Genetic testing in cardiovascular disease

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Disclosures

• Speaker – Quest/Cleveland HeartLab
9p21

- “The heart attack gene”
- 9p21 is a region of the genome on the short arm of chromosome 9
- Considered the “most robust genetic marker of coronary artery disease” \(^1\)
- Two SNPs associated with increased risk for CHD events
  - These two SNPs are highly correlated, with almost complete linkage disequilibrium
    - If one SNP has one mutated allele, it is highly likely the other SNP will have one mutated allele
- Biology of this region is not well understood
  - Contains elements that control gene transcription

# 9p21-associated risk and frequency

<table>
<thead>
<tr>
<th>Genotype*</th>
<th>Associated Risk</th>
<th>Population Frequency¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncarrier</td>
<td>No increased risk of early MI, AAA, or MI/CHD</td>
<td>27%</td>
</tr>
</tbody>
</table>
| Heterozygous | 25% increased risk MI/CHD  
49% increased risk early MI  
36% increased risk of AAA | 50% |
| Homozygous | 56% increased risk MI/CHD  
102% increased risk early MI  
74% increased risk of AAA | 23% |

*Genotypes for the rs10757278 and rs1333049 SNPs  
Due to high linkage disequilibrium, if one SNP is heterozygous the other is very likely to be heterozygous as well

(1.) Ivanova AA, Maksimov VN, Orlov PS, Ivanshchuk DE, Savchenko SV, Voevoda MI. Association of the genetic markers for myocardial infarction with sudden cardiac death. *Indian Heart J*. 2017;69 Suppl 1:S8-S11
9p21-associated risk is comparable to smoking and other accepted risk factors

<table>
<thead>
<tr>
<th>Risk Factor and End Point</th>
<th>Heterozygous Carriers</th>
<th>Homozygous Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>9p21 and early MI²</td>
<td>1.5-fold</td>
<td>2.0-fold</td>
</tr>
<tr>
<td>Current smoker (vs. nonsmoker)³</td>
<td>2.0-fold</td>
<td></td>
</tr>
<tr>
<td>9p21 and AAA⁴</td>
<td>1.4-fold</td>
<td>1.7-fold</td>
</tr>
<tr>
<td>9p21 and CHD / MI²</td>
<td>1.3-fold</td>
<td>1.6-fold</td>
</tr>
<tr>
<td>LDL-c (per SD increase)⁵</td>
<td>1.4-fold</td>
<td></td>
</tr>
<tr>
<td>HDL-c (per SD decrease)*⁵</td>
<td>1.3-fold</td>
<td></td>
</tr>
<tr>
<td>Age (per 5 years increase)³</td>
<td>1.2-fold</td>
<td></td>
</tr>
<tr>
<td>Lp(a) (per 10 mg/dL increase)³</td>
<td>1.1-fold</td>
<td></td>
</tr>
</tbody>
</table>

9p21 risk is independent of conventional risk factors for CAD¹

*derived from a risk ratio of 0.71 per SD decrease
Endpoint for all risk factors other than 9p21 in this table is CHD

9p21 improves risk assessment

- Which patients may benefit from the 9p21 risk SNPs test?
  - Patients who are of Caucasian, Chinese, Korean, Japanese, or East Indian descent with a family history of cardiovascular disease or who have traditional risk factors
  - The test may also be useful for risk stratification of those patients with diagnosed cardiovascular disease
- What does this test add to the risk profile of a patient?
  - This test has clinical utility in identifying those subgroups at higher genetic risk of cardiovascular disease, which may:
    - Allow for early detection and more aggressive monitoring, incorporation of lifestyle/behavioral changes, and treatment
    - Help guide therapy selection
    - Be of utility in family counseling
9p21 and population attributable risk (PAR)

- 9p21 has substantial PAR
- Although the risk levels associated with 9p21 are similar in magnitude to traditional risk factors, the PAR of 9p21 is substantial due to the high frequency of the risk-associated 9p21 variants
- Therefore, testing for 9p21 risk variants may have implications for early prevention of disease

<table>
<thead>
<tr>
<th>9p21 and Early MI</th>
<th>Population Attributable Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>9p21 and Early MI</td>
<td>31%</td>
</tr>
<tr>
<td>9p21 and AAA</td>
<td>26%</td>
</tr>
<tr>
<td>9p21 and CHD/MI</td>
<td>21%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp-PLA2 Activity</td>
<td>95 (normal &lt; 75)</td>
</tr>
<tr>
<td>LDL</td>
<td>229</td>
</tr>
<tr>
<td>Sweat</td>
<td>2.3 gallons (estimate)</td>
</tr>
</tbody>
</table>

