

Epigenetics of Cardiovascular Disease

Stella Aslibekyan, PhD

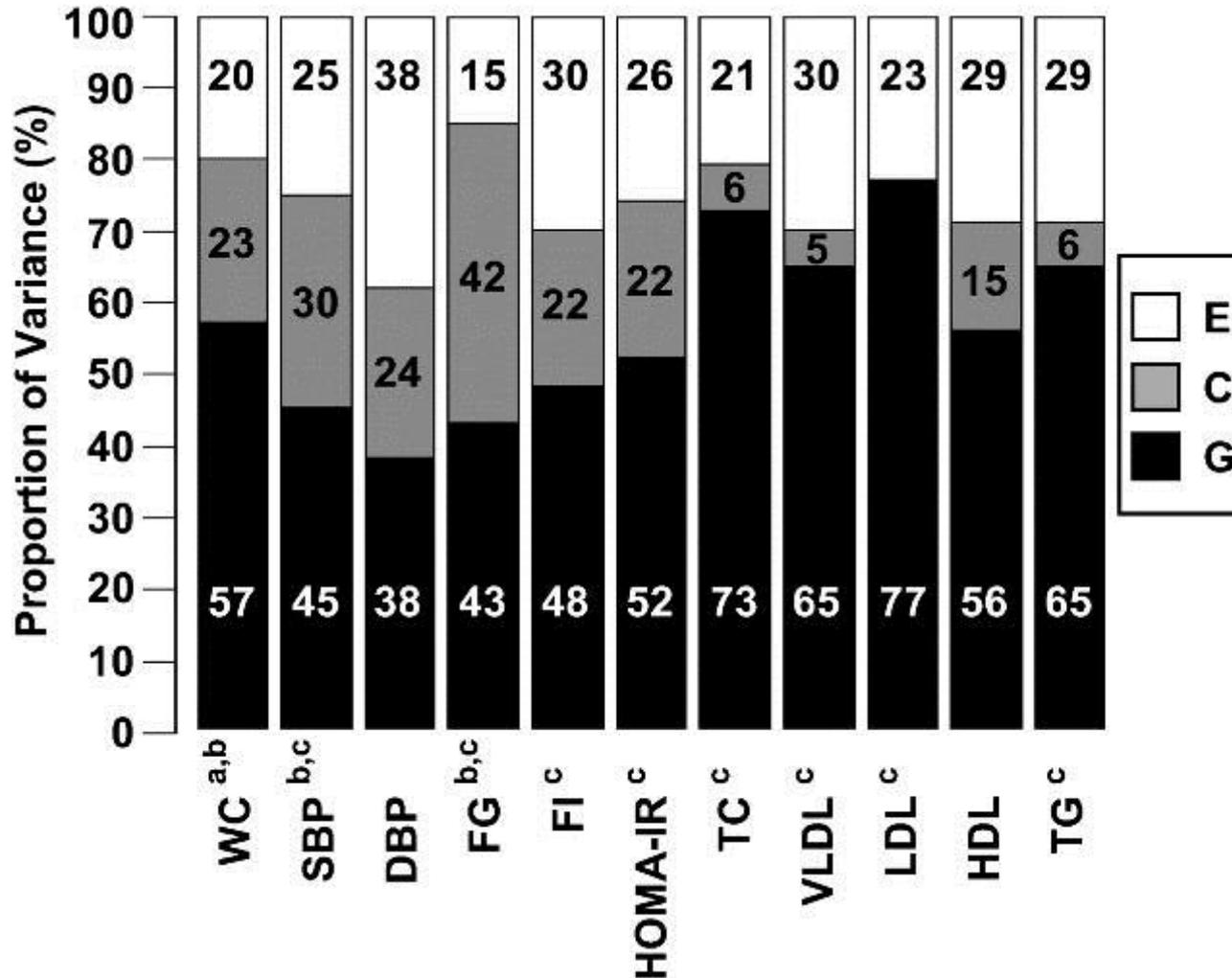
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Disclosures: NIH and AHA funding

Today

- **Overview of cardiovascular epigenetics**
- What have we found?
Example from our own GOLDN study
- Markers of cumulative stress?

