Optimizing Pharmacotherapy with Pharmacogenomics

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Objectives

• Describe basic pharmacogenomic concepts.
• Identify genetic variations influencing pharmacokinetic and pharmacodynamic properties.
• Recognize examples of genetic information in drug labeling.
• Explain how pharmacogenomic principles affect drug therapy decisions.

Current Pharmacotherapy Approach

Population with a given disease

Same therapy for all patients

Intolerance

Good response

Poor or non-response
### Factors Influencing Drug Response

- Age
- Race/ethnicity
- Pharmacokinetics
- Concomitant diseases
- Concomitant medications

### Inter-Patient Variability in Warfarin Response

<table>
<thead>
<tr>
<th>Patient #1</th>
<th>Patient #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American male</td>
<td>African American male</td>
</tr>
<tr>
<td>55 yo</td>
<td>53 yo</td>
</tr>
<tr>
<td>BMI 28 kg/m²</td>
<td>BMI 29 kg/m²</td>
</tr>
<tr>
<td>No interacting drugs</td>
<td>No interacting drugs</td>
</tr>
<tr>
<td>Normal liver function</td>
<td>Normal liver function</td>
</tr>
<tr>
<td>Low vitamin K intake</td>
<td>Low vitamin K intake</td>
</tr>
<tr>
<td>Taking warfarin 3.2 mg/day to maintain INR of 2-3.</td>
<td>Taking warfarin 10 mg/day to maintain INR of 2-3.</td>
</tr>
</tbody>
</table>

### Factors Influencing Drug Response

- Age
- Race/ethnicity
- Pharmacokinetics
- Concomitant diseases
- Concomitant medications
- GENOTYPE
Incorporating the Personal Genome in Clinical Assessment

• Analyzed complete genome sequence of a 40-yo man with a family h/o vascular disease and sudden cardiac death.
  – Analysis of 2.6 million variants showed an increased risk for MI, type 2 DM, and some cancers.
  – Had 3 rare mutations associated with SCD.
  – Had CYP2C19, HMGCR, SLCO1B1, and VKORC1 variants suggesting possible clopidogrel resistance, good response to statins, and need for lower warfarin dose requirements.

Pharmacogenetics

• Hereditary basis for inter-individual differences in drug response.
• Goal: optimize drug therapy and limit drug toxicity based on a person’s DNA.

PharmacogenETics vs. PharmacogenOMics

• Pharmacogenetics: a single gene that influences drug response.
• Pharmacogenomics: multiple genes that influence drug response.
History of Pharmacogenomics

1956: Discovery of glucose-6 phosphate dehydrogenase polymorphism

1957: "Inheritance might explain many individual differences in the efficacy of drugs and in the occurrence of adverse drug reactions." - Motulsky

1959: "Pharmacogenetics" introduced by Vogel


Human Genome

- Composed of 4 nucleotides
  - Adenine
  - Thymidine
  - Cytosine
  - Guanine

- Central dogma: one strand transcribed into RNA and translated to proteins

Single Nucleotide Polymorphism (SNP)
Other Types of Genetic Variants

- **Insertion/deletion polymorphism** – addition or removal of a strand of nucleotides
- **Tandem repeat polymorphism** – series of nucleotides that may be repeated in the genome a variable number of times (e.g. CAA repeat in GGCX)

What is the most common type of genetic variation?

1. SNP
2. Tandem repeat
3. Insertion/deletion

What is a SNP?

1. Addition or removal of a strand of nucleotides
2. Substitution of one nucleotide base by another
3. Series of nucleotide repeated a variable number of times
Pharmacogenomics

Drug Metabolizing Enzymes → Drug Transporter Proteins → Drug Target Proteins

PHARMACOKINETICS → PHARMACODYNAMICS

Variability in Efficacy/Toxicity

Thiopurine S-Methyltransferase (TPMT)

TPMT

6-Mercaptopurine → inactive metabolites

BONE MARROW CELL

Thioguanine

potent hematopoietic effects

Thiopurine S-Methyltransferase (TPMT)

6-Mercaptopurine

TPMT

inactive metabolites

BONE MARROW CELL

Thioguanine

Increased risk for serious anemias

10% of population carries a variant TPMT allele.

8/13/2010
Clinical Implications of TPMT Polymorphisms

- Genetic testing for TPMT is available for clinical use.
- 6-mercaptopurine dose reduction required for patients with a dysfunctional TPMT allele:
  - Moderate dose reduction required in heterozygotes.
  - 90%-95% reduction required in homozygotes.

