Pharmacogenetics of Cardiovascular Therapeutics

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The Concept

Genetic variation contributes to drug response – both therapeutic response and toxicity
Genetic Variation in Drug Metabolizing Enzymes and Drug Targets Influences Therapeutic Outcomes

Genes Determine Drug Effects

- Compound
- Absorption, Distribution, Metabolism, Excretion
- Concentration
- Adverse Reactions
- Beneficial Effects
- Cell
- G-Protein
- Receptor
- Gene
How does this work?

Chromosomes

Gene

Base pairs

SNP = single nucleotide polymorphism
Wild-type “normal”

DNA → Transcription → RNA → Translation → Protein
Normal activity

SNP Variant

DNA → Transcription → RNA → Translation → Protein
Reduced activity
No activity
Drug Metabolizing Enzymes
Warfarin
Metabolism and Site of Action of Warfarin

(Clin Pharmacol Therap 2006; 80:7-12)
Genetic Determinants of Warfarin Dose

CYP2C9
10% of variance in warfarin dose

VKORC1
35% of variance in warfarin dose
Average warfarin dose requirements, by ethnicity, to maintain a therapeutic INR

Johnson, J. A. Circulation 2008;118:1383-1393
### Ethnic Differences in Variant Allele Frequencies for Genes Important to Variable Warfarin Dose/Response (CYP2C9 and VKORC1)

<table>
<thead>
<tr>
<th>Variant</th>
<th>Whites</th>
<th>Blacks</th>
<th>Asians</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9*2</td>
<td>8% to 18%</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>CYP2C9*3</td>
<td>5% to 13%</td>
<td>1% to 2%</td>
<td>2% to 5%</td>
</tr>
<tr>
<td>Others</td>
<td>Rare/absent</td>
<td>2% to 4%</td>
<td>Rare/absent</td>
</tr>
<tr>
<td>VKORC1 variant</td>
<td>35% to 45%</td>
<td>8% to 10%</td>
<td>90% to 95%</td>
</tr>
</tbody>
</table>
Boxplot showing the distribution of warfarin dose by CYP2C9 and VKORC1 genotype

CYP2C9 & VKORC1 polymorphism for warfarin

Regression model using genotype, age, height

Caucasian population
Randomized PGx trial
Randomized PGx trial
Anderson et al. Circulation 2007;116:2563-70

<table>
<thead>
<tr>
<th>End Point</th>
<th>PG Group (n=101), %</th>
<th>STD Group (n=99), %</th>
<th>Absolute Percent Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out-of-range INRs,* all patients, mean (SD)</td>
<td>30.7 (22.9)</td>
<td>33.1 (22.9)</td>
<td>2.4</td>
</tr>
<tr>
<td>Out-of-range INRs, multiple variant patients</td>
<td>31.0 (21.4)</td>
<td>40.4 (25.4)</td>
<td>9.4</td>
</tr>
<tr>
<td>Out-of-range INRs, wild-type patients</td>
<td>28.1 (24.8)</td>
<td>36.9 (25.3)</td>
<td>8.8</td>
</tr>
<tr>
<td>Out-of-range INRs, wild-type and multiple variant patients</td>
<td>29.3 (23.4)</td>
<td>39.1 (25.2)</td>
<td>9.8</td>
</tr>
<tr>
<td>Out-of-range INRs, single variant patients</td>
<td>33.6 (22.1)</td>
<td>27.0 (17.8)</td>
<td>-6.6</td>
</tr>
</tbody>
</table>

PG indicates pharmacogenetic; STD, standard.
*Primary end point, intention-to-treat population.

