# Genetically-Mediated Alterations in Drug Response

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# Genetically-Mediated Alterations in Drug Response

Change in the response to the drug due to genetic factor.

- **Pharmacogenetics is the science of understanding how genetic variability influences drug treatment outcomes.**
- **It generally refers to the effects of a single genetic marker.**

# Genetically-Mediated Alterations in Drug Response

- **Pharmacogenomics is broader in context, referring to the collective influence of variability across the genome to modulate an individual's drug response profile.**
- **It refers to the effect of multiple genes.**
- **Some times these 2 terms are used interchangeably.**

# Genetically-Mediated Alterations in Drug Response

- **Genomic Variations led to the concept of "Personalised Medicine".**

. for example: slow metabolizer vs. extensive one should not get the same dose.

1 • **Variation can be caused by different concentrations at sites of drug action – pharmacokinetic variation.**

2 • **Or by different responses to the same drug concentration – pharmacodynamics variation.**

# Genetically-Mediated Alterations in Drug Response

- **In these cases, dose adjustment is needed to meet the individual's needs.**
- **Inter-individual variation in response to some drugs is a serious problem; if not taken into account.**
- **It can result in lack of or reduced effect or unexpected adverse effects.**

# Genetically-Mediated Alterations in Drug Response

- **Additive or synergistic influence of multiple gene variants can interact with environmental factors to result in a wide spectrum of inter-individual variation in drug response.**

or antagonistic

# Inherited Variation in Pharmacokinetics

ADME
Absorption, Distribution, Metabolism, Excretion.

A. Drug absorption disorders:

- Genetic defects in the "intrinsic factor" (secreted by the stomach) lead to impairment of vitamin $B_{12}$ absorption (in the terminal ileum) → megaloblastic anemia.

B. Drug metabolism disorders:

* Most imp enzymes for metabolism of drugs have genetic variation.
* Autosomal recessive.

- If a drug metabolizing enzyme is deficient, the drug will accumulate → adverse effects, which can be prevented by giving a smaller dose.

↳* if accumulate more and more → toxic effects

. If the drug was (prodrug) in drug metabolizing enzyme deficiency ∴ it will not work in the body

# Drug metabolism disorders

1. **Acatalasia:** (uncommon).

- **Lack of catalase in tissues and RBCs.** (antioxidant enzyme ($H_2O_2 \rightarrow H_2O + O_2$).)
- **$H_2O_2$ application → local tissue damage.** (used to clean wounds and debris → then it's hydrolyzed by catalase.)
- **Inherited in an autosomal recessive fashion.**

if there's acatalasia, $H_2O_2$ will cause local damage to the tissue.

# Drug metabolism disorders

2. **Atypical plasma cholinesterase:**

- **Failure to hydrolyze succinylcholine, a muscle relaxant used during surgery, → prolonged apnea that needs assisted ventilation until recovery.**
- **It affects mivacurium also.**
- **Inherited in an autosomal recessive fashion.**

# Drug metabolism disorders

3. **Genetic deficiency in acetylation:** (Common in our population)

- **Any given population can be divided into "slow" and "rapid" acetylators. Or "slow" "intermediate" and "rapid" acetylators.**
  - "slow" → ∴ drug accumulates → adverse rxns → toxic rxns.
  - "intermediate" → not affected
  - "rapid" → failure of drug.
- **Slow acetylation is inherited in an autosomal recessive fashion.**
  - In caucassian population
- **It affects 60-70% of the population.**

