Personalized Medicine – Is There a Future?

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Personalized Medicine
Practicing medicine using additional information from "omics"-based technologies such that a greater refinement in care is provided than would otherwise be possible.

"omics"-based technologies
- genomics
  - polymorphisms: noncoding, coding
    (synonymous, nonsynonymous)
  - copy number variation
  - mRNA expression
  - splice variants
  - methylation
- metabolomics
- proteomics

Potential "Direct" Application of Omics-based Clinical Data
- Diagnosis/risk
- Prognosis
- Define clinical subsets
- Response to therapy (pharmacogenetics or pharmacogenomics)
  - Identify those patients most likely to have a response
  - Identify those patients most likely to have a highly responsive phenotype
  - Identify those patients who are likely to have a severe adverse effect

![Graph showing the change in FEV1 from baseline for different treatments over weeks](image-url)
Some Problems with Polymorphism Association Studies

- Underpowered
- Lack of control for other clinical parameters
- Lack of correction for population stratification (i.e., ethnic differences in polymorphism frequency)
- Lack of correction for multiple comparisons
- Poor (or no) reproducibility by other investigative groups

Unidentified clinical subset in first report?
Spurious association in first report?
Different experimental conditions (LABA vs. SABA)

Human $\beta_2$-Adrenergic Receptor

\[
\text{Glu: Cas} = 0.45, \quad A-A = 0.25, \quad A-S = 0.33
\]

\[
\text{Ile: 0.05 (het)}
\]

1993

Effects of $\beta_2$AR Position 16 SNPs and AM PEFR During "as-needed" or Regular Albuterol

\[
\Delta \text{AM PEFR (L/min)}
\]

Weeks after Randomization
Position 16 Effect on PM PEFR

Exacerbations/patient/year

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Gly/Gly</th>
<th>Arg/Arg</th>
<th>As needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx Type</td>
<td>Regular</td>
<td>Regular</td>
<td>As needed</td>
</tr>
<tr>
<td>n</td>
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</tbody>
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β₂AR Polymorphisms are Associated with Asthma Exacerbations During Chronic Albuterol Treatment

Using Omics to Improve Medical Care: Discovering New Drug Targets

cells, disease model, tissue

expression of unsuspected gene
differential gene expression
copy number variation
polymorphisms

may not be useful for pharmacogenomics per se,
but can identify a new “drugable” pathway

At Least 6 TAS2Rs are Expressed in Human Airway Smooth Muscle

TAS2R Agonists Relax Human Bronchi ex vivo

Nature Medicine 16:1299-1304, 2010
**What About the Genomics of the Pathogen?**

- Human rhinovirus (HRV) infection causes ~50% of all asthma exacerbations
- There are >100 HRV serotypes; “pan-HRV” therapeutics have not been successful
- Can differences in HRV genomes define exacerbation subsets, for which conventional (early steroids?) or new therapy can be considered?
- Can HRV genomes be determined quickly?
- Is it necessary to sequence the entire HRV genome to gain prognostic/pharmacogenomic information?

**Human Rhinovirus (cont’d)**

Single stranded RNA virus

Genome: ~650b 5' UTR, ~6500b ORF, ~50b 3' UTR

ORF encodes a single protein that is subsequently cleaved to form II mature viral proteins

- 8 HRV complete genomes were known when study began
- Goal: sequence the complete genomes of all known HRVs
HRV Whole Genome Tree

~ 15 "miniclades"

Outgroup

Science 324:55-59, 2009

Of all Known HRV Serotypes

RNA-based Neighbor-Joining Bootstrap Consensus Tree

Nat Med 17:627-32, 2011

Of all Known HRV Serotypes

Entirely different base composition for each HRV strain

RNA synthesis

Converting genomes from translation to replication

Similar for all 115 HRV strains

Analogous tract in:

A: 5' cloverleaf and pyrimidine-rich tract

Longest for all HRV-B species

Poliovirus

Aphthovirus

Cardiovirus

Virulence

Nonsynonymous Mutations in the Coding Region From Field Samples Compared to the Analogous Reference HRV Sequence

VP4  VP2  VP3  VP1  2A  2B  2C  3A  3C  3D

1  12  207  467  1109  1476  1728  2174

Similar base composition for each HRV strain
From the reference set of HRVs, at least 23 recombination events were found, indicating a previously unrecognized mechanism of HRV diversity, ad demonstrating that "limited sequencing" may have "limited utility".

Summary

- Personalized medicine tools based on omics-technology have been applied to asthma
- Variability in patient genomes have been shown to identify:
  - Persons at risk
  - Clinical phenotypes
  - Response to therapy
- Reproducibility, effect size, and usefulness at point of care are issues that need to be addressed
- Omics-based technologies have identified new targets for asthma treatment
- Variability in pathogen (HRV) genome may provide actionable data during virus-promoted exacerbations