

DNA methylation clock and drift in aging

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Postdoctoral fellow

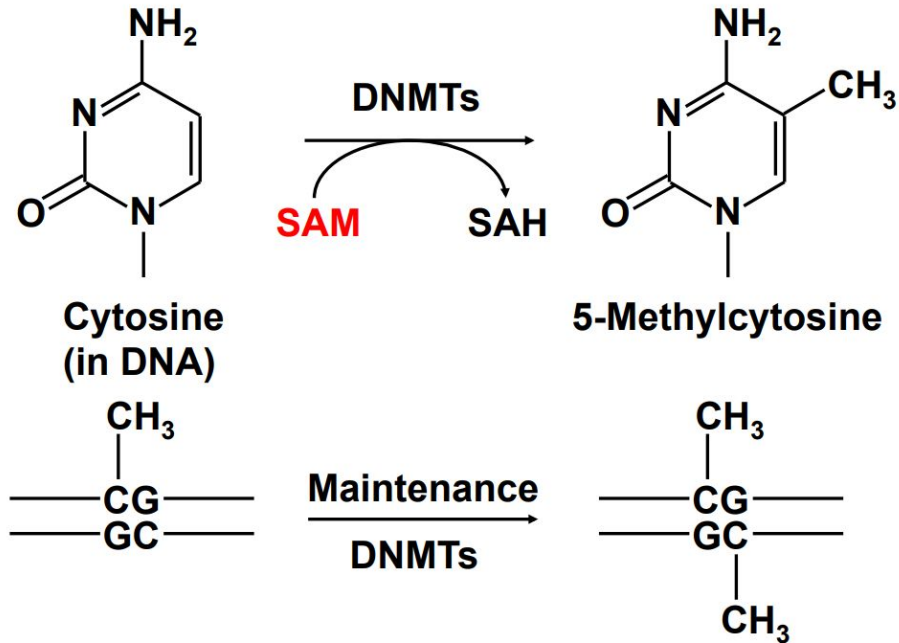
Matteo Pellegrini lab

Molecular cell and developmental biology

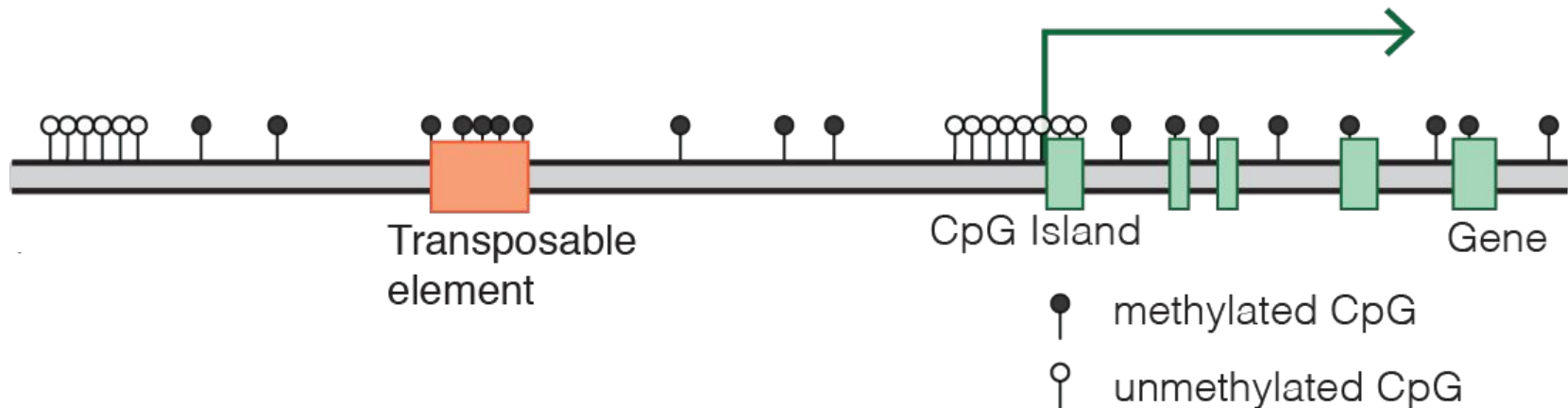
The UCLA logo consists of the letters "UCLA" in a bold, white, sans-serif font, centered within a solid blue rectangular background.