Warfarin

- Anticoagulant drug used for the prevention of thromboembolic disorders.
- Challenges with warfarin therapy:
  - Narrow therapeutic index.
  - Substantial inter-patient variability in warfarin dose requirements.
- S-isomer metabolized by CYP2C9.

Pharmacogenomics of Warfarin
What are the primary genes affecting warfarin dose requirements?
1. CYP2C19 and Prothrombin
2. CYP4F2 and Factor X
3. CYP2C9 and vitamin K epoxide reductase
4. CYP3A4 and calumenin

Warfarin Pharmacodynamics: Vitamin K Recycling

CYP2C9 Gene Alleles

<table>
<thead>
<tr>
<th>Allele</th>
<th>Amino acid change</th>
<th>Prevalence</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Caucasians</td>
<td>African Americans</td>
<td>Asians</td>
</tr>
<tr>
<td>*2</td>
<td>144Arg/Cys</td>
<td>20%</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>*3</td>
<td>359Ile/Leu</td>
<td>12%</td>
<td>2%</td>
<td>6-8%</td>
</tr>
<tr>
<td>*8</td>
<td>150Arg/His</td>
<td>&lt;1%</td>
<td>12%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
**CYP2C9 and Warfarin Dose Requirements in Caucasians**


![Bar chart showing median dose (mg/day) across different CYP2C9 genotypes with p<0.001.]

- **CYP2C9 and Warfarin Dose Response in African Americans**


![Bar chart showing median dose (mg/day) across different CYP2C9 genotypes with p=0.002.]

- **Vitamin K Epoxide Reductase (VKORC1) Gene and Warfarin**

- **VKORC1** encodes the warfarin-sensitive component of vitamin K epoxide reductase.
- `-1639G>A SNP in VKORC1 promoter region`
- 3 possible genotypes
  - GG – least sensitive
  - AG – intermediate sensitivity
  - AA – most sensitive
VKORC1 and Warfarin Dose Response


<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>*1/*2</td>
</tr>
<tr>
<td>GG</td>
<td>5-7</td>
</tr>
<tr>
<td>GA</td>
<td>5-7</td>
</tr>
<tr>
<td>AA</td>
<td>3-4</td>
</tr>
</tbody>
</table>

FDA Revises Warfarin Label in 2010

Clinical Implications of CYP2C9 and VKORC1 Polymorphisms

- Assist in choosing appropriate warfarin dosing for patients.
- May decrease the time to achieve optimal dosing.
- Reduce problems (bleeding) of high INRs during warfarin initiation.

Clopidogrel

• Thienopyridine that inhibits the P2Y12 receptor
• Reduces the risk for stent thrombosis
• Improves outcomes in:
  – Acute coronary syndromes
  – Percutaneous coronary intervention.
• Approximately 25% of patients are non-responders to clopidogrel.


Pharmacogenomics of Clopidogrel

Which gene is associated with response to clopidogrel?
1. CYP2C19
2. CYP1A2
3. CYP2B6
4. CYP2C9
### Clopidogrel Pharmacokinetics

**Clopidogrel**

- 85% → Inactive metabolite
- 15% → 2-oxo-clopidogrel → active metabolite
- CYP1A2 → CYP2C19 → CYP3A
- Esterases
- 85% → 15%

**Platelet**

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### Clopidogrel: CYP2C19

- **Loss of function alleles:** *2, *3, *4, *5
- **Phenotype**
  - **CYP2C19 alleles**
  - 2 loss-of-function alleles: **PM - Poor Metabolizer**
  - 1 loss-of-function allele: **IM - Intermediate Metabolizer**
- **Population prevalence**
  - **Race**
  - **PM**
  - **IM**
  - Caucasian: 2% 25%
  - African American: 4% 30%
  - Asian: 14% 50%

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### Clopidogrel: CYP2C19

- **Meta-analysis of 10 trials (9684 patients):**
  - **Outcome**
  - **Risk Ratio (95% CI)**
  - **1 variant vs *1/*1**
  - **2 variants vs *1/*1**
  - Major adverse cardiac events: 1.5 (1.1-2.1) 1.8 (1.2-2.7)
  - Stent thrombosis: 2.5 (1.6-4.0) 4.8 (2.0-11.4)

Clopidogrel Labeling

- Boxed warning added in March 2010
  - Warns of reduced effectiveness of clopidogrel in CYP2C19 PMs.
  - States availability of genetic testing.
  - Advises consideration of alternative treatment strategies in PMs.
- Labeling does not provide recommendations on specific strategies for PMs or include recommendations for IMs.

