“Precision Medicine” and the genetics of race

Wednesday, April 22nd
Holly Stessman
Objectives for today’s class

• Questions
  – What is “precision medicine”?
  – How is precision medicine used to treat patients?
  – What do we know about the genetics of race?

• Topics for today
  – Obama’s Precision Medicine Initiative
  – Precision medicine: Where are we now?
  – The first “ethnic” drug
  – Current genetic frameworks
    • 1000 Genomes Project
    • The HapMap Project
    • Rosenberg, et al.
Definitions

• “Precision medicine” = a medical model that proposes the customization of medical decisions and courses of treatment based on the individual patient.

• “Personalized medicine” = may refer to the creation of new treatments in response to a particular patients need.

• “Pharmacogenomics” = the study of the role genetics play in drug response.
Obama’s Precision Medicine Initiative

“Most medical treatments have been designed for the “average patient”. As a result of this ‘one-size-fits-all-approach,’ treatments can be very successful for some patients but not for others.”

The promise: $215 million investment split among the NIH, NCI, FDA, & ONC

The objectives:

• More and better treatments for cancer
• Creation of a voluntary national research cohort
• Commitment to protecting privacy
• Regulatory modernization
• Public-private partnerships

https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative
Genetics as a therapy tool in cancer

- Physician-ordered multigene assays can provide recurrence predictions and guide treatment options in node negative or node positive, ER-positive, HER2-negative invasive breast cancer

- Oncotype DX (16 cancer-related genes and 5 reference genes) analyzed for gene expression (mRNA)
The current state of affairs

In 2013, 114 genes were selected by a panel of experts as “medically actionable genetic conditions possibly undiagnosed in adults”.

In this study of 1,000 people the frequency of likely-high-impact variants in these genes was ~3.4% for European descent and ~1.2% for African descent.
Pharmacogenomics

<table>
<thead>
<tr>
<th>Gene product</th>
<th>Drug</th>
<th>Drug action linked to minor allele</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>Warfarin</td>
<td>Reduced anticoagulant effect</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Phenylbutazone</td>
<td>Increased toxicity</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Ticlopidine</td>
<td>Lower dose requirement</td>
<td>70</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Omeprazole</td>
<td>Increased adverse effects</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Meperidine</td>
<td>Enhanced cure rate of Helicobacter pylori</td>
<td>71</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Codesine</td>
<td>Decreased analgesia (poor metabolizers)</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>Euphoria, nausea (hypersensitive metabolizer)</td>
<td>72</td>
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<tr>
<td></td>
<td>Phenotiazines</td>
<td>Augmented β-blockade (poor metabolizer)</td>
<td>20,73,74</td>
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<tr>
<td></td>
<td>Desipramine</td>
<td>Variable antidepresant effect</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Debrisoquine</td>
<td>Excessive hypotension</td>
<td>75</td>
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<tr>
<td></td>
<td>Propafenone</td>
<td>Enhanced β-blockade</td>
<td>19</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Many</td>
<td>Varibly expressed; function not yet established</td>
<td>36</td>
</tr>
<tr>
<td>P-glycoprotein</td>
<td>Digoxin</td>
<td>Altered blood level and effect</td>
<td>33</td>
</tr>
<tr>
<td>N-acetyltransferase</td>
<td>Procarbazine</td>
<td>Slow acetylators, increased risk of the lupus syndrome</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Isoniazid</td>
<td>Slow acetylators, increased risk of hepatotoxicity</td>
<td>76</td>
</tr>
<tr>
<td>Thiopurine methyltransferase</td>
<td>6-mercaptopurine, azathioprine</td>
<td>Bone marrow aplasia (poor metabolizers)</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Thioguanine</td>
<td>Suboptimal therapeutic response (rapid metabolizers)</td>
<td>24, 58, 77</td>
</tr>
<tr>
<td>Pseudocholinesterase</td>
<td>Sucinylcholine</td>
<td>Prolonged apnoea</td>
<td>28</td>
</tr>
<tr>
<td>UGT-glucuronosyltransferase</td>
<td>Inositean</td>
<td>Enhanced toxicity</td>
<td>25</td>
</tr>
</tbody>
</table>

**Drug targets**

| Choline acetyltransferase | Tacrine | Decreased response in APOE4 homozygotes | 42 |
| HERG/MRP1 | QT-prolonging drugs | Increased risk of arrhythmias in MRP1 mutation carriers | 43 |
| β₂-adrenoceptors | β₂-agonists | Increased response in asthma | 78 |
| 5-lipoxygenase | 5-lipoxygenase inhibitor (Zileuton) | Diminished response among homozygotes for alleles reducing 5-lipoxygenase expression | 44 |