UCLA

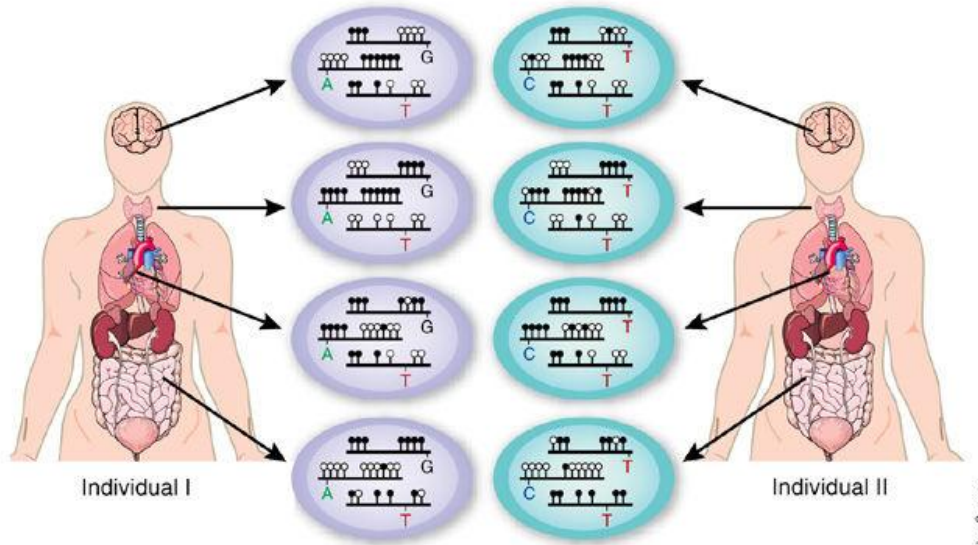
DNA methylation



Typical mammalian DNA methylation landscape

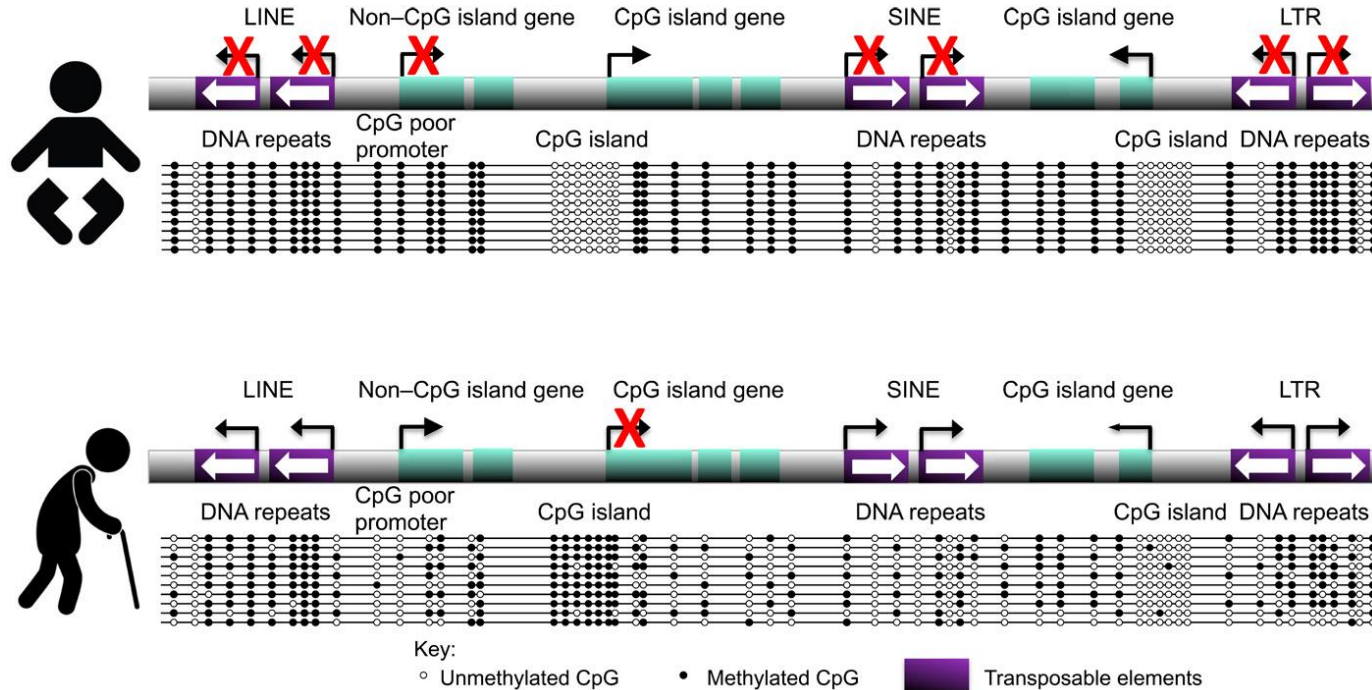


Why study DNA methylation?



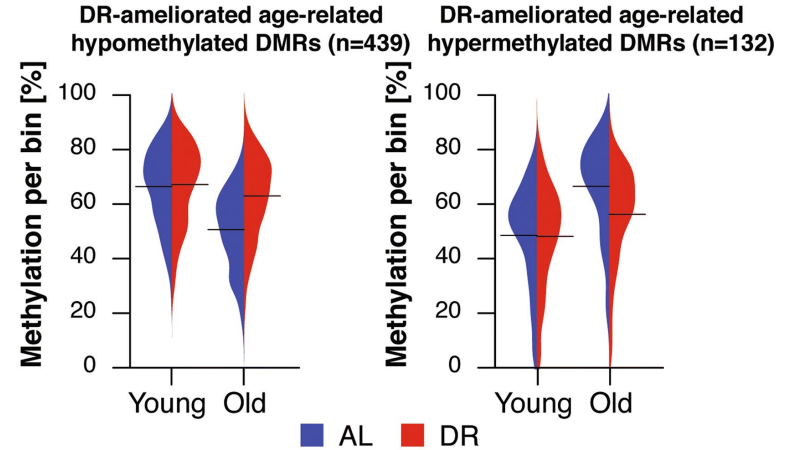
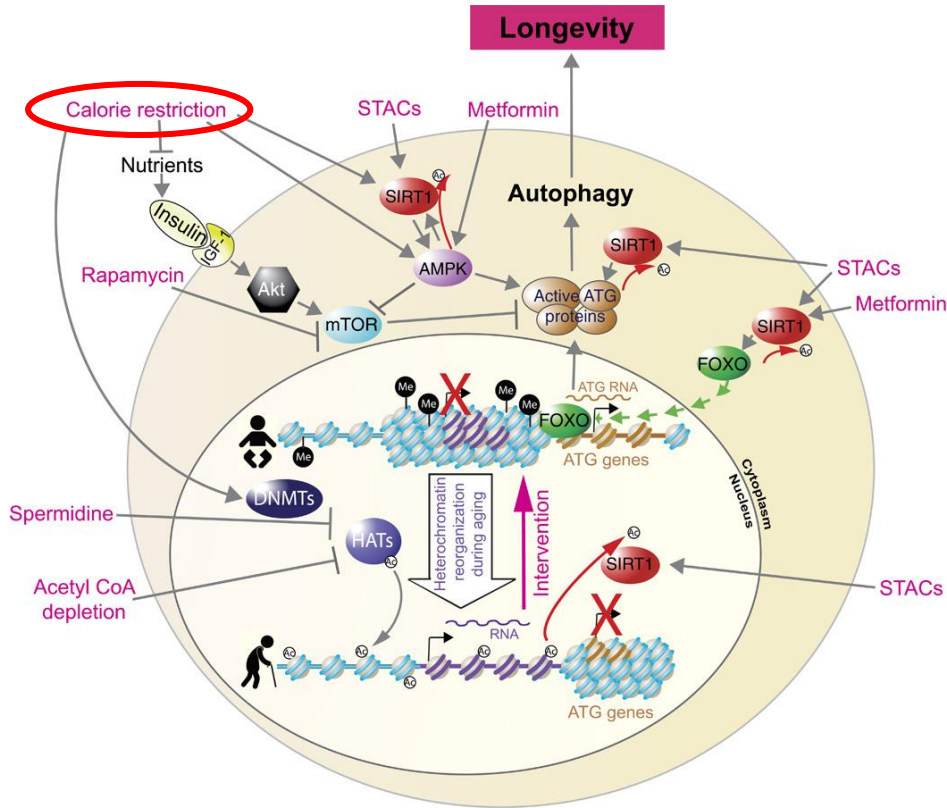
- Cell-type-, stage-specific
- Mutable, can be influenced by external factors
- Changes that occur over time
- Medium-term indicator, not as acute as transcription
- Regulates transcription and more....

Why study DNA methylation in aging?

