Genetic Individualization for Lipid Therapy: We Are Not There Yet

Sekar Kathiresan, M.D.
Director, Preventive Cardiology, Massachusetts General Hospital
Associate Professor of Medicine, Harvard Medical School
Associate Member, Broad Institute

March 15, 2014
Disclosures

• Research grants:
  – Merck, Pfizer

• Scientific Advisory Boards:
  – Celera, American Genomics, Catabasis
Monogenic vs Complex Disease

- Genotype $\rightarrow$ Phenotype correspondence nearly perfect
- Simple inheritance pattern
- Single causative gene
- Large effect of gene

- Genotype $\rightarrow$ Phenotype correlation imperfect
- No clear Mendelian inheritance pattern
- Multiple susceptibility genes
- Each gene with modest effect
- Environmental mimics (phenocopy)
Most MI and lipid disorders in the population is complex, not the result of a single gene defect.
41yo primary prevention patient seen by PCP in 2008

Total cholesterol: 217 mg/dL (5.56 mmol/L)
LDL cholesterol: 150 mg/dL (3.84 mmol/L)
HDL cholesterol: 41 mg/dL (1.06 mmol/L)
Triglycerides: 130 mg/dL (1.47 mmol/L)

BP 110/70
Fasting glucose 86, body mass index 24
No history of type 2 diabetes mellitus
No cigarette smoking
C-reactive protein 1.0 mg/L
Strong FH of MI/CAD

First MI at age 41

2 coronary stents at age 41
2 coronary stents at age 43
obstructive CAD on angio at age 51
Framingham risk score

Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack

The risk assessment tool below uses information from the Framingham Heart Study to predict a person’s chance of having a heart attack in the next 10 years. This tool is designed for adults aged 20 and older who do not have heart disease or diabetes. To find your risk score, enter your information in the calculator below.

<table>
<thead>
<tr>
<th>Age:</th>
<th>years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender:</td>
<td></td>
</tr>
<tr>
<td>Female □ Male □</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Cholesterol:</th>
<th>mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL Cholesterol:</td>
<td>mg/dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoker:</th>
<th>No □ Yes □</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Systolic Blood Pressure:</th>
<th>mm/Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No □ Yes □</td>
</tr>
</tbody>
</table>

Are you currently on any medication to treat high blood pressure.

[Calculate Your 10-Year Risk]
Framingham risk score:

4% risk for coronary heart disease over next 10 years
But, Framingham risk score doesn’t include family history
Reynolds Risk Score for Men

The value you entered for age is outside of the lower range. The result below is based on age 45.

As shown in the graph below, at Age 45, your chance of having a heart attack, stroke, or other heart disease event at some point in the next 10-years is 3 percent. This risk is approximately 3 times higher than that of a Man the same age who has optimal levels of all modifiable risk factors.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Age 45 Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Age</td>
<td>3</td>
</tr>
<tr>
<td>Age 55</td>
<td></td>
</tr>
<tr>
<td>Age 65</td>
<td></td>
</tr>
<tr>
<td>Age 75</td>
<td></td>
</tr>
</tbody>
</table>

- **Your 10-year risk (age 45)**: 3%
- **Your 10-year risk (age 45) if,**
  - Your cholesterol was 160 mg/DL (4.10 mmol/L): 2%
  - Your hsCRP was 0.5: 3%
  - All the above were optimal: 1%

The graph above also compares your risk to that of a Man of age 45 who has optimal levels for all modifiable risk factors, and shows what your risk would be if you improved your individual risk factors. For young Men, risk may appear to be low over the next 10-years, yet can be very high over a lifetime. Thus, to see what your risk would be as you get older if your risk factors remain the same, click on the buttons above.
Reynolds Risk Score for Men

The value you entered for age is outside of the lower range. The result below is based on age 45.

As shown in the graph below, at Age 45, your chance of having a heart attack, stroke, or other heart disease event at some point in the next 10-years is 3 percent. This risk is approximately 3 times higher than that of a Man the same age who has optimal levels of all modifiable risk factors.