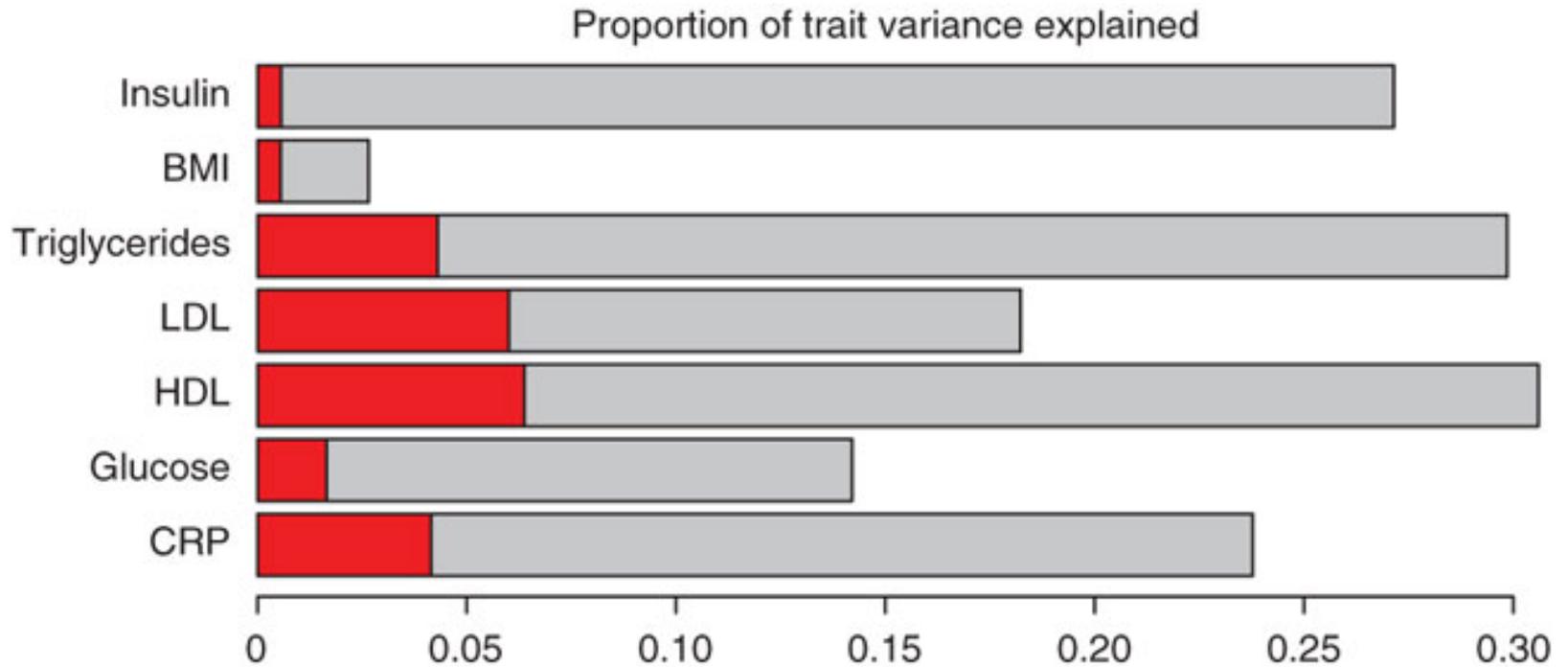
CVD Risk Heritability



Elder S J et al. J. Lipid Res. 2009;50:1917-1926



Known Genes Do Not Explain Heritable CVD risk

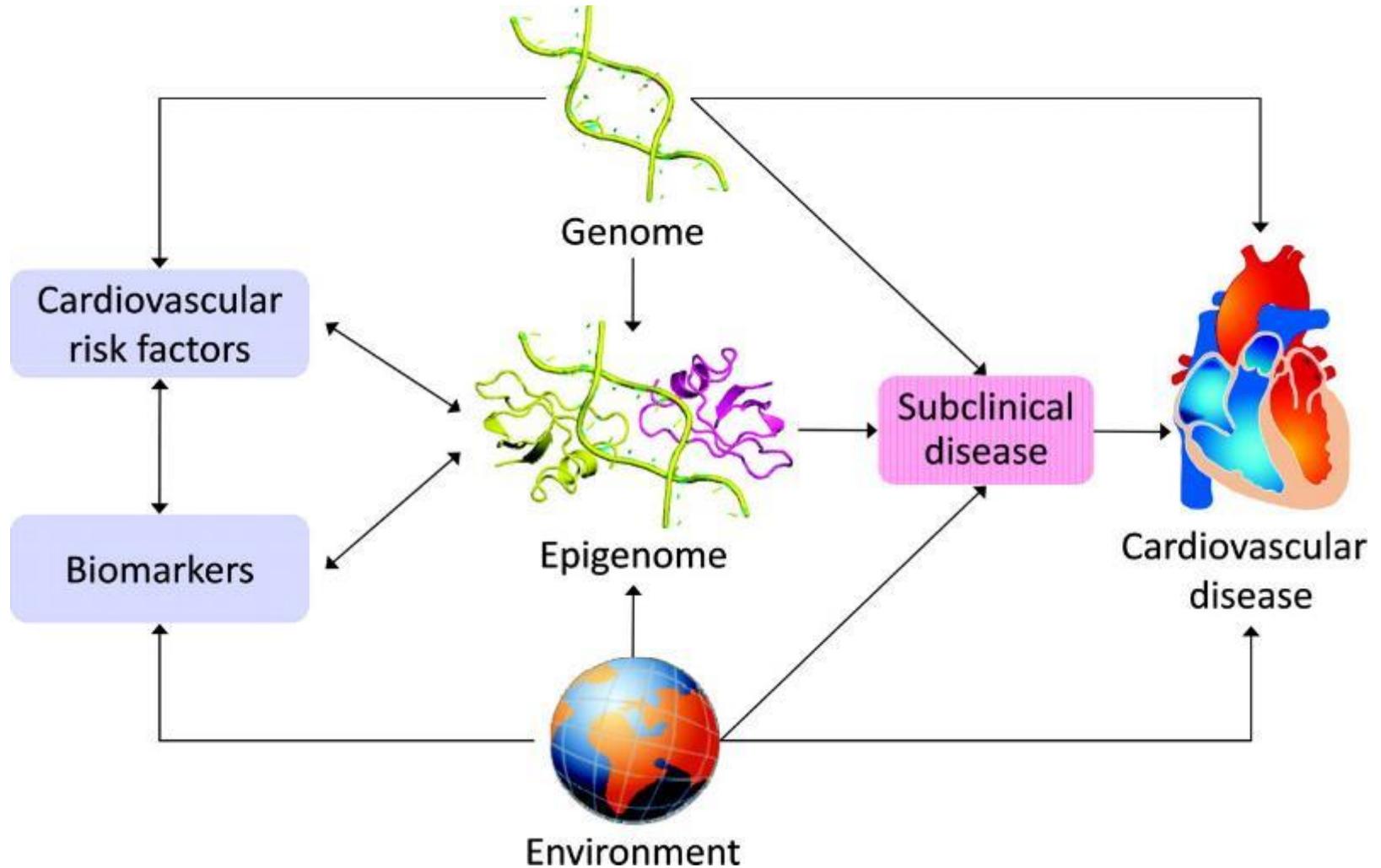


Why Epigenetics in CVD?

- 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.



Baccarelli A et al. *Circ Cardiovasc Genet* 2010;3:567-573

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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
 - ↑homocysteine ↓methylation ?CVD
- Candidate gene (e.g. *FTO*, *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

