



# Mapping Genetic Determinants of DNA Methylation Across Early Development

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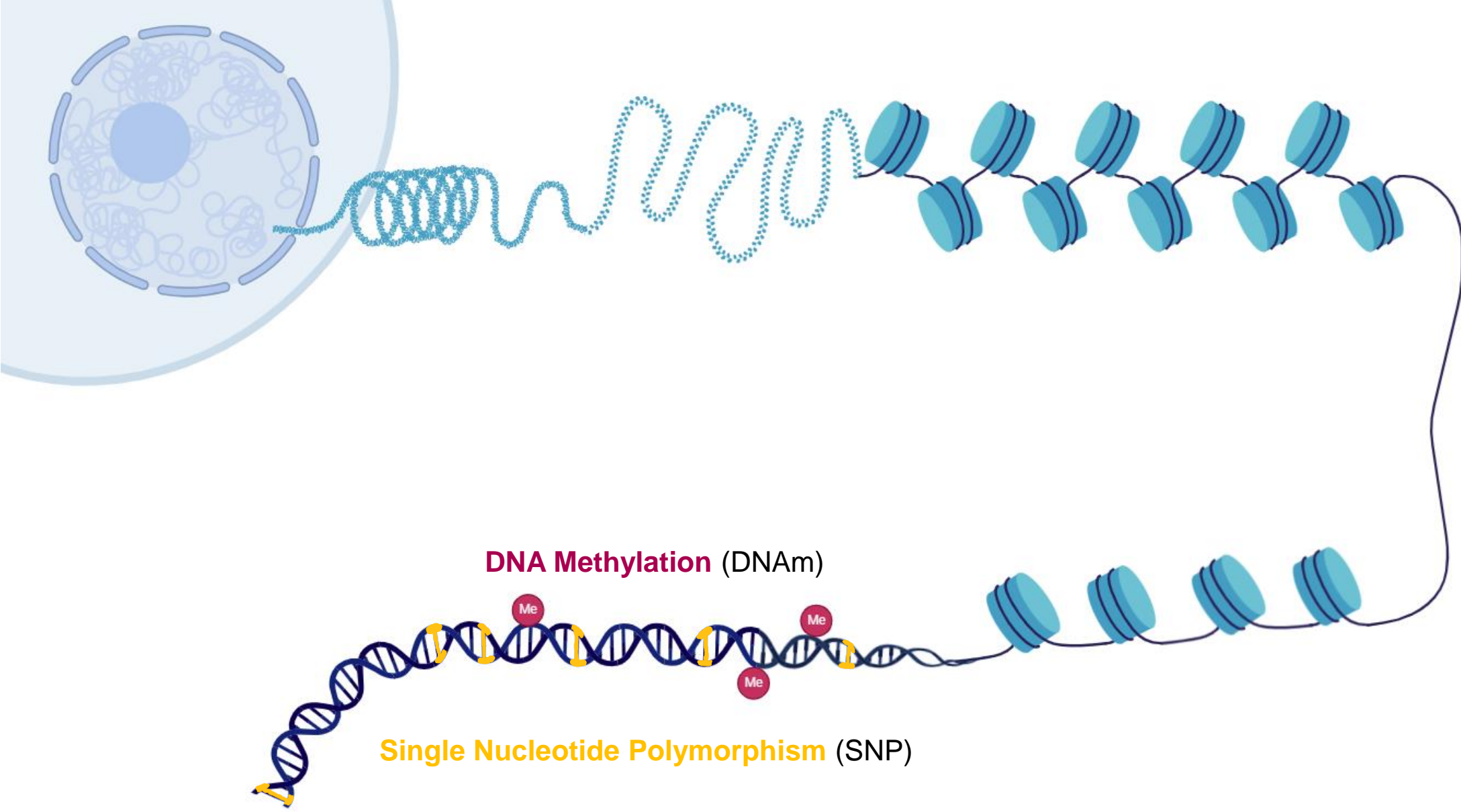
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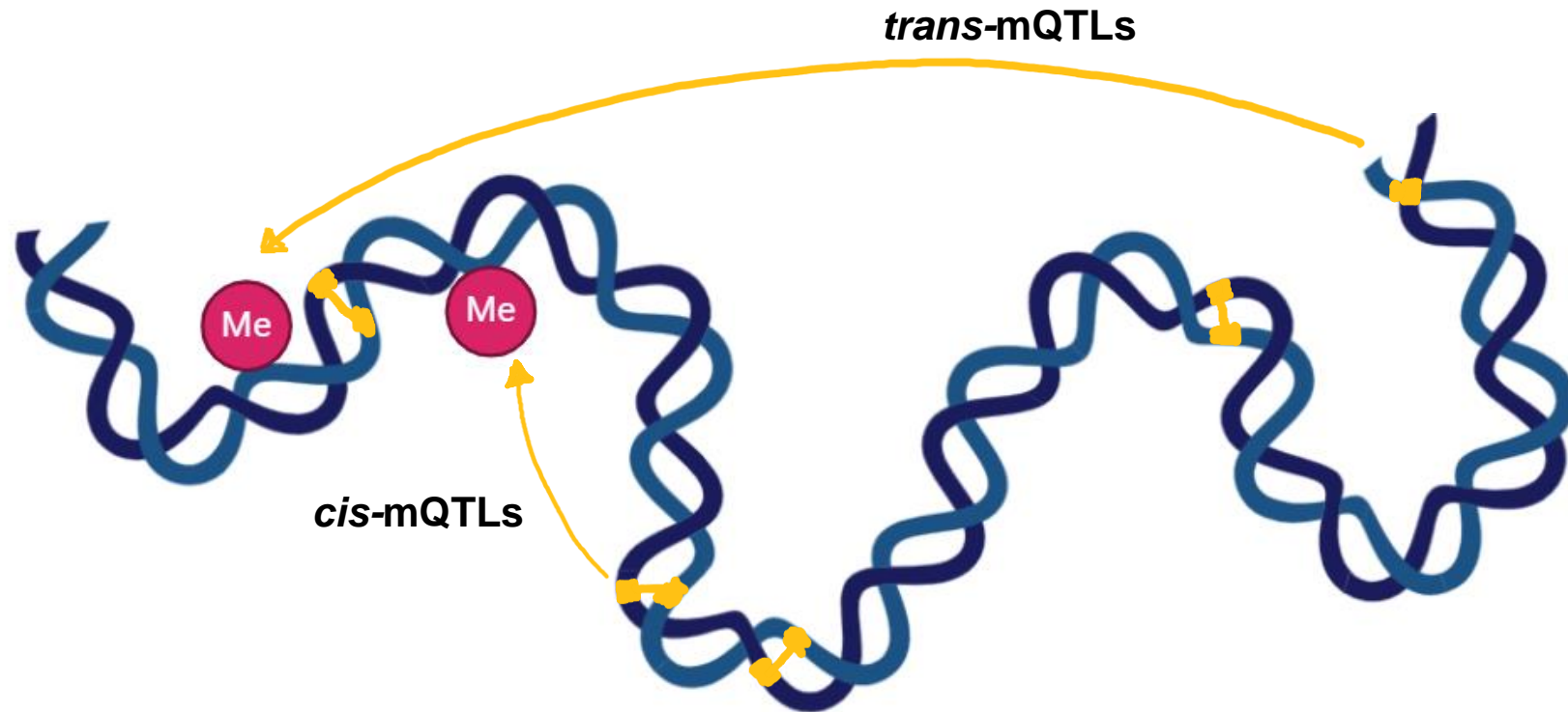


