PHARMACOGENETICS & DRUG IDIOSYNCRASY

M. Imad Damaj, Ph.D.
Associate Professor
Pharmacology and Toxicology
Smith 656A, 828-1676, mdamaj@hsc.vcu.edu

Oops! Too Much
↓ Dose
↓ Dose

Toxicity
↓ Dose

No Effect
↑ Dose

Too Little
↑ Dose

No effect
↑ Dose
Inter-individual Differences in Drug Efficacy

<table>
<thead>
<tr>
<th>Group</th>
<th>Incomplete/absent efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT2-antag</td>
<td>10-25%</td>
</tr>
<tr>
<td>SSRI</td>
<td>10-25%</td>
</tr>
<tr>
<td>ACE -I</td>
<td>10-30%</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>15-25%</td>
</tr>
<tr>
<td>Tricycl. AD</td>
<td>20-50%</td>
</tr>
<tr>
<td>HMGCoAR-I</td>
<td>30-70%</td>
</tr>
<tr>
<td>Beta-2-agonists</td>
<td>40-70%</td>
</tr>
</tbody>
</table>

May 1975: Five interns at St. Mary’s Hospital in London participated in a study of the effects of debrisoquine (40 mg), an antihypertensive agent.

Robert Smith only: dizziness and severe orthostatic hypotension
Pharmacogenetics

Same symptoms
Same findings
Same disease (?)

Same Drug....

Different Effects

Possible Reasons:
Non-Compliance...
Drug-drug interactions...
Chance...

Or....

Genetic Differences

PEOPLE ARE DIFFERENT!

Exposure  Exposure  Exposure
The Gene for...

The study of genetically controlled variations in drug response

Much individuality in drug response is inherited (polymorphism)

PHARMACOGENETICS
Human genome contains 30,000 to 40,000 genes

100,000 different proteins: possible drug targets

0.1% = almost 3 million single nucleotide polymorphism in which a nucleotide is exchanged for another at a given position

99.9% Identical

To be important SNPs must affect either function or amount of a protein
Ethnic Differences Correlate well with Genetic Background

GENETIC POLYMORPHISMS

Pharmacokinetic
- Metabolizing Enzymes
- Transporters
- Plasma protein binding

Pharmacodynamic
- Target Proteins
  - Receptors
  - Ion channels

Idiosyncratic Response
Variation in Target Proteins

Variations in target proteins or their pathways can influence the outcome of pharmacotherapy.

- **Amount**
- **Structure**
- **Function**

Variation in $\beta_2$-Adrenergic Receptor

- $\beta_2$-Receptor mediates the relaxation of smooth muscle in small airways.

$\beta_2$-Receptor agonists are used for asthma.
Variation in $\beta_2$-Adrenergic Receptor

$\beta_2$-Receptor is a G-protein receptor: highly polymorphic

Amino Acid 16:
60% Hispanic/Caucasian SNP for glycine G16
The other 40% arginine R16

Variation in $\beta_2$-Adrenergic Receptor

- Individuals with G16 variant acutely downregulate $\beta_2$-receptor in response to agonists
- Albuterol is less effective in G16 individuals
- First step toward developing an effective pharmacological strategy for such patients
Variation in Enzymes of Drug Metabolism

Poor Metabolizer \leftrightarrow Ultra-Metabolizer

- Deleted gene
- Multiple genes
- Toxicity
- Normal Response
- Diminished Response

PGt and Drug Metabolism

Same dose but different plasma concentrations

Patient A

\[ \text{GCCGCCTC} \]

Wild type

Patient B

\[ \text{GCCACCTC} \]

Mutation

Wild type

Mutation

CYP450

Concentration vs. Time
PGt: Possible Impact on PK and Dose-Response

Efficacy: reduction in anxiety and symptoms of depression
Example: Nortriptyline
Safety: tachycardia, arrhythmias and drowsiness

Individualizing Therapy is Important for Drugs with a Narrow Therapeutic Range

Some drugs have such a wide therapeutic range that individualizing the dose is not important

e.g. penicillin
Safe to prescribe dose effective for >90% of population

e.g. anticancer drug
Difficult to prescribe effective non-toxic dose
Atypical Plasma Cholinesterase

- a rapid acting, rapid recovery muscle relaxant - 1951
- usual paralysis lasted 2 to 6 min in patients
- occasional pt exhibited paralysis lasting hrs
- cause identified as an “atypical” plasma cholinesterase

Hydrolysis by pseudocholinesterase

- choline
- succinylmonocholine

Atypical Plasma Cholinesterase

- Atypical plasma cholinesterase has 1/100 the affinity for succinylcholine as normal enzyme
- occurs in 1:2500 individuals

Adapted from: Pharmac Ther 47:35-60, 1990.

