Epigenetic variation:
a promising biomarker in health and disease?

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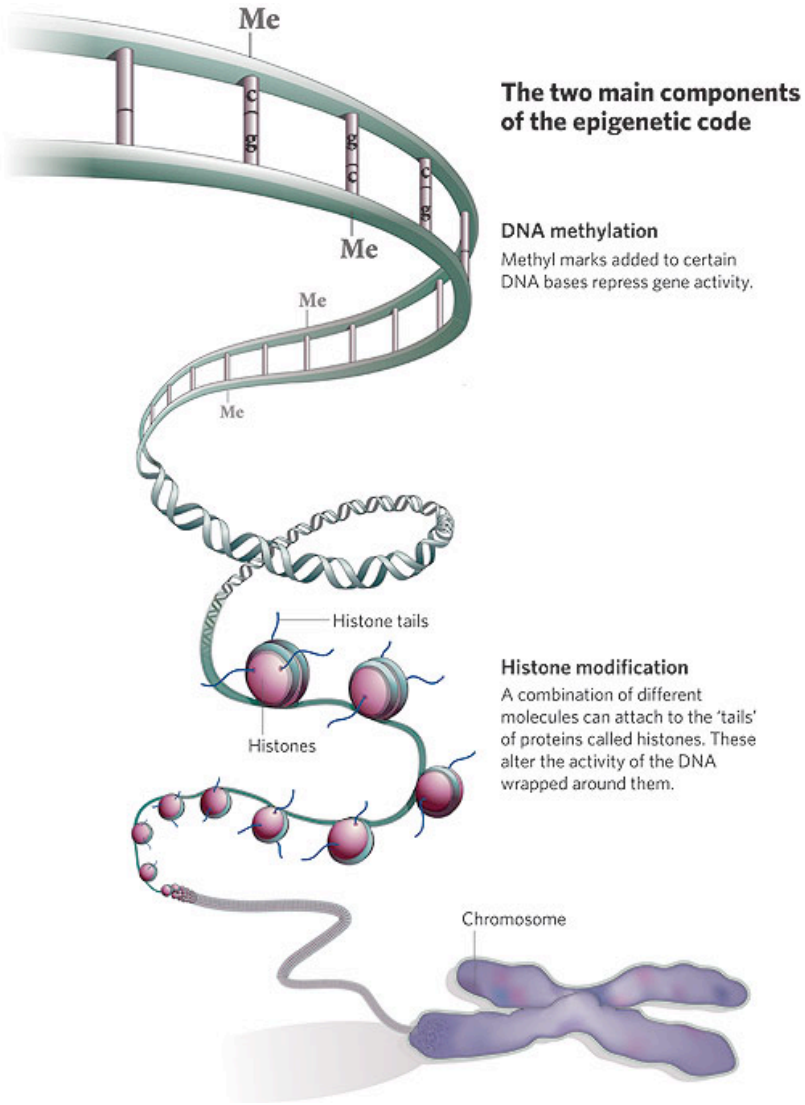
Epigenetics: a mechanism to explain how the genome 'memorises' environmental exposures