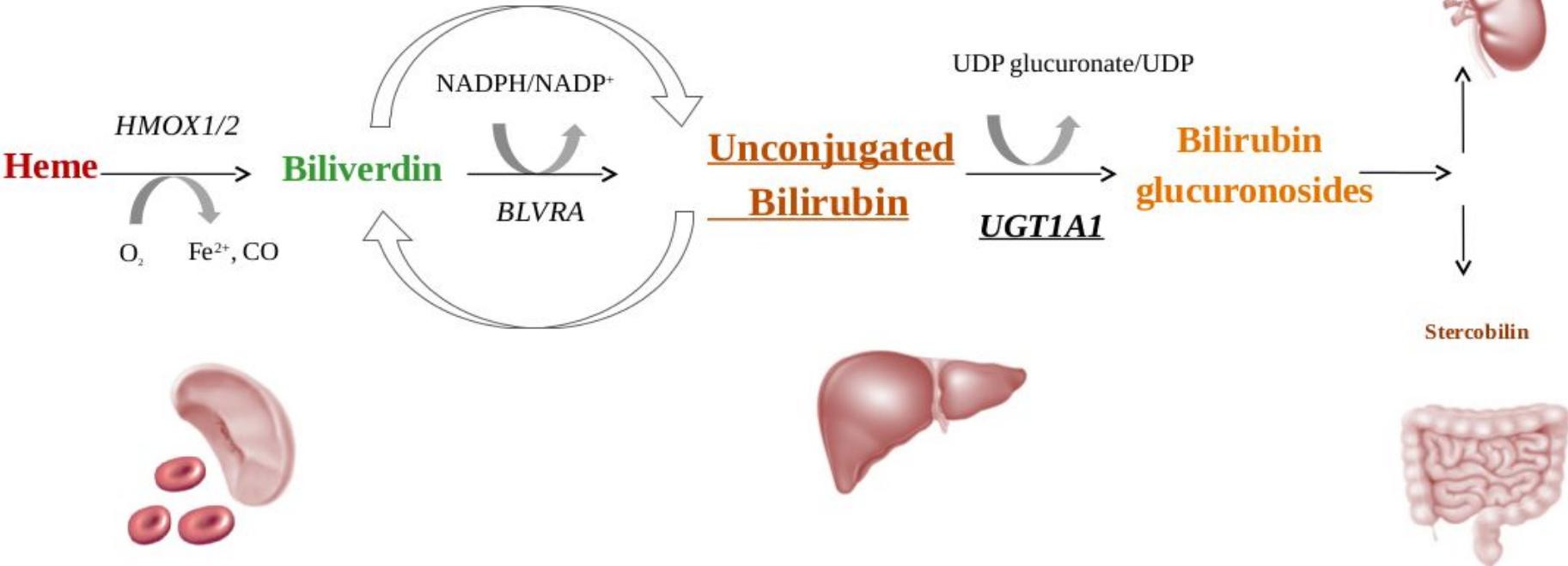


Aging is characterized by global HYPOMethylation!

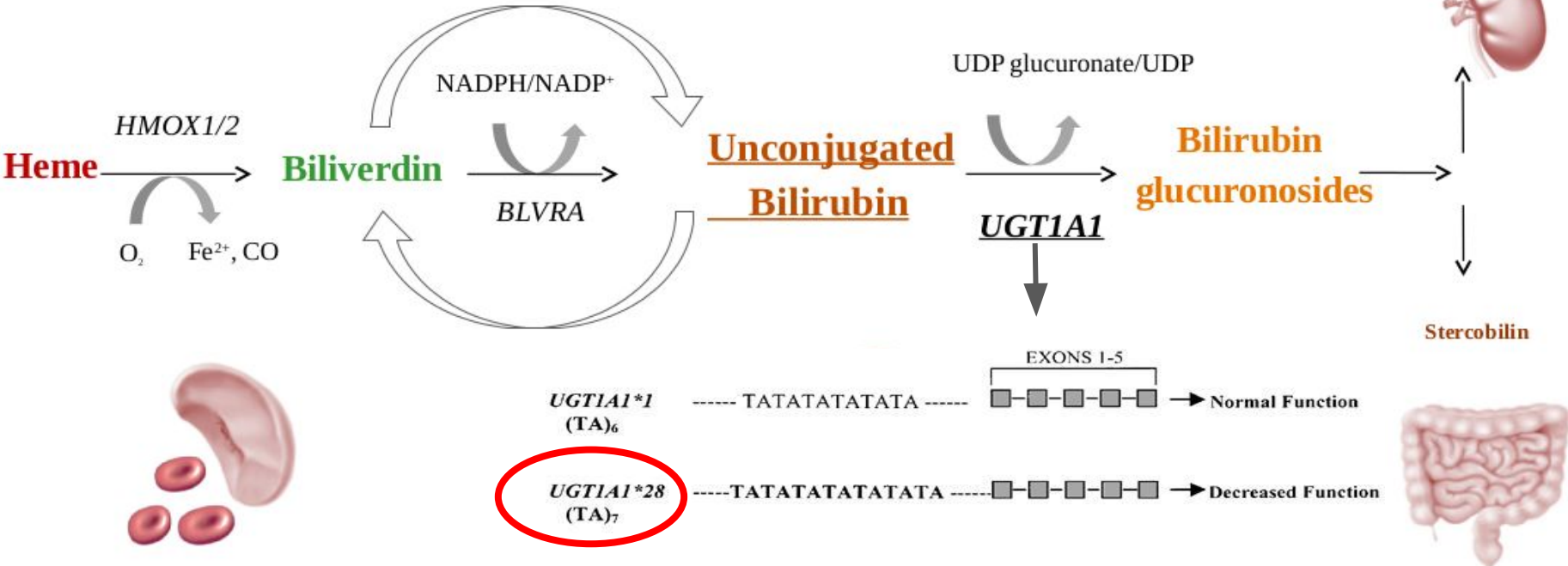
Caloric restriction (CR) and epigenetic drift



Increased endogenous bilirubin mimics CR



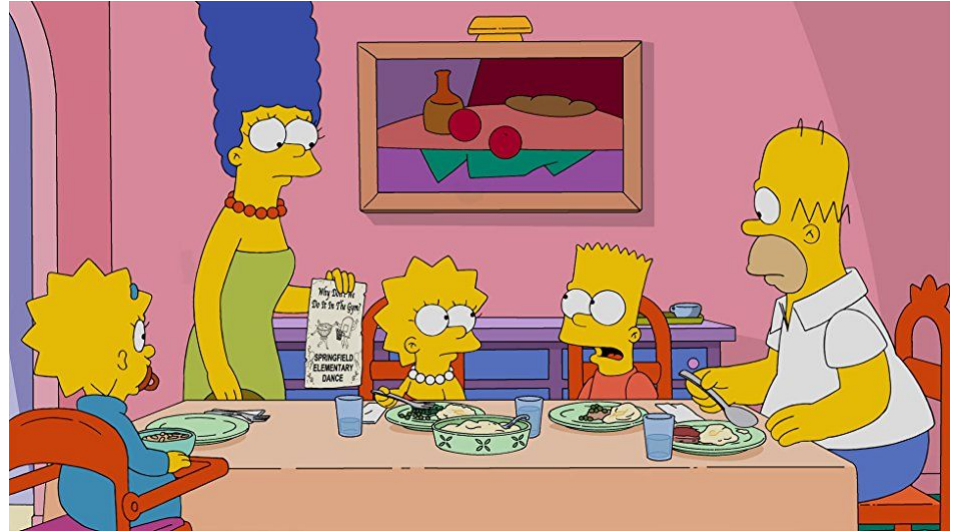
Gilbert's syndrome



Bilirubin: the key to longevity?