Log molar dibucaine conc.

Typical

Atypical

normal enzyme inhibited > 70%
abnormal inhibited ≤ 30%
Antianginal Drugs (Nitrates)

Nitroglycerin (Glyceryl Trinitrate); NITRO-BID NITROSTAT

Isosorbide Dinitrate; ISORDIL, SORBIRATE

Isosorbide -5-Mononitrate; IMDUR, ISMO

Antianginal Drugs & Methemoglobin Reductase

- Methemoglobin is hemoglobin that has been oxidized from the ferrous (Fe++) to the ferric (Fe+++) state, thus unable to bind oxygen.
- The NADH- methemoglobin reductase enzyme reduces methemoglobin to hemoglobin.
- Methemoglobinemia results from either inadequate enzyme activity or too much methemoglobin production.
Antianginal Drugs & Methemoglobin Reductase

- Deficiency of methemoglobin reductase is inherited as an autosomal recessive trait and occurs with increased frequency in Inuit and Alaskan Native Americans.
- Heterozygotes have approximately 50% enzyme activity but without cyanosis, although they are predisposed to the development of toxic methemoglobinemia when exposed to nitrates and other stress.

A family illustrating the inheritance of a deficiency in methemoglobin reductase.

N-ACETYLTRANSFERASE POLYMORPHISM

XENOBIOTICS SUBJECT TO POLYMORPHIC ACETYLATION IN MAN

**Hydrazines**
- isoniazid
- hydralazine
- phenylzine
- acetylhydrazine
- hydrazine

**Arylamines**
- dapsone
- procainamide
- sulfamethazine
- sulfapyridine
- aminogluthethimide

**Carcinogenic Arylamines**
- benzidine
- β-naphthylamine
- 4-aminobiphenyl

*Drugs metabolized to amines*
- sulfasalazine
- nitrazepam
- clonazepam
- caffeine

ETHNIC DIFFERENCES IN THE DISTRIBUTION OF ACETYLATOR PHENOTYPE

<table>
<thead>
<tr>
<th>Population</th>
<th>% Slow</th>
<th>% Hetero Fast</th>
<th>% Homo Fast</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Indians</td>
<td>59</td>
<td>35.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Caucasians</td>
<td>58.6</td>
<td>35.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Blacks</td>
<td>54.6</td>
<td>38.6</td>
<td>6.8</td>
</tr>
<tr>
<td>Eskimos</td>
<td>10.5</td>
<td>43.8</td>
<td>45.7</td>
</tr>
<tr>
<td>Japanese</td>
<td>12</td>
<td>45.3</td>
<td>42.7</td>
</tr>
<tr>
<td>Chinese</td>
<td>22</td>
<td>49.8</td>
<td>28.2</td>
</tr>
</tbody>
</table>

Many CYP450 Enzymes Are Polymorphic: Example CYP 2C19 & CYP 2D6

Family: CYP 2
Subfamily: CYP 2C19
Gene: CYP 2C19*3
• Responsible for metabolism of 40% of all Rx drugs

Family: CYP 2
Subfamily: CYP 2D6
Gene: CYP 2D6*3

OXIDATION POLYMORPHISM

CYP2C19 Polymorphism

- First detected from unusual response to anti-epileptic drug mephenytoin (dysphoria/sedation)
- 3-6% of Whites and African Americans, but up to 25% of Chinese/Japanese/Koreans are PMs
- The common true null mutations leading to PM status result from splicing defects (*2) or the loss of start (*4) and stop (*3) codons

<table>
<thead>
<tr>
<th>c.G636A</th>
<th>Exon 4</th>
<th>Pro Trp Ile Gln</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19*1</td>
<td>…CCC TGG ATC CAG gta…</td>
<td>Pro Trp Ile Gln</td>
</tr>
<tr>
<td>CYP2C19*3</td>
<td>…CCC TGA ATC CAG gta…</td>
<td>Pro Stop</td>
</tr>
</tbody>
</table>

(Truncation of protein at aa 211 - loss of heme/substrate binding domains)

<table>
<thead>
<tr>
<th>c.G681A</th>
<th>Exon 5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ile Cys</td>
<td></td>
</tr>
<tr>
<td>CYP2C19*1</td>
<td>…cttag ATA TGC…GGGAA</td>
</tr>
<tr>
<td>CYP2C19*2</td>
<td>…cttag atatgc………ag GAA</td>
</tr>
</tbody>
</table>

