NO Date 9th lec pharmacogenetics+pharmacogenomic

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

* polymorphism: variation in genome that occur at least in 1% in population (تعدد الأشكال من جين لآخر)

Types of polymorphisms

SNPs ("تبديل")

single base pair substitution

indels

→ Frame shift mutation

→ Missense SNP

chang amino acid codon → New protein

→ Sense SNP (silent)

pharmacogentics polymorphism may modify

pharmacokinetics

~ metabolism...

- Cytochrome P450 enzymes
- Succinylcholine apena
- Fast + slow acetylators of Isoniazid

pharmacodynamics

- Beta adrenergic receptor polymorphism
- polymorphism in HMG_COA reductase
- serotonin receptor polymorphism

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**
  metabolisim of anti-depressant + anti-sychotics

- **Pseudocholinesterase**
  metabolism of succinylcholine (muscle relaxant drug) ▲

- **N-acetyl transferase :**
  metabolisim of ISONiazid (TB drug)
  normal acetylator ⇝
  normal effect
  fast acetylator ⇝
  accumilation in liver

  slow acetylator
  accumilation of toxic metabolite

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Underlying Disease

① Acute intermittent porphyria: · AIP

Acute intermittent porphyria (mechanisim of disease):
↓ enzyme (porphobilinogen deaminase) essential to heme synthesis.
Barbiturates (drug mechanisim):
↑ 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 → ↑ accumilation in metabolites → Acute attacks (severe symptoms)

② Polymorphisim 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

⇒

Dynamics

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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 RBs more vulnerable, when pt takes Aspirin + Anti-malarial (quine) → Hemolysis

④ Malignant Hyperthermia MH

exposure to anesthetics drugs like (Halothan) trigger receptor of pt with mutation in it (Ryanodine receptor) in SR → secretion of Ca^{2+} (become extracellular) → muscle contraction uncontrolled → rapid rise in tempreture

treated by Dantrolene (antidote of MH) by inhibit abnormal C^{2+} relase [IV + ↑↑ dose]

- β adrenergic receptor polymorphism
- polymorphism in HMG-CO.A reductase

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

- serotonin receptor polymorphism