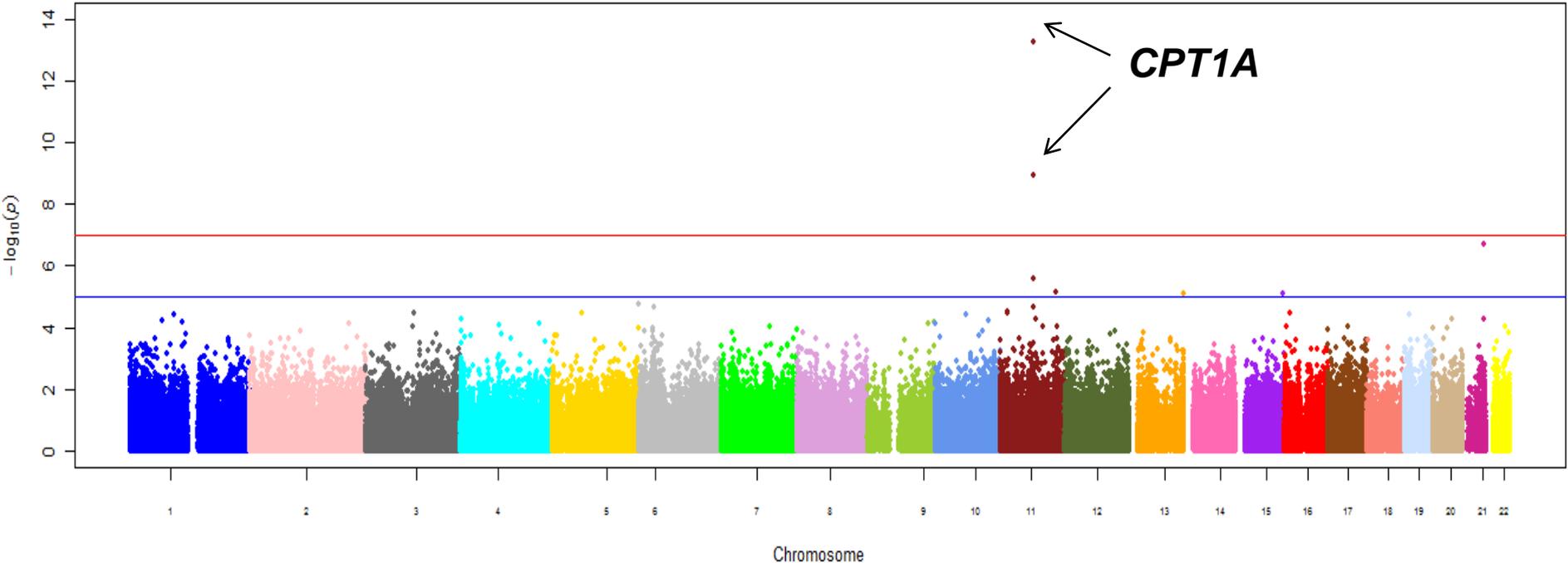
Statistical Methods

- Model:

**plasma lipids ~ methylation status at
450,000 loci + sex + age + family + technical
covariates**

- Additional models adjusting for BMI, alcohol, and current smoking status
- Replication cohort: Framingham Heart Study

Results: Fasting Triglycerides

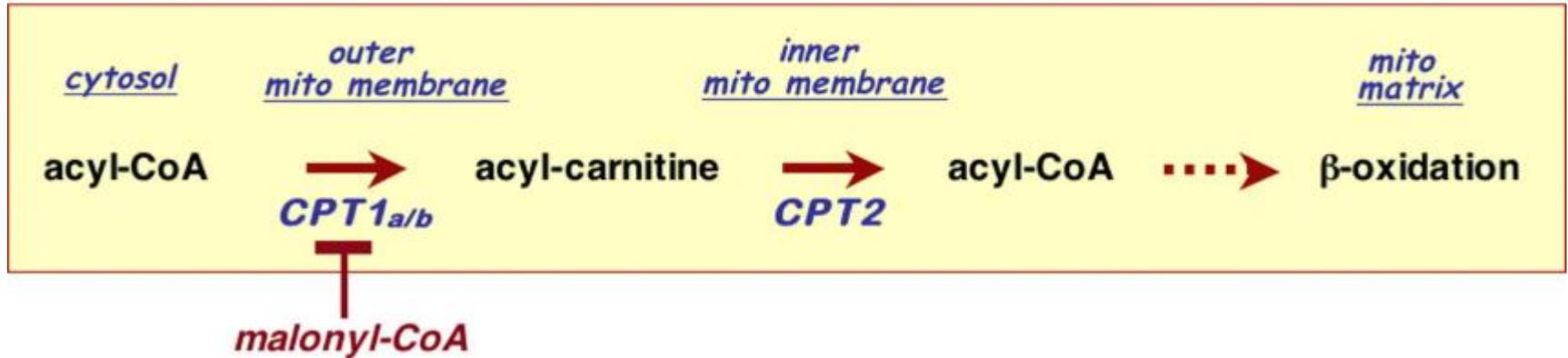


CpG-1:

