

*Pharmacogenetics: study of genetic basis for variation of drug response

*Polymorphism: variation in genome that occur at least in 1% in population (أعداد الأفراد من جين لآخر)

Types of polymorphisms

SNPs

"تعديل"

single base pair substitution

Indels

Frame shift mutation

Missense SNP

changing amino acid codon, New protein

Sense SNP (silent)

pharmacogenetics polymorphism

may modify

pharmacokinetics

metabolism...

Cytochrome P450 enzymes

succinylcholine esterase

alpha

Fast + Slow acetylators of Isoniazid

pharmacodynamics

Beta adrenergic receptor polymorphism

polymorphism in HMG-CoA reductase

serotonin receptor polymorphism

G6PD deficiency

Malignant Hyperthermia

Underlying Disease

Acute intermittent porphyria

polymorphism in ion channel

G6PD deficiency

Malignant Hyperthermia

Kinetics

NO Date



CYP2C9

metabolism of warfarin



CYP2C19

metabolism of proton pump inhibitors
(omeprazole + Lansprazole) drug to
cure peptic ulcer.



CYP2D6

metabolism of anti-depressants
+ anti-syphatics



Pseudocholinesterase

metabolism of succinylcholine (muscle relaxant
drug)



N-acetyl transferase :

metabolism of ISDNiazid (TB drug)

normal acetylator →

normal effect

fast acetylator →

accumulation in liver

slow acetylator

accumulation of toxic metabolite

① Acute intermittent porphyria: AIP

Acute intermittent porphyria (mechanism of disease):

↓ enzyme (porphobilinogen deaminase) essential to heme synthesis.

Barbiturates (drug mechanism):

↑ activity of hepatic enzyme involved heme production

→ excessive stimulation of heme biosynthesis →

metabolites such as porphyrin Precursor of porphobilinogen.

as we mentioned AIP pts have ↓ in the enzyme

→ ↑ accumulation in metabolites

→ Acute attacks (severe symptoms)

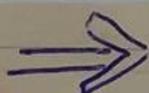
② Polymorphism in ion channels:

to these pts (antihistamine + antibiotics drugs) may cause death but how?

these drugs block K⁺ channels in the heart →

prolongation of QT interval in ECG →

ventricular fibrillation → life threatening arrhythmia



② Dynamics

NO Date

③ Glucose-6 phosphate dehydrogenase (G6PD) deficiency;
mechanism of disease: affects RBCs this deficiency,
cause this enzyme protect RBCs from oxidative damage
(normally), so this deficiency may leads to make RBCs more
vulnerable, when pt takes Aspirin + Anti-malarial (quine)
→ Hemolysis

④ Malignant Hyperthermia MH

exposure to anesthetics drugs like (Halothane) trigger
of pt with mutation in it (Ryanodine receptor)
in SR → secretion of Ca^{2+} (become extracellular)
→ muscle contraction uncontrolled → rapid rise in
temperature
treated by Dantrolene (antidote of MH) by inhibit
abnormal Ca^{2+} release [IV + ↑ dose]

⑤ β adrenergic receptor polymorphism

⑥ polymorphism in HMG-CO.A reductase

HMG-CO A reductase: key step in producing cholesterol
process. pt with this polymorphism takes Statin drug
to ↓ cholesterol level

⑦ serotonin receptor polymorphism