Pharmacogenetics: Challenges and Opportunities for Clinical Translation

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Disclosure

No Conflicts to Disclose

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Objectives

1. Definitions, potential of pharmacogenetics
2. Cardiovascular drugs as candidates for pharmacogenetics
3. Approaches to understanding genetic contribution to variable drug response
4. Intermediate endpoints vs. clinically meaningful outcomes
5. Ongoing studies, generating evidence
6. Challenges and opportunities in pharmacogenetics
How do we prescribe medications?

Patients with same diagnosis

One size fits all!

Predicted good response to tested drug

Predicted poor or nonresponse
Use different drug

Predicted increased toxicity risk
Decrease dose or use different drug
Drug response rate

- 30-60% response rate of drug therapies for Alzheimer’s, depression, rheumatoid arthritis, hypertension, osteoporosis

Adverse drug reactions (ADRs)

- Many ADRs are reported from medical errors, which could potentially be minimized when pharmacogenomic information is integrated into practice
- Up to 100,000 people/year die of medical errors in the U.S. (1999 IOM Report, To Err is Human)
  - ↑ Morbidity and Mortality
  - ↑ Cost
- Pharmacogenomics may improve drug response rate and minimize ADRs
What determines response or outcomes?

Prescribed dose

Administered dose

Concentration at sites of action

Intensity of responses

Administration
- medication errors
- patient compliance

Pharmacokinetics
- absorption
- distribution
- metabolism
- excretion

Sources of individual variation
- physiological variables
- pathological variables
- genetic variables
- drug interactions

Pharmacodynamics
- drug-receptor interaction
- patient's functional state
- placebo effects
Is variability in response common?

**LDL cholesterol changes by simvastatin 40 mg**

**Change in FEV\textsubscript{1} with inhaled corticosteroids in asthma**

study #1
study #2
study #3

**Blood pressure changes with β-blockade**

**QT changes with ibutilide**

Number of subjects

Mean: -7.8
SD: 8.01
Why do individuals respond differently?

- Variability in genes:
  - Drug metabolism genotype
  - Drug transporter genotype
  - Drug receptor genotype
  - Interactions

- Variability in environment:
  - Medications, Diet, Alcohol,
  - Exercise......
What is Pharmacogenetics?

- **Pharmacogenetics:** Effect of genetic variation in response to a drug in terms of therapeutic and adverse effects.
  - Primary candidate genes of interest include those encoding for drug receptors, metabolizing enzymes, and transporters.
- **Pharmacogenomics** more broadly involves genome wide analysis of the genetic determinants of drug efficacy and toxicity.
Drug Oxidation - Major Route of Drug Metabolism

Family of enzymes (CYPs) in liver

Proportion of Pharmaceuticals Metabolized by Individual Cytochrome P450’s

Major P450 Content of Human Liver

Shimada et al, 1994
Pharmacogenetics to Personalize Drug Therapy

- Assist in predicting risk of serious adverse events
- Assist in predicting efficacy/response
- Assist in determining which patients are/are not good candidates for therapy
- Assist in determining appropriate doses of medications
- Assist in improving therapy for large patient user groups
- Assist in determining which patients need more intensive or longer therapy
How do we understand the underpinnings of this variability?

- Clinical discriminators
- Small number of candidate polymorphisms in genes that regulate metabolism drug transport, drug targets
- Multiple variants in a drug pathway
- Whole genome association (GWA, exome)
Approach to assessing genetic variation

- **Single-gene approach**
  - Analyses the favourite candidate gene
  - Requires a large cohort to test the association
  - Carries the risk of not finding an association
  + Provides proof of principle if an association is found

- **Candidate-pathway-gene approach**
  - Analyses several functionally related candidate genes
  - Requires a smaller cohort to test the association
  - Carries the risk of missing important genes
  + Provides a more biologically meaningful association