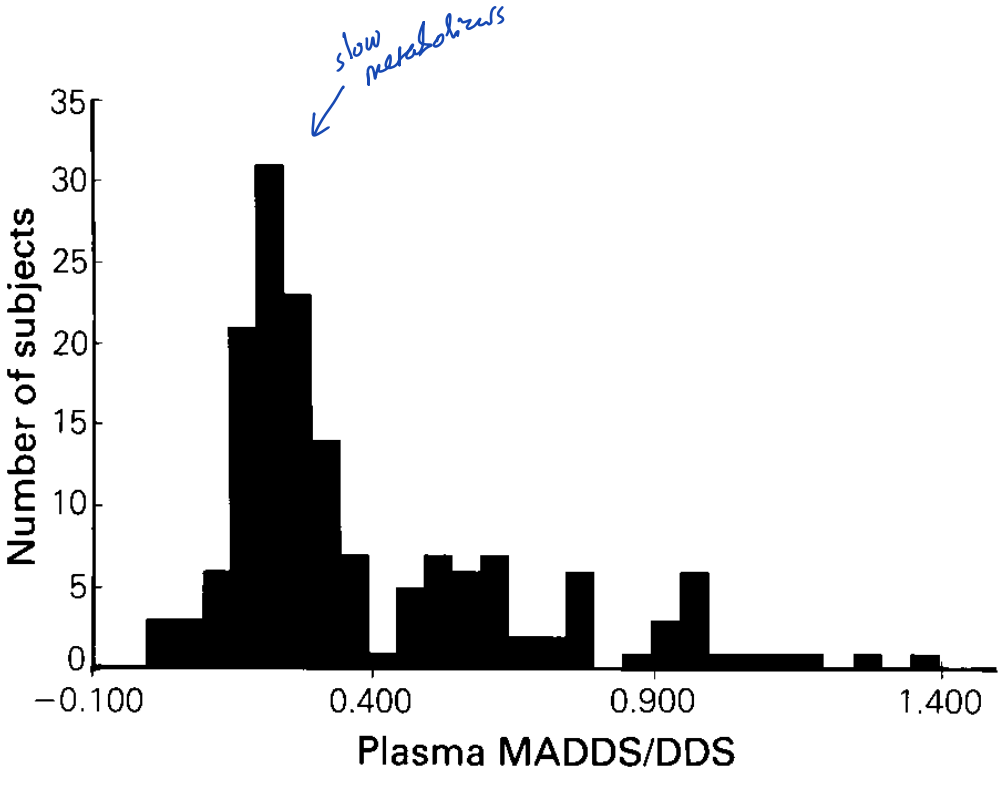



**Figure 2** Frequency distribution histogram of the plasma monoacetyldapsone to dapsone ratio in 160 unrelated Jordanian subjects.

# Examples of Drugs Affected

- **Caffeine, Clonazepam, Nitrazepam, Dapsone, Hydralazine, Isoniazid, Procainamide, Phenelzine, Sulfonamides.**

# Clinical Consequences of Acetylation Polymorphism

• It's an easy test to know the acetylation status of the patients (might take hours for the results).

1. **Slow acetylators of dapsone and sulfonamides may develop hemolytic anemia.**

- **This is because of deficiency in acetylation, allowing an alternative pathway of metabolism to predominate.**
- **Cytochromes P450 oxidize these drug to the hydroxylamine, which binds covalently to cells producing cellular toxicity.**

oxidative stressor

first cells affected - RBCs.

# Clinical Consequences of Acetylation Polymorphism

2. Slow acetylators of hydralazine and procainamide may develop drug-induced lupus erythematosus (autoimmune disease).
3. Rapid acetylators of procainamide produce excessive concentrations of N-acetlprocainamide (NAPA), which causes QT prolongation and life-threatening ventricular arrhythmias.

# Clinical Consequences of Acetylation Polymorphism

4. **Slow acetylators of isoniazid will have accumulation of the drug, which inhibits activation of pyridoxine to pyridoxal phosphate.**

Vit B6 (inactive) (active)

- **This leads to neurotoxicity, which is preventable by vitamin B6 administration.** (1)
- **Dose of isoniazid should be reduced, or the interval between administrations prolonged.** (2) (3)
- **Rapid acetylators of isoniazid may have therapeutic failure.**

This is a problem because TB could complicate to cause meningitis, osteomyelitis --- etc.

due to interindividual variations (but all are rapid).

