Genetically-Mediated Alterations in Drug Response

Yacoub M. Irshaid, MD, PhD, ABCP

Department of Pharmacology

Genetically-Mediated Alterations in Drug Response

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

Inherited Variation in Pharmacokinetics

A. **Drug absorption disorders:**

- **Genetic defects in the "intrinsic factor" lead to impairment of vitamin B_{12} absorption → megaloblastic anemia.**

B. **Drug metabolism disorders:**

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

Drug metabolism disorders

1. **Acatalasia:**

- **Lack of catalase in tissues and RBCs.**
- **H_2O_2 application → local tissue damage.**
- **Inherited in an autosomal recessive fashion.**

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:**

- **Any given population can be divided into "slow" and "rapid" acetylators. Or "slow" "intermediate" and "rapid" acetylators.**
- **Slow acetylation is inherited in an autosomal recessive fashion.**
- **It affects 60-70% of the population.**

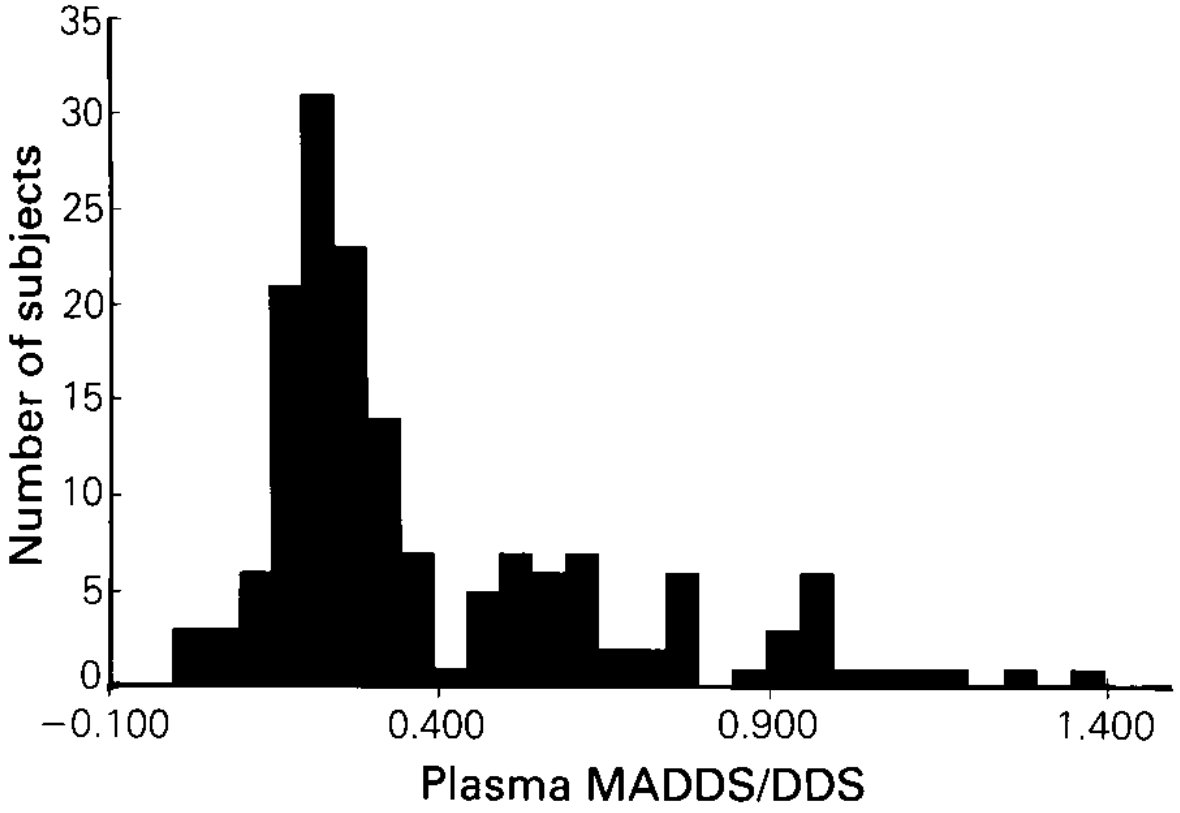


Figure 2 Frequency distribution histogram of the plasma monoacetyldapsone to dapsone ratio in 160 unrelated Jordanian subjects.

