Cardiovascular Genomics in 2012: Starting a Career in Genomic Epidemiology

Christopher J. O’Donnell MD MPH
No Disclosures
American Heart Association
November 3, 2012
An Unconventional Path to Sculpting a Cardiovascular Genomic Investigator

1987
- Medical School
  - Residency
  - 1st Clin Research

1997
- CV Fellowship
  - Epi Fellow+MPH
  - Faculty Job I
    - “50/50”
- Faculty Job IIa
  - “80/20” NIH+Hospital
  - “Major” in Genetic Epidemiology

2007
- Faculty Job IIb
  - “90/10” NIH+Hospital
  - Immerse in Gen Epi, Genomics & Programs

Contagious passion for epi & outcomes research

“What am I good at → move on → enjoy and succeed”

Focus on research, play focussed clinical role

Be rigorous, publish, focus on genetics and imaging

Join a collaborative genomic community

Lead novel genomic programs at Framingham & NHLBI
Summary: Perfecting your Plan

• Passion
  – Predict, Prevent, Pre-Empt, Pharmacogenomics
• Population to Study
• Phenotype of Focus
• Program: Genomic Approach
• Plan for Provision of Funding
• Project Design
• Perspective on the Evolving Field
• Plan, Plan, Plan
• Publish!
Atherosclerotic Plaque Development: From Healthy Vessel to Clinical CVD

Genetic/Genomic Determinants

Healthy Vascular State → Traditional Risk Factors, Novel Risk Factors → Subclinical Atherosclerosis → Clinical Cardiovascular Disease

Environmental Modifiers

Normal → Early Lipid rich → Internal rupture → Calcified shell, Calcified plaque → Vulnerable, Rupture, Thrombus, Myocardial Infarction, Obstructive Infarction

Fatty streaks, White blood cells, Red blood cells, Lipid rich plaque, Scar, White blood cells, Platelets, Fibrin

Inflammation and calcification, Scar development with calcification
Framingham Heart Study

Downtown Framingham, MA (circa 1960)

Factors of Risk in the Development of Coronary Heart Disease—Six-Year Follow-up Experience

The Framingham Study


Framingham, Massachusetts

Increasingly reliable estimates of the prevalence and incidence of coronary artery disease have been made possible by the Framingham Heart Study. Since it has been established that coronary atherosclerosis is present for many years before any evidence of clinical heart disease, recognition of the factors associated with coronary heart disease is of major public health importance.

- High Blood Pressure
- Increased Cholesterol
- Smoking
- Diabetes
- Male Gender
- Family History

Annals Internal Medicine 1961

Original cohort: N = 5209 men and women (ages 28-62)
1644 spouse pairs, 596 extended families

Offspring study: N = 5124 men and women (ages 5-70)
1576 spouse pairs, 3514 biological offspring

Third Generation study: N≈4000 men and women
A Brief History of Genomic Studies of Common CVD in Populations

Human Genome Project

Detailed Studies of Rare Mendelian Conditions

Genome-Wide (Microsatellite Linkage)

Detailed Studies of Candidate Gene/Locus Variation

HapMap, ENCODE

GWA Studies
  Case-Control Studies ➔
  Population Studies ➔

Deep Medical Resequencing Studies

GWAS Fundamentals:
• 10s of millions of SNPs in genome
• Nearby SNPs are correlated
• SNP “chips” with 50K to 5M SNPs
• GWAS to ID SNP assoc. w/phenotype
• Strong association $p < 5 \times 10^{-8}$
• GWAS meta-analysis boost power
# GWAS Discoveries for CAD/MI and CAD/MI Risk Factors: Update 2012

<table>
<thead>
<tr>
<th>Condition</th>
<th>N genes/loci</th>
<th>Consortium Name; Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD/MI</td>
<td>&gt;30*</td>
<td>CardioGRAM + C4D; Nat Genetics 2011.</td>
</tr>
<tr>
<td>Cigarette Use Behaviors</td>
<td>&gt;12</td>
<td>TAG; Nature Genetics 2010</td>
</tr>
<tr>
<td>Obesity/BMI</td>
<td>&gt;30*</td>
<td>GIANT; Nature Genetics 2010</td>
</tr>
<tr>
<td>Diabetes/ Glycemic Traits</td>
<td>&gt;25*</td>
<td>International Diabetes Genetics; Nat. Genetics 2010</td>
</tr>
<tr>
<td>Hypertension</td>
<td>&gt;25</td>
<td>Int. BP Genetics; Nature 2011.</td>
</tr>
</tbody>
</table>

