DNA methylation-based cardiovascular risk assessment

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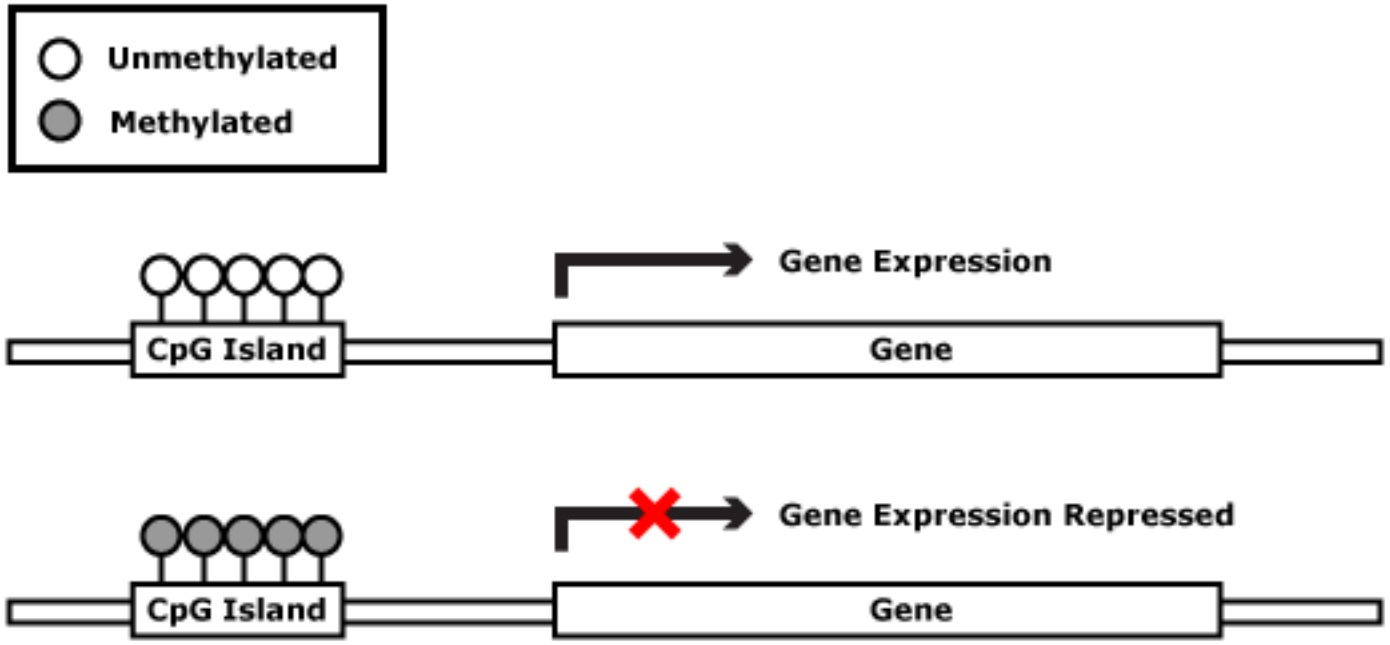
Foreshadowing

I. Background
II. Risk score construction
III. Evaluation
IV. The catch
V. Risk score biology

DNA methylation biology



A vast oversimplification of the functional consequences of DNA methylation

Illumina HumanMethylation450k microarray platform generates:

β ~ fractional methylation

M-value = $\log \frac{\beta}{1-\beta}$

DNA methylation is plastic…

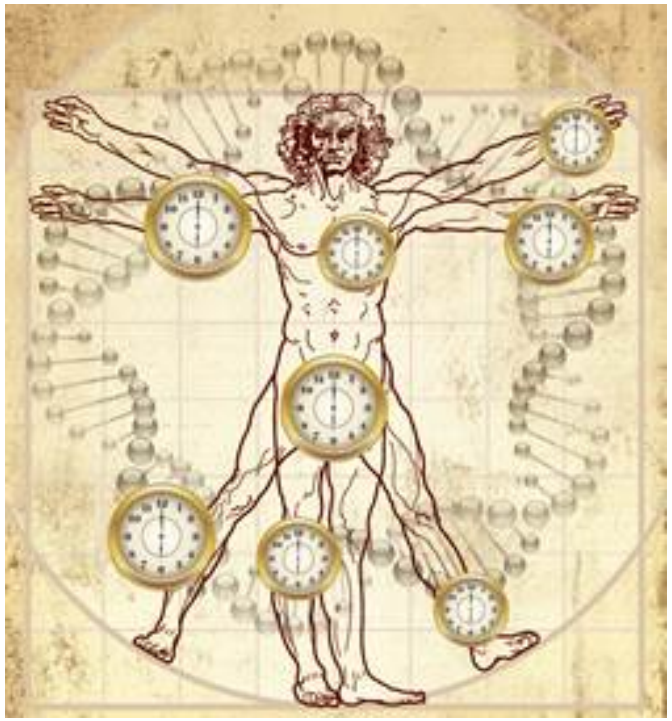
Associates with environmental exposures

- Smoking (observational)
- Pollution (observational)
- Exercise (RCT)

Changes with age

- Epigenetic clocks

(ex. Horvath 2013,
Hannum et al. 2013)



…but can be stable over short time frames

Biomarker of lead exposure and DNA methylation within retrotransposons (Wright et al. 2010)

	Alu β (95% CI)	LINE-1 β (95% CI)
Tibia lead (IQR = 15 g/g)		
Model 1 (n = 787)	0.01 (−0.08 to 0.10)	−0.11 (−0.28 to 0.05)
Model 2 (n = 762)	0.01 (−0.09 to 0.11)	−0.06 (−0.23 to 0.12)
Model 3 (n = 694)	0.02 (−0.10 to 0.13)	−0.07 (−0.29 to 0.14)
Patella lead (IQR = 19 g/g)		
Model 1 (n = 772)	−0.01 (−0.10 to 0.07)	−0.20 (−0.36 to −0.05)*
Model 2 (n = 747)	−0.01 (−0.10 to 0.08)	−0.17 (−0.33 to 0.00)*
Model 3 (n = 679)	−0.03 (−0.14 to 0.08)	−0.25 (−0.44 to −0.05)*
Blood lead (IQR = 2 g/dL)		
Model 1 (n = 716)	0.03 (−0.04 to 0.11)	−0.01 (−0.15 to 0.13)
Model 2 (n = 694)	0.03 (−0.05 to 0.10)	0.04 (−0.10 to 0.19)