Homozygous Positive 9P21
Jenny

Homozygous Positive 9P21

LDL on Pravastatin 40 mg and Ezetimibe 10 mg Daily

LDL

Target

0 50 100 150 200 250

9/1/2016 10/1/2016 11/1/2016 12/1/2016 1/1/2017

229
135
70
70
70
Jenny

Homozygous Positive 9P21

LP-PLA2 Activity on Pravastatin/Ezetimibe

LP-PLA2 Activity

Normal

0 10 20 30 40 50 60 70 80 90 100
9/1/16 10/1/16 11/1/16 12/1/16 1/1/17

95 90 80 70 60 70 70
Dr. Sachdev’s Sweat Level (in gallons)

Jenny

Homozygous Positive 9P21
- One SNP in the *KIF6* gene associated with increased CHD risk and event reduction with statin therapy
- *KIF6* is a member of the kinesin superfamily
  - Mediates the transportation organelles, proteins, and messenger RNA
  - Mutation at the SNP can effect function of the cargo-binding domain
  - Expressed in coronary arteries and vascular cells

KIF6- associated CHD risk

- Carriers: 55% greater CHD risk *independent* of other risk factors
  - Risk is reduced with 40mg pravastatin
    - NNT = 10 (PROVE-IT)
    - 40-60% RRR (CARE; WOS)
- Non Carriers: Risk defined by prevalence and severity of other risk factors
  - Minimal response to statins
    - NNT = 125 (PROVE-IT)
    - 6-20% RRR (CARE; WOS)

Atorvastatin reduces events more effectively in KIF6 carriers

- **PROVE-IT-TIMI 22 Trial**
  - 40 mg pravastatin vs 80 mg atorvastatin
  - Endpoint of death or major CVD events
  - Double-blind trial of ACS patients
  - N=1,778
  - Primarily middle-aged men with ACS in stable condition
    - Intensive statin therapy (80 mg atorvastatin) was found to reduce events more effectively in KIF6 carriers than in noncarriers
      - Relative risk reduction was 41% in KIF6 carriers and 6% in noncarriers
  - **NNT** was 25 for all patients (on atorvastatin)
    - NNT was 10 for KIF6 carriers with atorvastatin (vs. pravastatin)
    - NNT was 125 for noncarriers

Support for KIF6

- **CARE: Cholesterol and Recurrent Events**
  - N=2,715
  - Secondary prevention in patients with a prior MI
  - 40 mg pravastatin vs placebo

- **WOSCOPS: West of Scotland Coronary Prevention Study**
  - N=1,561
  - Primary prevention
  - 40 mg pravastatin vs placebo

- **ARIC: Atherosclerosis Risk in Communities**
  - N=13,907
  - Population-based observational study; CHD endpoint

- **CHS: Cardiovascular Health Study**
  - N=3,849
  - Population-based observational study; MI endpoint

- **WHS: Women's Health Study**
  - N=25,283
  - Randomized, double-blind, placebo-controlled trial
  - Women > 45 years of age without previous history of CHD risk independent of other risk factors

- **PROVE-IT-TIMI 22 Trial**
  - N=1,778
  - 40 mg pravastatin vs 80 mg atorvastatin
  - Double-blind trial of ACS patients; death or major CVD event endpoint

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## KIF6 summary and clinical implications

<table>
<thead>
<tr>
<th>KIF6 Genotype</th>
<th>Associated Risk</th>
<th>Treatment Consideration</th>
<th>Population Frequency¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier Arg/Arg or Trp/Arg</td>
<td>CHD risk increased up to 55%</td>
<td>Atorvastatin or pravastatin</td>
<td>60%</td>
</tr>
<tr>
<td>Noncarrier Trp/Trp</td>
<td>No increased CHD risk</td>
<td>--</td>
<td>50%</td>
</tr>
</tbody>
</table>

- **KIF6 Noncarriers**
  - No increased risk of CHD events
  - No significant event reduction from statin therapy
  - KIF6 noncarriers may still have standard risk factors that justify statin therapy
  - Clinicians may want to consider combination therapy with other drugs that have been proven to reduce CHD events.

- **KIF 6 Carriers**
  - Carriers are at increased CHD risk
  - Risk can be reduced with statin therapy, independent of LDL-C lowering
  - KIF6 helps clinicians provide patients with information about their CHD risk and individualized response to statin therapy.

