Pharmacogenomics
Treating the Individual Asthma Patient
Elliot Israel, M.D.
Professor of Medicine
Harvard Medical School
Brigham & Women’s Hospital
Partners’ Asthma Center

Too much of a good thing?
- 27 yo male with severe asthma with multiple hospitalizations
- Unable to reduce prednisone below 15 mg/d
- Uses nebulized and MDI beta-agonists 10-12 times a day
- Unable to tolerate inhaled corticosteroids because they make him wheeze
- Not working and rarely leaving the house

Stepwise Approach for Managing Asthma in Patients ≥ 12 Years of Age

Patient Education and Environmental Control at Each Step

45% of Patients Do Not Have an FEV₁ Response to ICS

OUTLINE

GOAL: Bring you up to date on techniques that are allowing us to specify particular medications for individual patients
- Define pharmacogenomics and techniques
- Review developments in pharmacogenomics as they relate to use of beta agonists, leukotriene modifiers, and corticosteroids
- Review how we will use this information for treatment decisions in the future

PHARMACOGENOMICS

Study of how genetic differences influence the variability in patients' responses (therapeutic and adverse) to drugs
- 50-60% of genetic variability associates with variability in therapeutic responses

What Polymorphisms Do We Look For?
- SNPs - Single Nucleotide Polymorphisms e.g. Guanine to Cytosine
- Insertions - additional gene sequences
  - CNVs - Copy Number Variants
    - Change in the number of repeats of a sequence
- Deletions - removal of a nucleotide or nucleotides
- Genomic/Non-Genomic
  - Genomic - in areas of the gene that are known to code for or regulate a gene
  - Macro-level - Race

How Do We Look?
- Candidate Gene and Pathway Approaches
- GWAS
- Expression profiling in cells of responsive and non-responsive individuals

How Do We Confirm?
- Prospective studies
  - Labor-intensive
  - Less subject to confounding
- Association studies
  - Require large numbers
  - Allow easy replication in multiple populations

Beta-Agonists
BAGS Genetic Analysis
AA16 Locus

Exacerbations/Subject/Year by Genotype

Effect of Race for LABA Add-On vs. ICS or LTRA (KIDS)

Treatment Failures in Subjects Not Taking LABA’s Across ACRN
Treatment Failures in Subjects Taking LABA’s Across ACRN

Caucasian
Black

Treatment Failure for Long-Acting Beta-Agonist

p = 0.0314

Wechsler & ACRN, AJRCCM, 2011

Treatment Failures in Subjects Taking LABA + ICS

Caucasian
Black

Treatment Failure for Long-Acting Beta-Agonist + ICS

p = 0.0028

Wechsler & ACRN, AJRCCM, 2011

Table 1. LABA added to ICS are not as effective in Blacks: Effect of LABA Added on to ICS in Blacks vs. mixed populations

<table>
<thead>
<tr>
<th></th>
<th>Blacks Bailey 08</th>
<th>Blacks Species 11</th>
<th>Blacks Brown 12</th>
<th>Mixed Shapes 09</th>
<th>Mixed Ind 03</th>
<th>Mixed Keck 09</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>239</td>
<td>341</td>
<td>242</td>
<td>84</td>
<td>150</td>
<td>92</td>
</tr>
<tr>
<td>Duration</td>
<td>12 mo</td>
<td>3 mo</td>
<td>12 mo</td>
<td>3 mo</td>
<td>6 mo</td>
<td>3 mo</td>
</tr>
<tr>
<td>ICS dose (mg/day)</td>
<td>290</td>
<td>040</td>
<td>042</td>
<td>500</td>
<td>509</td>
<td>200</td>
</tr>
<tr>
<td>Δ FEV1 (%predicted)</td>
<td>0.91 (7%)</td>
<td>9.09 (10%)</td>
<td>0.23 (10%)</td>
<td>-</td>
<td>0.23 (10%)</td>
<td></td>
</tr>
<tr>
<td>Δ AIR PEF Limits</td>
<td>16</td>
<td>18</td>
<td>10</td>
<td>20</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>Δ Rescue puff/s</td>
<td>0.2 (ms)</td>
<td>6</td>
<td>-</td>
<td>1.4</td>
<td>-</td>
<td>1.5</td>
</tr>
<tr>
<td>Δ% Sx free days</td>
<td>1.9 (ms)</td>
<td>1.9 (ms)</td>
<td>18.4</td>
<td>21</td>
<td>15.4</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

