Human Genetics and CV Risk Assessment

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Disclosures

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2. Consultant: Aegerion Pharmaceuticals
Genetic risk of CAD

**Mendelian (monogenic)**

Most notable examples involve disorders of cholesterol metabolism

Minority of CAD in population

**Complex (polygenic)**

Clustering within families but not due to single gene mutations

Majority of CAD in population

Focus for today
Case presentation

• Chief complaint: “I am homozygous for the risk allele at 9p21”

• 43 yo male
  • Otherwise healthy
  • Family history:
    • Paternal uncle: MI in 50s
    • Paternal aunt: MI in 50s
  • No medications
  • Physically active without chest discomfort
  • BP 112/60, exam unremarkable
  • TC 180, LDL 115, normal hsCRP
This means that you are, irrespective of age or gender, at 135% increased risk of having MI (heart attack) relative to the average risk of the white population. This test measures 8 variants in the DNA sequence you were born with.

About 0.2% of the white population will have the similar risk results as you whereas about 0.0% have higher risk and about 99.8% have lower risk than you.

Note: An individual who has higher genetic risk is not destined to have a heart attack and a patient at lower genetic risk is not free of heart attack risk. This is a risk test, not a determinative test.

A more complete 10 year risk estimate for coronary heart disease can be derived by multiplying the risk derived from commonly used risk scoring algorithms with the relative genetic risk results of the deCODEMI™ test. The scoring algorithms take into account the individual's age, sex, blood pressure, smoking history and blood lipids. Consult with your physician.

MI SAME AS HEART ATTACK
Myocardial infarction (MI) is the same as heart attack and is one of the ways that coronary heart disease presents itself.

REFERENCE POPULATION
These results only apply to white individuals of European ancestry.

PROFESSIONAL COUNSELING
Professional counseling is recommended for interpretation of the deCODEMI™ risk results.
How should we manage this patient?

Can genetics inform our decision?
Why would we want to improve risk stratification?

Problem is current approach:

Target treatment to highest risk based on clinical factors (mainly those with established disease older individuals)
Why might genetics improve risk stratification?

Genetic factors have unique properties:
- Represent fixed risk over lifetime
- Can be measured early in life before the development of traditional risk factors
~3500 subjects < 35 years old

15-20 years

Piers et al. BMC Cardiovascular Disorders 2008 8:38
Prevalence of Coronary Calcification

Prevalence of coronary calcium by lipid exposure before age 35 years, by race and sex.

*Values above bars are P-values represent the trend for increasing odds of calcification by category. Values above bars are

White Men

White Women

Black Men

Black Women

LDL levels and risk of disease

- <1.81 mmol/L (<70 mg/dL)
- 1.81–2.56 mmol/L (70–99 mg/dL)
- 2.59–3.34 mmol/L (100–129 mg/dL)
- 3.37–4.12 mmol/L (130–160 mg/dL)
- ≥4.14 mmol/L (≥160 mg/dL)

P < 0.001

16* 3*

41 164 368 228

Pletcher et al. Ann Intern Med 2010 153(3)
Can genetics inform risk assessment?

What genetic factors associate with CAD?

Stratifying CAD risk

Modifying genetic CAD risk
Can genetics inform risk assessment?

- What genetic factors associate with CAD?
- Stratifying CAD risk
- Modifying genetic CAD risk
Fundamental challenge in human genetics:

What genetic changes are related to health and disease?
Genetic association study

Measure genotypes:
- Blue squares = G
- Red squares = A
Genotype → Phenotype association

Homozygous for risk allele

Heterozygous

Risk of MI

Association

No association
Recent genome-wide association studies (GWASs) have localized the effect of multiple common variants contributing to polygenic dyslipidemia. Common variants associated with blood LDL cholesterol, HDL cholesterol, and triglycerides varied according to an allelic dosage score. The proportion of individuals exceeding clinical cut points for high LDL cholesterol, low HDL cholesterol, and high triglycerides varied according to an allelic dosage score. The success of this approach has been partially due to the identification of 64 genetic loci for CAD (58 published). Common variants at 30 loci contribute to polygenic dyslipidemia.
64 genetic loci for CAD (58 published)

1/3 map to known risk factors (genes for lipids and BP)

2/3 potentially provide additional information beyond traditional risk factors
Can genetics inform risk assessment?

What genetic factors associate with CAD?

Stratifying CAD risk

Modifying genetic CAD risk
9p21 and risk for CAD

Lead polymorphism at 9p21: G and T alleles

Risk of MI

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**GENETIC TEST RESULTS – PATIENT HANDOUT**

**YOUR GENETIC RELATIVE RISK**

This means that you are, irrespective of age or gender, at 135% increased risk of having MI (heart attack) relative to the average risk of the white population. This test measures 8 variants in the DNA sequence you were born with.