(40 bp deletion from mRNA and premature stop 20 aa downstream in new exon-5)
Phenytoin

Phenytoin Metabolism

Aromatic hydroxylation

Deficient para-hydroxylation will lead to increase phenytoin levels
Increased toxicity: nystagmus, ataxia and motor impairment
## Frequency of CYP2C19 Poor Metabolizers

<table>
<thead>
<tr>
<th></th>
<th>Phenotype</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africans</td>
<td>4.1</td>
<td>3.8</td>
</tr>
<tr>
<td>African-Americans</td>
<td>1.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Caucasians</td>
<td>2.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Chinese</td>
<td>13.6</td>
<td>13.8</td>
</tr>
<tr>
<td>Japanese</td>
<td>20.3</td>
<td>17.0</td>
</tr>
<tr>
<td>Koreans</td>
<td>13.7</td>
<td>16.8</td>
</tr>
<tr>
<td>Amerindians</td>
<td>5.7</td>
<td></td>
</tr>
</tbody>
</table>

## CYP2C19 Substrates

- S-mephenytoin
- hexobarbital
- R-mephobarbital
- phenytoin
- diazepam
- citalopram
- omperazole
- lansoprazole
- pantoprazole
- R-warfarin (8-OH)
- propranolol (in part)
- imipramine
- clomipramine
- amitryptyline
- proguanil
- teniposide
- nilutamide
- indomethacin
- moclobemide
Cure rates for H. pylori infections may depend upon CYP2C19 genotypes

- 62 patients with duodenal or gastric ulcer
- treated with omeprazole 20 mg and amoxicillin
- 20% of Asian and 4% of whites are homo. variant

**CYP 2D6 POLYMORPHISM**

The polymorphismus of CYP 2D6 (debrisoquine 4-hydroxylase) has been studied in great detail, as metabolic differences have first been described for debrisoquine and sparteine (antipsychotics)

Of the 75 alleles, 26 exprime CYP2D6 proteines

see http://www.imm.ki.se/CYPalleles/cyp2d6.htm
**CYP 2D6 Polymorphism (II)**

<table>
<thead>
<tr>
<th>Designation</th>
<th>Characteristic mutation(s)</th>
<th>Enzyme activity</th>
<th>Allelic frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6*1</td>
<td>Wild type</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>CYP2D6*2</td>
<td>G_{1740}C, C_{298}T, G_{480}C substitutions</td>
<td>Normal</td>
<td>30</td>
</tr>
<tr>
<td>CYP2D6*3</td>
<td>A_{2877} deletion</td>
<td>Deficient</td>
<td>2</td>
</tr>
<tr>
<td>CYP2D6*4</td>
<td>G_{Val238}A substitution</td>
<td>Deficient</td>
<td>22</td>
</tr>
<tr>
<td>CYP2D6*5</td>
<td>Gene deletion</td>
<td>Deficient</td>
<td>2</td>
</tr>
<tr>
<td>CYP2D6*6</td>
<td>T_{PvuII} deletion</td>
<td>Deficient</td>
<td>2</td>
</tr>
<tr>
<td>CYP2D6*7</td>
<td>A_{3021}C substitution</td>
<td>Deficient</td>
<td>0.1</td>
</tr>
<tr>
<td>CYP2D6*8</td>
<td>G_{InvT} substitution</td>
<td>Deficient</td>
<td>0.1</td>
</tr>
<tr>
<td>CYP2D6*9</td>
<td>(A_{2171}T-A_{2186}) or (G_{2303C2306}) deletion</td>
<td>Decreased</td>
<td>1.5</td>
</tr>
<tr>
<td>CYP2D6*10</td>
<td>C_{184}T, G_{144}C, G_{658}C substitutions</td>
<td>Decreased</td>
<td>1.5</td>
</tr>
<tr>
<td>CYP2D6*11</td>
<td>G_{Glu37}A substitution</td>
<td>Deficient</td>
<td>0.1</td>
</tr>
<tr>
<td>CYP2D6*12</td>
<td>G_{Glu12}A substitution</td>
<td>Deficient</td>
<td>0.1</td>
</tr>
<tr>
<td>CYP2D6*13</td>
<td>Hybrid: 2D7 exon 1, 2D6 exons 2-9</td>
<td>Deficient</td>
<td>0.1</td>
</tr>
<tr>
<td>CYP2D6*14</td>
<td>G_{1846A} substitution</td>
<td>Deficient</td>
<td>0.1</td>
</tr>
<tr>
<td>CYP2D6*15</td>
<td>T_{PvuII} insertion</td>
<td>Deficient</td>
<td>0.1</td>
</tr>
<tr>
<td>CYP2D6*16</td>
<td>Hybrid: 2D7 exons 1-7, 2D6 exons 8-9</td>
<td>Deficient</td>
<td>0.1</td>
</tr>
<tr>
<td>CYP2D6*1×2</td>
<td>Gene duplication</td>
<td>Increased</td>
<td>1</td>
</tr>
<tr>
<td>CYP2D6*1×2</td>
<td>Gene duplication</td>
<td>Increased</td>
<td>1.5</td>
</tr>
<tr>
<td>CYP2D6*1×2</td>
<td>Gene duplication</td>
<td>Deficient</td>
<td>0.5</td>
</tr>
</tbody>
</table>