# Drug metabolism disorders

5. **Polymorphic oxidation:**

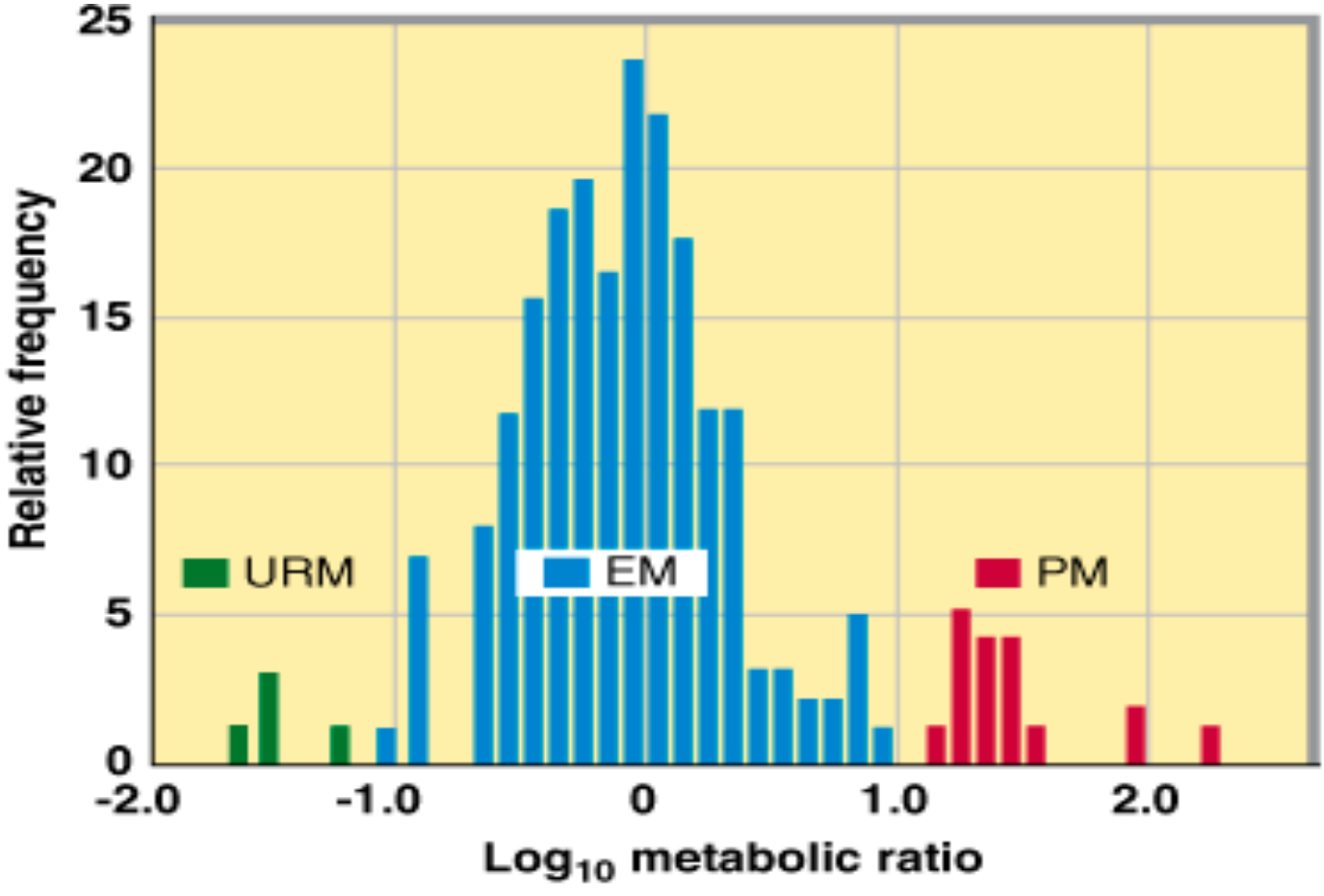
- **Involves deficiencies in cytochrome P450.**
- **All are inherited in an autosomal recessive fashion.**

A very old Antihypertensive agent.

# CYP2D6 ( Debrisoquine Hydroxylase)

- **Highly polymorphic** not white and black (slow and rapid).
- **200-fold variability in the metabolism of > 100 drugs**
- **Metabolizes 25-30% of clinically used drugs**
- **Involved in the metabolism of ~ 50% of all psychoactive drugs.**
- **The population can be divided into ultrarapid, extensive, intermediate or poor metabolizers.**
- **It affects 7% of the population.**

most imp metabolizing isoenzymes: CYP2D6 → 25%; CYP3A4 → 50%




Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

# Examples of Drugs Affected

selective β1 (commonly used in congestive heart failure).

