Pharmacogenomics: a first stage of personalized medicine

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TAKE TWO GENES AND CALL ME IN THE MORNING.
Sir William Osler (1849-1919): Medicine is a science of uncertainty and an art of probability
Eric Lander (1957-): Genes are only a small part of our makeup; the environment has a spectacular impact
DEFINITIONS

Pharmacogenetics = study on genetic factors involved in drug response

Pharmacogenomics = the use of genomic methods in drug research and discovery
PHARMACOGENOMICS

Pharmacogenetics with 2 SNPs

PHARMACOGENOMICS

PHARMACOGENETICS

U Mayer 2001
Pharmacogenetics: to deliver ‘right medicine, right dose, to right patient’
Why study pharmacogenomics?

As low as 30% of individuals get adequate therapeutic response from a prescribed medicine.
All patients with same diagnosis

1. Remove non-responders and toxic responders

2. Treat responders and patients not predisposed to toxicity
Unusual drug reactions can result from

Pharmocokinetic factors
- variations in drug-metabolising enzymes

Pharmacodynamic factors
- variations in drug targets (receptors etc)
Pharmacokinetics
How does the body affect the drug?

**ABSORPTION**
- Gastrointestinal tract

**DISTRIBUTION**
- Bound drug
- Free drug

**ELIMINATION**
- Excretion
- Metabolism

**= ADME**

Plasma

Storage site
Site of action
Example of a clinically relevant pharmacokinetic polymorphism: CYP2D6

- A hepatic CYP enzyme (<10% of total CYP)
- Metabolises ~ 100 clinically used drugs
- 1977: polymorphism of debrisoquine and sparteine metabolism
- 1988: 1st genetic basis for polymorphism
- 2002: > 70 variant CYP2D6 alleles
Polymorphism of CYP2D6: clinical significance
Nortriptyline as an example

- Nortriptyline - tricyclic antidepressant
- Large inter-individual variations in plasma concentrations observed early
- Phenotyping studies confirmed polymorphism
- Metabolised by polymorphic CYP2D6
- In vivo and in vitro studies
Mean plasma concentrations of nortriptyline in different CYP2D6 genotype groups after a single oral dose of nortriptyline. Bertilsson et al. BJCP 53, 111, 2002
Examples of dose adjustments based on pharmacogenomics

Kirchheiner et al 2005
The consequences of outlier CYP2D6-dependent drug metabolism.

35–50 million Europeans are either CYP2D6 poor metabolizers (PMs) or ultrarapid metabolizers (UMs).

As a result of the use of population-based dosing, drug treatment can result in many different effects in these subjects. Abbreviation: ADRs, adverse drug reactions.

Ingelman-Sundberg TIPS 25, 2004
Figure 2. Important pharmacogenomic biomarkers influencing treatment response and/or ADR incidence. For details and abbreviations, please see the main text.
Farmakogeneettisiä testejä

Lääke
- Atsatiopriini/6-MP
- Varfariini
- Trastutsumabi
- Abakaviiri
- Irinotekaani

Geenitesti
- TPMT
- CYP2C9/VKORC1
- HER2
- HLA-B*5701
- UGT1A1*28
New Target Protein for Warfarin

VKORC, 2 SNP:
-1639Ala ja 1173Thr

CYP2C9, 2 SNP:
CYP2C9*1 (Arg144Ile359) = wt
CYP2C9*2 (Cys144Ile359)
CYP2C9*3 (Arg144Leu359)
Welcome to WarfarinDosing.org, a free Web site to help doctors and other clinicians begin warfarin therapy by estimating the therapeutic dose in patients new to warfarin. This site is supported by the Barnes-Jewish Hospital at Washington University Medical Center, the NIH, and donations. Estimates are based on clinical factors and (when available) genotypes of two genes: cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase (VKORC1).

Recommendations on this Web site are based on data from over 1000 patients. Once information is entered onto the next page, the initial estimate of therapeutic dose explains 53% of the variability in a warfarin dose. If you return to the Web site and enter an INR value after 3 and/or 4 warfarin doses, the dose refinement is even more accurate.

Initial Information

Is this patient new to WarfarinDosing.org?

- New patient
- Existing patient

Click here to go to Clinical Trial Home.

Warfarin doses taken so far*: -Select-

*Required
Example of a clinically relevant pharmacodynamic polymorphism: her/neu oncogene

- Trastuzumab (Herceptin®)
- Monoclonal antibody against her/neu
- her/neu overexpressed in some breast cancers
- First determination of her/neu expression
- If +, treatment with Herceptin
- ”Theranostics”
HER-2/neu testing in breast cancer

(a) HER-2/neu gene amplification detected by fluorescent in situ hybridization (FISH; Ventana Inform System).

(b) HER-2/neu gene amplification detected by chromogenic in situ hybridization (CISH; Zymed).