<table>
<thead>
<tr>
<th>Age</th>
<th>Your 10-year risk (age 45)</th>
<th>Your 10-year risk (age 45) if,</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>3%</td>
<td>your cholesterol was 160 mg/DL (4.10 mmol/L) 2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>your hsCRP was 0.5 3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>all the above were optimal 1%</td>
</tr>
</tbody>
</table>

The graph above also compares your risk to that of a Man of age 45 who has optimal levels for all modifiable risk factors, and shows what your risk would be if you improved your individual risk factors. For young Man, risk may appear to be low over the next 10-years, yet can be very high over a lifetime. Thus, to see what your risk would be as you get older if your risk factors remain the same, click on the buttons above.

3% risk for heart attack, stroke, PCI, CABG, or CV death over next 10 years.
## U.S. national guidelines for cholesterol management in 2008

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk</th>
<th>LDL goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>&lt; 10%</td>
<td>&lt; 160</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>10-20%</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt; 20%</td>
<td>&lt; 100 or &lt; 70</td>
</tr>
</tbody>
</table>

ATP III, *Circulation* 2002; Grundy et al., *Circulation* 2004
<table>
<thead>
<tr>
<th>Category</th>
<th>Risk</th>
<th>LDL goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>&lt; 10%</td>
<td>&lt; 160</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>10-20%</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt; 20%</td>
<td>&lt; 100 or &lt; 70</td>
</tr>
</tbody>
</table>

U.S. national guidelines for cholesterol management in 2008

ATP III, *Circulation* 2002; Grundy et al., *Circulation* 2004
Recommendations of PCP

Patient’s LDL is 150 mg/dL

Goal LDL < 160 mg/dL
Drug therapy if LDL > 190 mg/dL

Therapeutic lifestyle change

Exercise, weight loss, diet modification
December 2010
inferior ST-segment elevation MI

Can we improve our ability to predict risk for MI?
Why attempt to improve prediction for MI?
Atherosclerosis: long, asymptomatic phase
Effective intervention: statins

- Block endogenous production of cholesterol
- Lower blood LDL cholesterol
- Treatment during asymptomatic phase reduces risk for MI
Statins: who to target and how early?

Current approach:
Target treatment to those at highest absolute risk (basically, older individuals)

Problem:
Waiting until advanced phase of disease
Clinical need

Marker(s) for early identification of higher risk individuals

Potential value of genotype
Principal advantages of genetic markers

• Fixed over lifetime

• Can be measured early in life
Risk assessment for MI

- Traditional Risk Factors
  - Blood biomarkers
  - Noninvasive cardiovascular testing
- Blood biomarkers
- Genetic profile

Myocardial Infarction
Inherited risk for myocardial infarction

If your mother or father had a history of early-onset cardiovascular disease, what is the increase in risk to you?
Inherited risk for myocardial infarction

If your mother or father had a history of early-onset cardiovascular disease, what is the increase in risk to you?

Men 3.2 (2.1 – 5.0); Women 2.9 (1.6 – 5.3)

Lloyd-Jones, JAMA 2004
If we knew the DNA sequence variants that influenced MI risk, would that improve our ability to assess risk for MI?
Discovery of DNA sequence variants for MI

Testing variants in prospective cohort studies

Next steps
Discovery of DNA sequence variants for MI

Testing variants in prospective cohort studies

Next steps
3.2 billion nucleotides in human DNA sequence

Which ones confer risk for MI?
Common variant genetic screens for the MI/CAD phenotype

A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction

Anna Helgadottir,1* Gudmar Thorleifsson,2 Blondal,1 Aslaug Jonasdottir,1 Adil Bjornsson,3 Grilli Masson,4 Daniel Gudbjartsson,1 M. Backman,5 Sigurberg Mathiasdotir,5 Steinunn Gudmundsdottir,5 Arnaldur G.,5 Christopher B. Granger,5 Harland Au Gulch5
1deCO MedC University of Utah,
2The University of Utah, Salt Lake City, Utah, USA
3University of Oxford, Oxford, United Kingdom
4The University of Yale, New Haven, CT, USA
5The University of Utah, Salt Lake City, Utah, USA

New susceptibility locus for coronary artery disease on chromosome 3q22.3

Jeanette Erdmann,1 Anika Grothoborg2, Peter S Brundt3, Inke R König3, Christian Hengstenberg3, Alistair S Hall4