Examples of Drugs Affected

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

Clinical Consequences of Acetylation Polymorphism

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.**

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

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

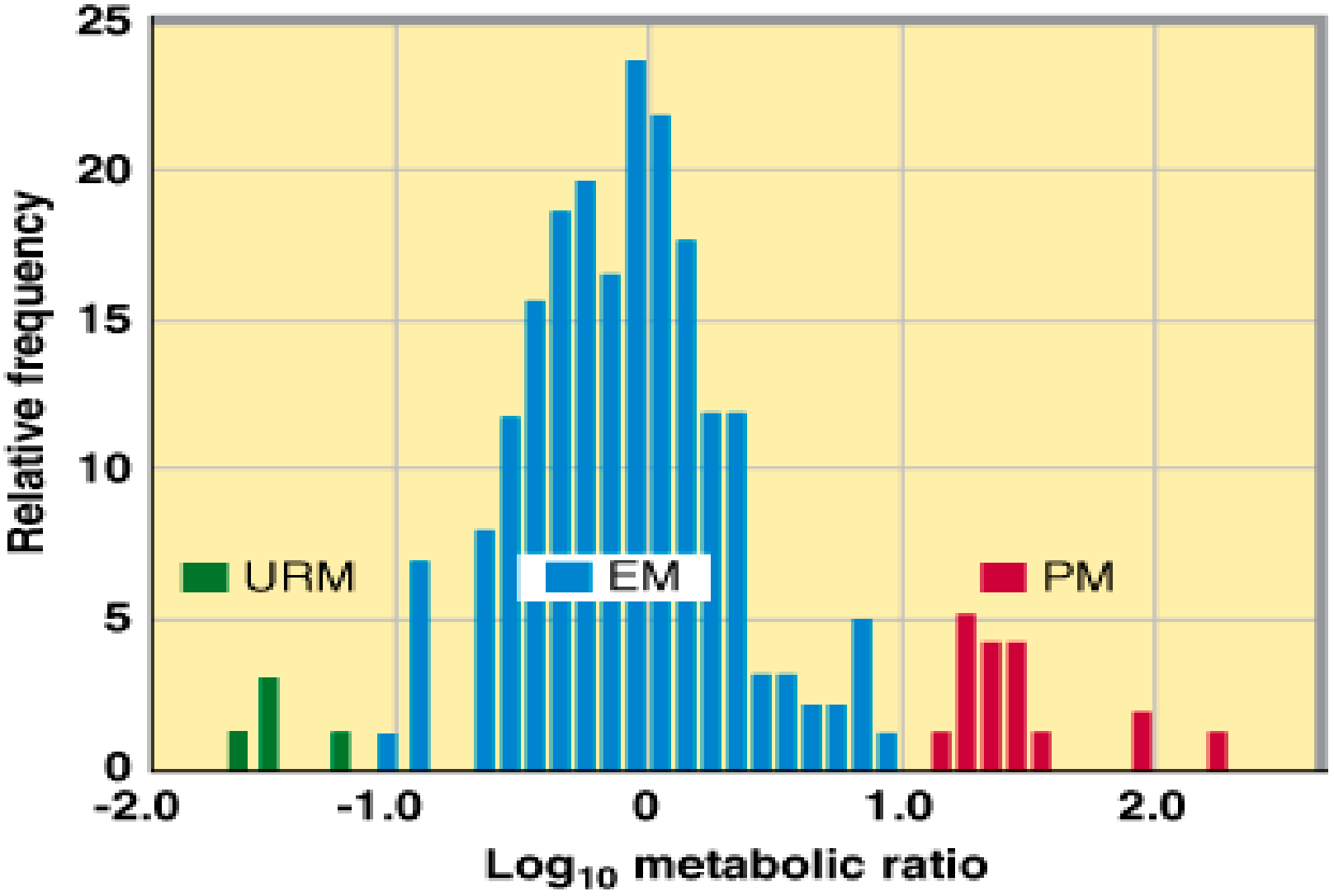
Drug metabolism disorders

5. **Polymorphic oxidation:**

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

CYP2D6 (Debrisoquine Hydroxylase)

- Highly polymorphic
- 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.



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

Examples of Drugs Affected

1. **β-Blockers: Metoprolol, Propranolol**
2. **Antiarrhythmics: Propafenone, Mexiletine, Lidocaine.**
3. **Antihypertensives: Debrisoquine, R-Carvedilol.**
4. **Neuroleptics: Fluphenazine, Thioridazine, Clozapine, Risperidone.**
5. **Antitussives: Dextromethorphan.**
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.