**DNA Methylation (DNAm)**

**Single Nucleotide Polymorphism (SNP)**



## Methylation Quantitative Trait Loci (mQTLs)



**Aim:** Characterize the genetic determinants of DNA Methylation patterns across early childhood

# The Drakenstein Health Child Study (DCHS)

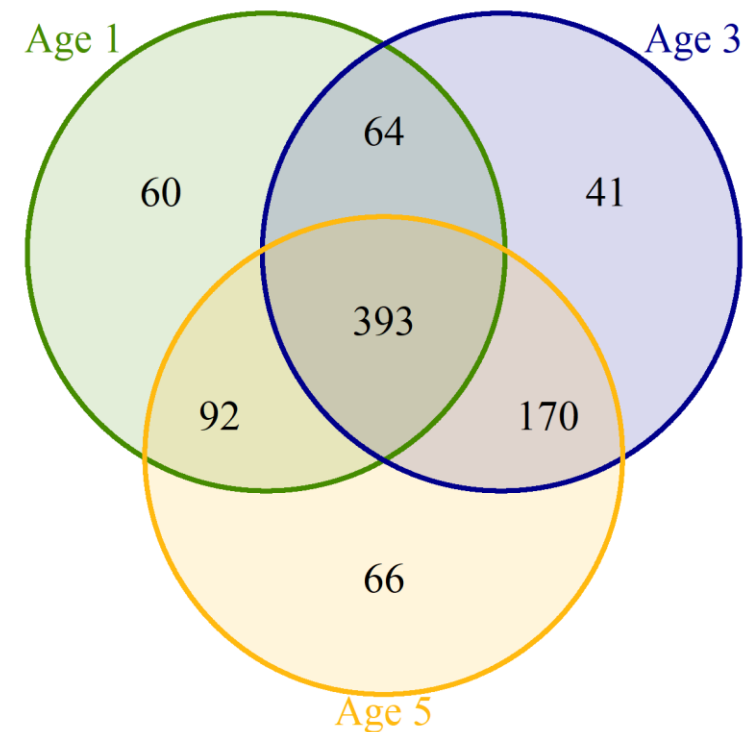


## ❖ Genetic data (SNPs)

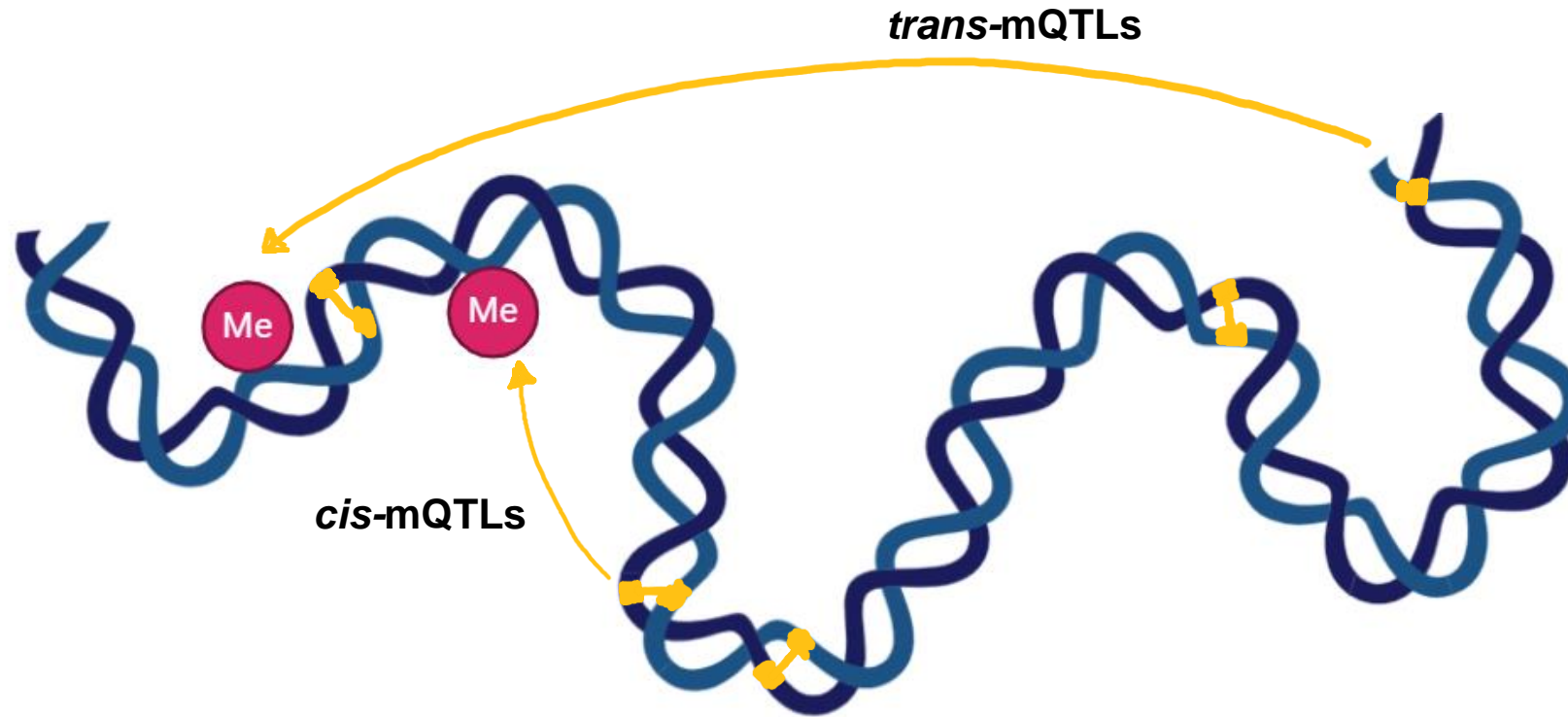
- Genotyped using the Illumina PsychArray and Global Screening Array
- > 6 million SNPs per sample