We present a three-stage analysis of genome-wide SNP data in 1,222 German individuals with myocardial infarction and 1,296 controls, in silico replication in three additional genome-wide datasets of coronary artery disease (CAD) and subsequent replication in ~25,000 subjects. We identified a new CAD risk locus on 3q22.3 in the MABAS (P = 7.44 x 10^-13) OR = 1.15, 95% CI = 1.11-1.19), and suggestive association with a locus on 12p24.31 near PHNA1 (12056) P = 4.81 x 10^-5

Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease

Nilesh J. Samani, F.Med.Sc, Jeanette Erdmann, Ph.D., Marialma Mangino, Ph.D., Riccardo Cooper, M.D., Richard H. Ethel Wichmann, M.D., Jennifer H. Barrett, Ph.D., Inke R. König, David A. Tregouet, Ph.D., David M. Isles, Ph.D., Frithjof C. Tien, M.D., Marcus Fischer, M.D., W. Anthony Balmforth, Ph.D., Andrea Baessler, Ingrid Braune, M.Sc., Christian Gieger, Ph.D., Panos Deli, John R. Thompson, Ph.D., and Herbert Schunkert,

Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction

Daniel F. Gudbjartsson,1 D. Unnur S. Bjornsdottir,1, Eva Halapi, Anna Helgadottir, Patrick Sulem,1

Genome-wide haplotype association study identifies the SLC22A3-LPA12-LPA gene cluster as a risk locus for coronary artery disease

David-Alexandre Tregouet1, Inke R König4, Jeanette Erdmann3, Alexandra Munteanu, Peter S Brundt3, Alistair S Hall4
CARDIoGRAMPlusC4D study: Validated markers now up to 45

CARDIoGRAMPlusC4D Consortium, Nat Genet 2013
## 45 gene regions mapped for MI/CAD

<table>
<thead>
<tr>
<th>19p13 LDLR</th>
<th>10q24 CYP17A1</th>
<th>5q31 SLC22A4</th>
<th>21q22 MRPS6</th>
<th>17p13 SMG6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p32 PCSK9</td>
<td>12q24 SH2B3</td>
<td>6p21 KCNK5</td>
<td>1p32 PPAP2B</td>
<td>17q21 GIP</td>
</tr>
<tr>
<td>2p24 APOB</td>
<td>4q32 GUCY1A3</td>
<td>6q26 PLG</td>
<td>6p21 ANKS1A</td>
<td>6q23 TCF21</td>
</tr>
<tr>
<td>2p21 ABCG5/G8</td>
<td>15q26 FURIN</td>
<td>13q12 FLT1</td>
<td>7q32 ZC3HC1</td>
<td>14q32 HHIPL1</td>
</tr>
<tr>
<td>12q24 HNF1A</td>
<td>10p11 KIAA1462</td>
<td>4q31 EDNRA</td>
<td>2q33 NBEAL1</td>
<td>15q25 ADAMTS7</td>
</tr>
<tr>
<td>11q23 APOA5</td>
<td>10q11 CXCL12</td>
<td>7p21 HDAC9</td>
<td>9p21 CDKN2BAS</td>
<td>17p11 RASD1</td>
</tr>
<tr>
<td>6q26 LPA</td>
<td>1q21 IL6R</td>
<td>7q22</td>
<td>1q41 MIA3</td>
<td>3q22 MRAS</td>
</tr>
<tr>
<td>9q34 ABO</td>
<td>2q22 ZEB2</td>
<td>10q23 LIPA</td>
<td>13q34 COL4A1</td>
<td>6p24 PHACTR1</td>
</tr>
<tr>
<td>8q24 TRIB1</td>
<td>8p21 LPL</td>
<td>2p11 GGCX</td>
<td></td>
<td>11q22 PDGFD</td>
</tr>
<tr>
<td>1p13 SORT1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Of 45, 10 relate to LDL cholesterol