- Inhibitors: Quinidine, Tamoxifen, Chlopromazine

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

1. **Hereditary Warfarin Resistance:**

- **True warfarin resistance is rare (< 0.1%).**
- **Associated with need for high warfarin doses to have therapeutic effect.**
- **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.**
- **Inherited in an autosomal dominant fashion.**

Inherited Variation in Pharmacodynamics

2. **Heparin Resistance Causes:**

A. **Inherited antithrombin III deficiency.**

B. **Acquired antithrombin III deficiency: Hepatic cirrhosis, Nephrotic syndrome & DIC (dissiminated intravascular coagulation).**

C. **Pregnancy: Elevated factor VIII. Prolongs aPTT (apparent resistance).**

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).

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

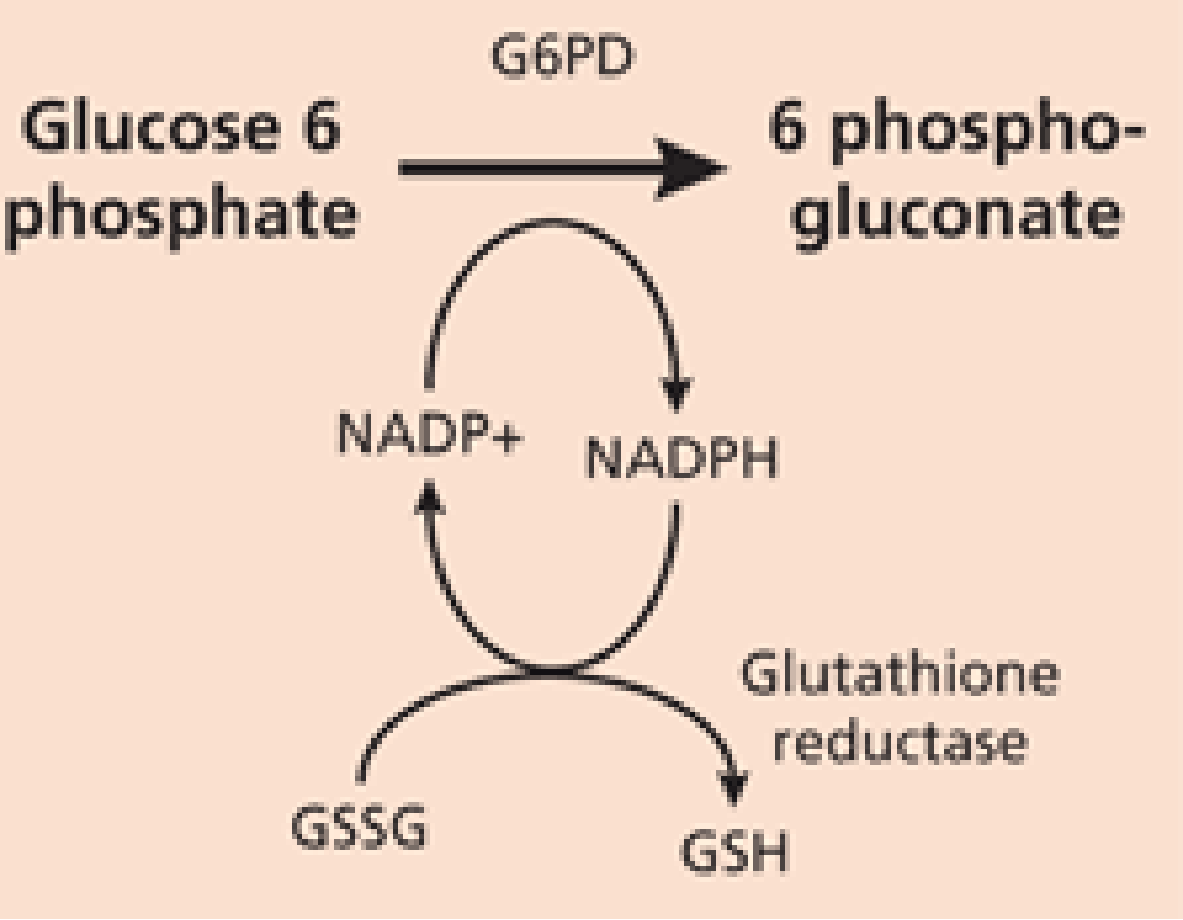
4. **Favism (drug-induced hemolytic anemia):**

- **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.**
- **Co-dominance means that both allelomorphic genes in a heterozygous individual have equal importance.**

Favism


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

Favism

Drugs Involved:

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

Inherited variation in Pharmacodynamics

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 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.**