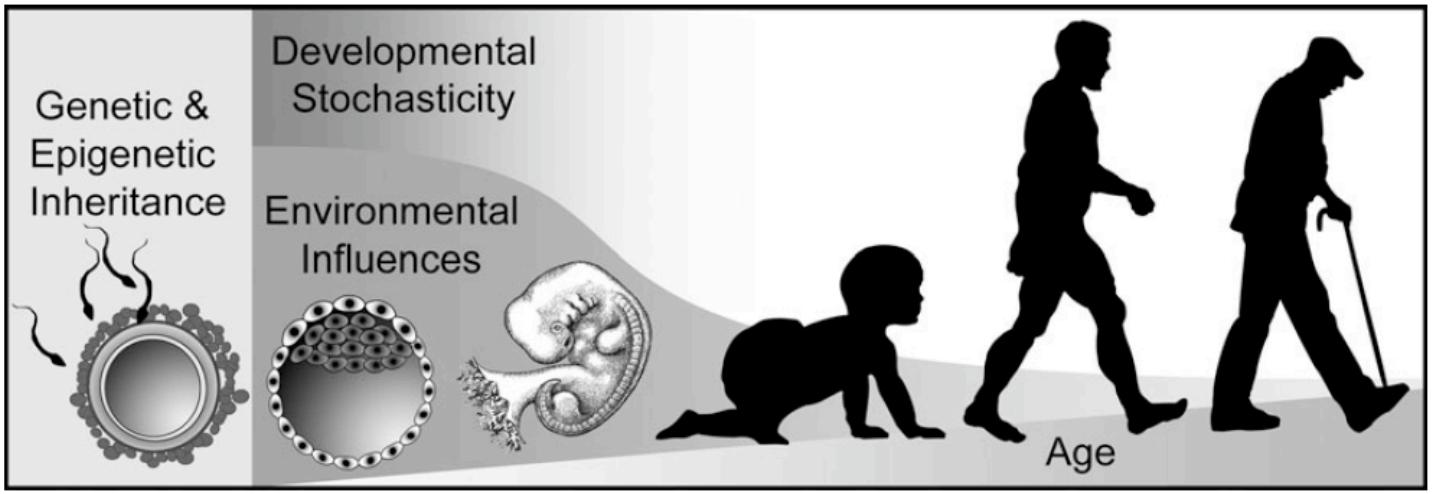
"Changes to the genome which are inherited from one generation to the next which alter gene expression but which do not alter the gene sequence"

- DNA methylation
- Histone modification
- microRNAs

- Somatic mitotic stability
- Germ-line epigenetic inheritance
- Trans-generational effects on phenotypic variation



