Nutrigenomics and Cardiovascular Disease

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Outline

• Introduction
• Candidate genes and nutri-genetic studies
• GWAS
• GWAS candidates and nutri-genetic
• Mouse studies
CVD is the leading cause of death in the US

In 2010, total costs of CVD were estimated to be $444 billion.

Treatment accounts for about $1 of every $6 spent on health care in the US.
1. As geneticist we know there are genetic factors
2. Clearly there are environmental factors
3. As nutrition scientist: diet is an important environmental factor
To diagnose metabolic syndrome, most doctors look for the presence of three or more of these components:

- **Central or abdominal obesity** (measured by waist circumference):
  - Men - greater than 40 inches
  - Women - greater than 35 inches

- **Triglycerides** greater than or equal to 150 milligrams per deciliter of blood (mg/dL)

- **HDL cholesterol**:
  - Men - Less than 40 mg/dL
  - Women - Less than 50 mg/dL

- **Blood pressure** greater than or equal to 130/85 millimeters of mercury (mmHg)

- **Fasting glucose** greater than or equal to 100 mg/dL
Differences between racial groups in metabolic syndrome

https://www.cdc.gov/pcd/issues/2017/16_0287.htm
Metabolic syndrome—complex interactions lead to diabetes and cardiovascular disease

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675814/
Candidate genes in lipoprotein metabolism and atherosclerosis

Atherosclerosis is a complex disease involving multiple genes, cell types and metabolic process at the vessel wall.
As you make daily food choices, base your eating pattern on these recommendations:

- Eat a variety of fresh, frozen and canned vegetables and fruits without high-calorie sauces or added salt and sugars. Replace high-calorie foods with fruits and vegetables.
- Choose fiber-rich whole grains for most grain servings.
- Choose poultry and fish without skin and prepare them in healthy ways without added saturated and trans fat.
- Eat a variety of fish at least twice a week, especially fish containing omega-3 fatty acids (for example, salmon, trout and herring).
- Select fat-free (skim) and low-fat (1%) dairy products.
- Avoid foods containing partially hydrogenated vegetable oils to reduce trans fat in your diet.
- Limit saturated fat and trans fat and replace them with the better fats, monounsaturated and polyunsaturated.
- Cut back on beverages and foods with added sugars.
- Choose foods with less sodium and prepare foods with little or no salt
- If you drink alcohol, drink in moderation. That means no more than one drink per day if you’re a woman and no more than two drinks per day if you’re a man.
- Follow the American Heart Association recommendations when you eat out, and keep an eye on your portion sizes.
FIGURE 2. Eicosapentaenoic acid (EPA) (1.8 g/d) reduced the incidence of major adverse coronary events in the Japan EPA Lipid Intervention Study (JELIS) by 19%. CI = confidence interval. From The Lancet, with permission from Elsevier.
Potential cardio-protective mechanisms of PUFA’s

Effect appears linear within ranges of typical dietary intake (<750mg/d), with smaller additional effects at higher levels.
- Effect appears linear across a wide range of intakes (at least up to 7g/d).
- Effect only appears potentially relevant at higher supplemental intakes (> 4g/d).
- Dose response relationship not established.

Figure 3  Physiological Effects of n-3 PUFA That Might Influence CVD Risk
PUFA’s are generally anti-inflammatory
Potential Gene x Diet interactions

Fig. 1 Nutrigenetic of omega 3 PUFAs in cardiovascular disease and related traits. See text for more details.
PUFA’s are generally anti-inflammatory
Genotype guided intervention

Participant recruiting

DNA isolation

PCR
Randomized Control Trial for NGx interactions

Placebo
60 AA females

1 gm Fish oil concentrate
60 AA females

dd
5d
55

dd
5d
55

20 AA females
20 AA females
20 AA females

20 AA females
20 AA females
20 AA females

ALOX5 Promoter Variants

20 AA females

five Sp1 element tandem repeats
Mean (±SEM) changes in oxylipid concentrations are shown from baseline to follow-up among the three ALOX5 genotype groups of interest in response to placebo and fish oil interventions.