---

**CYP 2D6 Polymorphism (III)**

**variability of debrisoquine-4-hydroxylation**

![Debrisoquine-4-hydroxylation diagram](image)

<table>
<thead>
<tr>
<th>MR-Wert</th>
<th>Metabolic rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>heterozygote extensive metabolizers</td>
</tr>
<tr>
<td>10</td>
<td>homozygote poor metabolizers</td>
</tr>
<tr>
<td>10</td>
<td>homozygote extensive metabolizers</td>
</tr>
</tbody>
</table>

Lit: T. Winkler *Deutsche Apothekerzeitung* 140 (2000) 38
### Frequency of CYP 2D6 Poor & Rapid Metabolizers

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Poor</th>
<th>Rapid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasians</td>
<td>5-10%</td>
<td>rare</td>
</tr>
<tr>
<td>Asians</td>
<td>1-2%</td>
<td></td>
</tr>
<tr>
<td>Ethiopians</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Spaniards</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

### CYP2 D6 Substrates

- Antidepressants
  - Haloperidol
  - β-Blockers
- Dextrometorphan
- Codeine
- Amphetamine
- Flecanide
- Phenformin
IDIOSYNCRATIC EFFECTS

- Not caused by variations in target proteins or metabolizing enzymes
- Chance interaction between the drug and some unusual aspect of the physiology
- Hard to predict

Types of Idiosyncratic Responses

- Drug toxicity due to deficient metabolism
- Increased sensitivity to drug effect
- Novel drug effect
- Decreased responsiveness to drug
- Abnormal distribution of material
**Increased Sensitivity to Drug Effect**

- Nitrites and other drugs causing methemoglobinemia (due to oxidizing effects) - basis is abnormal hemoglobins (M and H)
- Aminoglycoside antibiotic-induced deafness* -- basis unknown; apparent transmission by females
- Chloramphenicol-induced bone marrow depression* -- basis unknown

**Drugs and Chemicals Unequivocally Demonstrated to Precipitate Hemolytic Anemia in Subjects with G6PD Deficiency**

<table>
<thead>
<tr>
<th>Acetanilide</th>
<th>Nitrofurantoin</th>
<th>Primaquine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylene Blue</td>
<td>Sulfacetamide</td>
<td>Nalidixic</td>
</tr>
<tr>
<td>Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naphthalene</td>
<td>Sulfanilamide</td>
<td></td>
</tr>
<tr>
<td>Sulfapyridine</td>
<td>Sulfamethoxazole</td>
<td></td>
</tr>
</tbody>
</table>
Glucose-6-Phosphate Dehydrogenase Activity

Effects >100 million worldwide

INCIDENCE OF G6PD DEFICIENCY IN DIFFERENT ETHNIC POPULATIONS

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Incidence(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazic Jews</td>
<td>0.4</td>
</tr>
<tr>
<td>Sephardic Jews</td>
<td></td>
</tr>
<tr>
<td>Kurds</td>
<td>53</td>
</tr>
<tr>
<td>Iraq</td>
<td>24</td>
</tr>
<tr>
<td>Persia</td>
<td>15</td>
</tr>
<tr>
<td>Cochin</td>
<td>10</td>
</tr>
<tr>
<td>Yemen</td>
<td>5</td>
</tr>
<tr>
<td>North Africa</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Iranians</td>
<td>8</td>
</tr>
<tr>
<td>Greeks</td>
<td>0.7-3</td>
</tr>
</tbody>
</table>
INCIDENCE OF G6PD DEFICIENCY IN DIFFERENT ETHNIC POPULATIONS