Epigenetic patterns alter through the lifecourse



Germline epimutation

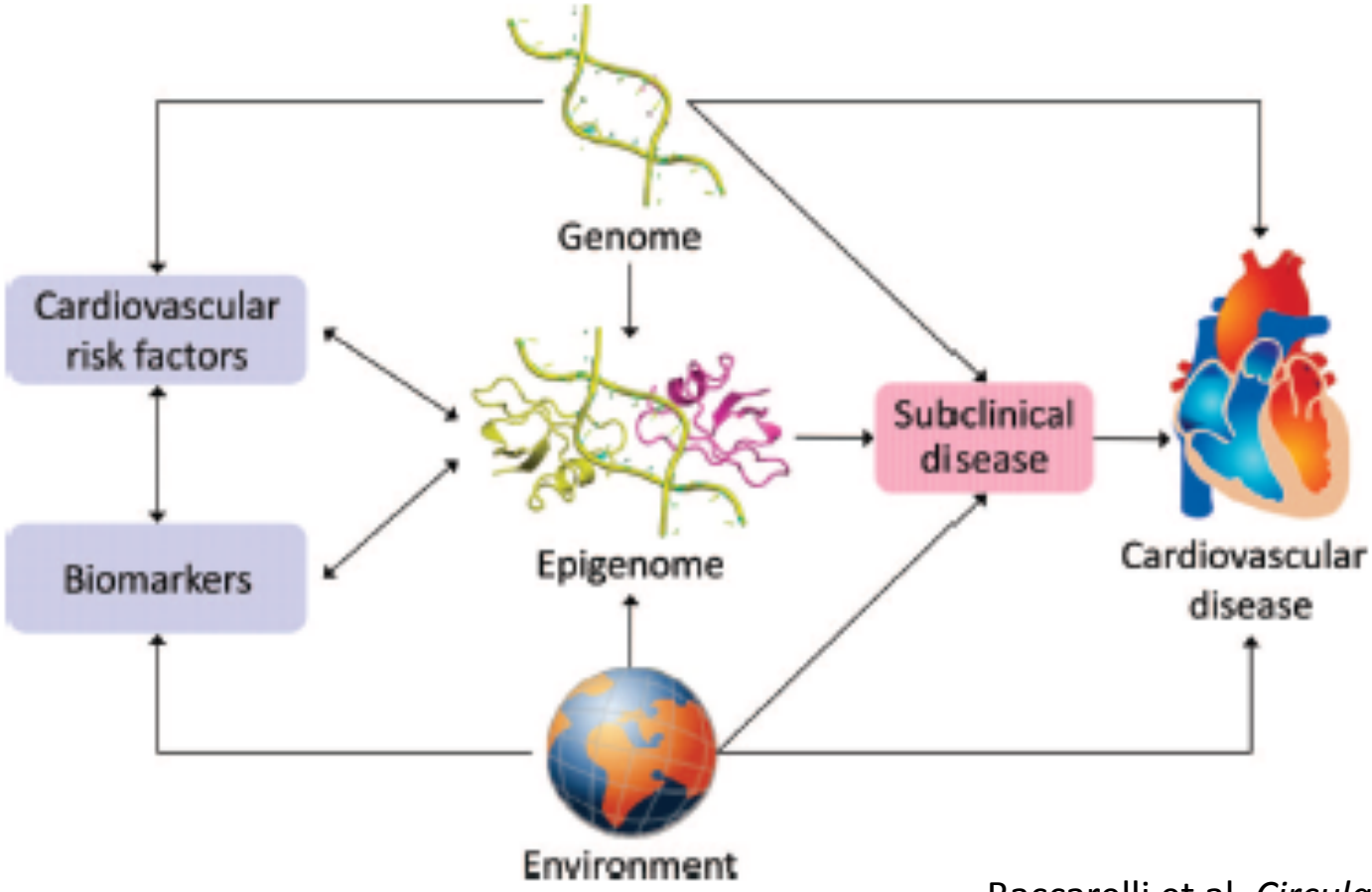
Parental genomic demethylation

Epigenetic drift / somatic epimutation

Developmental epigenetic programming

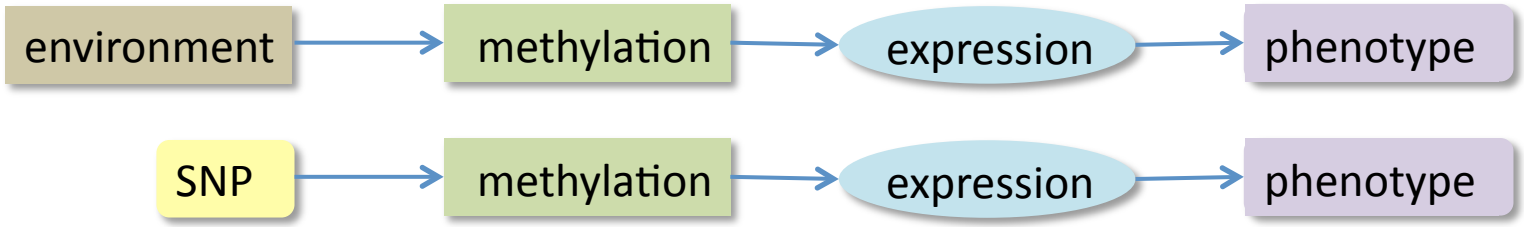
Waterland *Nutr Rev* 2008

A conceptual model linking epigenetics to cardiovascular disease and cardiovascular risk factors



Baccarelli et al. *Circulation* 2010

The causal pathway



- Epigenetic patterns are phenotypic, there is nothing inherently different than studying any other socially or behaviourally patterned phenotype
- Extravagant claims of the utlity of intermediate phenotypes have been made before – in the field of gene expression - that failed to replicate
- Rigorous approaches are essential to ensure that meaningful inferences are made about causality

Epigenetic variation – fundamental issues

- Can we identify epigenetically variable regions of the genome?
- Can we measure variation accurately in individuals and populations?
- How to we assess temporal stability?
  - Developmentally determined changes
  - Stochastic variation
  - Environmentally-induced, exposure-related fluctuations
  - Stable/persistent vs labile changes

Does smoking impact upon DNA methylation?

