Genetic Testing for Analgesic Optimization in Pain Management

Jauchia Blythe, Ph.D.
Scott Miscovich, M.D.
Pain

- Very personal experience
- Most common reason for physician consultation in US
- Varies with type of stimulation, pathways, sensitivity, tolerance, side of body, hair color
"A stabbing pain, you say?"
Pain Management with Opioids

- Not one size fits all
- Analgesic effect varies with weight, age, gender, diet, smoking, general health, genetics, prior opioid use, opioid formula
Genetic Testing – Early Years

- Mostly for prenatal and newborn screenings, disease diagnosis, and carrier identification
- Phenylketonuria, trisomy 21, hemophilia, sickle cell, Tay-Sachs, cystic fibrosis, Huntington disease
Genetic Testing – New Era

- Predictive testing – breast and colorectal cancers
- Forensic testing – IDs criminals, victims, biological relationships
- Pharmacogenetic testing (PGT) – detects genetic variations to predict response to medication
Currently Available PGT

- Cytochrome P450 enzymes (CYPs)
  - CYP1-3 oxidize 75% of all meds
- Glucuronyltransferase (UGTs)
  - Important for phase II metabolism
- HER2 – trastuzumab (cancer)
- VKORC1 – warfarin (thrombosis)
- HLA-B – abacavir (HIV)
## Pain Med Enzymes

<table>
<thead>
<tr>
<th>CYP2D6</th>
<th>CYP3A4</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Fentanyl</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Pethidine</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
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</tr>
</tbody>
</table>
What Does PGT Provide?

- Patient enzyme genotypes
- Patient drug metabolizing ability
What Do Physicians Do?

- Provide personalized medicine
- Choose more effective meds
- Choose safer dosage
- Minimize adverse drug reactions and toxicity
- Avoid drug interaction
- Prevent overdose and death
"You gotta be kidding! Your back still hurts?!"
Alleles

- Single nucleotide polymorphisms or SNPs are caused by DNA mutations
- Combinations of normal (wild type) and common SNP (variant) alleles produce enzymes of different effectiveness
Metabolizer Type

- Poor metabolizer (PM)
  - No/very slow metabolism
- Intermediate metabolizer (IM)
  - Slow metabolism
- Extensive metabolizer (EM)
  - Normal metabolism
- Ultra-rapid metabolizer (UM)
  - Fast metabolism
## Distribution of Metabolizers

<table>
<thead>
<tr>
<th></th>
<th>CYP2D6</th>
<th>CYP2C9</th>
<th>CYP2C19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PM</strong> (none)</td>
<td>10%</td>
<td>3%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>IM</strong> (slow)</td>
<td>35%</td>
<td>35%</td>
<td>29%</td>
</tr>
<tr>
<td><strong>EM</strong> (normal)</td>
<td>48%</td>
<td>60%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>UM</strong> (fast)</td>
<td>7%</td>
<td>2%</td>
<td>30%</td>
</tr>
</tbody>
</table>
### CYP2D6 Ethnic Distribution

<table>
<thead>
<tr>
<th>Type</th>
<th>Ethnic Groups</th>
</tr>
</thead>
</table>
| **PM** (none) | 9% Caucasians  
4% African Americans  
1% Asians           |
| **IM** (slow)  | 10% Caucasians  
50% Asians                             |
| **UM** (fast)  | 20% N Africans + Mediterranean  
3% Caucasians       |
When Rx is Drug

- Analgesic effect occurs before metabolism

Methadone $\xrightarrow{\text{CYP3A4}}$ EDDP

- EM?
- PM and IM?
- UM?
When Rx is Pro-Drug

- Analgesic effect occurs after metabolism

- EM?
- PM and IM?
- UM?
## Which is What?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enzyme</th>
<th>Metabolite</th>
</tr>
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<tbody>
<tr>
<td>Codeine</td>
<td>CYP2D6</td>
<td>Morphine</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>CYP2D6</td>
<td>Hydromorphone</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>CYP2D6</td>
<td>Oxymorphone</td>
</tr>
<tr>
<td>Tramadol</td>
<td>CYP2D6</td>
<td>O-desmethyltramadol</td>
</tr>
<tr>
<td>Morphine</td>
<td>UGT2B7</td>
<td>M-3-glucuronide</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>UGT2B7</td>
<td>HM-3-glucuronide</td>
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<tr>
<td>Fentanyl</td>
<td>CYP3A4</td>
<td>Norfentanyl</td>
</tr>
<tr>
<td>Methadone</td>
<td>CYP3A4</td>
<td>EDDP</td>
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Drug Interactions

- When presence of substances affects function of enzymes

- Two ways
  - Inducers – enhance enzyme activity
  - Inhibitors – reduce enzyme activity
# Potent Inducers and Inhibitors

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Inducers</th>
<th>Inhibitors</th>
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<tbody>
<tr>
<td>CYP2D6</td>
<td>rifampin</td>
<td>amiodarone, Benadryl, fluoxetine</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>carbamazepine, St John’s wort, phenobarbital</td>
<td>clarithromycin, diltiazem, erythromycin</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>carbamazepine, phenytoin, rifampin</td>
<td>amiodarone, fluconazole, fluoxetine</td>
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Good Candidates for PGT

- Patients with
  - High dosage of pain meds
  - Severe adverse drug reactions
  - Unsuccessful drug trials
  - Multiple health issues or drug types
  - Unexplained urine drug test results
Pros

- Done once in life time
- Test several enzymes at once
- No need to stop current meds
- Non-invasive
Cons

- No magic bullet
- Environmental factors
- Drug transporters and receptors
- Education
Metabolizer Type and Opioid Dosage in Pain Patients

A Cross-sectional Study using Pharmacogenetic Testing
Hypothesis

Patients who require higher dosage of opioid Rx to maintain analgesic effect are likely to be poor or intermediate metabolizers.
Methods

Subjects

N=20 (10 men + 10 women)
Matched by age ± 5 yrs
Opioid Rx ≥ 100 mg morphine eq.

Pharmacogenetic Testing

CYP2D6 and CYP3A4 genes
Pacific Toxicology Laboratories
## Results

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<tr>
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