Genotyping vs. expert coagulation clinic: realistic model for majority?
Warfarin Pharmacogenetics: Clinical Implications

• Genotyping has potential to achieve therapeutic INR more quickly and with less risk of bleeding
• Benefit of genotype-guided therapy depends on comparator group – specialized anticoagulation clinic vs. primary care physician
• Cost vs. benefit remains to be determined
Metoprolol

Carvedilol

Propafenone
CYP2D6

- Genetically poor metabolizers
  7-10% Caucasians and
  1-2% Asians and African Americans
- Medication-induced poor metabolism
  (strong inhibitors)
  fluoxetine
  paroxetine
  ritonavir
Metoprolol and CYP2D6

• Extensive 1\textsuperscript{st} pass metabolism via CYP2D6

• Oral bioavailability increased 2-4 fold in CYP2D6 PMs
METOPROLOL LEVELS IN POOR AND EXTENSIVE METABOLIZERS
Carvedilol and CYP2D6

- **Racemic mixtures**
  - $S(-) = \alpha + \beta$ blocker
  - $R(+) = \alpha$ blocker – metabolized CYP2D6

- **CYP2D6 PMs**
  - greater $\alpha/\beta$ blocker ratio and more hypotension
Propafenone and CYP2D6

• Racemic mixture
• Both isomers type IC actions
• One isomer has β-blocking activity and is metabolized by CYP2D6
• CYP2D6 PMs have more toxicity, especially bradycardia
PROPAFENONE DOSE AND TROUGH PLASMA CONCENTRATIONS IN POOR AND EXTENSIVE METABOLIZERS
Statins
KIF-6

- *KIF6* encodes kinesin-like protein 6, a member of the molecular motor superfamily.
- These proteins are involved in the intracellular transport of organelles, protein complexes, and mRNA.
- 719Arg mutation results in a mutated protein that affects binding.
KIF6 and CVD: Women’s Health Study
Shiffman et al. JACC 2008;51:444-8.
KIF-6 predicts statin efficacy
Iakoubova et al. JACC 2008;51:449-58
Statin-induced muscle injury

Statins induce myalgias in about 5-10% of subjects

ACC/AHA definitions:
1. Myalgia (complaints without serum CK)
2. Myositis (complaints with CK elevations)
3. Rhabdomyolysis (CK>10 URL)
4. Death (0.15 per 1 million)
SEARCH Trial “Study of the Effectives of Additional Reductions in Cholesterol and Homocysteine”  
(SEARCH Collaboration Group, NEJM 2008)

• 12,084 patients with AMI randomized to simvastatin 80 or 20mg
• 96 with myopathy on 80 mg simvastatin vs. matched controls with myopathy
• Genome-wide association study
SLCO1B1 Genotype Predicts Risk of Myopathy
Organic Anion-Transporter OAT1B1

- Encoded by SLC01B1 gene
- Mediates hepatic uptake of statins
- Higher statin blood concentrations with C allele
- Prevalence of C allele was 15%
- 60% of myopathy cases could be attributed to the C variant
## Determinants of Statin-Induced Myopathy

*(SEARCH NEJM 2008)*

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>8.8</td>
</tr>
<tr>
<td>SLC01B1 rs4149056</td>
<td></td>
</tr>
<tr>
<td>CC genotype</td>
<td>17.4</td>
</tr>
<tr>
<td>CT genotype</td>
<td>4.3</td>
</tr>
</tbody>
</table>

60% cases attributed to C variant
Clinical Implications

• Avoiding high dose simvastatin in carriers of C allele (15% of population) would reduce myopathy by 60%
• Avoiding high dose simvastatin in C allele homozygote (2% of population) would reduce myopathy by 25%
Clopidogrel
The Problem

Up to 30% of patients do not display adequate antiplatelet response to clopidogrel
Mechanisms of Action
(Nguyen 2005)
Enzymes That Convert Clopidogrel to Active Metabolites

CYP2C19
CYP3A
Pharmacogenetics of CYP2C19

- Low activity alleles: 2C19*2 and *3
- Prevalence of poor metabolizers
  - 3% Caucasians
  - 20-30% Asians
- Inhibited by omeprazole and other proton pump inhibitors
Plasma Clopidogrel Concentrations after 300 mg Loading Dose
(Kim Clin Pharmacol Therap 2008)
% Inhibition of Platelet Aggregation
(Kim Clin Pharmacol Therap 2008)
EXCELSIOR Trial
“Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate”
(Trenk IACC 2008)