- **Genome-wide approach**
  - Analyses the whole genome (expression and SNP)
  - Requires smaller cohorts to test associations
  - Biological meaning is difficult to assess because this approach carries a risk of false positives
  + Might identify new associations

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Evans 2006
Nature Reviews Cancer
Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect

Strong effect; Low PAR

? Aggregate effect ? PAR

Weak effect; High PAR
Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labels may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
<table>
<thead>
<tr>
<th>Drug</th>
<th>Biomarker</th>
<th>Label Selections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol (Coreg)</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
</tr>
<tr>
<td>Clopidogrel (Plavix)</td>
<td>CYP2C19</td>
<td>Boxed Warning, Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology</td>
</tr>
<tr>
<td>Isosorbide (Imdur) and Hydralazine (Apresoline)</td>
<td>NAT1; NAT2</td>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td>Metoprolol (Lopressor)</td>
<td>CYP2D6</td>
<td>Precautions, Clinical Pharmacology</td>
</tr>
<tr>
<td>Propafenone (Rhythmol)</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td>Warfarin (Coumadin)</td>
<td>CYP2C9</td>
<td>Dosage and Administration, Precautions, Clinical Pharmacology</td>
</tr>
<tr>
<td>Warfarin (Coumadin)</td>
<td>VKORC1</td>
<td>Dosage and Administration, Precautions, Clinical Pharmacology</td>
</tr>
<tr>
<td>Atorvastatin (Lipitor)</td>
<td>LDL receptor</td>
<td>Indications and Usage, Dosage and Administration, Warnings and Precautions, Clinical Pharmacology, Clinical Studies</td>
</tr>
</tbody>
</table>
Warfarin: An Overview

- Warfarin is the most widely used oral anticoagulant. It is used to prevent and treat clots (stroke, heart attack, atrial fibrillation (abnormal heart rhythm) and venous thromboembolism (formation/migration of blood clots in the veins).
- Warfarin prolongs the clotting time. It is monitored using the International Normalized Ratio. Most indications require an INR range of 2-3.

\[
\text{INR} = \left( \frac{\text{Patients Prothrombin Time}_{\text{seconds}}}{\text{Mean Normal Prothrombin Time}_{\text{seconds}}} \right)^{1/\text{ISI}}
\]

- Why do patients need different doses?
  - Age, gender, weight, other diseases, genes, dietary vitamin K, medications (e.g. CYP2C9 inhibitors-amiodarone) etc. One size does not fit all!

- Why is accurate dosing important?

- 54% of patients need about 5mg/day
- 34% of patients need <3 mg /day
- 12% patients need > 7 mg /day


Measure INR

Adjust dose

Repeat until INR is 2-3
Main Genes Involved in Warfarin Response

- **CYP2C9**
- **Warfarin**
- **VKORC1**

**Reduced Vitamin K**
- Hypofunctional Factors II, VII, IX, X
- Protein C, S, Z

**Oxidized Vitamin K**
- Activated Factors II, VII, IX, X
- Protein C, S, Z

**7-OH Warfarin**

**Pharmacogenetic approach vs Clinical approach vs Fixed-dose approach**

- Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data
- The International Warfarin Pharmacogenetics Consortium

Predicted Dose within 20% of Actual Dose (% patients)

