Pharmacogenetics of CYP-mediated drug metabolism

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Objectives

• Describe the role of drug metabolism in the activation and inactivation of drugs

• Explain the nomenclature of cytochrome P450 enzyme phenotypes and genetic variants

• List examples of CYPs and drugs with pharmacogenetic associations, and how they would be used to guide drug and dose selection
Drug response reflects both pharmacokinetic and pharmacodynamic processes.

Pharmacodynamics

Assessed by measuring concentrations of drug analytes in timed biological specimens (e.g. blood)

Drug Response

Pharmacokinetics
Factors that affect the concentration of drug analytes in the blood

- Drug formulation, dose, route administered
- Drug-drug and food-drug interactions
- Clinical status, age, gender
- Genetic variation
- Rate of absorption
- Rate of metabolism
- Rate of elimination
Drug metabolism

- Metabolism = biochemical modification, usually mediated by specialized enzymes

  - **Phase I reactions**: oxidation, reduction, hydrolysis
    (e.g. CYP2C9, CYP2C19, CYP2D6, DPYD)
  - **Phase II reactions**: conjugation (e.g. UGT1A6, TPMT)

- Phase I and II reactions may occur independently or in sequence

- Reaction products usually have different pharmacological activity or potency than the parent drug
Cytochrome P450 (CYP) nomenclature

Gene/enzyme name

“Star” allele name

CYP2D6*4E

Family
Subfamily
Polypeptide
Allele
Allele subtype

100C>T
1661G>C
1846G>A
4180G>C

*1 suggests that no variants were detected

http://www.cypalleles.ki.se/
Functional status of common CYP2D6 alleles

- **Increased function**: xN
- **Normal function**: *1, *2
- **Decreased function**: *9, *10, *17, *29, *41

http://www.cypalleles.ki.se/
Genetic variation in drug metabolizing enzymes is used to predict the metabolic phenotype

<table>
<thead>
<tr>
<th>Allele 1</th>
<th>Allele 2</th>
<th>Gene duplication</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function</td>
<td>Normal function</td>
<td>Yes</td>
<td>Ultra-rapid metabolizer</td>
</tr>
<tr>
<td>Normal function</td>
<td>Increased function</td>
<td>No</td>
<td>Rapid metabolizer</td>
</tr>
<tr>
<td>Normal function</td>
<td>Normal function</td>
<td>No</td>
<td>Normal metabolizer</td>
</tr>
<tr>
<td>No function</td>
<td>Decreased function</td>
<td>No</td>
<td>Intermediate metabolizer</td>
</tr>
<tr>
<td>No function</td>
<td>No function</td>
<td>No/Yes</td>
<td>Poor metabolizer</td>
</tr>
</tbody>
</table>

Genetic variation in drug metabolizing enzymes is also used to predict the CYP2D6 activity score

<table>
<thead>
<tr>
<th>Allele functional status</th>
<th>Allele activity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function</td>
<td>1</td>
</tr>
<tr>
<td>Decreased function</td>
<td>0.5</td>
</tr>
<tr>
<td>No function</td>
<td>0</td>
</tr>
</tbody>
</table>

*The CYP2D6 activity score is a quantitative value based on the sum of the allele activity scores*

\[(\text{Allele 1 Score}) + (\text{Allele 2 Score}) = \text{Total Score}\]
Range of CYP2D6 activity scores based on diplotype (combinations of alleles)

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Diplotype (combinations of alleles)</th>
<th>Activity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid metabolizer</td>
<td>2 normal function alleles + gene duplication</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Normal metabolizer</td>
<td>2 normal function alleles</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1 normal function + 1 decreased function alleles</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>1 normal function + 1 no function alleles</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>1 no function + 1 decreased function alleles</td>
<td>0.5</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>2 no function alleles</td>
<td>0</td>
</tr>
</tbody>
</table>
Pharmacogenetics of drug metabolism can increase accuracy of drug and dose selection

• Perform testing to predict metabolic phenotypes (per gene)

• Apply relevant clinical and gene-based dosing guidelines (per drug)

• Counsel and monitor
  – Avoid interactions
  – Evaluate response
  – Optimize dose
Sources of dosing guidance

Pharmacogenomics Knowledge Base (pharmgkb.org)
  – Gene-based dosing guidelines
    • Clinical Pharmacogenetics Implementation Consortium (CPIC)
    • Dutch Pharmacogenomics Working Group (DPWG)
  – Clinical annotations (>3000)