1989



2018

Study design

UGT1A1*1 / Control

UGT1A1*28 / GS

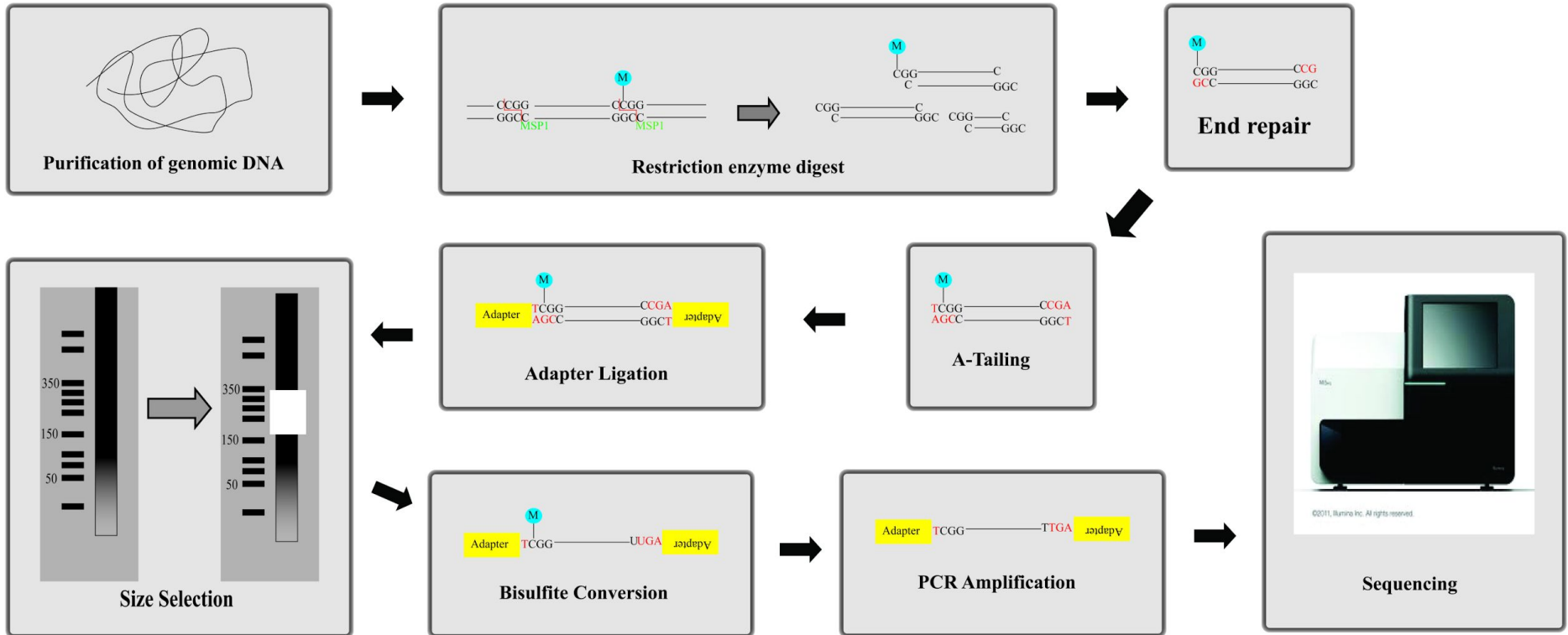
20-34 y.o.
(n = 22)



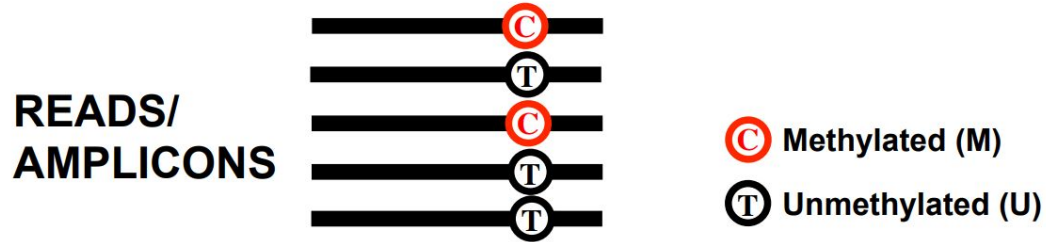
35-70 y.o.
(n = 20)



Reduced Representation Bisulfite Sequencing



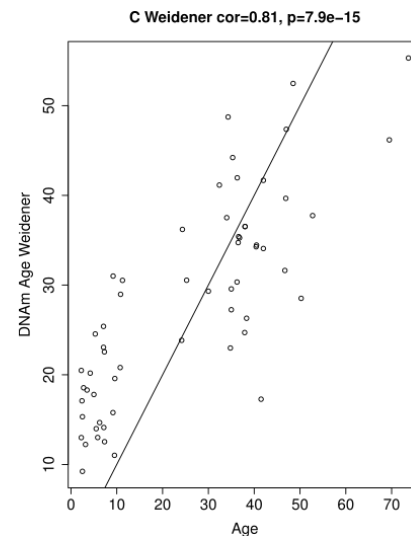
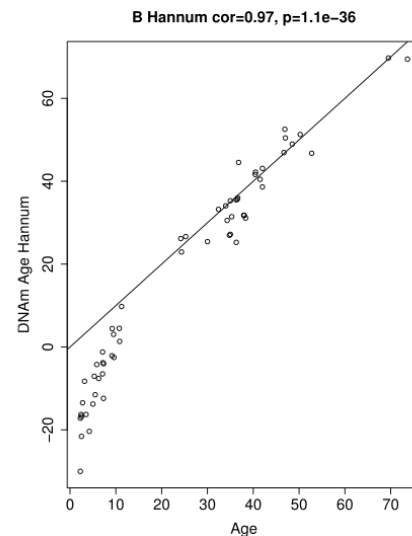
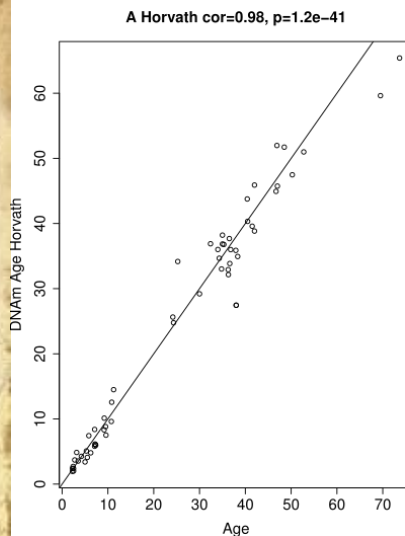
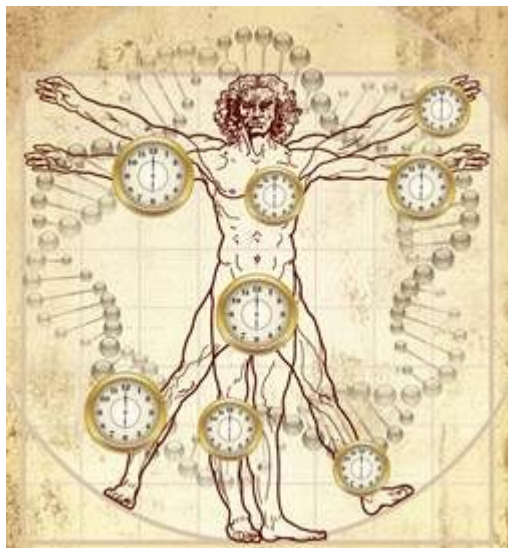
Calculating DNA methylation