## ❖ Epigenetic data (DNAm)

- Repeated measures at ages 1, 3, and 5
- Epigenotyped using the Illumina EPIC v2
- > 900,000 CpG sites per sample

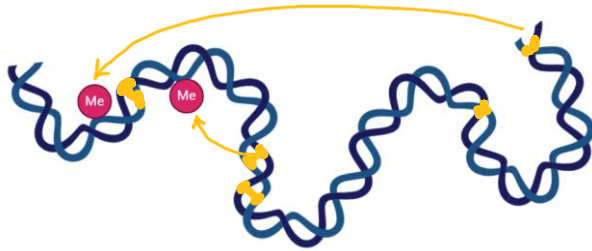


$$y_{DNAm} = \beta_0 + \beta_1 x_{SNP} + \epsilon$$

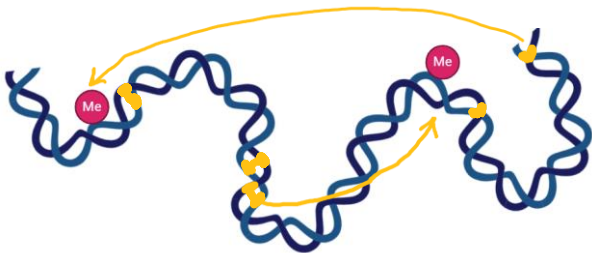


# Age-specific mQTL Analysis

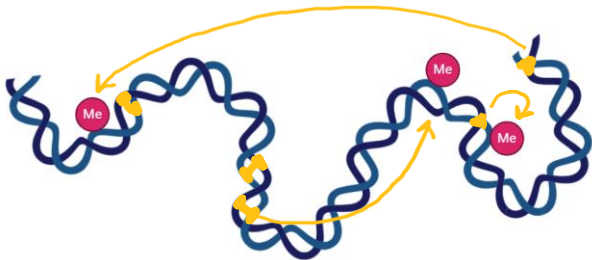
Age 1



Age 3



Age 5



## 1. Residualize beta values

Regress methylation state at each CpG site on covariates:

$$y_i = \beta_0 + \beta_1 Sex_i + [\beta_2 PC1_i + \dots + \beta_{11} PC10_i] + \beta_{12} Batch_i + \beta_{13} Site_i + [\beta_{14} CellProp1_i + \dots + \beta_{19} CellProp6_i] + \beta_{20} Smoking_i + \epsilon_i$$

