Race, Ethnicity, and Treatment Response in HIV-infected Patients

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Ethnicity vs Race

Race
- “…a social invention rather than a biological reality.”

Ethnicity
- Refers less to biological or visible traits; connotes more in the way of shared experience

Only 10-20% of human genetic diversity stems from populations

Pharmacogenetics / Pharmacogenomics
- Study of the genetic basis underlying variable drug response (efficacy vs toxicity) in individual patients

“It is becoming more and more clear that pigeon-holing patients into ‘races’ or ethnic groups is not only genetically imprecise, but –if extended to predictions about drug responses…based on ethnicity- such provincial thinking could lead to serious morbidity or mortality”

– D. Nebert, University of Cincinnati Medical Center, OH, USA

Pharmacogenetics: Historical Perspective

<table>
<thead>
<tr>
<th>Condition</th>
<th>Genetic Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suxamethonium toxicity</td>
<td>Pseudocholinesterase deficiency</td>
</tr>
<tr>
<td>Primaquine hemolysis in African American soldiers</td>
<td>G6PD deficiency</td>
</tr>
<tr>
<td>INH &amp; procainamide toxicity</td>
<td>Slow acetylator phenotype</td>
</tr>
<tr>
<td>Debrisoquine hypotension</td>
<td>CYP2D6 Poor Metabolizers (PM)</td>
</tr>
</tbody>
</table>

Mancinelli L et al. Pharmacogenomics: The promise of personalized medicine 2000;2 (1) Article 4 (http://www.aapspharmsci.org/)
# Relationship between Drug Response and Genetic Polymorphisms in HIV

<table>
<thead>
<tr>
<th>Gene/Genetic Region</th>
<th>Protein Function</th>
<th>Influence of Polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY: (NOT ALL HAART RECIPIENTS BENEFIT EQUALLY)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCR5</td>
<td>Chemokine receptor</td>
<td>virological response</td>
</tr>
<tr>
<td>MDR1</td>
<td>P-gp (drug transporter)</td>
<td>immune response + drug conc.</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>CYP450 enzyme</td>
<td>drug conc.</td>
</tr>
<tr>
<td><strong>TOXICITY: (SOME HAART RECIPIENTS EXPERIENCE ADRS; OTHERS DO NOT)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-B*5701, DR7, DQ3</td>
<td>MHC</td>
<td>abacavir hypersensitivity</td>
</tr>
<tr>
<td>SREBP-1C</td>
<td>Chol / TG regulation</td>
<td>hyperlipidemia</td>
</tr>
</tbody>
</table>

Multi-Drug Resistance Gene (MDR-1) and P-glycoprotein (P-gp)

MDR-1 encodes for: P-glycoprotein (P-gp)

- Member of the large ATP-binding cassette (ABC) super family of transport proteins
- An energy-dependent multidrug efflux pump
- Ejects substrates before reaching cytoplasm (acts as a “hydrophobic vacuum cleaner”)
- Identified in cancer cells resistant to antineoplastic therapy
Hypothetical Model of Human P-glycoprotein

POINT MUTATIONS ( ), PHOTOAFFINITY LABELED REGIONS ( ), AND PHOSPHORYLATION SITES ( P )
Simplified example of P-gp Activity

“A lot of P-gp”

“Intermediate amount of P-gp”

“A little of P-gp”
<table>
<thead>
<tr>
<th>Tissue</th>
<th>Localization</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small intestine &amp; colon</td>
<td>Apical membrane of epithelial cells</td>
<td>Secretion of drugs into gut lumen</td>
</tr>
<tr>
<td>Liver</td>
<td>Canalicular membrane of hepatocytes</td>
<td>Secretion of drugs into bile</td>
</tr>
<tr>
<td>Kidney</td>
<td>Apical membrane of epithelial cells of proximal tubule</td>
<td>Secretion of drugs into tubules lumen</td>
</tr>
<tr>
<td>CNS</td>
<td>Luminal membrane of endothelial cells forming the BBB</td>
<td>Protection of CNS from xenobiotics</td>
</tr>
<tr>
<td>Testis</td>
<td>Endothelial cells of capillary blood vessels</td>
<td>Blood-testis barrier</td>
</tr>
<tr>
<td>Placenta</td>
<td>trophoblasts</td>
<td>Protection of fetus from xenobiotics</td>
</tr>
<tr>
<td>Lymphocyte subsets</td>
<td>CD56+ NK, CD4+, CD8</td>
<td>Extrusion of drugs from cell</td>
</tr>
</tbody>
</table>
MDR-1 Polymorphisms and P-gp Expression and Function

