Epigenetics of Cardiovascular Disease

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Today

• Overview of cardiovascular epigenetics

• What have we found?
  Example from our own GOLDN study

• Markers of cumulative stress?
CVD Risk Heritability


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Known Genes Do Not Explain Heritable CVD risk

Sabatti C et al. Nat Genet 2009;41:35-46
Why Epigenetics in CVD?

- Evidence from animal and *in vitro* studies
- Translational success in other settings
- Cost of epigenetic analysis is decreasing

So… why not?
A conceptual model linking epigenomics to cardiovascular disease and cardiovascular risk factors.

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- Overview of epigenetics and why it matters for cardiovascular disease

- **What have we found?**
  Example from our own GOLDN study

- Translational challenges and future directions
Epigenetic Studies

- Global methylation
  \[\uparrow\text{homocysteine} \quad \downarrow\text{methylation}\quad ?\text{CVD}\]

- Candidate gene (e.g. \textit{FTO}, \textit{F2RL3})

- Epigenome-wide assays
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GOLDN

- 1200 participants of the NHLBI FHS at two sites
- Extended pedigrees
- Epigenetic data subset
  - N=991
  - Quantified on CD4+ T-cells
Statistical Methods

• Model:

  plasma lipids \sim \text{methylation status at 450,000 loci} + \text{sex} + \text{age} + \text{family} + \text{technical covariates}

• Additional models adjusting for BMI, alcohol, and current smoking status

• Replication cohort: Framingham Heart Study
Results: Fasting Triglycerides

CpG-1: $P_{\text{discovery}} = 1.8 \times 10^{-21}$
$r^2 = 11\%$

$P_{\text{replication}} = 4.1 \times 10^{-14}$
$r^2 = 5\%$
• Encodes carnitine palmitoyltransferase 1A
• Key in β-oxidation of long-chain fatty acids
Expression

![Scatter plot showing relative CPT1A expression vs. cg00574958 - corrected % methylation.](image-url)
Mouse Model

- \textit{Cpt1A}^{-/-}: embryonic lethal
- \textit{Cpt1A}^{+/−}: liver expression \downarrow by \sim 50\%, triglycerides (TG) decrease

BUT…

The effect of expression changes on TG levels is opposite in mice vs. humans
CPT1A Methylation Finding

• Also came up as significant for:
  - VLDL-C (GOLDN)
  - BMI (GOLDN and ARIC and FHS)
  - Adiponectin (GOLDN and HAPI Heart)

Pleiotropic effects?
Other Genes

• *ABCG1*
  - Glucose metabolism
  - Lipid metabolism
  - Obesity traits

• *HIF3A*
  - Obesity traits
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The Double Edged Sword

• Time- and tissue-specific

• Reversible; when to measure?

• Susceptible to both genes and environment
Biomarker Challenges

• Most evidence is from cross-sectional studies

• Only as good as the risk marker they represent (no “hard endpoint” studies)

• Aging is a confounder

• Require extensive validation
Future Directions

- Large consortia studies
- Prospective studies of prognostic ability
- Novel markers
- Specific therapeutic approaches

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