	Addition or deletion of bases in the genome.
Types	- Silent: no amino acid change - Missense: amino acid change affects protein function(malfunction) - Nonsense: creates a stop codon, producing a nonfunctional protein	
Examples	- SNP in non-coding region may increase cancer risk - Missense mutation in CFTR gene linked to cystic fibrosis	Indel mutation associated with Bloom syndrome in jerwish,japanese



Phenotype: الصفة الظاهرة

The phenotype is determined by genotype.

Examples of polymorphism: Pharmacokinetcs

Drug/Condition	Gene/Protein Involved	Variation Type	Impact
Clopidogrel	15% from drug metabolized into active form by CYP2C19 (NOTE: 85% by esterase)	Pharmacokinetic	**Poor metabolizers** have reduced anticoagulant effect, risking clotting.
Antidepressants	CYP2D6	Pharmacokinetic	**Poor metabolizers** have increased drug toxicity; **ultra-rapid metabolizers** may have decreased efficacy.
Succinylcholine **Tx: fresh blood transfusion(imp)**	Butyrylcholinesterase (BCHE) also known as plasma cholinesterase or pseudocholinesterase)	Pharmacokinetic	Mutations can cause prolonged muscle paralysis and respiratory failure (scoline apnea).
Isoniazid (INH)	N-acetyltransferase 2 (NAT2)	Pharmacokinetic	**Slow acetylators** have increased risk of **hepatotoxicity**; rapid acetylators have decreased drug efficacy.

حفظ مهم

Most important enzymes of CYP450 family are
CYP3A4
CYP2C9
CYP2C19
CYP2D6

Pharmacodynamics and disease modifying examples:

Beta Receptor Drugs	Beta-adrenergic receptor genes	Pharmacodynamic	**Tachyphylaxsis** – like in salbutamol
Some antidepressants that target serotonin	Serotonin receptor genes	Pharmacodynamic	Variations affect antidepressant efficacy and patient response.
G6PD Deficiency (Fauvism) More in males	G6PD enzyme	Disease-modifying	Deficiency leads to hemolysis, anemia when exposed to oxidizing agents. Life threatining
Malignant Hyperthermia **Tx:Dantrolene(imp)** (Dantrolene antagonize RYR1)	RYR1 (Ca release channel)	Disease-modifying	Susceptibility to severe reaction during anesthesia; causes muscle rigidity, fever,tachycardia,metabolic acidosis and Complications like muscle breakdown and high blood pottasium

G6PD protect RBCs against oxidizing agents: antibiotics,fava beans,aspirin,chloroquine....etc

MH occur Due to genetic mutations in RYR1 gene response to particular medications used during general anesthesia **(volatile anesthetic agents and succinylcholine)** (RYR1): functions as calcium release channel in the sarcoplasmic reticulum

Good luck ☺

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