“Genome-Wide Association Studies: A Pharmaceutical Research Perspective”

Patrice M. Milos, Ph.D.
Executive Director, Molecular Profiling
Pfizer Global Research and Development

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Challenges In Delivering New Medicines

• Cost of Drug Discovery and Development:
  – R&D productivity challenges business model
  – Need to deliver target portfolio with human relevance to disease
  – Need to identify best indications for targets
  – Need to enhance our clinical trial designs to make better/faster decisions

• Market Forces:
  – We aim to deliver the medicines which are best in class
  – Delivering the best medicine for the right patient

• Increased expectations:
  – Regulators
  – Shareholders
  – Public perception
Productivity Improvement Becomes Key Focus on **Quality** and Quantity

- **45 Preclinical Starts**
- **31 First in Humans**
- **24 First in Patients**
- **6 Phase III Starts**
- **5 NDAs**
- **4 Products**

Need to **Reduce Attrition**

- 70% reduction
- 66% reduction
- 28% reduction
- 80% reduction
- 90% reduction
Pharmacogenomics at Pfizer

Vision...

Genetics and genomics will revolutionize the diagnosis and treatment of disease and will be crucial for the successful discovery, development and delivery of effective new medicines

CETP Inhibitor

JAK3 Inhibitor

CCR5 Antagonist
Therapeutic Area

Imperatives

Portfolio Needs

Understand Disease

External Environment

Adding Value With Pharmacogenomics

Improve Drug Discovery & Development Efficiency

More Precise and Effective Therapies
Pharmacogenomics Across the Pipeline

Choosing the Best Targets

Better Understanding of Our Targets

Genetic-based Selection of Optimal Population

Predicting Efficacy and Safety

Differentiating and Defending our Brands
The Pharmacogenomics Opportunity

Clinical Samples: DNA Linked with Phenotype

Exploration of Discovery Targets to Add Human Relevance

Building the Infrastructure to Support Pharmacogenomics

Application to Clinical Development
Human Genetics and Disease Definition

Human genetics can decipher the genetic differences in clinical phenotypes

- Disease risk - align therapeutic with genetic risk
- Disease outcome risk - predict subjects likely to express rapid disease progression
- Biomarker variability - identify genetic causes to intersubject variation in biomarkers
- Safety risk – identify subjects at increased risk for safety event
Using Whole Genome Scans for Therapeutic Targets

- SNPs across genome
- Evaluate every gene in the genome in one experiment

- Identify new targets for common diseases
- Identify molecular signatures predictive of response
Metabolic Syndrome

ATP III* Guidelines set by the NCEP
National Heart, Lung, and Blood Institute of NIH

- Abdominal obesity
  - Men >40 in
  - Women >35 in
- Trigs >150 mg/dL
- HDL cholesterol
  - Men <40 mg/dL
  - Women <50 mg/dL
- Blood pressure >130/85 mm Hg
- Fasting glucose >110 mg/dL

*Metabolic Syndrome defined as having three or more of the five component phenotypes
Study Design

Metabolic syndrome and its component phenotypes

**Case** vs. **Control**

Two genome-wide screens: > 200,000 SNPs
(Two populations: Indian Asian males and Caucasian males)

Replication screen: 5,800 SNPs
(Four populations: Indian Asian females, Caucasian females, Mexican females, and Mexican males)
## Genome-wide Scans – Populations
### Indian Asian and Caucasian Males

* ATPIII criteria

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<th>No.</th>
<th>Age</th>
<th>Waist &gt; 40 inches</th>
<th>TG ≥150 mg/d</th>
<th>HDL &lt;40 mg/d</th>
<th>SBP &gt;130 mmHg</th>
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<td>±17.54</td>
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<td>±19.08</td>
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Measurements for component phenotypes as well as other biometrics and environmental confounders
Individuals chosen to perform case-control study of Metabolic Syndrome based on ATP III criteria

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Our Approach to Genome Scans

First Genome Scan
Samples: 500 cases, 500 controls males of Indian Asian ancestry

SNPs
- 248,000 SNPs attempted
  - Common haplotype tagging SNPs: blocks defined by >80% coverage of patterns with freq>0.1
  - Haplotype map based on re-sequencing 24 individuals of mixed ancestry, ~1 million common SNPs
  - Additional SNPs selected from dbSNP to obtain uniform spacing (every 13.5 Mb) across the genome

Second Genome Scan
Samples: 500 cases, 500 controls of European ancestry

SNPs
- 267,000 SNPs attempted
  - SNPs selected to tag European LD bins:
    - $r^2 > 0.8$, MAF > 0.10
  - LD map based on genotyping 1.7 million SNPs in 24 samples of European descent, contained ~1 million SNPs with MAF > 0.10
**Univariate analyses** - Models included terms for age and key environmental confounders

- Logistic regression for discrete outcomes
  
  Metabolic syndrome status $\sim$ age + genotype

- Linear regression for quantitative outcomes

  log (waist) $\sim$ age + genotype
  
  1/sqrt (trig) $\sim$ age + alcohol + genotype
  
  sqrt (hdl) $\sim$ age + alcohol + genotype
  
  log(sbp) $\sim$ age + (blood pressure meds)*genotype
  
  log(sbp) $\sim$ age + (blood pressure meds)*genotype
  
  log(HOMA) $\sim$ age + (diabetes mellitus)*genotype
5800 SNPs Chosen for Replication Screen