Tobacco-Smoking-Related Differential DNA Methylation: 27K Discovery and Replication

Lutz P. Breitling,[1,*] Rongxi Yang,[2,4] Bernhard Korn,[3,5] Barbara Burwinkel,[2,4] and Hermann Brenner[1]

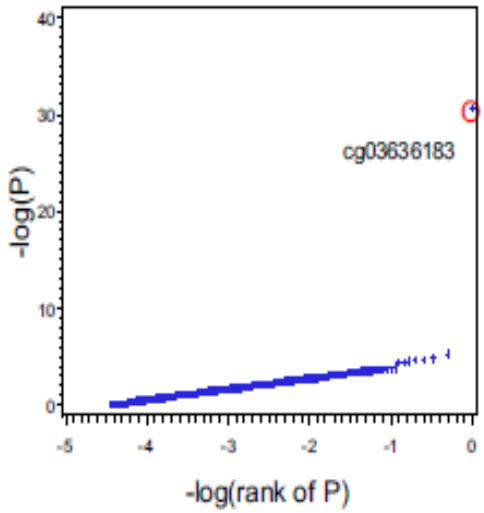
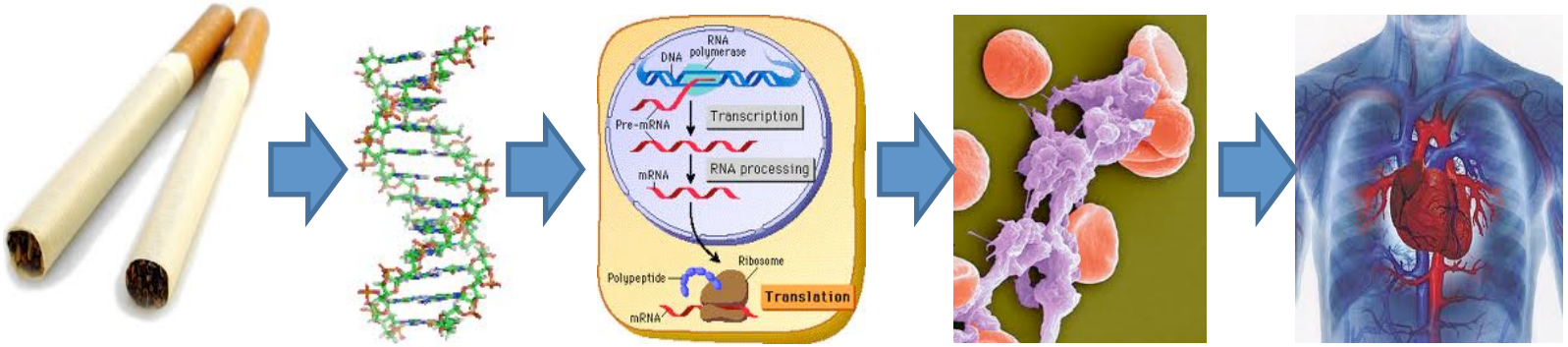


Figure 1. Mixed Linear Regression p Values of the Sex-Adjusted Association of Smoking Status with Methylation Intensities at 27,578 CpG Sites