- > 20 SNPs have been identified in the MDR-1 gene; 9 alter the amino acid sequence of P-gp\textsuperscript{1,2}
- The silent mutation, C3435T, is often linked with G2677T (Ala893Ser)
  - C3435T often associated with altered P-gp expression and function

Epidemiology (C3435T)\textsuperscript{2}
- Caucasian: CC 21-28%; TT 24-28%; CT 48-51%
- African American: CC 61-68%; TT 1-5%; CT 31-34%

\textsuperscript{1} Hoffmeyer et. al. Proc Natl Acad Sci USA 2000;97:3473-78.
MDR-1 Genotype: C3435T SNPs

CC Genotype

CT Genotype

TT Genotype
### Influence of MDR-1 SNPs on P-gp Expression or Function in Various Normal Tissues

<table>
<thead>
<tr>
<th>Tissue (SNP)</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small intestine (C3435T)</td>
<td>CC&gt;CT&gt;TT</td>
<td>Western Blotting in Caucasians</td>
</tr>
<tr>
<td>Small intestine (C3435T)</td>
<td>CC&lt;CT&lt;TT</td>
<td>RT-PCR in Japanese subjects</td>
</tr>
<tr>
<td>Placenta (G2677[A/T]) (C3435T)</td>
<td>GG&gt;G/mut&gt;mut/mut (n.s.)</td>
<td>Western Blotting</td>
</tr>
<tr>
<td>Placenta (G2677[A/T]) (C3435T)</td>
<td>CC&gt;CT&gt;TT (n.s.)</td>
<td></td>
</tr>
<tr>
<td>CD56+ NK (C3435T)</td>
<td>CC&gt;CT&gt;TT</td>
<td>RT-PCR/rhodamine 123 efflux</td>
</tr>
<tr>
<td>PBMC (C3435T)</td>
<td>CC&gt;CT&gt;TT</td>
<td>RT-PCR and FACS</td>
</tr>
</tbody>
</table>

## MDR-1 Polymorphisms and Drug Disposition

<table>
<thead>
<tr>
<th>Drug (population)</th>
<th>SNP</th>
<th>Result</th>
<th>Comment</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin (Caucasians)</td>
<td>C3435T</td>
<td>CC&lt;CT&lt;TT</td>
<td>Cmax @ cpss</td>
<td>Hoffmeyer et. al.</td>
</tr>
<tr>
<td>Digoxin (Japanese)</td>
<td>C3435T</td>
<td>GG/CC &lt; GT/CT&lt; TT/TT</td>
<td>F (iv and PO digoxin given)</td>
<td>Kurata et. al.</td>
</tr>
<tr>
<td>Digoxin (Japanese)</td>
<td>C3435T</td>
<td>CC&gt;CT&gt;TT</td>
<td>AUC$_{0-4}$ single PO dose</td>
<td>Sakaeda et. al.</td>
</tr>
<tr>
<td>Fexofenadine (European Americans)</td>
<td>C3435T</td>
<td>CC&gt;TT</td>
<td>AUC$_{0-4}$ single dose</td>
<td>Kim et. al.</td>
</tr>
<tr>
<td>Nelfinavir (Caucasians)</td>
<td>C3435T</td>
<td>CC&gt;CT&gt;TT</td>
<td>NFV trough</td>
<td>Fellay et. al.</td>
</tr>
</tbody>
</table>

Potential effect of P-gp modulation and variable expression may:

- Alter drug distribution into anatomical sites: CNS, testes, lymphocytes
- Influence HIV viral replication & immune recovery
- Contribute to drug-drug interactions & toxicity: P-gp substrates; inhibitors; inducers
- Genetic differences in MDR1 expression (SNPs)
Influence of *MDR1* Genotype on NFV and EFV Pharmacokinetics

Immune Recovery and *MDR1* 3435 Genotype

- Prevention of CD4+ cell apoptosis with P-gp overexpression?
- 40-70 fold decrease in HIV replication with P-gp expression?


