New Frontiers in the Evolving Field of Omics: From Generic to a Personalized Cardiovascular Disease Management

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THE HUMAN GENOME
COMPLETED APRIL 2003

NUMBER OF NUCLEOTIDES (BASES) 3.2 Billion
GENES Estimated 20,000
99.5% of the DNA sequences in the human genome are identical.
Evidence indicates the single nucleotide polymorphisms (SNP) account for 80% of human variation, including predisposition to disease.
The number of SNPs in the human genome is constant at 3.5 million.
DNA is copied every few days and reconstituted with an error rate of 1 base pair per billion generated.

94% of the errors result in substitutions of single nucleotides which is responsible for the 3.5 million Single Nucleotide Polymorphisms (SNPs) per human genome.

Nat Gen 2012;44:1161-5  JACC 2013:61;2029-37
Despite the low error rate, of one base pair per 1 billion, it leads to a mutation rate of $1.2 \times 10^{-8}$ resulting in approximately 40 to 60 new mutations per individual per generation.

Nat Gen 2012;44:1161-5  JACC 2013:61;2029-37
In a human population of 7 billion, there are over 300 billion new mutations in the current generation.
9p21 genetic risk variant is extremely common with one or two copies occurring in 75% of the population.

9p21 risk allele is estimated to be present in 4.5 billion people.

Homozygotes carry increased risk of 50% for CAD.
Heterozygotes carry increased risk of 25% for CAD.

Mapping the genome with a million SNPs, a p-value of 0.05 would give 50,000 false positives so we needed a correction.

\[ p\text{-value} \ 0.00000005 \ (5 \times 10^{-8}) \]
International Consortium for Genome-Wide Association Studies of CAD

Coronary ARtery DIsease
Genome-wide Replication And Meta Analysis

CARDIoGRAMplusC4D
CARDIoGRAM International Consortium

University of Ottawa Heart Institute
Stanford University
University of Pennsylvania
University of Schleswig-Holstein
Cambridge University
University of Utah
Harvard University
University of Leicester
Boston University
University of Massachusetts
University of Texas
Iceland (deCODE Genetics)
CARDIoGRAM

The largest collaboration undertaken in the history of cardiology
Discovery Population: 194,527
Replication Population: 15,613
TOTAL: 210,140

CARDIoGRAMplusC4D

Nature Genetics 2013 Jan;45(1):25-33
58 genetic risk variants for CAD of genome-wide significance have been discovered and replicated in independent populations.

What have we learned from genetic risk factors?
GWAS proved there is a genetic predisposition to CAD and other common diseases.
1. They are common with 50% of the variants occurring in 50% of the population
2. 30% occur in 75% of the population
3. Each mediates minimal risk averaging 17% increased relative risk for CAD
4. 80% are in nonprotein coding DNA
Distribution of Genetic Risk Variants Associated with CAD

Ottawa Heart Genomic Study (n=14,495)

Genetic Risk Score (cGRS) based on 21 genetic variants

Roberts, Circ Res. 2014 Jun 6;114(12):1890-903
Genetic Risk of Coronary Artery Disease and Myocardial Infarction

Risk is proportional to the number of genetic risk variants, rather than a specific risk variant

Nature Genetics Jan 2013;45(1):25-33
Two thirds of genetic risk variants for CAD mediate their risk through unknown mechanisms.
Has management of CAD been influenced by genetic variants?

Genetic Risk of Coronary Artery Disease and Myocardial Infarction
Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol

41% - 58% reduction in LDL-C levels
No significant side effects

Stein. NEJM 2012;366:1108-18
Randomized clinical trial provides exposure for 3-5 years.

Mendelian randomization enables assessment of causation, safety and efficacy over a lifetime.
Genetics of Lipids

- Plasma LDL-C and HDL-C levels are 70% to 80% determined by your genes.
- Plasma triglyceride levels are 50% determined by your genes.