1. **β-Blockers: Metoprolol, Propranolol**
2. **Antiarrhythmics: Propafenone, Mexiletine, Lidocaine.**
3. **Antihypertensives: Debrisoquine, R-Carvedilol.** (β-blocker)
4. **Neuroleptics: Fluphenazine, Thioridazine, Clozapine, Risperidone.**
5. **Antitussives: Dextromethorphan.** (for dry cough only not wet.)
6. **Tricyclic antidepressants: Desipramine, Imipramine, Tomoxetine, Doxepin.**

# CYP2D6 Substrates (Contd)

6. **MAOIs: Methoxyphenamine**
7. **SSRIs: Paroxetine, Fluoxetine, Citalopram.**
8. **Opioids: Codeine, Hydrocodone,**
9. **Miscellaneous: Methoxyamphetamine, Diltiazem, Simvastatin, Chlopheniramine, Metoclopramide.**

metabolized to morphine (In slow acetylators it fails bc it's a weak analgesic unlike morphine).

- **Inhibitors: Quinidine, Tamoxifen, Chlopromazine**

other drug interactions with CYP2D6 — Anti-arrhythmic — Estrogen receptor modifier - Breast cancer — Antipsychotic drug.

thus their conc. in the blood ↑ due to inhibited metabolism.

# CYP2C19 (Mephenytoin Hydroxylase)

- PMs had increased somnolence and intellectual impairment after mephenytoin.
- Concentration in PMs was ~ 2 times higher than in EMs.
- It affects 4-5% of the population.

# Examples on Drugs Affected

- S-Mephenytoin, Diazepam, Amitriptyline, Imipramine, Citalopram, Proguanil, Chloroguanide, Propranolol, Omeprazole, Lansoprazole, R-Methadone.

# CYP2C9 Polymorphism

- The population can be divided into "poor", "intermediate" and "extensive" (normal) metabolizers.
- Affects the metabolism of NSAIDs (ibuprofen, piroxicam, celocoxib …) and fluoxetine, losartan, phenytoin, tolbutamide, torsemide, S-warfarin.
- It affects 10-20% of the Caucasian population.

# Inherited Variation in Pharmacodynamics

Effects on Receptors - variation. (Not the drugs conc)

1. **Hereditary Warfarin Resistance:** (uncommon) — you need even a dose of 80 mg!

Normal warfarin dose < 10 mg.

- **True warfarin resistance is rare (< 0.1%).**
- **Associated with need for high warfarin doses to have therapeutic effect.** and you need to monitor through INR to figure this problem (INR won't be increased at normal or even high doses like 40-60mg)
- **Patients need much smaller doses of vitamin K to reverse the effect of warfarin.**
- **Warfarin does not irreversibly inhibit vitamin $K_1$ 2,3-epoxide reductase.** due to genetically modified Vit K-reductase
- **Inherited in an autosomal dominant fashion.**

- oxidation of vit K so carboxylation of clotting factors occurs.
  - converted into vit-K epoxide so recycling it through this reductase so it's used again to aid in carboxylation of clotting factors.
- Normally, Warfarin's MoA: inhibition of vit K epoxide reductase thus no carboxylation of clotting factors → Anticoagulation occurs ✓.
- If the enzyme is not inhibited due to genetic modification thus warfarin won't bind to it and inhibit it so there'll be carboxylation of clotting factors ∴ coagulation and failure of warfarin

# Inherited Variation in Pharmacodynamics

2. **Heparin Resistance Causes:** ↑ thrombosis status

A. **Inherited antithrombin III deficiency.** ↓ site of action of heparin

B. **Acquired antithrombin III deficiency: Hepatic cirrhosis, Nephrotic syndrome & DIC (dissiminated intravascular coagulation).** protein loss occurs. ; it's consumed

C. **Pregnancy: Elevated factor VIII. Prolongs aPTT (apparent resistance).** but still we give them heparin in VTE.

# Inherited Variation in Pharmacodynamics

D. **Oral contraceptives: Elevated factor V-Leiden.**
E. **Thrombocytosis.**
F. **High levels of basic heparin-binding proteins in plasma: (Histidine-rich glycoproteins, Vitronectin, Platelet factor-4).**

bound_ inactive

# Inherited Variation in Pharmacodynamics

3. **Vitamin D resistance: Patients develop rickets despite adequate vitamin D. 1000X the normal dose is needed to treat rickets in this case.**

