Genetics of Polygenic Disorders

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It is estimated there are 6,000 single gene disorders of which 2,000 genes have been identified.

Nucleic Acids Res. 2002;30;52
Am. J. Med. Gent. 2004;125C;50
Am. J. Hum. Gent. 2006;79:421-426
Just don’t expect it to roar.
CARDIAC STRUCTURE IN β-MyHC-Q\textsuperscript{403}
TRANSGENIC RABBIT MODEL OF HUMAN FHCM
THE TRANSGENIC RABBIT MODEL OF HCM SIMULATES HUMAN FHCM

• Hypertrophy
• Interstitial fibrosis
• Myocyte disarray
• Ventricular diastolic and systolic dysfunction
In single gene disorders, a single gene is both necessary and sufficient to induce the phenotype.
Single gene disorders are rare occurring in 1/10th of 1% of the population.
GENETICS AND MEDICINE

• 20 diseases account for over 80% of all deaths in the world

• It is estimated thousands of genes are responsible for these diseases
The cause of Death in Canada

Cardiovascular diseases: 33.7%
Cancer: 29.5%
Other chronic diseases: 26.5%
Injuries: 5.7%
Communicable diseases: 4.6%

Identifying the Genes Responsible for common chronic diseases such as CAD was not feasible until recently.

Common chronic diseases are due to multiple genes each contributing minimal to moderate effects.
Genome-wide scanning for Case Control Studies

Kruglyak using simulation studies postulated in 1999 it would require DNA markers spanning the genome every 6,000 base pairs to detect genes predisposing to common diseases.

This would require 500,000 DNA markers.
Identifying the Genes Responsible for CAD has been prohibitive until recently. WHY?

- Genome-wide scanning requires hundreds of thousands of DNA markers.
- Requires a sample size of thousands of unrelated controls and affected individuals.
- Such high throughput genotyping and phenotyping until recently was prohibitive.
99.5% of the DNA sequence of all human beings is identical.
Individual genetic variation and susceptibility to Polygenic Diseases

3,000,000 SNPs are responsible for individual variations and susceptibility to polygenic diseases
A Reminder

Each gene has multiple forms referred to as alleles.

Most alleles differ from each other by only 1 or 2 nucleotides (SNPs)
SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs)

ATCGTGCAGAT
TAGCAGCTA

Normal Wild Type

ATCGTGCAGAG
TAGCAGGCTC

Single Nucleotide Polymorphism (SNP)
Definition of a SNP

Single Nucleotide Polymorphism (SNPs)

A mutation due to a single nucleotide that occurs at a frequency $\geq 1\%$
The first technological breakthrough making GWAS possible was the development of thousands of DNA markers in the form of SNPs on a microarray.
AFFYMETRIX 500,000 DNA MARKERS
ON TWO CHIPS

250,000 SNPs 250,000 SNPs

2005 - $1,640.00
Affymetrix 500,000 Chip
2005

2005 - $1,640.00
Case Control Association Studies

Affected (Cases)

Unaffected (Controls)
Mapping and Identification of Genes for Common Multigene Disorders

Case Control Association Studies

• Candidate Gene Approach
• Genome-wide Scans
Parameters used to calculate Sample Size

- Minor allele frequency (MAF) ≥ 10%
- Risk ratio of ≥ 1.3
- 1,000,000 SNPs for screening
- Power function of 0.90
- Association requires a p-value ≤ 0.00000001 (5 x 10^{-8})
Bonferroni Correction

\[ P\text{-value} = \frac{0.05}{1,000,000} = 0.000000005 \]
Sample Size with Allele Frequency of $\geq 10\%$

Sample size 12,000

6,000 cases versus 6,000 controls
Sample Size with Allele Frequency of $\geq 5\%$

Sample size 25,200
12,600 cases versus 12,600 controls
Sample Size with Allele Frequency of $\geq 20\%$

Sample size 8,000

4,000 cases versus 4,000 controls
Sample Size with Allele Frequency of $\geq 30\%$

Sample size 6,000

3,000 cases versus 3,000 controls
Sample Size (total cases + controls) by MAF

![Graph showing the relationship between MAF and total sample size. The graph indicates a decreasing trend in sample size as MAF increases.]
Sample Size for Replication

This would depend on the number of SNPs taken forward. If taking forward a single SNP then a p-value of 0.01 would be stringent.
Genome wide Association Studies

Case Control Association studies require replication in an independent population similar to the initial discovery population.
RUDDY CANADIAN CARDIOVASCULAR GENETICS CENTRE

DNA Extractor

Affymetrix 450 Station
1,000,000 Chip Analyzer
Fast CT Scanner (64 Slice)
Non-invasive Coronary Angiograms
GENOME WIDE SCAN FOR GENES ASSOCIATED WITH CORONARY ARTERY DISEASE

72,864 SNPs Genome wide scan

Ottawa Heart Population 1 (322 vs 312)
(2,586 SNPs, p .02)