HLA allele and Stevens Johnson Syndrome (SJS)

- SJS/Toxic epidermal necrolysis (TEN)
  - Severe adverse reactions to carbamazepine.
  - Serious blistering reactions of the skin and mucous membranes that can be permanently disabling or fatal.
  - ~10 times more common among Asians.
- Human Leukocyte Antigen-B*1502 allele
  - Found almost exclusively in patients with Asian ancestry.
  - Associated with increased risk of SJS/TEN from carbamazepine.

Carbamazepine Labeling

- Updated in 2007.
- Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine. If they test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions.
- Because this new data suggests a possible association between HLA-B*1502 and phenytoin-induced SJS, healthcare providers should consider avoiding phenytoin as alternative for carbamazepine in patients who test positive for HLA-B*1502.
Clinical Application of Pharmacogenomics

- Individualize therapy based on genotype.
  - Predict likelihood of response and risk for toxicity based on DNA (e.g. warfarin, carbamazepine).
  - Choose drug therapy accordingly.
- Potential to eliminate trial-and-error approach to drug prescribing (e.g. antihypertensive drugs).
- Streamline treatment for complicated diseases (e.g. heart failure)

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Clinical Application of Pharmacogenomics

<table>
<thead>
<tr>
<th>Population with disease</th>
<th>Predicted response</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Toxicity</td>
<td>Adjust dose or use different drug</td>
</tr>
<tr>
<td></td>
<td>Good response</td>
<td>Traditional therapy</td>
</tr>
<tr>
<td></td>
<td>Poor response</td>
<td>↑ dose or alternative therapy</td>
</tr>
</tbody>
</table>

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Drugs with Genetic Labeling

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Effect</th>
<th>Testing Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine, Phenytoin</td>
<td>HLA-B</td>
<td>Increased risk for Stevens Johnson</td>
<td>Recommended for at-risk persons</td>
</tr>
<tr>
<td>Warfarin</td>
<td>CYP2C9; VKORC1</td>
<td>Altered metabolism and sensitivity</td>
<td>Suggested</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>CYP2C19</td>
<td>Determines efficacy</td>
<td>Suggested</td>
</tr>
<tr>
<td>Rasburicase</td>
<td>G6PD</td>
<td>Severe hemolysis</td>
<td>Recommended for at-risk persons</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2</td>
<td>Determines efficacy</td>
<td>Mandated</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
<td>Determines efficacy</td>
<td>Mandated</td>
</tr>
<tr>
<td>Azathioprine (6MP)</td>
<td>TPMT</td>
<td>Increased risk for myelotoxicity</td>
<td>Recommended</td>
</tr>
</tbody>
</table>
CASE 1: A 4 yo boy is diagnosed with acute lymphoblastic leukemia and is prescribed 6-mercaptopurine. Basing dosing decisions on TPMT genotype may result in which of the following?

1. Eliminate need for hematologic monitoring
2. Decreased risk for anemia
3. Shorten course of chemotherapy
4. Decreased need for multi-drug chemotherapy regimens

CASE 2: A 60 yo, 62 kg female is started on warfarin for stroke prevention in a. fib. Her other meds are metoprolol and atorvastatin. Genetic testing shows the CYP2C9*1/*3 and VKORC1 -1639 A/A genotypes. What is the most appropriate warfarin starting dose?

1. 2.5 mg/day
2. 5 mg/day
3. 7.5 mg/day
4. 10 mg/day

CASE 3: JM is a 55 yo male who suffers an ACS. He undergoes PCI with placement of a drug-eluting stent. He weighs 80 kg and has NKDA. Genotyping shows the CYP2C19*2/*2 genotype. What do you recommend?

1. Standard dose clopidogrel
2. Prasugrel
3. High dose clopidogrel
4. Platelet aggregation testing
CASE 4: JB is an Asian male with newly diagnosed epilepsy. The physician is considering starting carbamazepine in this patient. What do you recommend?

1. Genotype for HLA-B*1502 allele and start carbamazepine if present.
2. Genotype for the HLA-B*1502 allele and start phenytoin if present.
3. Genotype for HLA-B*1502, and avoid both carbamazepine and phenytoin if present.
4. Genotyping is not necessary as JB is at low risk for having the HLA-B*1502 allele.

Bibliography