**Modulators of drug action**

| ACE inhibitor | Decreased response in DD subjects | 50 |
| β-blockers | Augmented response to β-blockers in DD subjects | 51 |
| QT-prolonging drugs | Increased risk of arrhythmias | 45–48 |
| Fluoxetine | Decreased drug response | 79 |
| Penicillamine | Regression of atherosclerosis | 80 |

**Genetics of CYP2D6**

- **Poor metabolizers**
  - CYP2D6 Activity: None
- **Intermediate metabolizers**
  - CYP2D6 Activity: Low
- **Extensive metabolizers**
  - CYP2D6 Activity: Normal
- **Ultrarapid metabolizers**
  - CYP2D6 Activity: High

**Ethnic Differences (Approximate)**
- Caucasians: 6%-10%
- Mexican Americans: 3%-6%
- African Americans: 2%-5%
- Asians: ~1%
- Not established
- Most people are extensive metabolizers
- Finns and Danes: 1%
- North Americans (white): 4%
- Greeks: 10%
- Portuguese: 10%
- Saudis: 20%
- Ethiopians: 30%

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Dr. Prof. Gideon Koren, FRCP
d, James Cairns, MD, Prof. David Chitayat, FRCP, Andrea Gaedigk, PhD, Steven J. Leeder, PhD

Nature Reviews Drug Discovery 2004 3: 749-761
The treatment of congestive heart failure (HF)

- ~ 5.1 million people in the U.S. have HF
- More common in African Americans**
- About half of people with HF will die within 5 years of diagnosis
- Treating HF costs the nation ~ $32 billion/year

http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/
BiDil for the treatment of congestive heart failure (HF)

**HOW BiDIL TREATS HEART FAILURE**

Unlike a healthy person’s heart, a failing heart gets larger as it struggles to pump blood and causes fluid to accumulate in the lungs' alveoli. BiDil is thought to slow the progress of the disorder by dilating narrow blood vessels, which can ease the burden on the heart.

**Healthy Heart and Lungs**
- Aorta
- Left atrium
- Right atrium
- Left ventricle
- Right ventricle
- Alveoli
- Fluid-filled alveoli

**Constricted Blood Vessel**
- Narrow arteries and veins make it harder to pump blood, putting additional strain on the heart.
- Nitric oxide (NO) can relax the vessels, but free radicals such as superoxide (O$_2^-$) counteract its beneficial influence.

**Theorized Mechanism of BiDil**
- BiDil consists of isosorbide dinitrate, which enhances the production of NO and hydralazine, which inhibits the creation of superoxide. Blood vessels dilate as they get more NO$_2$, making it easier for the heart to push blood through them.
BiDil for the treatment of congestive heart failure (HF)

BiDil = Isosorbide dinitrate/hydralazine

Used for the treatment of congestive heart failure

Drug trials 1980-2004 (V-HeFT I, V-HeFT II)

http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4145B2_02_01-NitroMed-Background.htm
BiDil for the treatment of congestive heart failure (HF)

**BiDil** = Isosorbide dinitrate/hydralazine

Used for the treatment of congestive heart failure


The V-HeFT trial data suggested greater efficacy in self-identified African Americans.

http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4145B2_02_01-NitroMed-Background.htm
The A-HeFT Trial

- Multicenter, double-blind, placebo-controlled, randomized (H + ISDN=BiDil) vs. placebo
- Population = self-reported black (or of African descent)
- New York Heart Association Class III-IV HF on standard therapy
- Left ventricular ejection fraction (LVEF) ≤ 35%

<table>
<thead>
<tr>
<th>Visit No.</th>
<th>Screening</th>
<th>Baseline</th>
<th>Titration</th>
<th>Treatment &amp; Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>0</td>
<td>0+</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>-2 Wk.</td>
<td>0</td>
<td>3-5 Days</td>
<td>3 Mo.</td>
<td>6 Mo.</td>
</tr>
</tbody>
</table>

* All patients seen every 3 months until last patient completes visit No. 2.

BiDil: The first approved “ethnic” drug

A-HeFT results:
• 43% reduction in mortality in the treatment arm
• 39% reduction in first hospitalization from HF in the treatment arm
• Improved quality of life

BiDil approved by the FDA in June 2005.

The genetic underpinnings of BiDil efficacy are still being determined

*NEJM* 2004 351(20): 2049-2057.
Drug development can take decades

http://www.mdlingo.com/article/fda-approval-process-for-new-drugs