2.35

equals 135% increased risk, over general population risk of 1.0

**POPULATION RISK DISTRIBUTION**

About 0.2% of the white population will have the similar risk results as you whereas about 0.0% have higher risk and about 99.8% have lower risk than you.

**Note:** An individual who has higher genetic risk is not destined to have a heart attack and a patient at lower genetic risk is not free of heart attack risk. This is a risk test, not a determinative test.

**YOUR OVERALL RISK**

A more complete 10 year risk estimate for coronary heart disease can be derived by multiplying the risk derived from commonly used risk scoring algorithms with the relative genetic risk results of the deCODEMI™ test. The scoring algorithms take into account the individual's age, sex, blood pressure, smoking history and blood lipids. Consult with your physician.

**NOTE**

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**PROFESSIONAL COUNSELING**

Professional counseling is recommended for interpretation of the deCODEMI™ risk results.
Does knowledge of 9p21 status improve risk prediction?

Cardiovascular Disease Risk Prediction With and Without Knowledge of Genetic Variation at Chromosome 9p21.3

Nina P. Paynter, PhD; Daniel I. Chasman, PhD; Julie E. Buring, ScD; Dov Shifman, PhD; Nancy R. Cook, ScD; and Paul M Ridker, MD, MPH

>20,000 white women from Women’s Genome Health Study: Median age 52

No improvement over traditional risk factors

Impact of Adding a Single Allele in the 9p21 Locus to Traditional Risk Factors on Reclassification of Coronary Heart Disease Risk and Implications for Lipid-Modifying Therapy in the Atherosclerosis Risk in Communities Study

Ariel Brautbar, MD; Christie M. Ballantyne, MD; Kim Lawson, MS; Vijay Nambi, MD; Lloyd Chambless, PhD; Aaron R. Folsom, MD; James T. Willerson, MD; Eric Boerwinkle, PhD

~10,000 white men and women from ARIC: Median age 54

Minimal improvement over traditional risk factors
Top loci associated with MI or CAD

Odds ratio of CAD at most loci: between 1.05 – 1.3

1. Individual loci of weak effect unlikely to effectively stratify risk

2. What if we could combine information from all CAD loci together?
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.
Calculated genetic risk for >48,000 participants of four statin therapy trials

Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial

Peter S Sever, Börn Dahlof, Neil R Poulter, Hans Wedel, Gareth Beevers, Mark Caulfield, Rory Collins, Sverre E Kjeldsen, Arni Kristinsson, Gordon T McKinnes, Jesper Mehlsen, Markku Nieminen, Eoin O’Brien, Jan Östergren, for the ASCOT investigators*

The New England Journal of Medicine

Established in 1812

November 20, 2008

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Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Genetic risk score

27 genetic markers associated with MI

Number of risk alleles

0

54

Increasing risk

“Low risk”
Bottom 20%

“Intermediate risk”

“High risk”
Top 20%

Genetic risk score
In placebo arms, genetic score stratifies risk.

*Adjusted for traditional CV risk factors
Can genetics inform risk assessment?

- What genetic factors associate with CAD?
- Stratifying CAD risk
- Modifying genetic CAD risk
There are genetic markers that are definitively associated with CAD in collected studies

1. Do those genetic factors prospectively predict risk in independent populations?
   Yes

2. Is genetic risk useful to measure and is genetic risk modifiable?
Monogenic risk assessment and modification

Figure 8  LDL cholesterol burden in individuals with or without familial hypercholesterolaemia as a function of the age of initiation of statin therapy. Data derived from Huijgen et al.\textsuperscript{20} and Starr et al.\textsuperscript{21} LDL, low-density lipoprotein; LDL-C, LDL cholesterol; HDL-C, high-density lipoprotein cholesterol; CHD, coronary heart disease; FH, familial hypercholesterolaemia.

Can we modify polygenic risk if 2/3 of loci are non-lipid?

Nordestgaard et al. \textit{EHJ} 2013
Gold standard: Randomized trial

- Test the hypothesis that genetic information will improve risk stratification and that those individuals benefit from early therapy

Young individuals without ASCVD
Men 30-40, Women 40-50

- High genetic risk
- Randomize: Statin vs Placebo

- Low genetic risk
- Randomize: Statin vs Placebo

Follow for clinical events Many years
Calculated genetic risk for >48,000 participants of four statin therapy trials

Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial

Methods

We enrolled 4162 patients who had been hospitalized for an acute coronary syndrome and who had average or lower-than-average cholesterol concentrations. Participants were randomly assigned to pravastatin (40 mg per day) or placebo. These patients formed the lipid-lowering arm of the ASCOT study. We planned follow-up for an average of 5 years, the primary end point was the combination of death and non-fatal myocardial infarction; cardiovascular disease events (death from cardiovascular causes, myocardial infarction, coronary revascularization, unstable angina, rehospitalization for coronary heart disease), or any coronary event. We report the results from the planned 5-year follow-up and the effects of pravastatin on serum lipids and other biochemical and clinical variables.