Immune Recovery and \textit{MDR1} 3435 Genotype

- Retrospective analysis in ARV naïve individuals

- PI + 2 NRTIs (n = 106)
  - 84\% with HIV-RNA < 50 copies/mL
  - CC: 30.2\%, CT: 49.1\%, TT: 20.7\%

- NNRTI + 2 NRTIs (n = 43)
  - 84\% with HIV-RNA < 50 copies/mL
  - CC: 34.9\%, CT: 39.5\%, TT: 25.6\%

Changes in Plasma Viral Load According to *MDR1* 3435 Genotype

Changes in Plasma Viral Load According to MDR1 3435 Genotype

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  - 84% with HIV-RNA < 50 copies/mL
  - CC: 30.2%, CT: 49.1%, TT: 20.7%

- **NNRTI + 2 NRTIs (n =43)**
  - 84% with HIV-RNA < 50 copies/mL
  - CC: 34.9%, CT: 39.5%, TT: 25.6%

MDR1 Polymorphism and Viral Decay

Plasma phase-1 viral decay reflects CD4+ cell turnover

Methods:
- 48 HIV+ subjects (mostly Caucasian); RTV + ZDV + 3TC; frequent HIV-RNA measurements, CD4+ & CD8+ cell subsets, RTV troughs
- 3435: CC (23%), CT (45%), TT (32%) (n = 31)
- 2677: GG (26%), GT (58%), TT (16%) (n = 31)

Results:
- No association between MDR1 genotype and phase 1 or 2 viral decay, T cell subset changes over time, or RTV troughs

Haas et al. 43rd ICAAC. September 14-17, 2003. Chicago, IL [abstract H-449]
Response to ARV treatment According to *MDR1* 2677 Genotype

<table>
<thead>
<tr>
<th>MDR-1 2677 (HIV+ pts)</th>
<th>GG</th>
<th>TT</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl/F (L/h/kg)</td>
<td>0.82</td>
<td>0.48</td>
<td>.02</td>
</tr>
<tr>
<td>Dose-normalized Cmax (mg/kg/dose)</td>
<td>0.62</td>
<td>0.93</td>
<td>.04</td>
</tr>
<tr>
<td>52-week response (RNA log copies/mL)</td>
<td>-2.2</td>
<td>-3.7</td>
<td>.04</td>
</tr>
</tbody>
</table>

- Cl/F was also lower (0.49 vs 0.84 L/h/kg) in the 3435 TT patients vs. the CC patients.
- Study confirmed intuitive link between drug conc. & response

**MDR-1 Genotype**

- Variably expressed in different populations
- May or may not influence:
  - HIV PI concentrations
  - Immune recovery
  - Rate of HIV-RNA decline
  - HIV replication
  - Susceptibility to drug interactions with PIs
  - Transmissibility of infection?
  - PI-related toxicities?