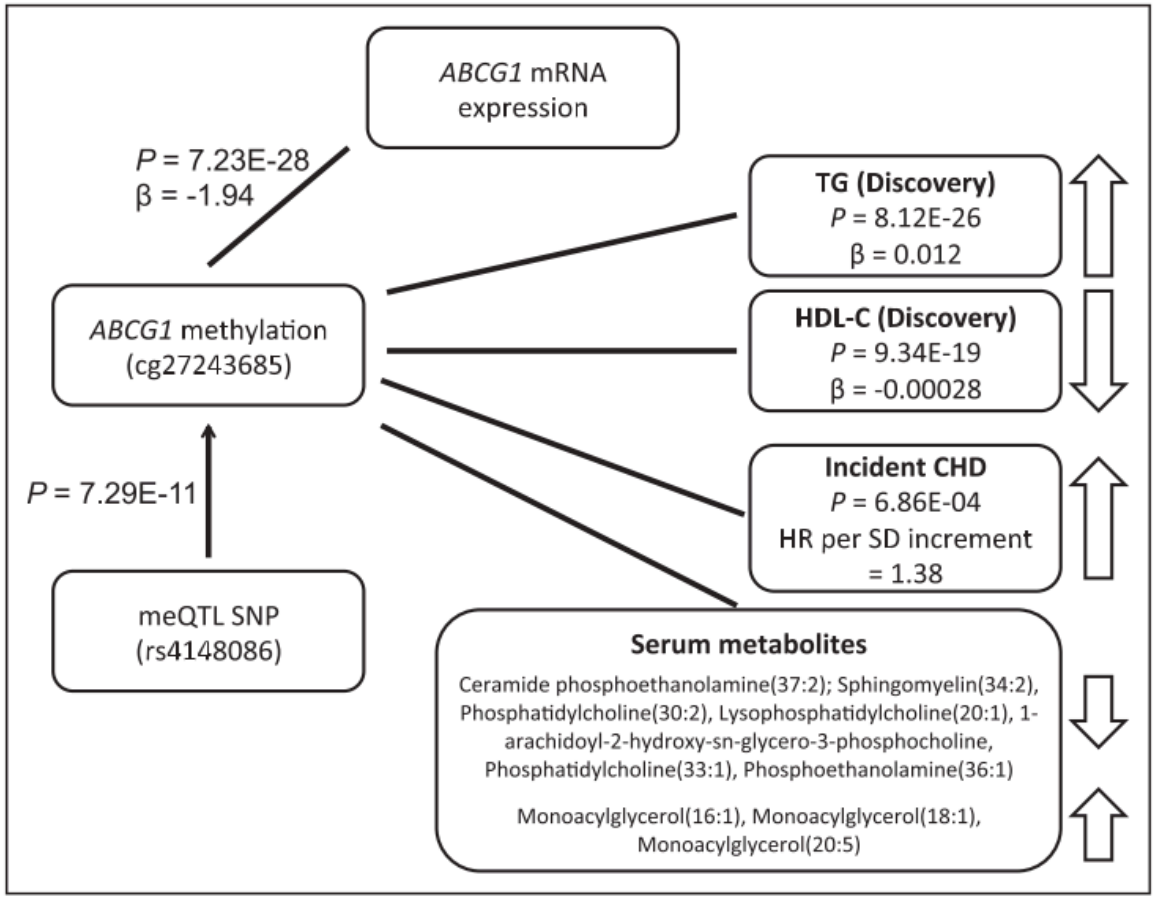
No association of DNA methylation levels with blood lead levels (transient)

Significant association with patella lead levels (bone: proxy for cumulative past lead exposure)

Methylation risk scores for prognosis

Stability + Plasticity → Ideal for biomarkers of modifiable risk

EWAS link methylation & CVD risk factors

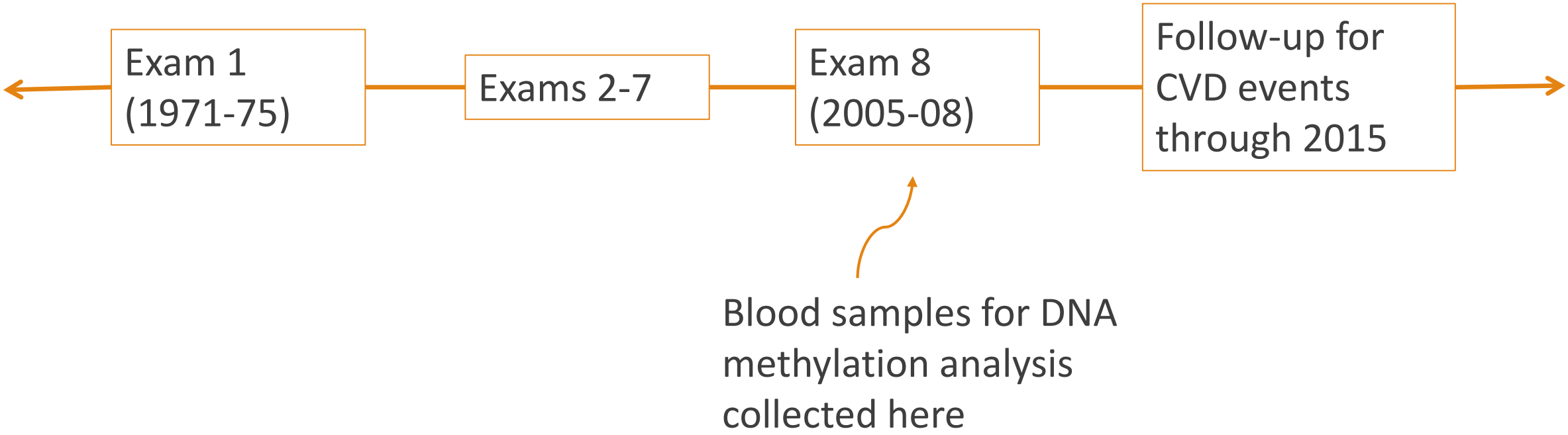


Hedman et al., Circ-Cardiovasc. Gene. (2017)