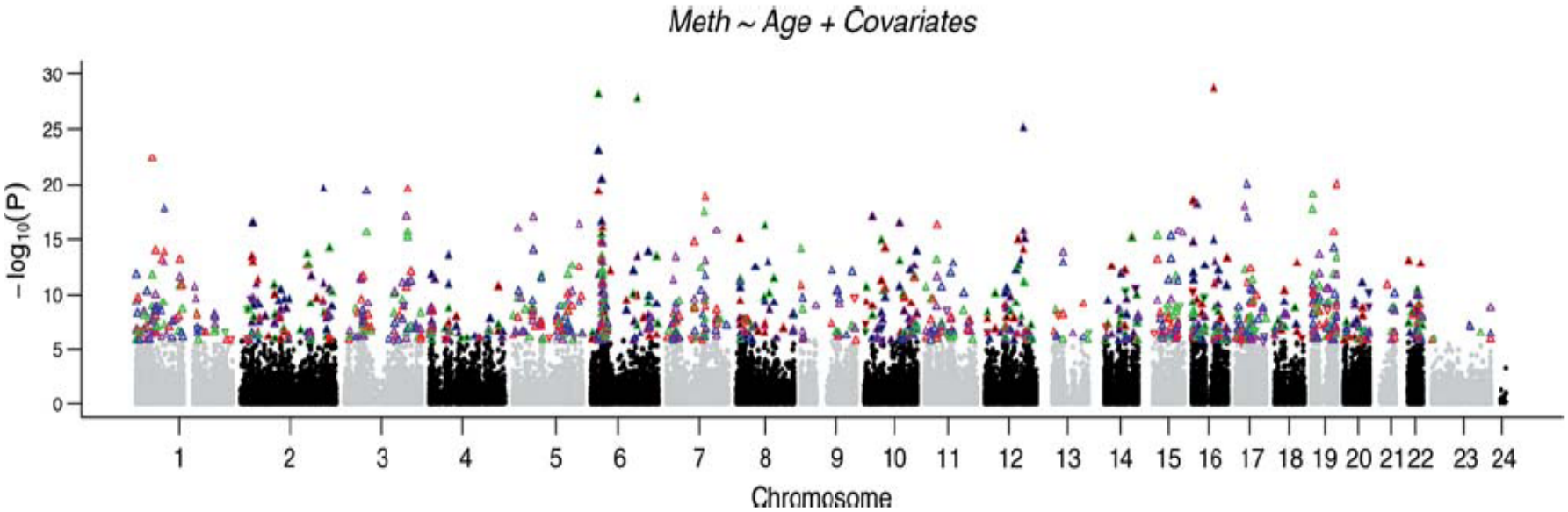
Epigenetic mediation of smoking and cardiovascular disease

- Smoking associated with decreased methylation of the coagulation factor II receptor-like 3 gene (*F2RL3*)
- Prompt increased expression of the protease-activated receptor-4 (PAR4)
- Induces platelet activation (aggregation)
- Plausible mechanism of smoking induced myocardial pathology



↑ smoking → ↓ methylation *F2RL3* → ↑ expression PAR4 → ↑ platelet aggregation → ↑ risk CVD

Age-related change in methylation



Manhattan plot showing association between methylation at individual CpG sites and chronological age. Plotted are P-values indicating strength of association between DNA methylation levels at >27 000 CpG sites and age in cerebellum (purple), frontal cortex (green), pons (blue) and temporal cortex (red). For each point, a positive association between DNA methylation and chronological age is indicated by upward pointing triangles; a negative association is indicated by downward pointing triangles.

