Pharmacogenetics of Drug Metabolism: Part 1

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Disclosure

• I declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

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Pharmacogenetics of Drug Metabolism

• Genetic polymorphisms of important drug metabolizing enzymes
• Broadly classified into
  — Oxidative drug metabolism (Phase I)
  — Conjugative drug metabolism (Phase II)
• Phase I enzymes include CYP, esterases
Classification system for Cytochrome P450 enzymes

- Root ‘CYP’ + number designating the family + letter for the subfamily + number for the individual P450 form.
- P450s from the same family share more than 40% sequence homology
- P450s from the same subfamily share more than 55% sequence homology
## Cytochrome P450 Enzyme Classification

**CYP2D6  Enzyme name (classification)**

<table>
<thead>
<tr>
<th>CYP</th>
<th>Cytochrome P450</th>
<th>&gt; 40% homology</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Family</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Subfamily</td>
<td>&gt; 55% homology</td>
</tr>
<tr>
<td>6</td>
<td>Enzyme</td>
<td>unique aa sequence</td>
</tr>
</tbody>
</table>
Human cytochrome P450 allele nomenclature committee

• “Wild type” enzyme designated *1
  – CYP2D6*1
  – Reference allele
  – “normal” activity or metabolism

• Variants sequentially numbered
  i.e., CYP2D6*4 is 3rd variant identified
CYP Enzyme Expression

Liver

- CYP2B6: 1%
- CYP2A6: 6%
- CYP2C8, 2C9, 2C19: 25%
- CYP2C19: 2%
- CYP2D6: 2%
- CYP2E1: 9%
- CYP3A4, 3A5: 40%
- CYP1A2: 18%

Intestine

- CYP2C9: 14%
- CYP2D6: 1%
- CYP2J2: 1%
- CYP3A: 82%

Contribution of CYPs to Drug Metabolism

CYP3A (48%)
- Cyclosporine
- CCBs (Nifedipine)
- Midazolam
- Ritonavir
- Statins

CYP2B6 (2%)
- Efavirenz
- Methadone

CYP2C8/2C9/2C19 (18%)
- Losartan
- Phenytoin
- NSAIDs
- Warfarin
- PPIs

CYP2A6 (2%)
- Nicotine

CYP2D6 (25%)
- Antidepressants
- Beta-Blockers
- SSRIs

CYP2E1 (3%)
- Inhalational Anesthetics
- Chlorzoxazone
Sources of Variation in Drug Metabolism

- Pharmacogenetics
- Concomitant drug therapies or environmental factors
  - Induction or inhibition
- Disease states
  - Liver Disease
CYP Pharmacogenetics

- Genetic variation is a major cause of inter-individual variability in drug response.
- Genetic variation has now been described for all of the major CYP enzymes that contribute to human drug and xenobiotic metabolism.
CYP Pharmacogenetics

• For some enzymes (e.g., CYP2D6 and CYP2C19), allelic variants produce “loss-of-function” alleles

• Broadly, can be categorized as:
  – fairly well conserved
    (e.g., CYP1A2, CYP2E1, CYP3A4)
  – highly polymorphic
    (e.g., CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A5)
CYP Pharmacogenetics

- **Nonsynonymous SNPs:** amino acid change often associated with enzymes having catalytic activity altered as compared to the fully functional *1 allele.
  - CYP2C9*2
  - CYP2D6*10

CYP2A6
CYP Enzymes

Phenotypes

• PMs: Poor metabolizers
• IMs: Intermediate metabolizers
• NMs: Normal metabolizers
• UMs: Ultrarapid metabolizers
CYP2D6-Dependent Polymorphic Metabolism

(adapted from Dahl et al., Pharmacogenetics 3:61, 1993)
$DBRR = \frac{Au_{4OHDEB}}{Au_{4OHDEB} + Au_{DEB}}$

$CMR = \frac{PX}{CAF}$

Index of Enzyme Activity
DBRR = \frac{Au_{4OHD}}{Au_{4OHD} + Au_{DEB}}

Index of Enzyme Activity
Clinical Consequences of CYP Genetic Polymorphisms

- Toxicity
  - NTI drugs that are inactivated
    - Phenytoin
- Reduced efficacy or therapeutic failure
  - Drugs that are activated
    - Codeine
Pharmacogenetics and Drug Metabolism

Same dose – different plasma concentrations

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genetic Mechanisms</th>
<th>Pharmacokinetic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Metabolizer (PM)</td>
<td>2 inactive alleles</td>
<td></td>
</tr>
<tr>
<td>Intermediate Metabolizer (IM)</td>
<td>2 decreased-activity alleles OR one active allele and one inactive allele OR one decreased-activity allele and one inactive allele</td>
<td></td>
</tr>
<tr>
<td>Normal Metabolizer (NM)</td>
<td>2 functional alleles (wild type)</td>
<td></td>
</tr>
<tr>
<td>Ultrarapid Metabolizer (UM)</td>
<td>Gene duplication in the absence of inactive or decreased alleles</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. Genetic mechanisms for CYP450 metabolic phenotypes and their pharmacokinetic implications (van der Welde et al., 2005).
Sources of Variation in Drug Metabolism

• Pharmacogenetics
• Concomitant drug therapies or environmental factors
  – Induction or inhibition
• Disease states
  – Liver Disease
CYP2D6 Inhibition by Quinidine


P < 0.0001
Sources of Variation in Drug Metabolism

• Pharmacogenetics
• Concomitant drug therapies or environmental factors
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• Disease states
  – Liver Disease

\( r_s = -0.794 \)
CPIC

• Formed in 2009
• Detailed gene-drug pharmacogenetic clinical practice guidelines
• CPIC guidelines are peer-reviewed and published in *Clinical Pharmacology and Therapeutics*
• PharmGKB posts supplemental information/data and updates.
• **Goal**: address some of the barriers to implementation of pharmacogenetic tests into clinical practice.
CPIC GUIDELINES

• Designed to help clinicians understand **HOW** available genetic test results should be used to optimize drug therapy, not **WHETHER** tests should be ordered.

• **Key Assumptions:**
  – Clinical genotyping will become more widespread
  – Genotype information available
<table>
<thead>
<tr>
<th>CPIC Level</th>
<th>Clinical Context</th>
<th>Level of evidence</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Genetic information should be used to change prescribing of affected drug</td>
<td>Preponderance of evidence is high or moderate in favor of changing prescribing</td>
<td>At least one moderate or strong action (change in prescribing) is recommended.</td>
</tr>
<tr>
<td>B</td>
<td>Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing</td>
<td>Preponderance of evidence is weak with little conflicting data</td>
<td>At least one optional action (change in prescribing) is recommended.</td>
</tr>
<tr>
<td>C/D</td>
<td>No prescribing actions are recommended because (a) clinical data absent or not clear, (b) dosing based on genetics convincingly makes no difference, or (c) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical.</td>
<td>Evidence levels can vary</td>
<td>No prescribing actions are recommended.</td>
</tr>
</tbody>
</table>
CPIC GUIDELINES

- Tables in guidelines
- Translate genotype information to phenotype to clinical recommendation
Additional Resources

- [http://www.cypalleles.ki.se/](http://www.cypalleles.ki.se/)
- [https://cpicpgx.org/](https://cpicpgx.org/)
- [https://www.pharmgkb.org/](https://www.pharmgkb.org/)
- [https://www.pharmgkb.org/page/pgxImplementationResources](https://www.pharmgkb.org/page/pgxImplementationResources)
  - Includes genotype-function translation tables.