$$\% \text{Methylation} = \frac{M}{M + U} \times 100$$

In the above example, the methylation level of the locus is **40%**

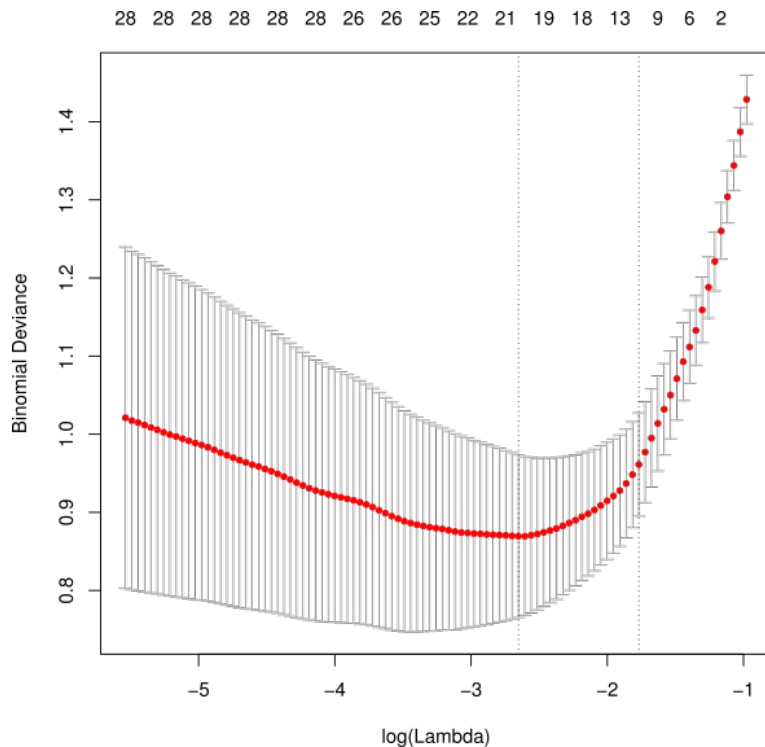
The Horvath epigenetic aging clock



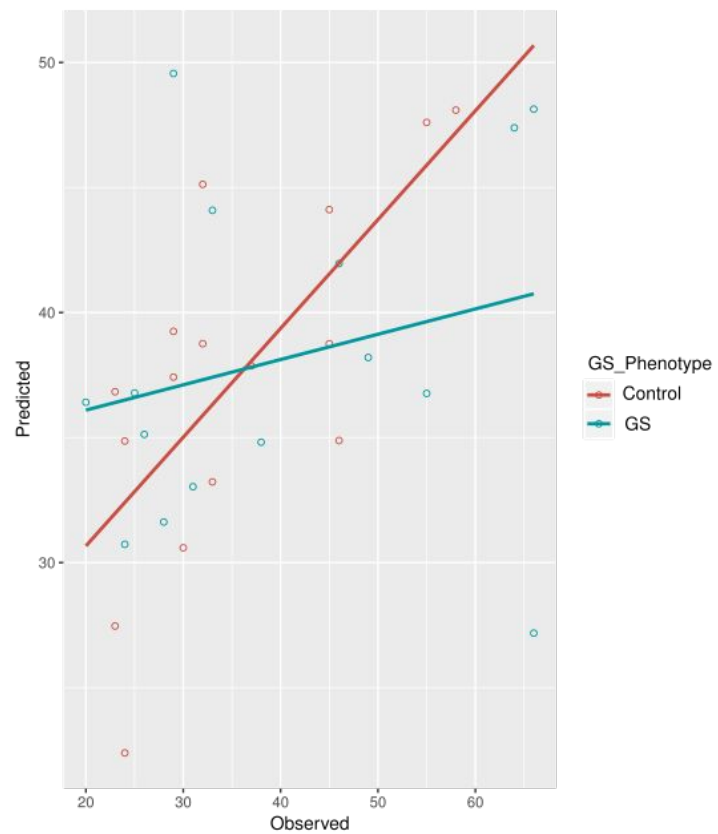
Based on Illumina 27K or 450K bead arrays; overlap with RRBS poor: 5628 and 66224 sites, respectively, out of more than 1 million sites in RRBS.

How to find CpG sites from RRBS data that can predict age?