Charles B. Stephensen et al. J. Lipid Res. 2011;52:991-1003
• this placebo-controlled intervention trial, randomized within genotypes,
• identified a significant gene–diet interaction
• genotype-determined differences in response to omega-3 intake
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Published GWA Reports, 2005 – 6/2012

Through 6/30/12 postings
Published Genome-Wide Associations through 07/2012
Published GWA at $p \leq 5 \times 10^{-8}$ for 18 trait categories

NHGRI GWA Catalog
www.genome.gov/GWAStudies
www.ebi.ac.uk/fgpt/gwas/
Cardiogram results
Initial GWAS Finding

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

Ruth McPherson,1*† Alexander Pertsemidis,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†
Initial GWAS Finding

**Screening**

Genome-wide Association Scan (75,000 SNPs/person)

*Ottawa Heart Study-1 (OHS-1)*
- 322 Cases : 312 controls

Replicate Association Study 1: SNPs with P < 0.025

*Ottawa Heart Study-2 (OHS-2)*
- 311 cases : 326 controls

Replicate Association Study 2: SNPs with P < 0.025

*Atherosclerosis Risk in Communities Study (ARIC)*
- 1,347 cases : 9,054 controls

→ rs10757274 and rs2383206

**Validation**

*Copenhagen City Heart Study (CCHS)*
- 1,525 cases
- 9,053 controls

*Dallas Heart Study (DHS)*
- 154 cases
- 527 controls

*Ottawa Heart Study-3 (OHS-3)*
- 647 cases
- 847 controls
Fine mapping of the genomic interval on chromosome 9 associated with CHD. (A) SNPs spaced ~5 kb apart in the interval extending 175 kb upstream and downstream of rs10757274 and rs2383206 were assayed in 500 cases and 500 controls from the OHS population with GeneChip Human Mapping 500K Array Sets (Affymetrix, Santa Clara, CA).

R McPherson et al. Science 2007;316:1488-1491
## 9p21 locus- Associations reported

<table>
<thead>
<tr>
<th>Disease/Trait</th>
<th>Reported Gene(s)</th>
<th>Strongest SNP-Risk Allele</th>
<th>P-value</th>
<th># pubs</th>
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<tbody>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>CDKN2A,CKDN2B</td>
<td>rs2383207-G</td>
<td>2 x 10^-8</td>
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<td>Ankle-brachial index</td>
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<td>rs10757269-G</td>
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<td>Breast cancer</td>
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<td>Coronary artery calcification</td>
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<td>Coronary heart disease</td>
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<td>Type 2 diabetes</td>
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<td>rs2383208-A</td>
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</tr>
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</table>

http://www.genome.gov/gwastudies/index.cfm
9p21.3 locus- structure varies by population

Kelly A. Frazer, Sarah S. Murray, Nicholas J. Schork & Eric J. Topol
Nature Reviews Genetics 10, 241-251 (April 2009)
Can 9p21 Risk Be Modified by Dietary Intake?

The Effect of Chromosome 9p21 Variants on Cardiovascular Disease May Be Modified by Dietary Intake: Evidence from a Case/Control and a Prospective Study

Ron Do¹, Changchun Xie²,³, Xiaohe Zhang², Satu Männistö⁴, Kennet Harald⁴, Shofiqul Islam²,³, Suneke D. Bailey¹, Sumathy Rangarajan², Matthew J. McQueen², Rafael Diaz⁵, Liu Lisheng⁶, Xingyu Wang⁷, Kaisa Silander⁴,³, Leena Peltonen⁴,³, Salim Yusuf², Veikko Salomaa⁴, James C. Engert¹,⁹,¹⁰*, Sonia S. Anand²,³*, on behalf of the INTERHEART investigators
Can 9p21 Risk Be Modified by Dietary Intake?

- Five ethnicities
- Retrospective Case-Control study → Risk factors for acute non-fatal MI
- Recruitment → within 24 hours of being admitted to a coronary care unit with clinical characteristics of acute MI. → Control matched for age and sex.

Four SNPs (rs10757274, rs2383206, rs10757278, rs1333049) from the Chromosome 9p21 region were selected based on previous results from genome-wide association studies for coronary heart disease/MI

Genotypes: 1,744 Europeans, 1,867 South Asians, 2,231 Chinese, 1,100 Latin Americans, and 1,172 Arabs (a total of 8,114 samples).
The Effect of a Prudent Diet is most pronounced in individuals with Risk Allele

An analysis of the rs2383206 genotype and tertiles of the prudent diet score in the INTERHEART samples demonstrated that individuals with two copies of the risk allele (GG) and with a low prudent diet score had a 2-fold increase in MI risk when compared to the reference group of individuals with two copies of the protective allele (AA) and a high prudent diet score.
Conclusions

• Metabolic syndrome is complex and multigenic
  – Candidate genes regulate metabolism
  – Diet is also important

• Genotype guided interventions
  – Demonstrate differences in metabolism
  – Changes effect of diet

• Main effect alleles of GWAS demonstrate potential benefit effects of diet