Came from two categories:

1. SNPs significantly associated with metabolic syndrome or component phenotypes in genome-wide scans
   - \( p < 0.0001 \) in either scan
   - \( p < 0.001 \) in both scans

2. SNPs chosen
   - To improve coverage of intervals containing SNPs associated in genome-wide scans
   - In genes of interest due to previously identified associations with metabolic syndrome or component phenotypes
### SNP Replications: Metabolic Syndrome Populations defined by ATP III criteria

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Univariate analyses - models allowed for heterogeneity of genotype effects across populations

- Logistic regression for discrete outcomes
  Metabolic syndrome status $\sim$ age + pop*genotype

- Linear regression for quantitative outcomes
  log (waist) $\sim$ age + pop*genotype

False discovery rates - estimated across subset of SNPs selected for each component phenotype
## Subphenotype: HDL Cholesterol Replicated Associations

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<td>[LPL]</td>
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<td>8</td>
<td>19829997</td>
<td>[LPL]</td>
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<td>rs325</td>
<td>8</td>
<td>19829601</td>
<td>[LPL]</td>
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Results

- Significant – FDR ≤ .007
  Thirteen SNPs all located within genes previously shown to be associated with component phenotypes
  - HDL levels – CETP, ABCA1, and LPL
  - Triglyceride levels - the apoAI/apoAV/apoCIII gene cluster and LPL

- FDR ≤ 0.35
  Eleven additional SNPs
  - HDL levels – three in LPL, one novel
  - Triglyceride levels – two in LPL, one novel
  - Diastolic blood pressure – one novel
  - HOMA / Insulin – three novel
Coverage of the Genome-wide Scans

- Used HapMap Phase II data to estimate power
  - Determine direct power based on CEU allele frequency and disease model parameters
  - Determine maximum $r^2$ with a genotyped SNP and adjusted power
  - Conservative $\alpha = 10^{-4}$ level
- Disease model parameters
  - 500 cases & 500 controls
  - Multiplicative risk
  - Discrete trait with prevalence 0.2
• Several genes previously shown to be associated with component phenotypes, such as CETP with HDL levels and LPL and the chromosome 11 Apo gene cluster with triglyceride levels had genome-wide significance in our study

• Some new loci with smaller effect sizes were associated with component phenotypes but examination in additional populations is required to distinguish from false positives

• We identified no genetic risk factors for metabolic syndrome, suggesting that analyzing the individual component phenotypes may be a better means of studying this disease
The Need to Accelerate Our Pace and Our Learnings

GAIN: The Genetic Information Association Network

A Unique Public/Private Partnership
Pfizer/Perlegen’s Goals in Funding and Supporting GAIN

• Accelerate our understanding of the genetic basis of human diseases – many of which remain major medical needs for patients

• Generate and quickly release genotype data (pre-competitive) for several these important human diseases

• Encourage analysts around the world to participate in the analysis of these important disease data sets and thereby advance the science of whole genome analyses for the entire scientific community

• Finally, build the foundation for more precise therapies where the potential exists to better diagnosis and treat human disease
Why Are Whole Genome Methods So Important?
The Challenges in Drug Development: Applying Pharmacogenomics – Why We Need to Examine the Whole Genome

Discovery

- Increase target selection by using human genetics to understand disease etiology
- Evaluate how common variants in the target will influence the efficacy of the compound
- Select subjects or stratify populations in early efficacy studies to improve quality of decision making
- Prediction of efficacy and adverse events based on a subject’s genotype

Development
Torsade de Pointes

Normal QT

Prolonged QT

Torsade de Pointes (TdP)
Business Drivers for Genetic Studies

- Low incidence of drug-induced *torsade de pointes* during development of dofetilide resulted in alteration of dosing scheme for patients

- Phenotype mimics the phenotype of inherited long QT syndrome

- Does the genetic basis of Long QT Syndrome provide any insight into drug-induced TdP?
## Can Familial Genes Teach Us About Drug-Induced TdP?

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<th>Gene</th>
<th>Product</th>
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Can Genetics Predict TdP Prior to Therapy?

- DNA samples not collected during dofetilide clinical trials
- Heroic efforts made to collect DNA post-trial
- 40 Patients/families consented to DNA analysis
- For some, only plasma was available (Whole genome amplified for residual DNA where possible)
- All exons of 7 LQT genes scanned for mutations in 34 individuals who developed drug-induced TdP

- All TdP patients, 95 controls from the same study, and 595 controls from another study genotyped for all common amino acid changing SNPs and rare SNPs identified via SNP scanning
Highlighted in red are familial variants linked to long QT syndrome.
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A single genetic variant does not account for drug-induced TdP.

LQT genotypes alone could not be used to completely predict susceptibility to TdP, even when used in conjunction with phenotype.

Statistical modeling using genotypic and phenotypic variables was unable to predict all adverse events.

Current research suggests genetic variation can be identified in one of the LQT candidate genes, approximately only 20% of the time.

In other subjects the effect is mediated by other undetermined factors.

Additional research through whole genome approaches may offer opportunity for defining other genes involved in TdP.

Statistical modeling using genotypic and phenotypic variables was unable to predict all adverse events.

Candidate gene analyses, even though strongly based in selection, provides limited opportunity to define genetic basis of outcome.
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  Nick Staten
  Rich Mazzarella
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  John Wetterau

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