<table>
<thead>
<tr>
<th>Chromosome Location</th>
<th>Gene</th>
<th>Chromosome Location</th>
<th>Gene</th>
<th>Chromosome Location</th>
<th>Gene</th>
<th>Chromosome Location</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>19p13</td>
<td>LDLR</td>
<td>10q24</td>
<td>CYP17A1</td>
<td>5q31</td>
<td>SLC22A4</td>
<td>21q22</td>
<td>MRPS6</td>
</tr>
<tr>
<td>1p32</td>
<td>PCSK9</td>
<td>12q24</td>
<td>SH2B3</td>
<td>6p21</td>
<td>KCNK5</td>
<td>1p32</td>
<td>PPAP2B</td>
</tr>
<tr>
<td>2p24</td>
<td>APOB</td>
<td>4q32</td>
<td>GUCY1A3</td>
<td>6q26</td>
<td>PLG</td>
<td>6p21</td>
<td>ANKS1A</td>
</tr>
<tr>
<td>2p21</td>
<td>ABCG5/G8</td>
<td>15q26</td>
<td>FURIN</td>
<td>13q12</td>
<td>FLT1</td>
<td>7q32</td>
<td>ZC3HC1</td>
</tr>
<tr>
<td>12q24</td>
<td>HNF1A</td>
<td>8p21</td>
<td>LPL</td>
<td>4q31</td>
<td>EDNRA</td>
<td>2q33</td>
<td>NBEAL1</td>
</tr>
<tr>
<td>11q23</td>
<td>APOA5</td>
<td>10q11</td>
<td>CXCL12</td>
<td>7p21</td>
<td>HDAC9</td>
<td>9p21</td>
<td>CDKN2BAS</td>
</tr>
<tr>
<td>6q26</td>
<td>LPA</td>
<td>1q21</td>
<td>IL6R</td>
<td>7q22</td>
<td></td>
<td>1q41</td>
<td>MIA3</td>
</tr>
<tr>
<td>9q34</td>
<td>ABO</td>
<td>2q22</td>
<td>ZEB2</td>
<td>10q23</td>
<td>LIPA</td>
<td>13q34</td>
<td>COL4A1</td>
</tr>
<tr>
<td>8q24</td>
<td>TRIB1</td>
<td>10p11</td>
<td>KIAA1462</td>
<td>2p11</td>
<td>GGCX</td>
<td>11q22</td>
<td>PDGFD</td>
</tr>
<tr>
<td>1p13</td>
<td>SORT1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Of 45, 10 relate to LDL cholesterol, 4 to BP, and 1 to TG/HDL

<table>
<thead>
<tr>
<th>19p13 LDLR</th>
<th>10q24 CYP17A1</th>
<th>5q31 SLC22A4</th>
<th>21q22 MRPS6</th>
<th>17p13 SMG6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p32 PCSK9</td>
<td>12q24 SH2B3</td>
<td>6p21 KCNK5</td>
<td>1p32 PPAP2B</td>
<td>17q21 GIP</td>
</tr>
<tr>
<td>2p24 APOB</td>
<td>4q32 GUCY1A3</td>
<td>6q26 PLG</td>
<td>6p21 ANKS1A</td>
<td>6q23 TCF21</td>
</tr>
<tr>
<td>2p21 ABCG5/G8</td>
<td>15q26 FURIN</td>
<td>13q12 FLT1</td>
<td>7q32 ZC3HC1</td>
<td>14q32 HHIPL1</td>
</tr>
<tr>
<td>12q24 HNF1A</td>
<td>8p21 LPL</td>
<td>4q31 EDNRA</td>
<td>2q33 NBEAL1</td>
<td>15q25 ADAMTS7</td>
</tr>
<tr>
<td>11q23 APOA5</td>
<td>10q11 CXCL12</td>
<td>7p21 HDAC9</td>
<td>9p21 CDKN2BAS</td>
<td>17p11 RASD1</td>
</tr>
<tr>
<td>6q26 LPA</td>
<td>1q21 IL6R</td>
<td>7q22</td>
<td>1q41 MIA3</td>
<td>3q22 MRAS</td>
</tr>
<tr>
<td>9q34 ABO</td>
<td>2q22 ZEB2</td>
<td>10q23 LIPA</td>
<td>13q34 COL4A1</td>
<td>6p24 PHACTR1</td>
</tr>
<tr>
<td>8q24 TRIB1</td>
<td>10p11 KIAA1462</td>
<td>2p11 GGCX</td>
<td></td>
<td>11q22 PDGFD</td>
</tr>
<tr>
<td>1p13 SORT1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Remaining 30 don’t map to known risk factors