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Sharon (72 y/o WF)

Homozygous Negative KIF-6 on Pravastatin 80 mg daily

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp-PLA2</td>
<td>207 (normal &lt; 200)</td>
</tr>
<tr>
<td>LDL</td>
<td>75</td>
</tr>
<tr>
<td>Pulse</td>
<td>140 bpm</td>
</tr>
</tbody>
</table>
Sharon

Homozygous Negative KIF-6

LDL-C on Lovastatin 20 mg Daily

- LDL-C
  - 3/1/2012: 75
  - 4/1/2012: 75
  - 5/1/2012: 75
  - 6/1/2012: 75
  - 7/1/2012: 80

- Target
  - 3/1/2012: 70
  - 4/1/2012: 70
  - 5/1/2012: 70
  - 6/1/2012: 70
  - 7/1/2012: 70
Sharon

Homozygous Negative KIF-6

Lp-PLA2 on Lovastatin 20 mg Daily

LP-PLA2

9/1/2016 10/1/2016 11/1/2016 12/1/2016 1/1/2017

Target Range

Lp-PLA2

Sharon

Homozygous Negative KIF-6

Dr. Sachdev’s Pulse Rate

Pulse Rate Graph for Dr. Sachdev from 9/1/2016 to 1/1/2017.
The role of ApoE in lipid metabolism

- ApoE serves as the ligand to LDL receptors
- ApoE mediates the hepatic uptake of chylomicron remnants, very-low density lipoprotein, and intermediate density lipoproteins

3 ApoE isoforms and their effect on plasma lipids

- ApoE3 has average affinity for hepatic LDL-receptors (LDL-R)
  - No genotype impact
- ApoE2 has reduced affinity for LDL-R
  - Associated with slow conversion of IDL to LDL
  - Decreased LDL
  - Elevated triglycerides (TG)
- ApoE4 has increased affinity for LDL-R and limits HDL-binding
  - Inhibits normal cholesterol clearance process (reverse cholesterol transport or RCT)
  - Elevated total cholesterol, LDL, and TG
  - Decreased HDL

# ApoE-associated CVD risk

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Population Frequency(^1)</th>
<th>CVD Risk</th>
<th>Treatment Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/2</td>
<td>1%</td>
<td>No increased risk(^2) to slightly reduced risk(^3)</td>
<td>Moderate fat diet (35%) if elevated triglycerides(^4) Statin therapy(^5)</td>
</tr>
<tr>
<td>2/3</td>
<td>10%</td>
<td>Normal dietary modifications</td>
<td></td>
</tr>
<tr>
<td>2/4</td>
<td>2%</td>
<td>No increased risk(^2)</td>
<td>Statin therapy</td>
</tr>
<tr>
<td>3/3</td>
<td>62%</td>
<td>Increased risk (42%)(^2)</td>
<td>Very low-fat diet (20%) if elevated LDL-C(^6) Statin therapy(^7)</td>
</tr>
<tr>
<td>3/4</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/4</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ricky (38 y/o WM)

Apo E 3/4 Drinking Red Wine Daily

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<thead>
<tr>
<th>Parameter</th>
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</tr>
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<tbody>
<tr>
<td>Lp-PLA2 Activity</td>
<td>93 (normal &lt; 75)</td>
</tr>
<tr>
<td>LDL</td>
<td>158</td>
</tr>
<tr>
<td>LDL-P</td>
<td>1983</td>
</tr>
<tr>
<td>Alcohol Intake</td>
<td>1-2 glasses wine/day</td>
</tr>
</tbody>
</table>
Ricky

ApoE 3/4 on No Alcohol

LDL-C Without Daily Alcohol

![Graph showing LDL-C levels over time for Ricky, with target LDL-C of 70 and actual levels fluctuating between 158 and 143 over the period from 6/1/2016 to 10/1/2016.]
Ricky

ApoE 3/4 on No Alcohol

LDL-P Without Daily Alcohol

LDL-P

<table>
<thead>
<tr>
<th>Date</th>
<th>LDL-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/1/2016</td>
<td>850</td>
</tr>
<tr>
<td>7/1/2016</td>
<td>850</td>
</tr>
<tr>
<td>8/1/2016</td>
<td>850</td>
</tr>
<tr>
<td>9/1/2016</td>
<td>850</td>
</tr>
<tr>
<td>10/1/2016</td>
<td>850</td>
</tr>
</tbody>
</table>

Target Range

LDL-P without daily alcohol ranges from 1983 to 1983 with a target range of 850.
Ricky

Apo E 3/4 No Alcohol

Lp-PLA2 Activity Without Daily Alcohol

Lp-PLA2 Activity

Target Range

0 10 20 30 40 50 60 70 80 90 100
6/1/2016 7/1/2016 8/1/2016 9/1/2016 10/1/2016"
Other Useful Genetic Tests

The Genetic Toolbox

- 4q25: Atrial Fibrillation Risk
- IL-1: Heightened Response to Inflammation
- Haptoglobin: CV Risk in Diabetics
- LPA Aspirin: CV Risk and Aspirin Response
- LPA-Intron 25: Independent Risk Factor for CV Disease related to LP(a)
- And More…..
The End