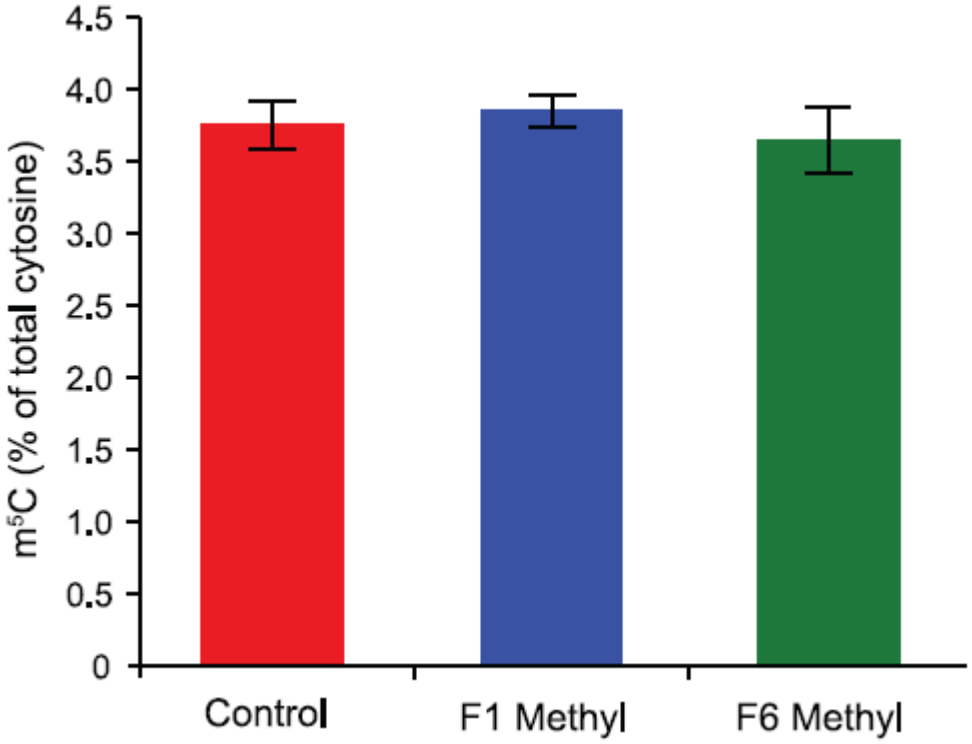
Hernandez et al. *Hum Mol Genet* 2011

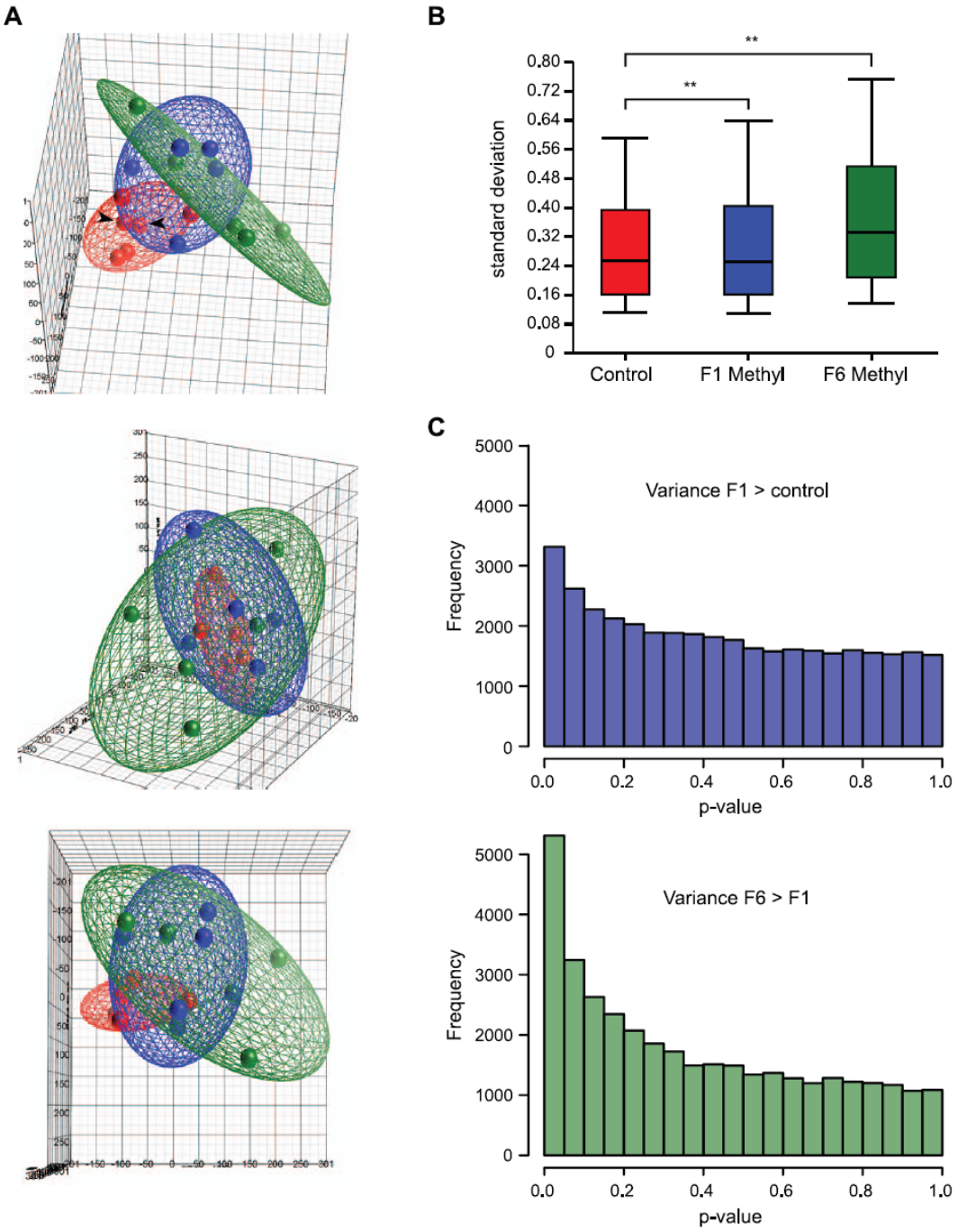
Dietary influences on epigenetic variance in isogenic mice