<table>
<thead>
<tr>
<th>19p13 LDLR</th>
<th>10q24 CYP17A1</th>
<th>5q31 SLC22A4</th>
<th>21q22 MRPS6</th>
<th>17p13 SMG6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p32 PCSK9</td>
<td>12q24 SH2B3</td>
<td>6p21 KCNK5</td>
<td>1p32 PPAP2B</td>
<td>17q21 GIP</td>
</tr>
<tr>
<td>2p24 APOB</td>
<td>4q32 GUCY1A3</td>
<td>6q26 PLG</td>
<td>6p21 ANKS1A</td>
<td>6q23 TCF21</td>
</tr>
<tr>
<td>2p21 ABCG5/G8</td>
<td>15q26 FURIN</td>
<td>13q12 FLT1</td>
<td>7q32 ZC3HC1</td>
<td>14q32 HHIPL1</td>
</tr>
<tr>
<td>12q24 HNF1A</td>
<td>8p21 LPL</td>
<td>4q31 EDNRA</td>
<td>2q33 NBEAL1</td>
<td>15q25 ADAMTS7</td>
</tr>
<tr>
<td>11q23 APOA5</td>
<td>10q11 CXCL12</td>
<td>7p21 HDAC9</td>
<td>9p21 CDKN2BAS</td>
<td>17p11 RASD1</td>
</tr>
<tr>
<td>6q26 LPA</td>
<td>1q21 IL6R</td>
<td>7q22</td>
<td>1q41 MIA3</td>
<td>3q22 MRAS</td>
</tr>
<tr>
<td>9q34 ABO</td>
<td>2q22 ZEB2</td>
<td>10q23 LIPA</td>
<td>13q34 COL4A1</td>
<td>6p24 PHACTR1</td>
</tr>
<tr>
<td>8q24 TRIB1</td>
<td>10p11 KIAA1462</td>
<td>2p11 GGCX</td>
<td></td>
<td>11q22 PDGFD</td>
</tr>
<tr>
<td>1p13 SORT1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Many contributors to atherosclerosis in humans: *not previously appreciated* *seem to operate outside known risk factors*
One specific variant to highlight: common, large effect size
Genetic marker on chromosome 9p21

CARDIoGRAMPlusC4D Consortium, Nat Genet 2013
### Variant at 9p21 – first discovered

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>19p13</td>
<td>LDLR</td>
<td>10q24</td>
<td>CYP17A1</td>
<td>5q31</td>
<td>SLC22A4</td>
</tr>
<tr>
<td>1p32</td>
<td>PCSK9</td>
<td>12q24</td>
<td>SH2B3</td>
<td>6p21</td>
<td>KCNK5</td>
</tr>
<tr>
<td>2p24</td>
<td>APOB</td>
<td>4q32</td>
<td>GUCY1A3</td>
<td>6q26</td>
<td>PLG</td>
</tr>
<tr>
<td>2p21</td>
<td>ABCG5/G8</td>
<td>15q26</td>
<td>FURIN</td>
<td>13q12</td>
<td>FLT1</td>
</tr>
<tr>
<td>12q24</td>
<td>HNF1A</td>
<td>10p11</td>
<td>KIAA1462</td>
<td>4q31</td>
<td>EDNRA</td>
</tr>
<tr>
<td>12q24</td>
<td>KIAA1462</td>
<td>10q11</td>
<td>CXCL12</td>
<td>7p21</td>
<td>HDAC9</td>
</tr>
<tr>
<td>11q23</td>
<td>APOA5</td>
<td>10q11</td>
<td>CXCL12</td>
<td>7p21</td>
<td>HDAC9</td>
</tr>
<tr>
<td>6q26</td>
<td>LPA</td>
<td>1q21</td>
<td>IL6R</td>
<td>7q22</td>
<td></td>
</tr>
<tr>
<td>6q26</td>
<td>LPA</td>
<td>1q21</td>
<td>IL6R</td>
<td>7q22</td>
<td></td>
</tr>
<tr>
<td>9q34</td>
<td>ABO</td>
<td>2q22</td>
<td>ZEB2</td>
<td>10q23</td>
<td>LIPA</td>
</tr>
<tr>
<td>8q24</td>
<td>TRIB1</td>
<td>8p21</td>
<td>LPL</td>
<td>2p11</td>
<td>GGCX</td>
</tr>
<tr>
<td>1p13</td>
<td>SORT1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **9p21** CDKN2BAS
- **15q25** ADAMTS7
- **17p11** RASD1
- **3q22** MRAS
- **6p24** PHACTR1
- **11q22** PDGFD
Polymorphism on 9p21
At single site on 9p21, two alleles
At single site on 9p21, two alleles