Molecular Medicine Today 2000:6;170-175
Science 2004:305;869-872
It has been the dogma since 1964 that plasma HDL-C protects again CAD and myocardial infarction.
Interventions such as statins, niacin, exercise, alcohol and fibrates that increase plasma HDL-C also tend to decrease plasma LDL-C.
Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study

A polymorphism (SNP) in the endothelial lipase gene (LIPG Asn396Ser)

Associated with an increase in plasma HDL-C of 0.14 mmol/L per copy

No change in plasma LDL-C or triglycerides

These studies indicate that a lifelong exposure to isolated increased plasma HDL-C is **NOT** associated with any decrease in risk for myocardial infarction.

Results of Mendelian Randomization

**MR has shown the following are not causative of CAD:**

- C-reactive protein
- Lipoprotein-associated phospholipase A2 (Lp-PLA2)
- Secretory phospholipase A2 (sPLA2)
- Uric acid
- Cystatin C
- Fibrinogen
- Folic acid
- Pentraxin 3
Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials


Summary

Background Genetic variants have been associated with the risk of coronary heart disease. In this study, we tested whether or not a composite of these variants could ascertain the risk of both incident and recurrent coronary heart disease events and identify those individuals who derive greater clinical benefit from statin therapy.

www.thelancet.com Published online March 4, 2015 http://dx.doi.org/10.1016/S0140-6736(14)61730-X
In this study, 27 of the known genetic variants for CAD were genotyped and analyzed in a sample size of 48,421 selected from clinical trials.
Clinical Application of Genetic Variants for CAD

Population Genotyped

Primary prevention clinical trial
- JUPITER
- ASCOT

Secondary prevention clinical trial
- CARE
- PROVE-IT-TIMI 22

Community cohort
- Malmo diet and cancer study
Clinical Application of Genetic Variants for CAD to Predict Cardiac Events

Traditional risk factors adjusted for in the analysis:

- Age
- Sex
- Smoking
- Hypertension
- FAMILY HISTORY
- HDL and LDL cholesterol
- Diabetes
- Race
Genetic Risk Score Delineates Categories of Low to High Risk

<table>
<thead>
<tr>
<th>Genetic risk score category</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>1.34 (1.22-1.47)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High risk</td>
<td>1.72 (1.55-1.92)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

www.thelancet.com  Published online March 4, 2015  http://dx.doi.org/10.1016/S0140-6736(14)61730-X
Genetic Risk Variants Predict Response to Statin Therapy in Each Risk Group
Genetic Risk Variants Can Be Used to Select CAD Candidates Who Will Receive the Greatest Therapeutic Benefit

<table>
<thead>
<tr>
<th>Genetic Score</th>
<th>Prevention of Primary Event (number to treat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>66</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>42</td>
</tr>
<tr>
<td>High risk</td>
<td>25</td>
</tr>
</tbody>
</table>
GRS predicted cardiac events independently of clinical risk factors (FRS) and were significantly more discriminating than FRS (p<0.001)

Primary Prevention of CAD

Framingham Risk Score is based on age dependent factors: age, cholesterol, BP

Genetic Risk Score, based on DNA variants, is independent of age and other clinical factors
Genetic Risk Score Predicts CAD Risk

Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

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Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

• Sample size of 55,685
• Healthy lifestyle – no smoking, no obesity, regular physical activity and healthy diet
• Population was genotyped for 50 genetic variants proven to be associated with risk for CAD
• Genetic risk score (GRS) derived from these variants was used to stratify participants into high, medium or low risk
Stratification of risk for cardiac events by the genetic risk score was confirmed to be independent of conventional risk factors.

A 50% lower incidence of cardiac events was observed in those individuals with high GRS and a favorable lifestyle.
This study shows lifestyle can modify genetic risk and eliminates the myth that whatever is in your genes is fixed and cannot be modified.

Genetic Risk Score based on DNA variants will be the same at birth as at death. DNA does not change in one's lifetime.
Utilizing the Genetic Risk Score to detect CAD risk will represent a paradigm shift in primary prevention of CAD.
A premenopausal, asymptomatic 49 yr. old female on routine checkup has LDL-C of 160 mg/dl (4.0 mm/l) with no other risk factors
I would like to express my appreciation to all my collaborators involved with CARDIoGRAMplusC4D
Acknowledgements

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