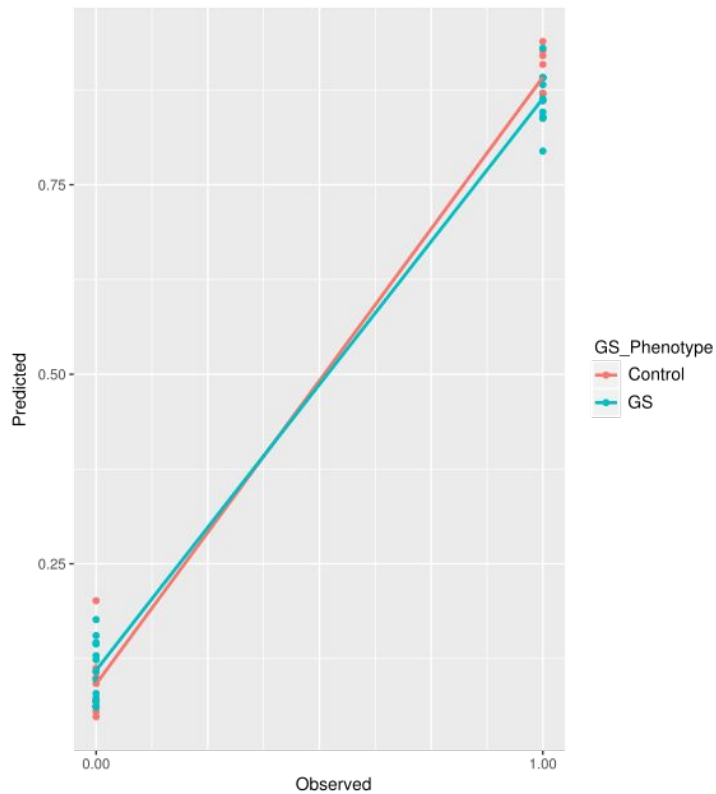
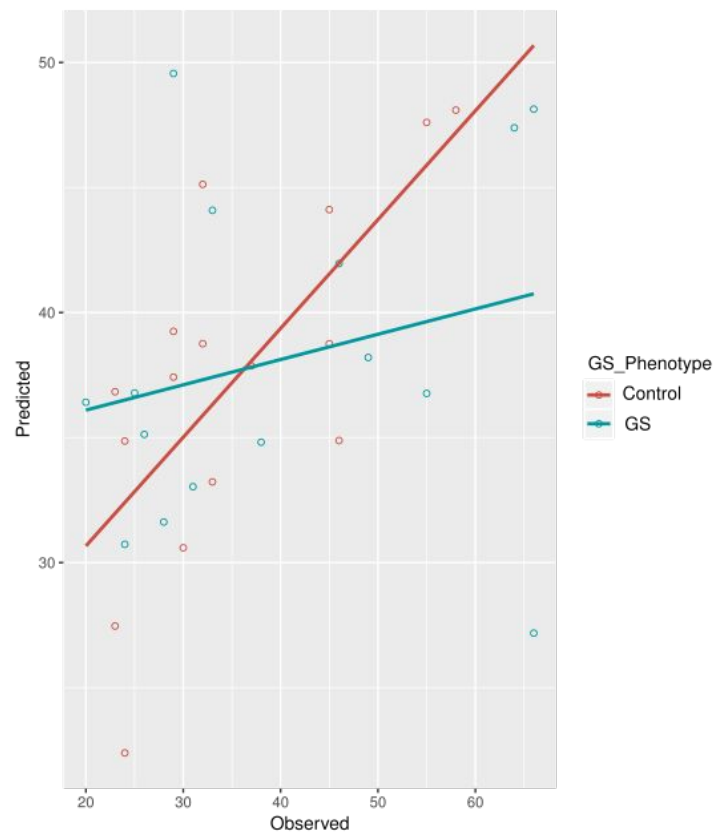
Prediction models with elastic net regularisation



Linear model for age prediction



Logistic model for age prediction

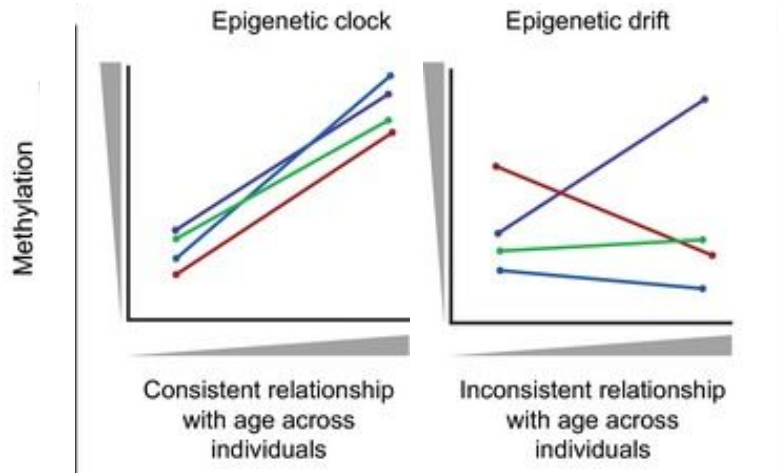


How to find CpG sites that act as age clocks in healthy individuals but drift with age in GS?

Epigenetic clock vs. epigenetic drift

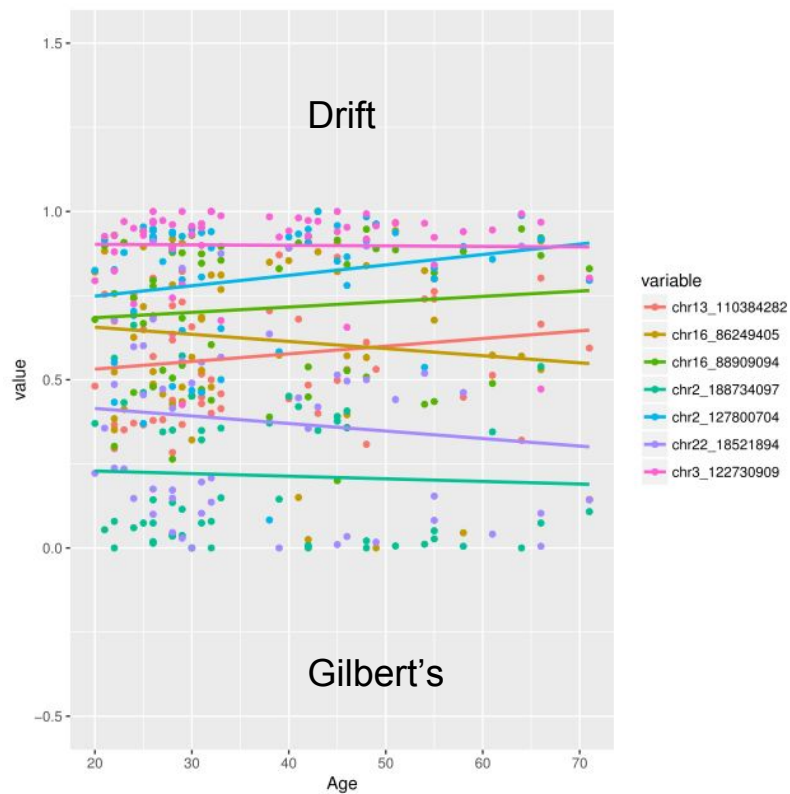
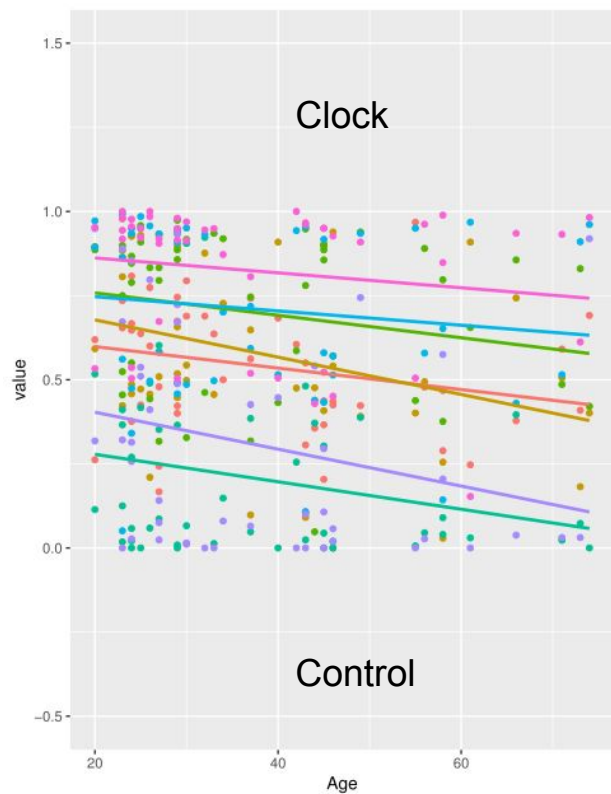
UGT1A1*1 / Control