Methylation levels are unchanged after methyl donor supplementation

Whole-genome 5-methylcytosine (m^5C) content in liver DNA from control, F1 supplemented and F6 supplemented mice

Li et al *PLoS Genetics* 2011



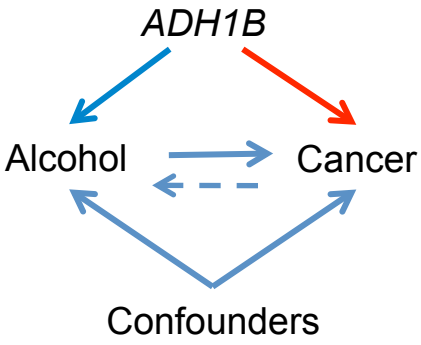


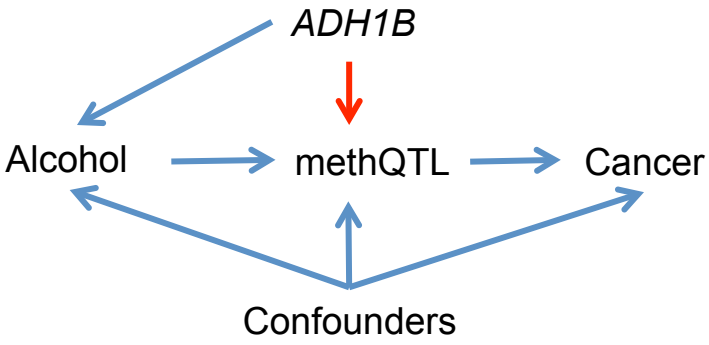
Methyl donor supplementation increases epigenetic variation in exposed mice

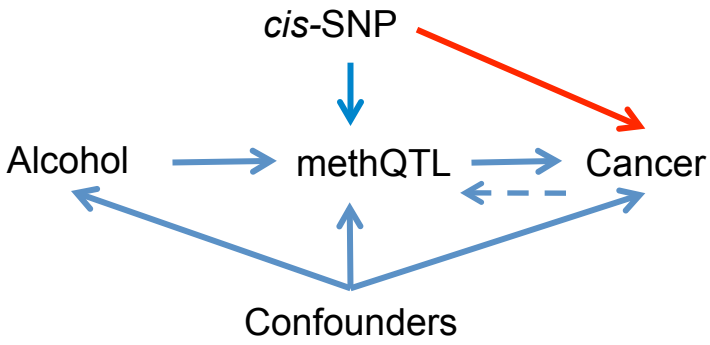
Pseudo three-dimensional plot showing PCA of microarray data from **control** and **F1** and **F6** supplemented mice. The ellipsoids around the PCA scores of each group were determined by standard deviations, so that their size is indicative of the overall variance within the group.