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Incidence(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asiatics</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>2</td>
</tr>
<tr>
<td>Filipinos</td>
<td>13</td>
</tr>
<tr>
<td>Indians-Parsees</td>
<td>16</td>
</tr>
<tr>
<td>Javanese</td>
<td>13</td>
</tr>
<tr>
<td>Micronesians</td>
<td>&lt;1</td>
</tr>
<tr>
<td>African-Americans</td>
<td>10</td>
</tr>
</tbody>
</table>

Primaquine

- Haemolysis is pronounced in individuals who are glucose 6-phosphate dehydrogenase deficient (~10% of black American males).
- Primaquine itself is not toxic to erythrocytes.
- It has been proposed that there is extensive metabolism to unstable catechols and quinones.
- Primaquine metabolites can place the erythrocyte under oxidative stress.
- If not rectified, oxidative stress results in oxidation of haemoglobin and critical protein thiols, with Heinz body formation and lysis.
Acute Intermittent Porphyria

- Porphyrias are associated with overproduction of porphyrins: acute abdominal pain, psychosis, “purple pee”.
- Acute intermittent porphyria the exacerbation is induced by barbiturates, sulfonamides, and griseofulvin

Malignant Hyperthermia & Halothane

- Malignant Hyperthermia- 1/20,000 with succinylcholine
- Classic-- rapid rise in body temperature, muscle rigidity, tachycardia, rhabdomyolysis, acidosis, hyperkalemia
- Life threatening- I.v. dantrolene
- Genetic defect in the muscle
- Mutations in the Ryanodine receptor (calcium release channel)
- Halothane induces potentiation of Ca activity in susceptible patients
### Distinguishing Toxic, Idiosyncratic and Allergic Responses to Drugs

<table>
<thead>
<tr>
<th></th>
<th>Toxic</th>
<th>Idiosyncratic</th>
<th>Allergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-related</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>What drugs</td>
<td>All</td>
<td>Few</td>
<td>Many</td>
</tr>
<tr>
<td>Prior exposure</td>
<td></td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Receptor</td>
<td>Receptor</td>
<td>Ag-Ab</td>
</tr>
<tr>
<td>Effect antagonized</td>
<td>Antagonists</td>
<td>Antagonists</td>
<td>Anti-H; SAD</td>
</tr>
</tbody>
</table>

### Allergic skin reaction

- Penicillin rash
PHARMACOGENETICS & CLINICAL PRACTICE

Genetically Based Optimization of Drug Dosing

- Responders
- Non-responders
- Toxic responders

Responders
Non-responders
Toxic responders
Genetically Based Optimization of Drug Dosing

Current Applications of Pharmacogenetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th>Gene</th>
<th>PGx Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-MP</td>
<td>ALL</td>
<td>TPMT</td>
<td>Safety &amp; Efficacy</td>
</tr>
<tr>
<td>Melacine</td>
<td>Melanoma</td>
<td>Not published</td>
<td>Safety</td>
</tr>
<tr>
<td>5-FU</td>
<td>Colorectal Cancer</td>
<td>TS</td>
<td>Safety</td>
</tr>
<tr>
<td>Herceptin</td>
<td>Breast Cancer</td>
<td>HER2</td>
<td>Efficacy</td>
</tr>
</tbody>
</table>
Pharmacogenetics: Use in drug delivery

ALL, 6MP and polymorphic TPMT

Children $\rightarrow$ TPMT $\rightarrow$ Toxicity

Children $\rightarrow$ TPMT $\rightarrow$ Poor response

**THE WALL STREET JOURNAL**

**MARKETPLACE**

**SCIENCE**

New Era of Personalized Medicine

Targeting Drugs For Each Unique Genetic Profile

By Robert Langreth

THE PHARMACEUTICAL industry makes billions of dollars a year selling over-the-counter medications, but now the trend is to come up with tailor-made drugs that will treat people based on their individual genetic makeup.
**Pharmacotherapy of Tomorrow?**

**today**
- empirical prescription
  - "mass market"

**future**
- rational prescription
  - "individualized"

- individual physician experience
  - Cost: time, money & well-being

- informed physician diagnosis
  - Savings: time, money & illness

**Pharmacogenetics: to deliver ‘right medicine, right dose, to right patient’**
Personalized Medication in the Future

In the future (? years), your doctor will be able to select the best drug to treat your disease and the appropriate dose based on knowledge of your specific genetic makeup!