# Inherited Variation in Pharmacodynamics

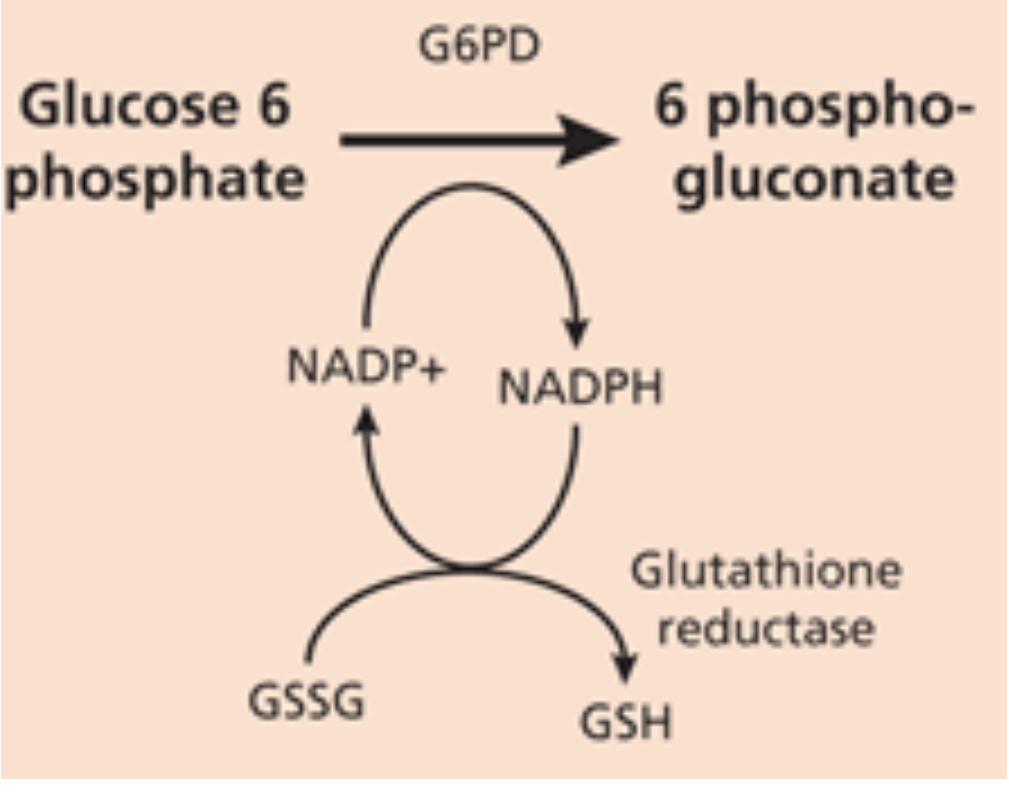
4. **Favism (drug-induced hemolytic anemia):**

- **Due to glucose-6-phophate dehydrogenase (G6PD) deficiency**
- **Two types:**
  a. **African type (10% of population): confers partial resistance to malaria.**
  b. **Mediterranian type (more severe).**

# Favism

- **Deficiency of G6PD leads to deficiency in NADPH,$H^+$, which is needed for regeneration of reduced glutathione (GSH), which is needed to protect cells against oxidative stress.**
- **The deficiency is sex-linked co-dominant.** but females are affected $\underline{X}\underline{X}$.
- **Co-dominance means that both allelomorphic genes in a heterozygous individual have equal importance.** (never are carriers)

# Favism


G6PD
Glucose 6 phosphate
6 phospho-gluconate
NADP+
NADPH
Glutathione reductase
GSSG
GSH

# Favism

means → Before using those drugs you have to test for G6PD.

**Drugs Involved:**

- **Sulfonamides and dapsone.**
- **Antimalarial drugs: primaquine**, Chloroquine.
- **Antibacterial agents: nitrofurantoin, p-aminosalicylic acid.**
- **Others.**

# Inherited variation in Pharmacodynamics

Screening through hx: Ask if they have fx of death during anaesthesia.

5. **Malignant Hyperthermia with Muscle Rigidity:**

- **Uncontrolled rise in body temperature during anesthesia (> 2°C/hour).**
- **Implicated drugs: halothane and succinylcholine.**
- **Mortality rate 50-60%.**
- **May be due to a disturbance in the intracellular distribution of $Ca^{2+}$.**

# Inherited variation in Pharmacodynamics

- **Inherited in an autosomal dominant fashion.**
- **Once it starts to happen, stop administration of the drugs, support vital signs, and give dantrolene which improves intracellular distribution of $Ca^{2+}$.**

# Inherited variation in Pharmacodynamics

6. Glaucoma (↑ IOP) due to abnormal response to intraocular steroids, or long-term use of systemic steroids.

- Occurs in 5% of USA population.
- Inherited in autosomal recessive fashion.