### GWAS for CVD and CVD Risk Factors: 2012

<table>
<thead>
<tr>
<th>CVD Anatomical Area</th>
<th>GWAS Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Artery</td>
<td>MI, CAD</td>
</tr>
<tr>
<td>Left Ventricle</td>
<td>Heart Failure, HF Death, Sudden Death, Vent. Fibrillation</td>
</tr>
<tr>
<td>Left Atrium</td>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td>Cerebral Arteries</td>
<td>Ischemic Stroke Intracranial Aneurysm</td>
</tr>
<tr>
<td>Peripheral Arteries</td>
<td>PAD</td>
</tr>
<tr>
<td>Peripheral Veins</td>
<td>VTE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Factor Domain</th>
<th>GWAS Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids</td>
<td>LDL, HDL, Triglycerides</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>SBP, DBP, Hypertension</td>
</tr>
<tr>
<td>Glycemia</td>
<td>Type 2 Diabetes Mellitus, Fasting Glucose and Insulin</td>
</tr>
<tr>
<td>Adiposity</td>
<td>BMI, Obesity, Waist Circumf.</td>
</tr>
<tr>
<td>Smoking Behavior</td>
<td>Cigarette Use</td>
</tr>
</tbody>
</table>

Pre-Genome Science Models

- Lone scientists in pursuit of basic knowledge
- Post-doc fellows toiling in a single lab/group
- Few collaborations, generally occur only when mutually beneficial (publish paper, patents, etc)
- Sharing of data discouraged
- RPG funded
- White male PIs
- Glory (Stockholm)

Hypercholesterolemia
(Familial) and MI
Post-Genome Epidemiology

- Common mission: scientific discovery for preventing and treating (complex) disease
- Multidisciplinary: epidemiologists, clinicians, statisticians, genome scientists, bioethicists
- Multinational PIs, multiethnic populations
- Data sharing required (by NIH) mostly embraced
- A village of scientists
- Communicate via WIKI
- Shared credit, resources
Prospective, longitudinal follow-up. Deep phenotyping for RFs and outcomes. Similar methods and QC for phenotyping. Available DNA, RNA, blood, imaging.

**CHARGE (Cohorts for Heart & Aging Research in Genome Epidemiology) Consortium, N~40,000**

- **FHS**
  - N~9,400
  - Affy 500K, 100K, 50Kg

- **CHS**
  - N~5,000
  - Illumina 370CNV

- **AGES**
  - n~5,000
  - Illumina 370CNV

- **ARIC**
  - N~16,000
  - Affy 6.0

- **Rotterdam**
  - N~12,000
  - Illumina Hap550

Common High Priority Disease Phenotypes


>600 Investigators, >80 Cohorts
>60 Phenotype Working Groups
Published Collaboration Principles
>140 Publications since 2008
Targeted & Genome-Wide Sequencing to Discover Causal DNA Variants

-----Protein-coding Gene A-----

Exon 1  Exon 2  Exon 3  Exon 4

-----Protein-coding Gene B-----

Exon 2  Exon 2  Exon 3

-Protein-coding Gene C-

Exon 1  Exon 2  Exon 3

Targeted to Exon(s)
Targeted to A Region(s)
Whole Exome
Whole Genome
Tools, Resources & Applications for Advancing Genomic Medicine

- Patient Cohorts
- Population Cohorts
- iPSCs
- Big Data - Ontologies
- Computational Models
- Predict, Prevent, Treat, and Pre-Empt Cardiovascular Disease
- Biorepositories
- Proteome/Metabolome
- Genome/Transcriptome/Epigenome
- Imaging
Systems and Network Approaches to Translate Genomics to Disease Phenotypes

Use networks to define common mechanisms underlying diseases across tissues.