Li et al *PLoS Genetics* 2011

'*Genetical epigenomics*': Extending the principles of Mendelian randomization

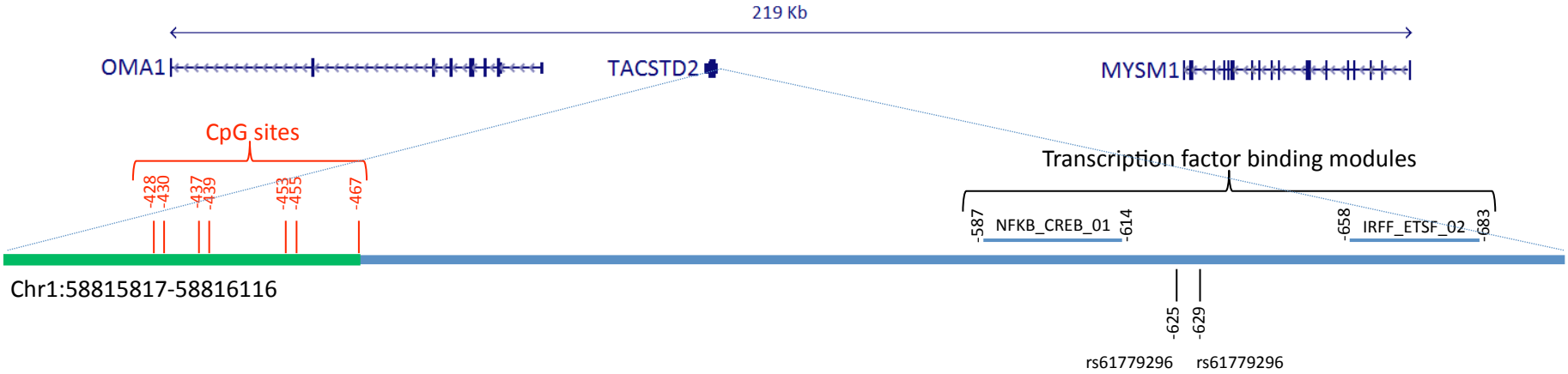


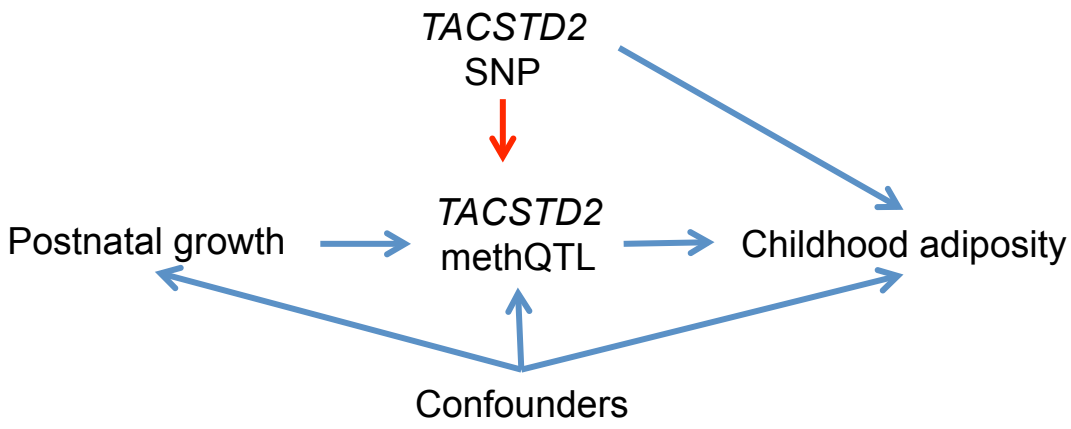




Relton & Davey Smith *PLoS Med* 2010

Using *cis* SNPs to strengthen causal inference in a study of postnatal growth and childhood adiposity





Applications in behaviour-related contexts

- Maternal / *in utero* effects of behavioural and lifestyle influences on offspring epigenetic patterns
- Adolescent alcohol consumption habits
- Eating disorders
- PTSD
- Conduct problems
- Early childhood adversity