Genomics-
Hope or Hype?

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April 12, 2006
April in Genetics

April 23, 1953 Watson and Crick published structure of DNA

April 25, 2003 Publication of Human Genome Sequence (declared DNA day)
Why Asthma Genomics?

“We think it has something to do with your genome.”
Objectives

- What is genomics
- How may genomics impact medicine and public health
- What is known about genetic factors and asthma
- How does the genome interact with the environment
- Future questions
Definitions

Genetics-The branch of biology that deals with heredity, especially the mechanisms of hereditary transmission and the variation of inherited characteristics among similar or related organisms.

Genomics-The study of genes and their function. Genomics aims to understand the structure of the genome, including the mapping genes and sequencing the DNA. Genomics examines the molecular mechanisms and the interplay of genetic and environmental factors in disease.
Human Genome Project
Human Genome Project: Biology’s Moonshot. Fifteen years, six countries, twenty centers. Three billion dollars, three billion letters. One dollar per letter—such a deal!

Twenty-three chromosomes. Supposed to contain 100,000 genes. Turns out to only have 30,000 genes—or maybe 25,000. But it could be 40,000—check back with us next year.

Said to have the answer to everything, absolutely everything. Diabetes, Asthma, Cancer, Evolution, Populations, Migrations, Life, Death, Taxes. Even the Boston Red Sox.

The only problem is: there’s no index.
Genome: Bought the book, hard to read.

Eric Lander IgNobel® Prize Nano-lecture

10/2/2003
What does this mean for medicine?
History of Medicine (abridged)

- 2000 BC  Here, eat this root
- 1000 BC  That root is heathen, say this prayer
- 1850 AD  Prayer is superstition, drink this potion
- 1940 AD  That potion is snake oil, swallow this pill
- 1990 AD  That pill has a narrow therapeutic window and low efficacy; take this biologically engineered drug
- 2000 AD  That drug is artificial; here eat this root
2010 AD  I want to study your genotype before prescribing anything.
Human Genome Project

- ~30,000 genes
- 3.7 proteins per gene
- 1/1000 base pair difference
- 3 billion base pairs
- Differ at 3 million places!!
- “Junk DNA”
A single nucleotide polymorphism (SNP) can be defined as a single base pair site in the human genome that is different from person to person.
Hypothesis

Patterns of polymorphisms predict predisposition to disease
Generic prevention vs. Personalized prevention

Generic therapy vs. Personalized therapy
Benefits

- More effective therapy
- Safer therapy
- More cost-effective therapy
- Decreased pharmaceutical utilization?
- Innovative therapies
Limitations/Risks

- Availability of information
- Availability of new technology
- Predictive accuracy
- Preparation of provider system
- Adoption of new technology
- Consumer demand/direct to consumer
- Cost implications
Economics of Genomic Medicine

- **Decrease costs**
  - Preventive measures
  - Earlier interventions
  - More effective interventions

- **Increase costs**
  - Treatments for the untreatable
  - Longevity
  - Pharmacy
  - Gene therapy and stem cell therapy
What Is Asthma

- **Asthma Triad**
  - Bronchial hyperresponsiveness
  - Increased mucous production in airway
  - Edema of airway epithelial cells

- **Asthma is a disorder of inflammation!!**

- **Treatment must control bronchospasm (rescue) and inflammation (controller)**
Is Asthma Genetic?

- Twin studies estimate heritability at 36-79%.
- Three times more likely to have asthma if mother has asthma.
- Seven times more likely if mother and father have asthma.
- 20 chromosomal regions linked to asthma (4 in >1 study).
Is Asthma Environmental?

- Prevalence of asthma increasing faster than can be explained by genetics
- Proposed factors
  - Air pollution
  - Allergens
  - Early infection
Genes and Environment

Diabetes
HIV/AIDS
Asthma
Diabetes
Cancer
Phenylketonuria
Cystic Fibrosis
Tay-Sachs
Lead
How do we sort it all out?
Asthma (pre-2003)

- How is asthma (a trait) inherited?
- How does a family history of asthma increase risk for a patient?
- Techniques include family studies, twin studies, adoption studies to sort out heritability and environmental effect
- Linkage studies
  - Hampered by definition of ‘phenotype’
Phenotype
Phenotype

Asthma Genes

Cold-induced asthma

Exercise-induced asthma
Phenotype

Asthma Genes

Asthma  Asthma  Asthma
Asthma (post-2003)