Goal

To develop a methylation-based score indicative of cardiovascular disease risk, and to investigate the potential biological significance of this biomarker.

Framingham Heart Study Offspring Cohort



Framingham Heart Study Offspring Cohort

Overall population

- Samples from 2590 unique subjects after sample quality control
- Most are 50-80 years old
- Even sex distribution
- All Caucasian

Cardiovascular events

- Defined here as MI, stroke, or death from CHD/CVD
- 280 subjects experienced an event between Exam 8 and the available ~3600 days of follow-up
- 82 had experienced a previous cardiovascular event

MRS characterization and evaluation

FHS Offspring dataset was split into training and testing sets

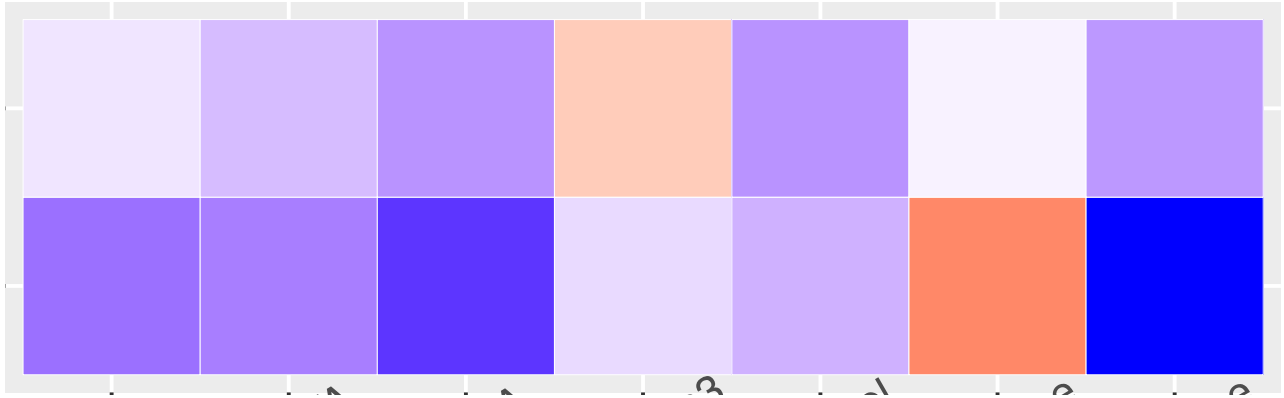
- 60% of sample to training, 40% to testing
- Proportional for number of incident events, otherwise random

MRS biology

Enrichment analysis of annotated genes

Reactome gene set	p	FDR
NCAM1 interactions	5.00E-07	3.34E-04
Platelet homeostasis	9.90E-07	3.34E-04
NCAM signaling for neurite outgrowth	1.21E-05	0.0027
Metabolism of RNA	4.38E-05	0.0070
Collagen formation	5.18E-05	0.0070
Metabolism of amino acids and derivatives	7.47E-05	0.0072
Glucagon signaling	7.49E-05	0.0072
Immune system	8.93E-05	0.0075
Nitric oxide stimulates guanylate cyclase	1.51E-04	0.010
GNAZ signaling events	1.75E-04	0.010

Correlations with dietary components



Preliminary conclusions

- DNA methylation data can be used to construct a significantly predictive biomarker of cardiovascular risk
- This risk score may provide a small improvement over current risk prediction methods
- The score may be acting as a proxy for prior cardiovascular events

Future directions

- Additional datasets for greater power and validation
- Gender stratification
- Longer-term: incorporate interactions with diet in risk prediction

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