HLA and Pharmacogenomics
The Abacavir Story

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\[ Rx + \text{sad} = \text{happy} \]

\[ Rx + \text{sad} = \text{sad} \]

\[ Rx + \text{sad} = \text{skull} \]

???
Differences in genetic constitution

\[ RX + \text{sad} = \text{happy} \]

\[ RX + \text{sad} = \text{sad} \]

\[ RX + \text{sad} = \text{death} \]
PHARMACOGENETICS

The study of genetically controlled variations in drug response
Clinical Potential of Pharmacogenomics

1. Predicted good response to tested drug
2. Predicted poor or nonresponse. *Use different drug*
3. Predicted increased toxicity risk. *Decrease dose or use different drug*

GENETIC POLYMORPHISMS

**Pharmacokinetic**
- Transporters
- Plasma protein binding
- Metabolism

**Pharmacodynamic**
- Receptors
- Ion channels
- Enzymes
- Immune molecules
Table 1. Pharmacogenomic Biomarkers as Predictors of Adverse Drug Reactions.

<table>
<thead>
<tr>
<th>Gene or Allele</th>
<th>Relevant Drug</th>
<th>Specificity of Biomarker</th>
<th>Percent of Patients with an Adverse Reaction to Drug*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>TPMT (mutant)</em></td>
<td>6-Mercaptopurines</td>
<td>Very good</td>
<td>1–10</td>
</tr>
<tr>
<td>UGT1A1*28</td>
<td>Irinotecan</td>
<td>Good</td>
<td>30–40</td>
</tr>
<tr>
<td>CYP2C9 and VKORC1</td>
<td>Warfarin†</td>
<td>Good</td>
<td>5–40</td>
</tr>
<tr>
<td>CYP2D6 (mutant)</td>
<td>Tricyclic antidepressants</td>
<td>Relatively good</td>
<td>5–7</td>
</tr>
<tr>
<td>HLA-B*5701</td>
<td>Abacavir</td>
<td>Very good</td>
<td>5–8</td>
</tr>
<tr>
<td>HLA-B*1502</td>
<td>Carbamazepine</td>
<td>Very good</td>
<td>10</td>
</tr>
<tr>
<td>HLA-DRB1<em>07 and DQA1</em>02</td>
<td>Ximelagatran</td>
<td>Good</td>
<td>5–7</td>
</tr>
</tbody>
</table>

* Percentages are of affected whites except that for HLA-B*1502, which is the percentage of affected Asians.
† Carriage of the CYP2C9 and VKORC1 alleles affects warfarin dosing.
Abacavir is a nucleoside reverse transcriptase inhibitor used in conjunction with other antiretroviral agents in the treatment of HIV infection.
Abacavir is generally well tolerated but can cause hypersensitivity in 5% to 8% of patients during the first 6 weeks of treatment.
Hypersensitivity to abacavir is immunologically mediated, driven by conventional MHC-I antigen presentation and activation of HLA-B*5701. Activation of HLA-B*5701 restricted CD8+ T cells results in the secretion of the inflammatory mediators TNF-alpha and IFN-gamma and induces the delayed-type hypersensitivity reaction.
Pharmacogenetics of Abacavir Hypersensitivity: Translation into Clinical Practice (Brighton Clinic)

Reeves et al. HIV Medicine 2006
## Abacavir Hypersensitivity and HLA Polymorphisms

<table>
<thead>
<tr>
<th></th>
<th>Abacavir Hypersensitive</th>
<th>Abacavir Tolerant</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B 5701</td>
<td>14 (78%)</td>
<td>4 (2%)</td>
<td>117</td>
</tr>
<tr>
<td>HLA-DR7, HLA-DQ3</td>
<td>13 (72%)</td>
<td>6 (3%)</td>
<td>73</td>
</tr>
<tr>
<td>HLA-B 5701,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-DR7, HLA-DQ3</td>
<td>13 (72%)</td>
<td>0 (0%)</td>
<td>822</td>
</tr>
</tbody>
</table>

HLA = human leukocyte antigen; OR = odds ratio.

SHAPE Study Design

**CASES**
Black and White subjects with clinically-suspected ABC HSR (CS-HSR)

ABC skin patch test & HLA-B*5701

- **Positive**
  - White: 42
  - Black: 5
- **Negative**
  - White: 85
  - Black: 63

**CONTROLS**
Black & White subjects enrolled in KLEAN, ALOHA, CNA30027, CNA30032

Identify ABC-tolerant subjects who provided PGx consent and sample

- White: 202
  - Black: 206

*HLA-B*5701 results available for all but one case

*Skin patch test results unavailable for 3 Whites, 1 Black*
HLA-B*5701 carriage frequency

- **INDIA**: 5-20%
- **JAPAN**: 0%
- **CHINA**: 0% (NB 2.5% N.E. provinces)
- **UK**: ~8%
- **MIDDLE EAST**: 1-2% (NB 5-7% Ashkenazi Jews)
- **AUSTRALIA**: ~8%
- **US Caucasian**: ~8%
- **US Asian**: ~1%
- **US African-American**: ~2.5%
- **US Hispanic**: ~2%
- **W. EUROPE**: 5-7%
- **MEDITERRANEAN**: 1-2%
- **S. AMERICAN**: 5-7%
- **Subsaharan AFRICA**: <1%
- **THAILAND**: 4-10%* (Urban Bangkok 3.6%, Thai Dai Lue (NE Thai) ~11%, Southern Thai Muslim 3%)
- **CHINA**: 0%
- **JAPAN**: 0%
- **THAILAND**: 4-10%*
- **AUSTRALIA**: ~8%
- **HLA-B*5701 carriage**: ~8%

*Nolan et al, J HIV Ther 2003; 8(2):36-41*
To recommend screening for HLA-B*5701 in European populations or of European origin but not in some Asian or African populations could be problematic?
Ancestry and Disease in the Age of Genomic Medicine
N Engl J Med 363;16 October 14, 2010

Figure 1. Variation in the HLA-B*5701 Locus in 11 HapMap Samples.
Screening for the HLA-B*5701 (rs2395029) allele substantially reduces the incidence of abacavir hypersensitivity in patients being treated for human immunodeficiency virus infection. Shown are the prevalences (with 95% confidence intervals) of the HLA-B*5701 variant in five U.S. ethnic groups (Panel A) and in six global ethnic groups (Panel B). This variant has a prevalence of 13.6% among the Masai in Kenya but a prevalence of 0% among the Yoruba in Nigeria, which indicates that the use of racial or continental labels such as “black” or “African” can sometimes obscure important, biomedically relevant variation.
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Virgin of the Rocks (1495 - 1508)

Virgin of the Rocks (Madonna and child, San Giovannino and angel) is an oil painting on a panel of 189.5 x 120 cm, executed between 1495 and 1508 by Leonardo da Vinci.

National Gallery

Louvre