- Pharmacogenetic approach
- Clinical approach
- Fixed-dose approach

## VKORC1 haplotype versus single SNP

<table>
<thead>
<tr>
<th></th>
<th>Predicted mean dose ± SD (mg/wk)</th>
<th>$R^2_{\text{full model}}$%</th>
<th>$R^2_{\text{VKORC1}}$%*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asians (n = 247)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$-1639G&gt;A$ (rs9923231)</td>
<td>21.55 ± 6.56</td>
<td>46.09</td>
<td>28.58</td>
</tr>
<tr>
<td>VKORC1 haplotype</td>
<td>21.55 ± 6.52</td>
<td>46.08</td>
<td>28.57</td>
</tr>
<tr>
<td><strong>Blacks (n = 365)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$-1639G&gt;A$ (rs9923231)</td>
<td>40.79 ± 8.18</td>
<td>27.02</td>
<td>4.15</td>
</tr>
<tr>
<td>VKORC1 haplotype</td>
<td>40.80 ± 8.13</td>
<td>27.41</td>
<td>4.54</td>
</tr>
<tr>
<td><strong>Whites (n = 556)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$-1639G&gt;A$ (rs9923231)</td>
<td>33.23 ± 11.02</td>
<td>50.94</td>
<td>23.16</td>
</tr>
<tr>
<td>VKORC1 haplotype</td>
<td>33.15 ± 11.06</td>
<td>51.53</td>
<td>23.75</td>
</tr>
</tbody>
</table>
Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes†

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/*1</td>
</tr>
<tr>
<td>GG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AA</td>
<td>3-4 mg</td>
</tr>
</tbody>
</table>

†Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the table. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

“The patient’s CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose. Table 5 describes the range of stable maintenance doses observed in multiple patients having different combinations of CYP2C9 and VKORC1 gene variants. Consider these ranges in choosing the initial dose.”
Genome Wide Association Studies

- Cooper et al 2008 (186 EA- CYP2C9 & VKORC1)
- Takeuchi et al 2009 (1,053 Swedes CYP2C9, VKORC1, CYP4F2)
## Warfarin Associated Hemorrhage

<table>
<thead>
<tr>
<th>Cohort Design</th>
<th>Polymorphisms Assessed</th>
<th>Risk of Hemorrhage, Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control</td>
<td>CYP2C9*2, *3</td>
<td>Minor: 2.7 (0.9–8.1)</td>
</tr>
</tbody>
</table>
| (36 cases, 52 controls)
|                |                        | Major: 3.7 (1.4–9.5)                    |
| Retrospective  | CYP2C9*2, *3           | Minor and major combined: 2.6 (1.2–5.7) |
| (n=180)        |                        |                                        |
| Retrospective  | CYP2C9*2, *3           | Minor: not evaluated or reported        |
| (n=186)        |                        | Major: 2.4 (1.2–4.9)                    |
| Prospective    | CYP2C9*2, *3, VKORC1 1173|                                        |
| (n=446; 227 African-Americans) |               | CYP2C9:                                 |
|                |                        | Minor: 1.3 (0.8–1.9)                    |
|                |                        | Major: 3.0 (1.2–7.5)                    |
|                |                        | VKORC1:                                 |
|                |                        | Minor: 0.8 (0.5–1.3)                    |
|                |                        | Major: 1.7 (0.7–4.4)                    |
Ongoing Studies: Warfarin

Clarification of Optimal Anticoagulation through Genetics

- 1,238 participant, multicenter, double-blind, RCT comparing two approaches to guiding warfarin therapy initiation:
  - 1) genotype-guided dosing
  - 2) clinical-guided dosing

- **Primary Outcome**: Percentage of time participants spend within the therapeutic INR range (1 month)
- **Secondary outcome**: Occurrence of INR greater than 4 or serious clinical event

Warfarin Adverse Event Reduction For Adults Receiving Genetic Testing at Therapy Initiation

- 7000 pts >65yoa, randomized and blinded, multi-center study
- 2300 pts with variants randomized to genotype-guided vs. clinical-guided dosing
- 1500 pts w/o variants will be followed through a registry for 30 days
- **Primary Outcome** to determine the utility of genetic testing in reducing the incidence of adverse events, both bleeding and thromboembolism at 30 days (60 and 90 days for 2° analysis)
Challenges and Opportunities

- Unique opportunity to improve patient care and decrease cost
- Translating findings from pharmacogenetic studies
- Evidence from large population based studies and/or clinical trials is needed
- Deluge of data informatics, analysis, methodology
- Implementation in practice
- Points that need to be considered
  - Population attributable risk
  - Cost of testing (payment)
  - Severity of the complication prevented and treatment benefit gained

Illustration: Roger Schillerstrom