Two flavors or “ALLELES”: G or T
At single site on 9p21, three genotypes

Three genotypes: GG GT TT
Risk for MI/CAD varies by genotype
1:2 people has one copy of the risk flavor

1:4 people carry 2 copies, these individuals are at \(~60\%\) increased risk
Discovery of DNA sequence variants for MI

Testing variants in prospective cohort studies

Next steps
Proof of concept (2008): Genetic risk score

Polymorphisms Associated with Cholesterol and Risk of Cardiovascular Events

Sekar Kathiresan, M.D., Olle Melander, M.D., Ph.D., Dragi Anevski, Ph.D., Candace Guiducci, B.S., Noël P. Burtt, B.S., Charlotta Roos, M.Sc., Joël N. Hirschhorn, M.D., Ph.D., Göran Berglund, M.D., Ph.D., Bo Hedblad, M.D., Ph.D., Leif Groop, M.D., Ph.D., David M. Altshuler, M.D., Ph.D., Christopher Newton-Cheh, M.D., M.P.H., and Marju Orho-Melander, Ph.D.

Genetic risk score: Additive combination of multiple common variants (each with small effect) contributes to risk for CVD
Effect size of genetic risk score may be over-estimated in initial discovery studies.
Effect size of genetic risk score may be over-estimated in initial discovery studies. Need to test in independent studies, preferably with prospective design.
We have tested the first 13 discovered MI SNPs in five prospective cohort studies
THE LANCET

A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses

Testing in prospective cohorts

Five Scandinavian studies
31,827 people, initially healthy
Follow-up ~9 years
1,294 incident CHD events
Adjusted for conventional risk factors (including family history)
Genetic risk score for each individual

- 13 SNPs
- 0, 1, or 2 copies of the risk ‘flavor’
- Score ranging from 0 to 26 for each person

Ripatti, *Lancet* 2010
Does the genetic risk score relate to future risk for MI?
Genetic risk score & incident MI

Ripatti, Lancet 2010
Relative Risk:

Difference in means between two distributions
Relative Risk:
Difference in means between two distributions

Discrimination:
Extent of overlap of two distributions (e.g., C-statistic)
Distribution of 4 biomarkers for CHD
Distribution of 4 biomarkers for CHD

- Genetic risk score
- LDL-C
- Blood pressure
- C-reactive protein
What about a risk scoring algorithm like the Framingham Risk Score?
What about a risk scoring algorithm like the Framingham Risk Score?
Genetic risk score effect size seems modest (HR of 1.7)

Will this be clinically useful?
Type 2 diabetics are treated as “MI-equivalent” for LDL cholesterol target.

What is the fold-increase in MI risk if you have type 2 diabetes?
Comparing genetic risk score to other cardiovascular risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio for Top Quintile versus Bottom Quintile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic risk score</td>
<td>1.7</td>
</tr>
<tr>
<td>Type 2 diabetes +</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Comparing genetic risk score to other cardiovascular risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio for Top Quintile versus Bottom Quintile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic risk score</td>
<td>1.7</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>2.1</td>
</tr>
<tr>
<td>Type 2 diabetes +</td>
<td>2.0</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.7</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>1.8</td>
</tr>
<tr>
<td>Framingham risk score</td>
<td>3.2</td>
</tr>
</tbody>
</table>
Should we have different LDL treatment thresholds for those with high genetic risk score?
Discovery of DNA sequence variants for MI

Testing variants in prospective cohort studies

Next steps
#1: Discovery of additional loci
45 common variants

Magnitude of effect

Frequency of minor allele in population

45 common variants
Discovery turning to variants rarer in frequency

- Low-frequency variants (>1% and <5%)
- 45 common variants
Discovery turning to variants rarer in frequency

- Rare mutations (<1%)
- Low-frequency variants (>1% and <5%)
- 45 common variants

Magnitude of effect vs. Frequency of minor allele in population
#2: Test utility of genetic risk scores in specific clinical settings
Our patient in 2008

41yo with family history of early-onset MI
Low 10-year risk
LDL 150 mg/dl

? Initiate statin
Statins: who to target and how early?