(c) Immunohistochemistry using Herceptest system (Dako Corporation) with continuous membranous 3+ positive immunostaining (i.e. the staining is restricted to the cytoplasmic membrane) for HER-2/neu protein.
Noin 7 % valkoihoisista on genotyyppiä, joilla on toimimaton CYP2D6-entsyymi (hitaat CYP2D6-metabloijat). Tämän genotyypin omaavien potilaiden altistus atomoksetiinille on moninkertainen verrattuna potilaisiin, joilla on normaali entsyymitoiminta. Hitailla metaboloijilla on näin ollen suurentunut riski saada haittavaikutuksia (ks. kohdat Haittavaikutukset ja Farmakokinetiikka). Jos potilaan tiedetään olevan hidas metaboloija, tulee harkita pienempää aloitusannosta ja hitaampaa annoksen titrausta.
Hitaat CYP2D6-metaboloijat (PM)
Seuraavia haittavaikutuksia esiintyi vähintään 2 %:lla potilaista, jotka olivat hitaita CYP2D6-metaboloijia (PM), ja ne olivat joko kaksi kertaa yleisempiä tai tilastollisesti merkitsevästi yleisempiä PM-potilailla kuin potilailla, jotka olivat nopeita CYP2D6-metaboloijia (EM):

<table>
<thead>
<tr>
<th>Haittatapahtuma</th>
<th>Hitaat metaboloijat (PM) % PM-potilaista</th>
<th>Nopeat metaboloijat (EM) % EM-potilaista</th>
</tr>
</thead>
<tbody>
<tr>
<td>ruokahalun väheneminen</td>
<td>24,1 %</td>
<td>17,0 %</td>
</tr>
<tr>
<td>unettomuus</td>
<td>10,5 %</td>
<td>6,8 %</td>
</tr>
<tr>
<td>keskiyön unettomuus</td>
<td>3,8 %</td>
<td>1,5 %</td>
</tr>
<tr>
<td>enureesi</td>
<td>3,0 %</td>
<td>1,2 %</td>
</tr>
<tr>
<td>masentuneisuus</td>
<td>3,0 %</td>
<td>1,0 %</td>
</tr>
<tr>
<td>vapina</td>
<td>5,1 %</td>
<td>1,1 %</td>
</tr>
<tr>
<td>aamuyön unettomuus</td>
<td>3,0 %</td>
<td>1,1 %</td>
</tr>
<tr>
<td>sidekalvotulehdus</td>
<td>3,0 %</td>
<td>1,5 %</td>
</tr>
<tr>
<td>pyörtyminen</td>
<td>2,1 %</td>
<td>0,7 %</td>
</tr>
<tr>
<td>mydriaasi</td>
<td>2,5 %</td>
<td>0,7 %</td>
</tr>
</tbody>
</table>
Pharmacogenetic testing in drug development
An example

Phase II trial
500 patients

- 30% reacts favorably
- 70% does not react

Phase III trial
5000 patients

- 100% reacts favorably

Pharmacogenetic testing
Selection of patients to phase III
Individual Genomes Instead of Race for Personalized Medicine

PC Ng¹, Q Zhao¹, S Levy¹, RL Strausberg¹ and JC Venter¹

The cost of sequencing and genotyping is aggressively decreasing, enabling pervasive personalized genomic screening for drug reactions. Drug-metabolizing genes have been characterized sufficiently to enable practitioners to go beyond simplistic ethnic characterization and into the precisely targeted world of personal genomics. We examine six drug-metabolizing genes in J. Craig Venter and James Watson, two Caucasian men whose genomes were recently sequenced. Their genetic differences underscore the importance of personalized genomics over a race-based approach to medicine. To attain truly personalized medicine, the scientific community must aim to elucidate the genetic and environmental factors that contribute to drug reactions and not be satisfied with a simple race-based approach.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Examples of substrates</th>
<th>James Watson</th>
<th>Craig Venter</th>
<th>Known effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Antipsychotics, caffeine, warfarin</td>
<td>*1F/*1F</td>
<td>*1F/*1F</td>
<td>*1F influences the induction of CYP1A2 activity</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Anti-inflammatory drugs, statins, warfarin, sulfonylurea (antidiabetic), angiotensin</td>
<td>*1A/*1A</td>
<td>*1A/*1B</td>
<td>*1B appears to be normal</td>
</tr>
<tr>
<td></td>
<td>receptor blockers (hypertension)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Proton pump inhibitors, tricyclic antidepressants</td>
<td>*1B/*1B</td>
<td>*1B/*1B</td>
<td>*1B has normal enzyme activity</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>β-Blockers, antiarrhythmics, antipsychotics, tricyclic antidepressants</td>
<td>*10/*10</td>
<td>*1A/*1A</td>
<td>*10 has decreased activity</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Calcium channel blockers, chemotherapeutic agents, statins</td>
<td>*1A/*1B</td>
<td>*1A/*1A</td>
<td>*1B may influence prostate cancer</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Immunosuppressive drugs, protease inhibitors, statins</td>
<td>*3/*3</td>
<td>*3/*3</td>
<td>*3 is nonfunctional because of a splicing defect</td>
</tr>
</tbody>
</table>
Why is pharmacogenetic information not used in clinical practice?

- Very few prospective studies on clinical benefits
- Questions about cost effectiveness
- Lack of clinical guidelines
- Lack of education among physicians
- ”Technology enables research, but not clinical practice”
"Here's my sequence..."

New Yorker