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

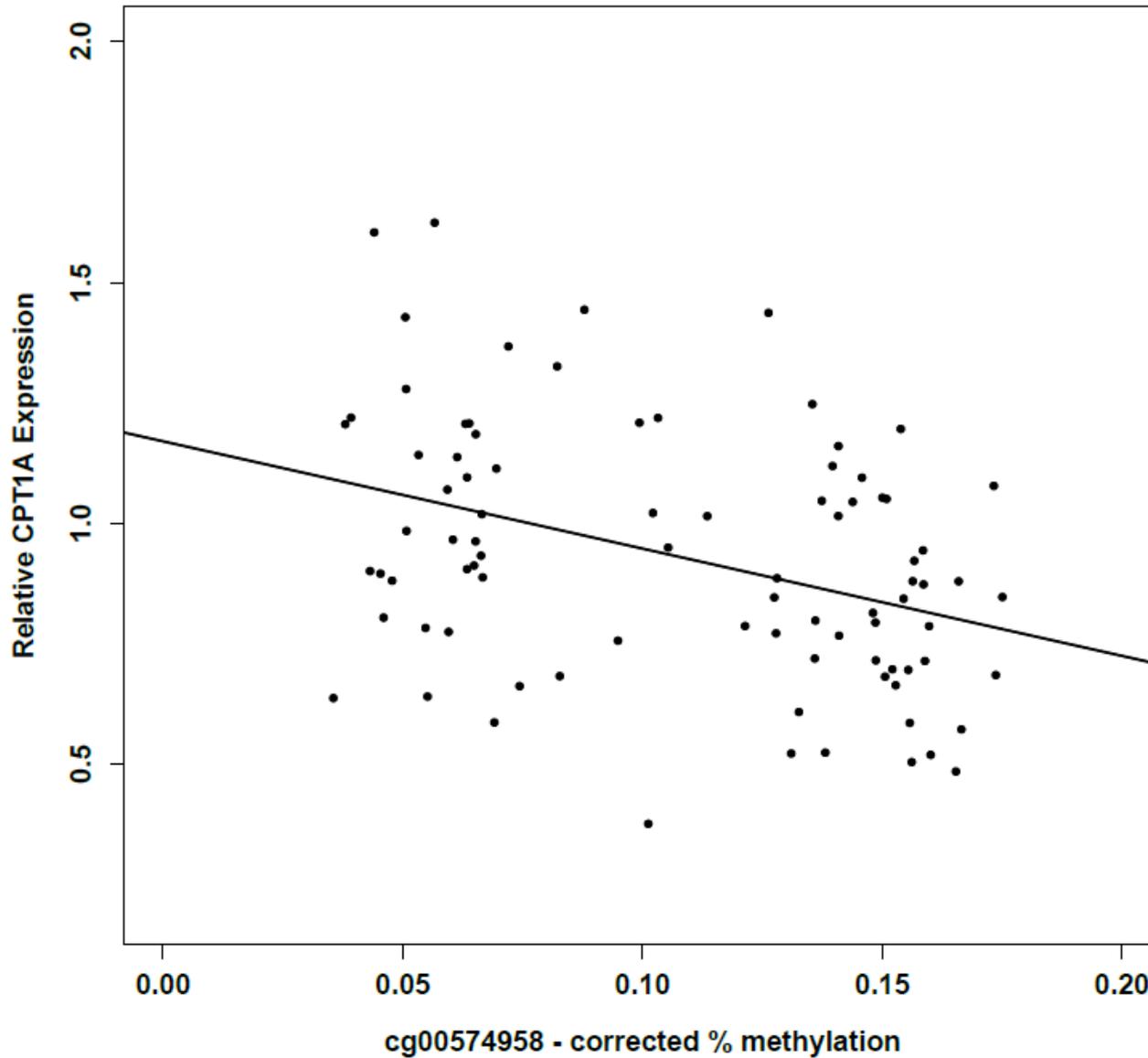
$$P_{\text{replication}} = 4.1 \times 10^{-14}$$
$$r^2 = 5\%$$

CPT1a liver
CPT1b skeletal muscle
CPT1c brain



- Encodes carnitine palmitoyltransferase 1A
- Key in β -oxidation of long-chain fatty acids

Expression



Mouse Model

- *Cpt1A* $-/-$: embryonic lethal
- *Cpt1A* $+/-$: liver expression ↓ by ~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

stella7@gmail.com