Ottawa Heart Population 2 (311 vs 326)
(50 SNPs, p .02)

ARIC Study (11,478)
(2 SNPs, p .02)

Dallas Study (527 vs 153)

Copenhagen Study (10,578)

Ottawa Heart Population 3 (647 vs 847)
A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

Ruth McPherson,1* Alexander Pertsemlidis,2* Nihan Kavaslar,1 Alexandre Stewart,1 Robert Roberts,1 David R. Cox,3 David A. Hinds,3 Len A. Pennacchio,4,5 Anne Tybjaerg-Hansen,6 Aaron R. Folsom,7 Eric Boerwinkle,8 Helen H. Hobbs,2,9 Jonathan C. Cohen2,10

Coronary heart disease (CHD) is a major cause of death in Western countries. We used genome-wide association scanning to identify a 58-kilobase interval on chromosome 9p21 that was consistently associated with CHD in six independent samples (more than 23,000 participants) from four Caucasian populations. This interval, which is located near the CDKN2A and CDKN2B genes, contains no annotated genes and is not associated with established CHD risk factors such as plasma lipoproteins, hypertension, or diabetes. Homozygotes for the risk allele make up 20 to 25% of Caucasians and have a 30 to 40% increased risk of CHD.

Science 2007:316(5830);1488 - 1491
A COMMON ALLELE ON CHROMOSOME 9 ASSOCIATED WITH CORONARY HEART DISEASE

rs10757274  rs2383206

9p21

Chromosome 9

Science, 2007: 316(5825)1488-91
9p21 LOCUS OCCURS COMMONLY IN THE CAUCASIAN POPULATION

- 9p21 locus is heterozygous in 50% of Caucasians

- 9p21 locus is homozygous in 20 – 25% of Caucasians
THE 9p21 LOCUS IS ASSOCIATED WITH SIGNIFICANT INCREASED RISK OF CORONARY ARTERY DISEASE IN THE CAUCASIAN POPULATION

• Homozygotes carries an increased risk of 30-40% for CHD
• Heterozygotes carry increased risk of 15-20% for CHD
A COMMON ALLELE ON CHROMOSOME 9 ASSOCIATED WITH CORONARY HEART DISEASE

9p21 locus risk is independent of known risk factors, namely, cholesterol, hypertension or diabetes
Progress of Genome wide Association Studies in identifying Disease loci

Over 200 loci associated with disease have now been identified by Genome wide Association Studies and replicated in independent populations

Donnelly P. Nature 2008;458:728-731
## Progress of Genome-wide Association Studies (2009)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Loci</th>
<th>2 years ago</th>
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<tbody>
<tr>
<td>Crohn’s Disease</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Height</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Obesity</td>
<td>6</td>
<td>1</td>
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</table>
Twelve Loci replicated for predisposition to CAD and Myocardial Infarction

<table>
<thead>
<tr>
<th>Chromosomal Locus</th>
<th>MAF Frequency (Minor Allele)</th>
<th>Odd Ratio</th>
<th>P-Value</th>
<th>Sample Size</th>
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<tbody>
<tr>
<td>9p21</td>
<td>75%</td>
<td>1.30</td>
<td>2.7 x 10^{-44}</td>
<td>600 – 23,000</td>
</tr>
<tr>
<td>3q22.3</td>
<td>40%</td>
<td>1.15</td>
<td>7.4 x 10^{-13}</td>
<td>2,520 – 25,000</td>
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<tr>
<td>6q26-q27</td>
<td>1 – 40%</td>
<td>1.20</td>
<td>4.2 x 10^{-15}</td>
<td>4,864 – 19,262</td>
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<tr>
<td>21q22</td>
<td>13%</td>
<td>1.19</td>
<td>6.0 x 10^{-11}</td>
<td>6,046 - 25,538</td>
</tr>
<tr>
<td>6p24</td>
<td>6%</td>
<td>1.13</td>
<td>1.0 x 10^{-9}</td>
<td>6,046 - 25,538</td>
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<tr>
<td>2q33</td>
<td>14%</td>
<td>1.17</td>
<td>1.0 x 10^{-8}</td>
<td>6,046 - 25,538</td>
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<tr>
<td>1p13</td>
<td>80%</td>
<td>1.17</td>
<td>7.9 x 10^{-12}</td>
<td>6,046 - 25,538</td>
</tr>
<tr>
<td>10q11</td>
<td>80%</td>
<td>1.17</td>
<td>7.4 x 10^{-9}</td>
<td>6,046 - 25,538</td>
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<tr>
<td>1q41</td>
<td>70%</td>
<td>1.13</td>
<td>1.4 x 10^{-9}</td>
<td>6,046 – 25,538</td>
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<tr>
<td>1p32</td>
<td>80%</td>
<td>1.15</td>
<td>9.6 x 10^{-9}</td>
<td>6,046 - 25,538</td>
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