• Arg16Arg polymorphism identifies patients who may not do as well with regular beta-agonists
  – It may identify Blacks who do less well with LABAs
• Blacks may not realize as much benefit from LABAs as Caucasians

Leukotriene Modifiers
Effect of promoter repeats of ALOX5 on the change in FEV₁ at end of active treatment with ABT-761

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Frequency (n)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>ALOX5 (repeat variant)</td>
<td></td>
<td></td>
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<tr>
<td>5/5</td>
<td>0.64 (37)</td>
<td>1.0</td>
<td>0.045</td>
</tr>
<tr>
<td>5/X</td>
<td>0.36 (21)</td>
<td>0.27 (0.08, 0.97)</td>
<td></td>
</tr>
<tr>
<td>LT4H (rs2660645)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>0.49 (28)</td>
<td>1.0</td>
<td>0.021</td>
</tr>
<tr>
<td>AG</td>
<td>0.44 (25)</td>
<td>4.0 (1.23, 12.99)</td>
<td>0.133</td>
</tr>
<tr>
<td>GG</td>
<td>0.08 (5)</td>
<td>4.5 (0.63, 31.95)</td>
<td></td>
</tr>
<tr>
<td>LTC4S (rs790012)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>0.51 (30)</td>
<td>1.0</td>
<td>0.023</td>
</tr>
<tr>
<td>AC</td>
<td>0.38 (22)</td>
<td>0.24 (0.07, 0.83)</td>
<td>0.106</td>
</tr>
<tr>
<td>CC</td>
<td>0.11 (6)</td>
<td>0.16 (0.02, 1.49)</td>
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</table>

Corticosteroid Responses

Corticotropin Releasing Hormone Receptor-1 Haplotype and Response to ICS

Arginase 1 and Change in FEV1 in Response to ICS
Additional Associations with Corticosteroid Responses

- TBX21 - encodes the transcription factor T-bet (induction of Th1 and suppression of Th2)
  - associated with large improvement in airway hyperresponsiveness in response to corticosteroid therapy. (Tantisira PNAS 2004 and Ye J Clin Pharm Ther. 2009)
  - Only 5% frequency
- Adenyl Cyclase 9 (AC9) - activated by ADRB2

Changes in Lung Function and GLCCI1 Polymorphism (glucocorticoid-induced transcript 1 gene)

Biologics

- No polymorphisms that associate with altered responses
- However there are polymorphisms that associate with the biology
  - FCER1 gene polymorphisms and IgE levels (Palmer, Clin Exp All 1999)
  - IL6R polymorphisms and circulating IL6R (Bleecker, JACI, 2012)

Additional Methods to Discover Candidate Genes

- In vitro expression profiling of cells from responsive and non-responsive populations
  - FK506 binding protein 51 gene (FKBP51) in bronchial epithelium (Woodruff PNAS 2007)

Conclusions

- Genetic polymorphisms do associate with differential responses to asthma medications

Potential Applications

- Predict responders
- Predict those with increased tendency for adverse effects
- Individualize dosing
- Allow introduction of medications that have effects in a predictable population
What prevents us from using this information now?

- Repeatable cross-sectional and prospective studies in multiple populations that will put the associations on a firm foundation of data **WHY?**
- Gene-gene interactions
  - May modify associations so that they may differ significantly among different populations and ethnic groups
- Gene-environment interactions
  - May result in differences among populations and ethnic groups

**SUMMARY**

- While we have not yet reached the level of specificity seen in cystic fibrosis, where a drug is targeted to one specific polymorphism, we are beginning to identify patterns of genetic change which will predict responses (or adverse effects) to asthma medications.
- Combining multiple studies in multiple populations with informatics for physicians will allow us to bring this information to the practice setting