Other Sources:
  – FDA labeling and “Table of Pharmacogenomic Biomarkers in Drug Labels” and “List of Cleared or Approved Companion Diagnostic Devices”
  – International drug labeling (European Union, Japan, Canada, etc.)
  – Professional Society Guidelines
  – Software tools and algorithms (public and proprietary)
Examples of dosing guidance

• *Drug avoidance* due to risk of toxicity

• *Drug avoidance* due to predicted lack of efficacy

• Dose adjustment and optimization

Must know what the consequence of metabolism is for an individual drug…
Drug analytes may be “active” or “inactive”
Drug analytes may be “active” or “inactive”
Simplified metabolism of codeine

Codeine -> Morphine (~10%) -> Morphine-3-glucuronide (~60%)

Drug effects

CYP2D6

UGT2B7
CYP2D6 phenotypes are associated with the amount of morphine generated from codeine

- **Poor metabolizer**: Higher than expected morphine concentration increases risk of dose-related toxicity!
- **Normal metabolizer**: Lower than expected morphine concentration increases risk of therapeutic failure!
- **Ultra-rapid metabolizer**: Bucharest...
CPIC guidance for extreme CYP2D6 phenotypes

- **Ultra-rapid metabolizers**: avoid codeine use due to potential for toxicity
- **Poor metabolizers**: avoid codeine use due to lack of efficacy

“Tramadol, and to a lesser extent hydrocodone and oxycodone, are not good alternatives because their metabolism is affected by CYP2D6 activity… To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone and hydromorphone, along with non-opioid analgesics, may be considered as alternatives for use in CYP2D6 poor and ultra-rapid metabolizers.”

https://www.pharmgkb.org/guideline/PA166104996
Examples of other CYP-based dosing guidelines

- CYP2D6
  - Tricyclic antidepressants
  - SSRI antidepressants
  - Antipsychotics
  - Opioids
  - Tamoxifen
  - Propafenone

- CYP2C9
  - Phenytoin
  - Warfarin
  - Antihyperglycemics

- CYP2C19
  - Tricyclic antidepressants
  - SSRI antidepressants
  - Clopidogrel
  - Voriconazole

- CYP3A4/CYP3A5
  - Tacrolimus

https://www.pharmgkb.org/
https://cpicpgx.org
Pharmacogenomics Research Network
Translational Pharmacogenetics Program

- University of Maryland
- University of Florida
- St Jude Children’s Research Hospital
- Vanderbilt University
- Mayo Clinic
- Ohio State University

Shuldiner et al., Clin Pharmacol Ther, 94(2):207-10, 2013
Metabolism isn’t always simple

- Most drugs are metabolized by many enzymes
- The balance of metabolic activity will influence the optimal dose of a drug
- Drug-drug and food-drug interactions can change the phenotype of one or multiple pathways
- Therapeutic concentrations of a drug does not guarantee response
Simplified metabolism of tamoxifen

- Involves multiple drug metabolizing enzymes
- Complicated interactions of genetic and non-genetic factors
- Therapeutic range not well established

Association of CYP2D6 phenotype and endoxifen concentrations

Multi-gene software/algorithmic approach

• Proprietary commercial products are available
  – GeneDose™ – many drug classes
  – YouScript® – many drug classes
  – GeneSight® – psychotropics, ADHD, analgesics
  – CNSDose – antidepressants

• Some integrate genetics with clinical and demographic data and/or offer interactive risk mitigation tools for polypharmacy

• All tools provide decision support tools but few are supported by randomized clinical trials, and no studies directly compare effectiveness of the clinical decision support

## Multi-gene software case example

### Medication Summary (more alternatives discoverable at GeneDose™ LIVE)

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-ADHD Agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidiabetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifungals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet Agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>*4/*4</td>
<td>Poor</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*2/*1</td>
<td>Intermediate</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*17/*1</td>
<td>Rapid</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>*3/*1</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

- **CYP2D6**: *4/*4 Poor
- **CYP2C19**: *2/*1 Intermediate
- **CYP2C9**: *17/*1 Rapid
- **CYP3A5**: *3/*1 Intermediate
GeneDose LIVE

- Cloud-based software tool
- Incorporates both genetic and nongenetic risk factors, lifestyle factors, drug-drug interactions, Beers criteria, etc.
- Includes >35,000 drug products
- Mitigates risk of adverse drug reactions
# Real time modeling of alternative drug choices