- Patient Phenotypes
- Traits
- Molecular Networks
- Genetics/Genomics

Tissue, organ, individual and population levels

Molecular and cellular levels

Figure adapted from Barabasi, *New Engl J Med* 357:404-7 (2007)
## NHLBI GWA & Exome Cohort/Prgms: 2012

<table>
<thead>
<tr>
<th>Program</th>
<th>GWAS Tot N</th>
<th>Exome Data*</th>
<th>Population(s): Sex; Ethnicity</th>
<th>Phenotypes Under Investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham SHARE</td>
<td>9,500</td>
<td>Yes</td>
<td>Men, Women; EA</td>
<td>CVD, Risk Factors, Lung, Blood**</td>
</tr>
<tr>
<td>Asthma SHARE</td>
<td>5,000</td>
<td></td>
<td>Men, Women; EA</td>
<td>Asthma</td>
</tr>
<tr>
<td>MESA SHARE</td>
<td>8,500</td>
<td>Yes</td>
<td>Men, Women; EA, AA, HA, CA</td>
<td>CVD, Risk Factors, Lung, Blood**</td>
</tr>
<tr>
<td>Women’s Health Initiative SHARE</td>
<td>12,000</td>
<td>Yes</td>
<td>Women; AA, HA</td>
<td>CVD, Risk Factors, Lung, Blood**</td>
</tr>
<tr>
<td>STAMPEED ARIC, CHS</td>
<td>~50,000</td>
<td>Yes, Yes</td>
<td>Men, Women; EA, AA, HA</td>
<td>CVD, Risk Factors, Lung, Blood**</td>
</tr>
<tr>
<td>CARe (CARe IBC)</td>
<td>~11,000 (~40,000)</td>
<td>Yes, var. cohorts</td>
<td>Men, Women; AA (EA, AA, HA, CA)</td>
<td>CVD, Risk Factors, Lung, Blood**</td>
</tr>
<tr>
<td>Women’s Genome Health</td>
<td>28,000</td>
<td></td>
<td>Women Only; Largely EA</td>
<td>CVD, Risk Factors, Blood**</td>
</tr>
<tr>
<td>COPD Gene</td>
<td>~10,000</td>
<td></td>
<td>Men, Women; EA, AA</td>
<td>COPD, CVD, Risk Factors</td>
</tr>
</tbody>
</table>

**Total Participants:** ~140,000 ~12,000
Starting a Career in Genomic Epidemiology: Some Key Questions

- Major versus Minor?
- What is Your Pressing Question and Your Key Phenotype?
- Population vs Clinical vs Translational Research?
- What is the Genomic and Analytic Method?
  - Genome/epigenome, proteome/metabolome, RNAome
  - Bioinformatics/statistical genetics
- What is the Broad Area of Translation?
  - Discovery of Disease Mechanisms
  - Clinical Trials
  - Prediction/Prognosis
  - Pharmacogenetics
  - Clinical Genetics
  - Outcomes/Clinical Effectiveness/Cost-Effectiveness Research
Starting a Career in Genomic Epidemiology: Some Key Questions

• What is Your Program for Supplemental Learning?
  – Genomics, stat. genetics, bioinformatics, epi, clinical research
  – Masters Program? PhD?

• Right Mentor, Right Environment, Right Time?
  – Post-Doc Fellowship (AHA, NIH, Other Gov’t Training)
  – Genetics Dept, Genomics Institute or School of Public Health
  – Cohorts and/or Consortia (eg, CHARGE Consortium)

• AHA Councils: Epi/NPAM, FGTB

• Fellowship and Career Opportunities at NIH?

• Pursue Training Grant and Map Fellow→Faculty Path

• Essential: your specific project should lead to specific, high quality first author manuscript(s)
Summary: Perfecting your Plan

• Passion
  – Predict, Prevent, Pre-Empt, Pharmacogenomics
• Population to Study
• Phenotype of Focus
• Program: Genomic Approach
• Plan for Provision of Funding
• Project Design
• Perspective on the Evolving Field
• Plan, Plan, Plan
• Publish!