UGT1A1*28 / GS

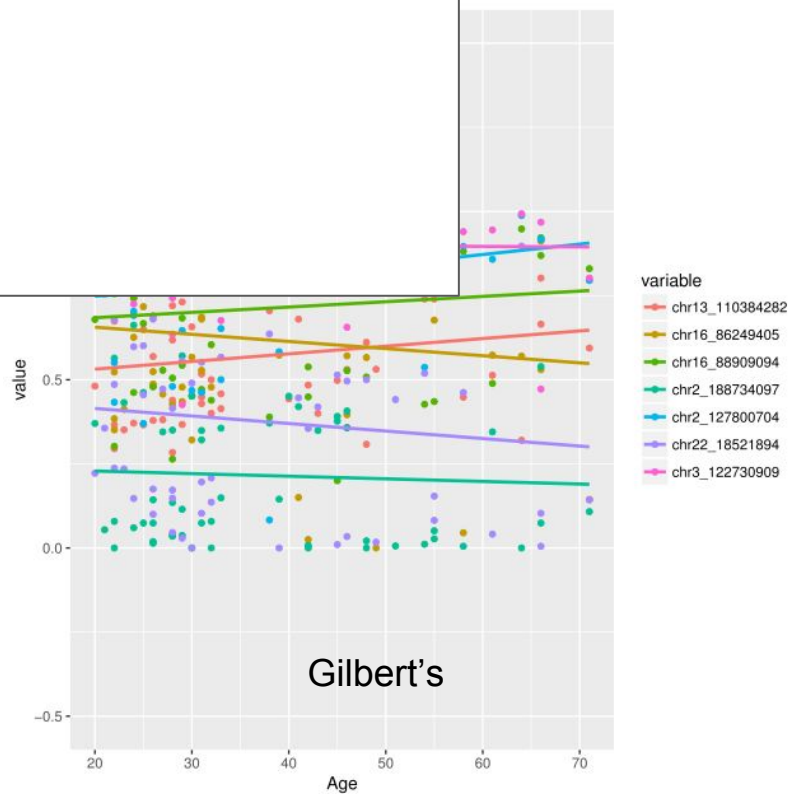
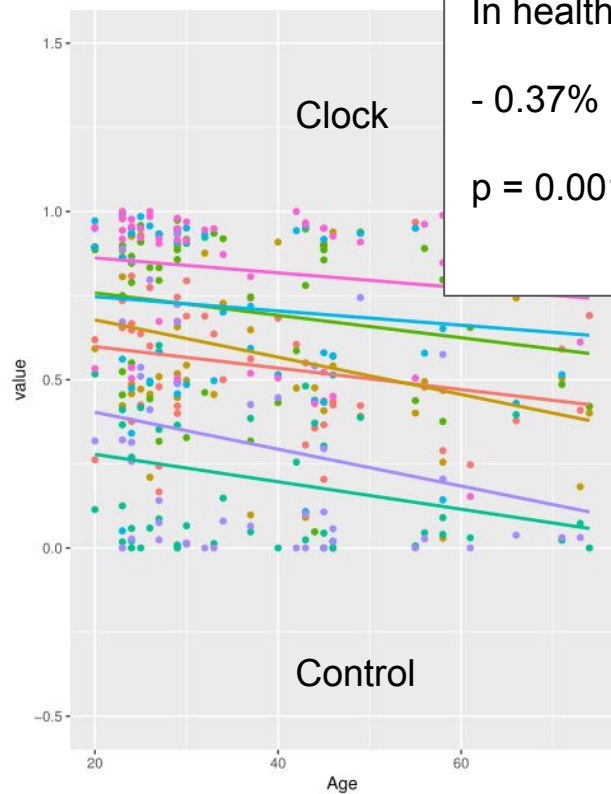


Differentially methylated sites
with $> 10\%$ diff, $p < 0.05$

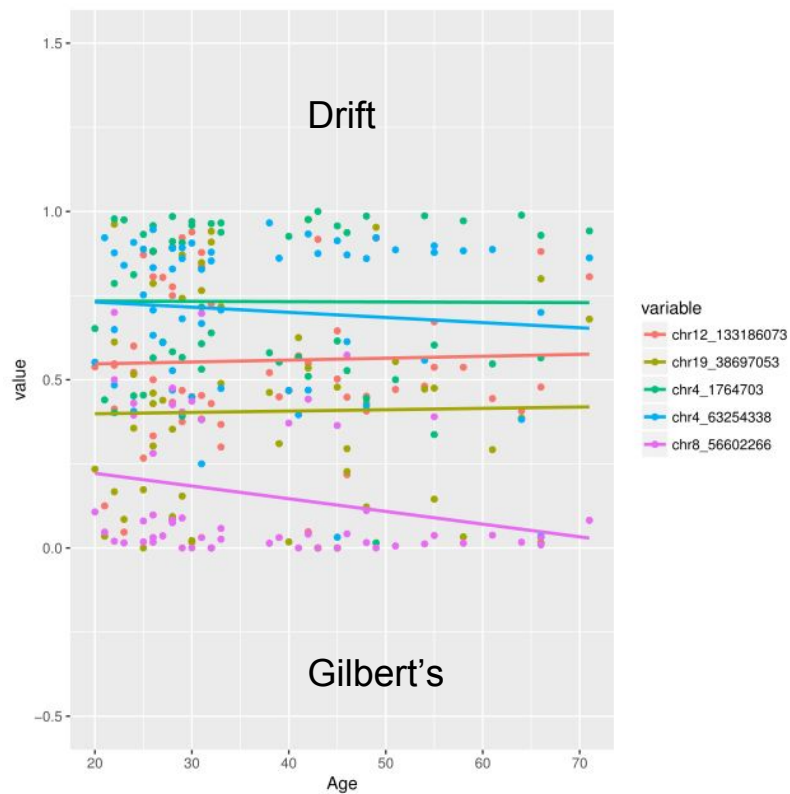
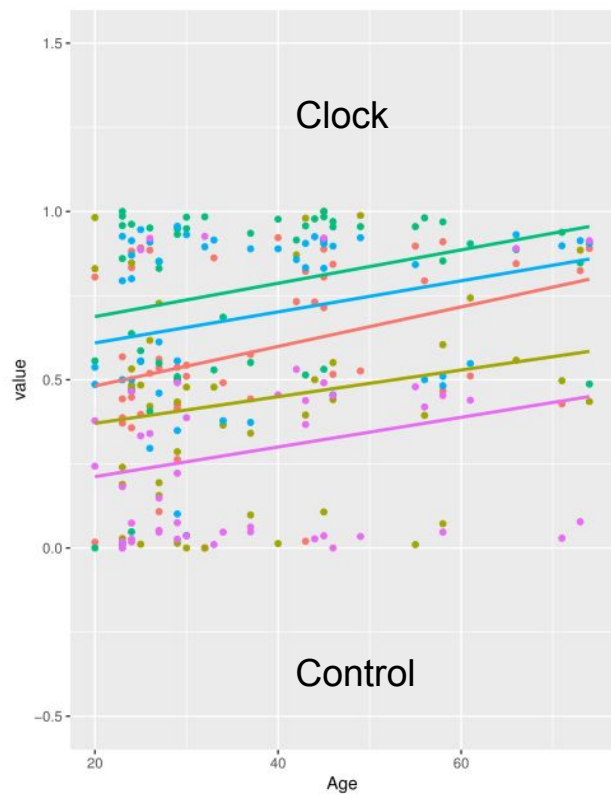
Hypomethylated sites with age