## Alternatives for Doxepin Hydrochloride 150mg Oral capsule

### Tricyclic and other cyclic Antidepressants

<table>
<thead>
<tr>
<th>Alternative drug</th>
<th>Δ drug</th>
<th>Δ regimen</th>
<th>Detail</th>
<th>Risk chart</th>
<th>Est. cost/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maprotiline Hydrochloride Oral tablet</td>
<td>-80</td>
<td>-90</td>
<td>☰</td>
<td><img src="image" alt="Risk Chart" /></td>
<td>Generic: $1.18</td>
</tr>
<tr>
<td>Mirtazapine Oral disintegrating tablet</td>
<td>-50</td>
<td>-60</td>
<td>☰</td>
<td><img src="image" alt="Risk Chart" /></td>
<td>Brand: $4.06, Generic: $0.94</td>
</tr>
<tr>
<td>Mirtazapine Oral tablet</td>
<td>-50</td>
<td>-60</td>
<td>☰</td>
<td><img src="image" alt="Risk Chart" /></td>
<td>Brand: $4.89, Generic: $0.44</td>
</tr>
<tr>
<td>Amitriptyline Hydrochloride Oral tablet</td>
<td>-40</td>
<td>-50</td>
<td>☰</td>
<td><img src="image" alt="Risk Chart" /></td>
<td>Generic: $0.65</td>
</tr>
<tr>
<td>Amoxapine Oral tablet</td>
<td>-35</td>
<td>-45</td>
<td>☰</td>
<td><img src="image" alt="Risk Chart" /></td>
<td>Generic: $1.02</td>
</tr>
<tr>
<td>Protriptyline Hydrochloride Oral tablet</td>
<td>-25</td>
<td>-35</td>
<td>☰</td>
<td><img src="image" alt="Risk Chart" /></td>
<td>Brand: $4.09, Generic: $1.64</td>
</tr>
<tr>
<td>Trimipramine Maleate Oral capsule</td>
<td>-20</td>
<td>-30</td>
<td>☰</td>
<td><img src="image" alt="Risk Chart" /></td>
<td>Brand: $5.73, Generic: $3.05</td>
</tr>
<tr>
<td>Imipramine Hydrochloride Oral tablet</td>
<td>-18</td>
<td>-28</td>
<td>☰</td>
<td><img src="image" alt="Risk Chart" /></td>
<td>Brand: $7.93, Generic: $0.13</td>
</tr>
</tbody>
</table>

Risk scores represent the cumulative total of warnings from sources such as the Food and Drug Administration, the American Geriatric Society, pharmaceutical labeling, medical publications, and research in genetics. Each risk has been weighted according to the impact severity associated with that risk. These results are intended to complement the complete medical records for this patient and should be used only by a qualified healthcare provider.
Models for implementation of multi-gene pharmacogenetic testing

- Application-based (e.g. psychiatry)
  - Pre-emptive
  - Reactive
- Not specific to an application
  - Elderly patients on polypharmacy
  - Personal or family history of adverse drug reactions
  - Wellness panels
Examples of positive outcomes from multigene pharmacogenetic testing

- Improved antidepressant efficacy
  - 2.52-fold greater rate of remission of major depressive disorder with testing (Singh, Clin Psychopharmacology Neuroscience, 2015)

- Reduced pharmacy costs
  - $1035.60 savings over 1 yr in total medication costs with testing in cohort of psychiatric patients (Winner et al, Current Medical Research & Opinion, 2015)

- Reduced rates of hospitalization
  - 9.8% with testing versus 16.1% without testing in cohort of patients ≥65 yrs (Brixner et al, J Medical Economics, 2015)

- Improved adherence with therapy
Are more genes better?

• In a review of 22 proprietary algorithms for clinical validity, there were 46 genes represented (Bousman, *Lancet Psychiatry*, 2016)
  – 25 (53%) were associated with supporting evidence graded by the PharmGKB databased as preliminary or low
  – 9 (20%) were associated with high levels of evidence, only 3 of which are relevant to psychotropics: CYP2D6, CYP2C19 and HLA-B
  – All algorithms include CYP2D6 and CYP2C19; most also include CYP2C9 and CYP3A4/5

• 39.1% of patients ≥65 receive at least one drug metabolized by CYP2D6, CYP2C19 and/or CYP2C9 (Kuch et al, *Health Informatics*, 2016)
Conclusions

• CYP pharmacogenetics can help guide drug and dose selection for an individual patient, particularly to minimize adverse drug reactions and therapeutic failure.

• Pharmacogenetic testing does not replace the need for dose optimization or clinical monitoring.

• Patients and providers should recognized that the field of clinical pharmacogenetics is evolving and guidelines continue to improve.