CPT1A Methylation is a Novel Epigenetic Marker of Cardiovascular Risk: An Update

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November 19, 2013

FINANCIAL DISCLOSURE:
No relevant financial relationship exists
Research Aim

To identify novel heritable correlates of cardiovascular risk traits through an epigenome-wide study of DNA methylation in CD4+ T-cells in a large population-based cohort.
Hypothesis

Genotype → DNA methylation → CVD risk phenotypes

Age/Sex
Obesity
Smoking
Alcohol
GOLDN

- 1200 participants of the NHLBI FHS at two sites
- Family study
- Epigenetic data subset: n=991
Statistical Methods

• Outcome: methylation status of ~470,000 CpGs
• Predictors: CVD risk phenotypes (plasma lipids, adipokines, anthropometric traits)

• Linear mixed models adjusted for:
  – Sex, age, cell purity, pedigree (family)
What We Have Shown Before

CpG sites in \textit{CPT1A} robustly associated with fasting TG, VLDL-C, adiponectin

Models were adjusted for age, sex, T-cell purity, pedigree, and study site
What We Have Done Since

• Validated results of the Illumina 450K chip using bisulfite sequencing
• Conducted $CPT1A$ expression analyses
• Tested for association with additional CVD phenotypes
• Attempted replication in adipose tissue
Validation

The image shows a scatter plot with the title "Validation". The plot compares two variables: Beta - Methyl1450 on the y-axis and Beta - BisSeq on the x-axis. The data points are scattered across the graph, and a line of best fit is drawn through them, indicating a positive correlation between the two variables.
Expression
CPT1A Methylation Linked to Other Disease Phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>7 x 10^{-11}</td>
</tr>
<tr>
<td>Glucose (Fasting)</td>
<td>2 x 10^{-10}</td>
</tr>
<tr>
<td>WC</td>
<td>3 x 10^{-10}</td>
</tr>
<tr>
<td>Insulin (Fasting)</td>
<td>2 x 10^{-8}</td>
</tr>
</tbody>
</table>

No associations were observed with TC, LDL-C, HDL-C, or inflammatory cytokines.
• Encodes carnitine palmitoyltransferase 1A
• Key in β-oxidation of long-chain fatty acids
After Adjustment for Triglycerides

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</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>$7 \times 10^{-11}$</td>
<td>$9 \times 10^{-6}$</td>
</tr>
<tr>
<td>Glucose (Fasting)</td>
<td>$2 \times 10^{-10}$</td>
<td>0.002</td>
</tr>
<tr>
<td>WC</td>
<td>$3 \times 10^{-10}$</td>
<td>$6 \times 10^{-5}$</td>
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<tr>
<td>Insulin (Fasting)</td>
<td>$2 \times 10^{-8}$</td>
<td>0.02</td>
</tr>
</tbody>
</table>

No associations retained statistical significance.
Adipose Tissue Replication

• LEEP Study (n=102)
• Tested only $CPT1A$ sites

  **Successful replication: BMI and waist circumference ($P<0.0001$)**

  **Did not replicate: TG, adiponectin**

• Did not measure: insulin, glucose, VLDL-C
Future Directions

• Further replication/ meta-analysis
• Repeated methylation measurements
• Development of risk stratification tools