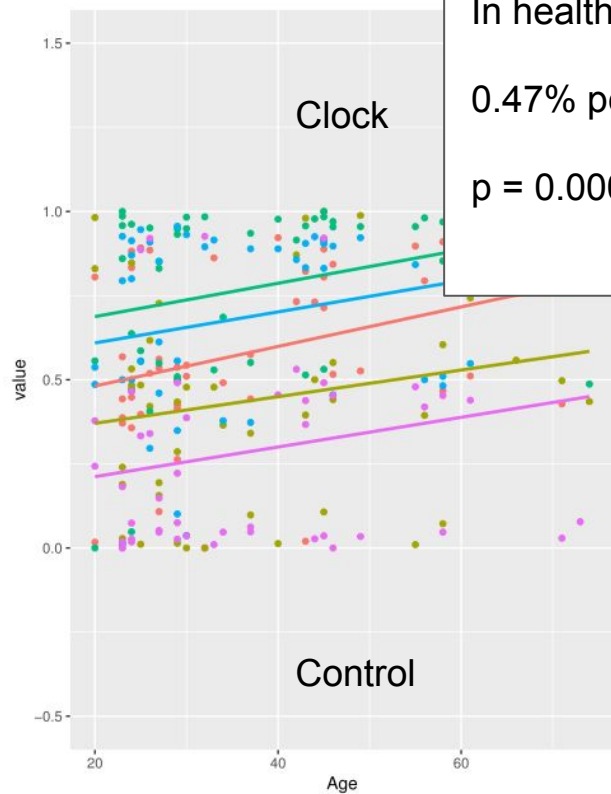
Hypomethylated sites with age



Hypermethylated sites with age



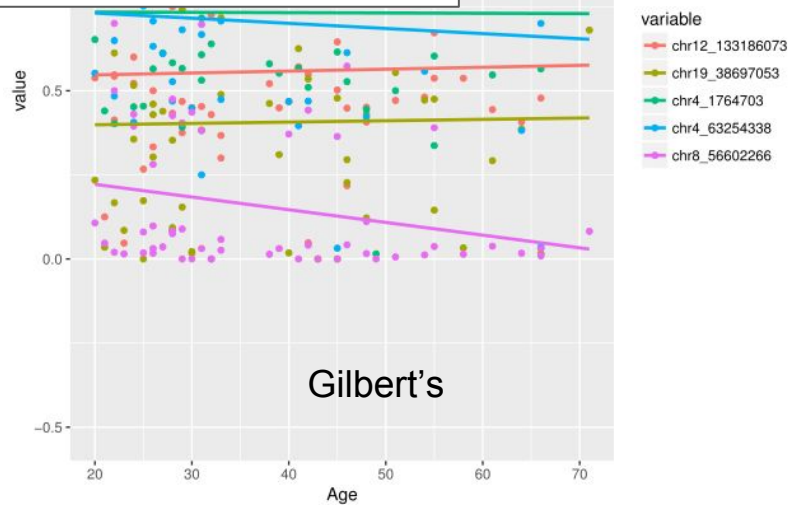
Hypermethylated sites with age



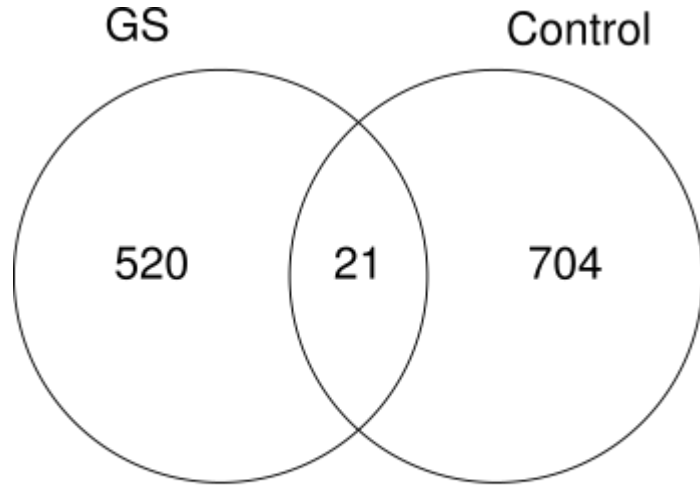
In healthy controls:

0.47% per year

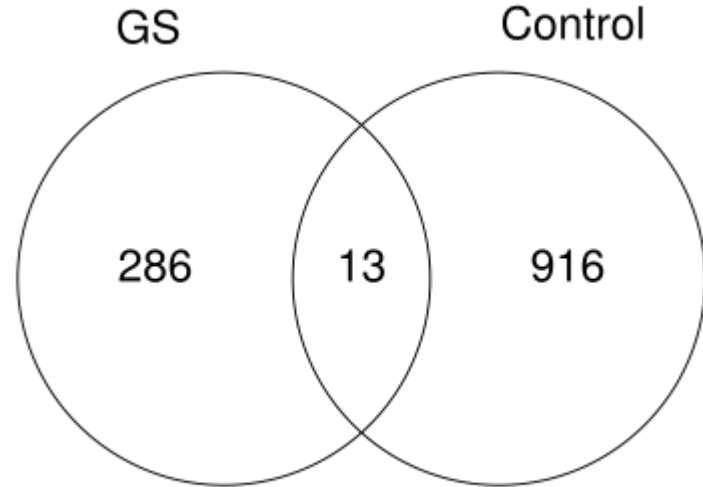
$p = 0.000629$



Overlap between clock CpG sites



Clock CpG sites
hypermethylated with age



Clock CpG sites
hypomethylated with age

Where are these sites located and what are their functions?

- Annotation in progress!!!
- No overlap with changes in RNA expression
- Only a very small fraction in gene promoter regions
- Many associate with gene bodies or lncRNAs
- High representation in transposable elements, especially Alu elements

Thanks!!!!