Relative risk reduction for statins consistent across nearly every subgroup
Statins: who to target and how early?

Relative risk reduction for statins consistent across nearly every subgroup

Degree of absolute benefit dependent on absolute risk
Statins: who to target and how early?

Relative risk reduction for statins consistent across nearly every subgroup

Degree of absolute benefit dependent on absolute risk

For young/middle-aged adults, can we cull out those at higher absolute risk using genotypes?
What if?
DNA from the subject indicated above has been tested for genetic variants on chromosome 9p21 which have been associated with myocardial infarction (MI), especially at the age before 50 in males and 60 in females.

SNPs RS10757278 and RS1333049 are located in the vicinity of the tumor suppressor genes CDKN2A and CDKN2B on chromosome 9p21 and were tested for the presence of a G and C allele respectively (the risk alleles). Homozygosity for the G allele at RS10757278 or the C allele at RS1333049 is what constitutes a positive test, associating with increased risk for MI.

All other genotype combinations constitute a negative result.

A **positive test means that the subject has a significantly increased risk above the general population of having a MI due to his/her genotype results. This increase is about two fold for a MI before the age of 55 for man and 60 for woman and about 1.6 fold (60 % increase) irrespective of sex or age.**

More specifically this individual's genotypes are G/G and C/G for RS10757278 and RS1333049 respectively, meaning that the subject is homozygous for the RS1057278 G allele of the risk alleles but not the RS1333049 C allele.
Patient carries two copies of risk allele at 9p21 locus
At ~60% increased risk for MI

RESULT
Positive

DNA from the subject indicated above has been tested for genetic variants on chromosome 9p21 which have been associated with myocardial infarction (MI), especially at the age before 50 in males and 60 in females.

SNPs RS10757278 and RS1333049 are located in the vicinity of the tumor suppressor genes CDKN2A and CDKN2B on chromosome 9p21 and were tested for the presence of a G and C allele respectively (the risk alleles). Homozygosity for the G allele at RS10757278 or the C allele at RS1333049 is what constitutes a positive test, associating with increased risk for MI. All other genotype combinations constitute a negative result.

A positive test means that the subject has a significantly increased risk above the general population of having a MI due to his/her genotype results. This increase is about two fold for a MI before the age of 55 for man and 60 for woman and about 1.6 fold (60 % increase) irrespective of sex or age.

More specifically this individual's genotypes are G/G and C/G for RS10757278 and RS1333049 respectively, meaning that the subject is homozygous for the RS1057278 G allele of the risk alleles but not the RS1333049 C allele.
Hypotheses

Early initiation of lipid lowering therapy will benefit young but higher-risk individuals
Hypotheses

Early initiation of lipid lowering therapy will benefit young but higher-risk individuals

Higher-risk individuals can be identified based on a combination of family history and genetic risk score
Potential Clinical Trial Design to Test the Value of Genotype

Patients with a Family History
Men 30-55, Women 40-65

Screen using Genotype Panel

High risk on Panel
(e.g. top 20% of genetic risk score)

Statin

Follow for clinical event

Y
N
Before clinical trial, we are first testing this hypothesis in completed statin trials
Preventive intervention based on high genetic risk score:

We are not there yet

BUT

possible role in selected clinical settings
Summary

- Principal advantages of genotype: fixed, measured once early in life, blood test
Summary

• Principal advantages of genotype: fixed, measured once early in life, blood test

• Genetic risk score identifies 20% of population at 1.7-fold increased risk for MI
Summary

• Principal advantages of genotype: fixed, measured once early in life, blood test

• Genetic risk score identifies 20% of population at 1.7-fold increased risk for MI

• Genetics may have a role in defining who to treat early with statin