“There’s something happening here; what it is ain’t exactly clear”

-Stephen Stills
(“For What it’s Worth”)
Abacavir hypersensitivity reaction:

- SX: rash, fever, GI SX (N, V, D)
- 3.7% incidence (0-14%)
- Usually occurs within first 6 weeks
- Symptoms worsen with continued therapy
- Symptoms improve when drug is DC’ed
- RECHALLENGE:
  - Recurrence of (severe) symptoms within hours
  - May result in hypotension and death

Hewitt RG. Clin Infect Dis 2002;34;1137-1142.
Genetic Predisposition to Drug Toxicity

Abacavir hypersensitivity reaction

• Who’s at risk?
  ✓ 40% reduction of risk in persons of African descent (n = 5,332)
  ✓ Hispanic ethnicity: OR = 2.77 (n = 540)
  ✓ White race: OR = 5.16 [1.16-22.97] (n = 91)

2 Hewitt RG. Clin Infect Dis 2002;34;1137-1142.
Genetic Predisposition to Drug Toxicity

### Association between MHC alleles & abacavir (ABC) hypersensitivity

<table>
<thead>
<tr>
<th></th>
<th>+ ABC HYPER (n = 18) all Caucasian</th>
<th>- ABC HYPER (n = 167) all Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B*5701+DQ3+DR7</td>
<td>72% (13/18)</td>
<td>0 %*</td>
</tr>
<tr>
<td>HLA-B*5701</td>
<td>78% (14/18)</td>
<td>2% *</td>
</tr>
<tr>
<td>HLA-DR7 + DQ3</td>
<td>72% (13/18)</td>
<td>3%*</td>
</tr>
</tbody>
</table>

* P < .0001

Mallal S et. al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse transcriptase inhibitor abacavir. Lancet 2002;359:727-32.
Genetic Predisposition to Drug Toxicity

Association between MHC alleles & abacavir (ABC) hypersensitivity

<table>
<thead>
<tr>
<th></th>
<th>+ ABC HYPER (n = 84)</th>
<th>- ABC HYPER (n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>78%</td>
<td>71%</td>
</tr>
<tr>
<td>Black</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>HLA-B*5701</td>
<td>46% (39/84)</td>
<td>3.5% (4/113)</td>
</tr>
</tbody>
</table>

* P < .0001

Predictive values of HLA markers will vary across populations

Genetic Predisposition to Drug Toxicity

Implications of MHC genotype and abacavir hypersensitivity data:

- S. Mallal et. al.: current practice is to **WITHHOLD ABACAVIR** in patients with HLA-B*5701 + HLA-DQ3 + HLA-DR7
- Predicted impact on preventing abacavir hypersensitivity reactions:
  - $9\% \rightarrow 2.5\%$ (72% reduction) with genotype screening

Mallal S et. al. Association between presence of *HLA-B*5701, *HLA-DR7*, and *HLA-DQ3* and hypersensitivity to HIV-1 reverse transcriptase inhibitor abacavir. Lancet 2002;359:727-32.
Genetic Predisposition to Drug Toxicity

What does this mean for the rest of us?

- Most data is in Caucasians
  - Must study ethnically diverse populations
- Further define pathogenesis
- Development of widely available, affordable test? (e.g. patch testing?)
- Currently, clinical monitoring and management of hypersensitivity RX to abacavir must remain unchanged

Mallal S et. al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse transcriptase inhibitor abacavir. Lancet 2002;359:727-32.
Genetic Predisposition to Drug Toxicity

• Fat Redistribution
Genetic Predisposition to Drug Toxicity

- Lipodystrophy and SNPs in promoter region of TNF-α gene? (increased TNF expression?)
  - ¹Case-control study in 191 Caucasians in Western Australia receiving HAART
    - G → A at -238 promoter region was found to be associated with earlier onset of lipodystrophy ($P = .014$).
  - ²Case-control study in 96 UK patients
    - G → A at -238 promoter region was more common in pts with lipodystrophy (9/61, 14.7%) than in those with no evidence of lipodystrophy (0/35, 0%; $P = .01$)

¹Nolan D et. al. AIDS 2003;17:121-3.
²Maher B et. al. XIIIth International AIDS Conference. Durban, 20002 [LB 113]
People of different races and ethnic backgrounds may respond differently to medications due to their individual genetic profiles.

Ethnicity and therapeutics: extremely important to diversify genetic studies, especially with ARVs becoming increasingly available.

A more comprehensive genetic analysis is needed (microarray analysis to assess multiple genes) for future studies.

Data thus far represent “...the first few drops before a downpour.”