- Identify all genes that contribute to asthma trait (phenotype)
  - Association studies
- Study all gene-gene and gene-environment interactions
- Identify different ‘phenotypes’
  - Environmental response (exercise, cold)
  - Drug response
Combined Approach

- Start with conventional mapping/linkage analysis
- Use genomic approaches (such as SNPs) to rapidly identify candidate genes
- Define role of candidate gene
- Assess for appropriateness as treatment target
First Success
ADAM33
First Success
ADAM33

- Locus on 20p13 identified on genome-wide screen of 460 Caucasian families
- Association increased when phenotype was tightened to focus on airway hyperresponsiveness
- Fine mapping with SNPs identified ADAM33
- ADAM33 expressed in lung (bronchial smooth muscle and fibroblasts) and lymph nodes
- Other ADAM proteins interact with inflammatory cytokines
Conclusions

- **ADAM33** is an excellent candidate gene for asthma susceptibility
- Represents a great target for drug development
First Success?  

**ADAM33**

- Linkage to 20p13 not seen in previous genome-wide screens
- Two cohorts were used in study and may not have been independent (favoring spurious results)
- Other methodologic concerns
- No functional data on role of gene variants reported
First Success?  
**ADAM33**

- Subsequently, three other groups have been unable to reproduce the study results, although some association in certain populations was seen.
- Role of **ADAM33** in asthma unclear.
Problems with Association

- Failure to replicate association studies very common

- Reasons
  - False association in study
  - Insufficient power
  - Population admixture
  - Heterogeneity of genetic and phenotypic factors
  - Environmental factors
Other Genes

- **PHF11**
  - Associated with IgE levels
  - Identified in multiple studies of atopic individuals
  - Association with asthma less impressive
  - Function of gene unknown
  - Two other genes in the region also possible candidates
Other Genes

- **DPP10**
  - Located adjacent to Interleukin-1 gene cluster
  - IL-1 variants known to be associated with asthma
  - Identified variant in promoter of gene, which could affect expression
  - No other convincing data at present
Gene-Environment Interaction?

- **CD14**
  - Plays a role in innate immune system response
  - Relationship between polymorphisms and IgE levels
  - Linkage strengthened if population stratified by exposure to cigarette smoke in infancy

- **TLR4**
  - Toll-like receptor 4
  - Signal similar to that seen in ILR
  - Association found between exposure to endotoxin in house dust and asthma
Where Are We?
Where Are We?

From Malerba and Pignatti J Appl Genet 46:93-104, 2005

Table 1. Asthma-related genes and their localization.

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Chromosomal and genomic locations have been extracted from the Ensembl Genome Browser - Ensembl v77 (http://www.ensembl.org). Genes were arbitrarily ordered by location from chromosome 1 to the sex chromosomes.
Where Are We Going?
Future Research in Asthma
NHLBI Working Group 2004

- 4 priorities and 2 initiatives
- Priority 4-Genetics/Gene-Environment interactions, Pharmacogenetics
  - To identify all relevant susceptible variants in environment-specific and population-specific contexts
  - To characterize the function of susceptible genetic variants
  - To incorporate genetics information into the clinical management of asthma
Population Differences

- Ethnic differences
- Understand genomic variation that underlies difference

**Age-Adjusted* Asthma Mortality Rates by Race, United States: 1979–1998**

- **Black**
- **Other**
- **White**

Source: Underlying Cause of Death dataset by the National Center for Health Statistics

* Age-adjusted to 2000 U.S. population
Genomic Approaches

- Refine asthma phenotypes
- More robust association studies
- Identify relevant pathways
Gene-Environment Interactions

- Define how environment affects gene regulation
- Can this effect be modified?
Gene-Environment Interactions

National Children’s Study

---Study Assembly-----
Pharmacogenomics

Differential response to drugs

- Response to β-agonists
- Response to Leukotriene receptor antagonists

The Arachidonic Acid Pathway

Membrane phospholipids

Phospholipase A₂

Arachidonic Acid

5-Lipoxygenase activating protein (FLAP)

5-Lipoxygenase

Cyclooxygenase

Prostaglandins

Thromboxanes

Other Inflammatory Diseases (e.g. arthritis)

Leukotrienes

LTC₄, LTD₄, LTE₄ (cysteinyl LTs)

Asthma
Asthma Genomics Hope or Hype?