Results

The median LDL cholesterol level achieved during treatment was 95 mg per deciliter (mean, 91 mg per deciliter) in the pravastatin group and 110 mg per deciliter (mean, 110 mg per deciliter) in the placebo group (P<0.001). These beneficial changes are also directly related to the pretreatment level of LDL cholesterol. The relative risk reduction was 25% (95% CI, 17 to 32; P<0.0001) for non-fatal myocardial infarction, 26% (17 to 34; P<0.0001) for the primary end point, 17% (9 to 25; P<0.0001) for coronary death, and 25% (14 to 33; P<0.0001) for total cardiovascular events, but the effect of lowering cholesterol levels below 240 mg per deciliter (mean, 156 mg per deciliter) was not statistically significant: 18% (9 to 26; P=0.003) for non-fatal myocardial infarction and 20% (10 to 28; P=0.003) for the primary end point.

Discussion

In intervention studies, however, the lowering of cholesterol concentration lowered by about 1·0 mmol/L corresponds to about 50% in the placebo group, an absolute difference of 5.9 percentage points in the pravastatin group (P<0.0001). In observational studies, however, the lowering of cholesterol concentration lowered by about 1·0 mmol/L corresponds to about 30% in the placebo group, an absolute difference of 0.6 percentage points in the pravastatin group (P=0.11).

Calculating the risk associated with the cholesterol lowering involved a digital calculation of the risk associated with the cholesterol lowering in the placebo group.

The New England Journal of Medicine

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein


Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Daniel J. Rader, M.D., Jean L. Rouleau, M.D., Rene Belder, M.D., Steven V. Joyal, M.D., Karen A. Hill, B.A., Marc A. Pfeffer, M.D., Ph.D., and Allan M. Skene, Ph.D., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators
### Summary

#### Primary prevention
- **Low risk**: JUPITER hazard ratio (HR) 0.68 (0.26–1.78), ASCOT 0.64 (0.26–1.56), Summary 0.66 (0.34–1.27).
- **Intermediate risk**: JUPITER HR 0.68 (0.42–1.10), ASCOT 0.68 (0.44–1.04), Summary 0.68 (0.49–0.94).
- **High risk**: JUPITER HR 0.41 (0.16–1.06), ASCOT 0.54 (0.29–1.01), Summary 0.50 (0.30–0.84).

#### Secondary prevention
- **Low risk**: CARE HR 0.79 (0.45–1.39), PROVE IT HR 1.24 (0.67–2.29), Summary HR 0.97 (0.63–1.51).
- **Intermediate risk**: CARE HR 0.79 (0.60–1.04), PROVE IT HR 0.63 (0.45–0.88), Summary HR 0.72 (0.58–0.90).
- **High risk**: CARE HR 0.54 (0.32–0.91), PROVE IT HR 1.51 (0.28–0.94), Summary HR 0.53 (0.35–0.78).

Comparison of hazard ratios across genetic risk score categories: p=0.0277
High genetic risk → greater benefit from statin therapy

- Low Genetic Risk
- Intermediate Genetic Risk
- High Genetic Risk

**JUPITER**

1. **ASCOT**

Absolute Risk Reductions (%)
High genetic risk $\rightarrow$ greater benefit from statin therapy

Number needed to treat

\[
\frac{1}{\text{Absolute risk reduction}}
\]
High genetic risk $\rightarrow$ greater benefit from statin therapy

Number needed to treat

$\frac{1}{\text{Absolute risk reduction}}$

Low genetic risk ASCOT trial

NNT $\sim$ 100
High genetic risk $\rightarrow$ greater benefit from statin therapy

Number needed to treat

$1 / \text{Absolute risk reduction}$

Low genetic risk ASCOT trial  
NNT $\sim 100$

High genetic risk ASCOT trial  
NNT $\sim 33$
Ongoing work

• Incorporate information from across the genome to improve risk stratification

• Preliminary results suggest modest but significant improvements
Summary: Genetics and CV risk

- Genetic factors identify graded risk of CAD
  - Top 20% of population: ~70% increased risk

- Independent of traditional risk factors

- Inexpensive; can be measured early in life

- May have a role in allocating preventive therapies
Thank you.

www.stitziellab.org