• 797 patients undergoing PTCA and stenting
• ADP-induced residual platelet aggregation assessed after 600mg clopidogrel loading dose
• CYP2C9 genotyping
• One year incidence of death and myocardial infarction
Odds Ratios for High On-Clopidogrel Platelet Reactivity by CYP2C19 Genotype
(Trenk, JACC, 2008)
Cumulative Incidence of Death and MI by Pre-Discharge RPA
(Trenk, JACC, 2008)

[Graph showing cumulative incidence of death and MI by pre-discharge RPA. The graph includes two lines: one for RPA > 14% and one for RPA ≤ 14%. The Log-Rank P value is 0.004. The number of patients at risk for different time points are listed in the table below.]

<table>
<thead>
<tr>
<th>Days after PCI</th>
<th>No. at Risk RPA &gt; 14%</th>
<th>No. at Risk RPA ≤ 14%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>217</td>
<td>548</td>
</tr>
<tr>
<td>120</td>
<td>211</td>
<td>540</td>
</tr>
<tr>
<td>240</td>
<td>205</td>
<td>537</td>
</tr>
<tr>
<td>360</td>
<td>200</td>
<td>520</td>
</tr>
</tbody>
</table>
Proton Pump Inhibitors Reduce Clopidogrel Effectiveness
(Aubert, Circulation S815, 2008)

• 14,383 who underwent stent placement with clopidogrel
• 30% were also taking PPI
• CV events observed over 12 months

<table>
<thead>
<tr>
<th></th>
<th>C = PPI</th>
<th>C alone</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No preceding CV event</td>
<td>32%</td>
<td>21%</td>
<td>1.70 (1.62-1.97)</td>
</tr>
<tr>
<td>Preceding CV event</td>
<td>40%</td>
<td>26%</td>
<td>1.86 (1.12-2.12)</td>
</tr>
</tbody>
</table>
Clopidogrel and CYP2C9
Clinical Implications

- CYP2C9 PMs have reduced antiplatelet effects and may have higher risk of recurrent CV events
- Omeprazole inhibits CYP2C9 and decreases the platelet inhibiting effect of clopidogrel (plus aspirin)
- Omeprazole and other PPIs associated with increased CV risk in patients taking clopidogrel
- Need to weigh benefits of preventing GIB vs. risk of more CV events by use of PPIs (prasugrel may be the answer)
Why Pharmacogenomics in Cardiovascular Therapeutics?

• Avoid serious drug toxicity.
• Improve drug selection and dosing.
• FDA is very interested in new drug labeling.
• High throughput genotyping becomes less expensive. Every patient can carry their SNP profile.
## FDA Re-labeling Initiative

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enzyme</th>
<th>Goal</th>
<th>Year</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-MP</td>
<td>TPMT</td>
<td>safety</td>
<td>2003</td>
<td>complete</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>TPMT</td>
<td>safety</td>
<td>2003</td>
<td>complete</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>CYP2D6</td>
<td>safety</td>
<td>2004</td>
<td>complete</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>UGT1A1</td>
<td>safety</td>
<td>2004</td>
<td>complete</td>
</tr>
<tr>
<td>Warfarin</td>
<td>CYP2C9, VKORC1</td>
<td>safety</td>
<td>2005</td>
<td>complete</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>CYP2D6</td>
<td>efficacy</td>
<td>2006</td>
<td>pending</td>
</tr>
<tr>
<td>Abacavir</td>
<td>HLA-B*5701</td>
<td>safety</td>
<td>2007</td>
<td>completed</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-B*1502</td>
<td>safety</td>
<td>2007</td>
<td>completed</td>
</tr>
</tbody>
</table>