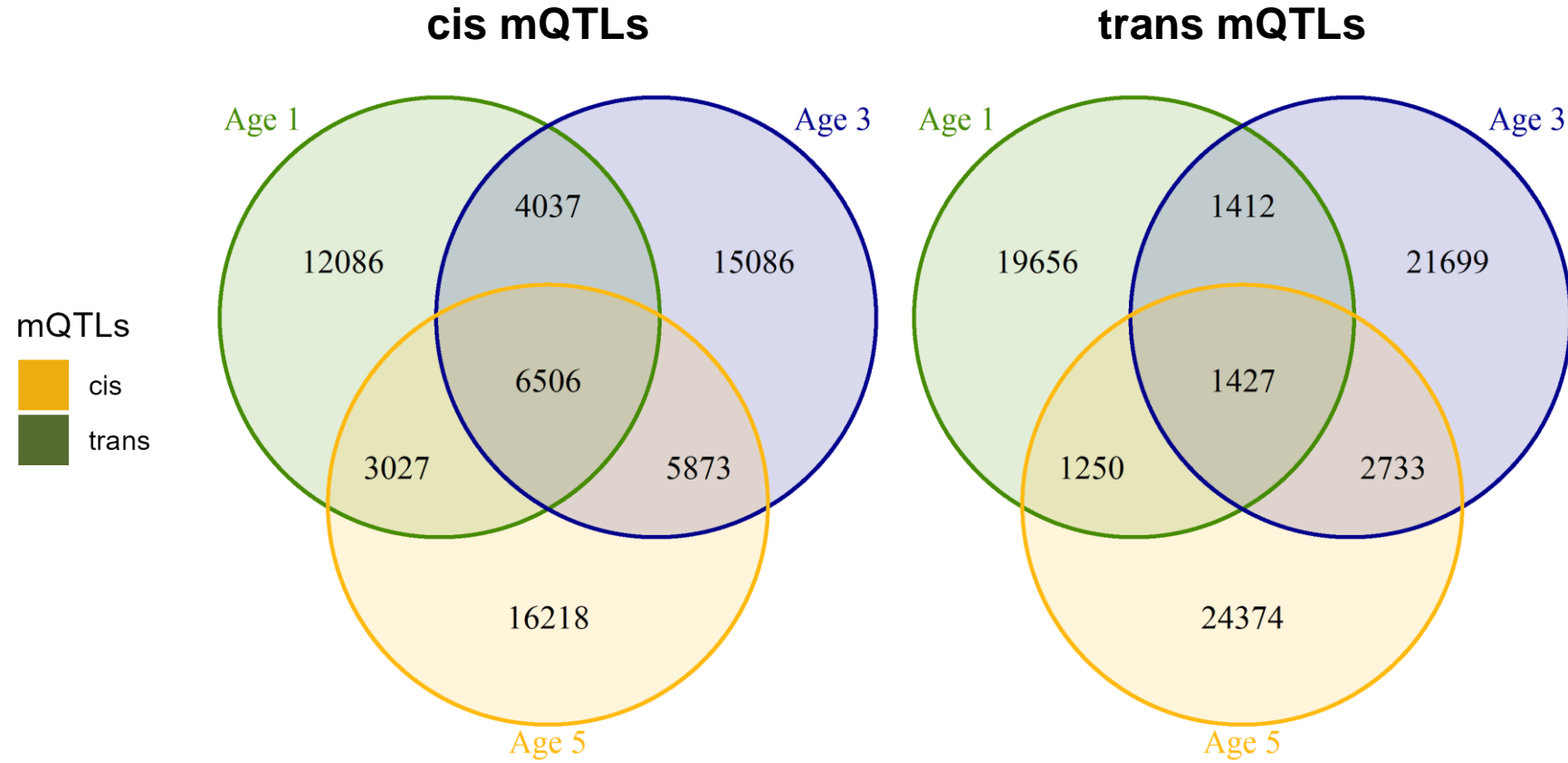
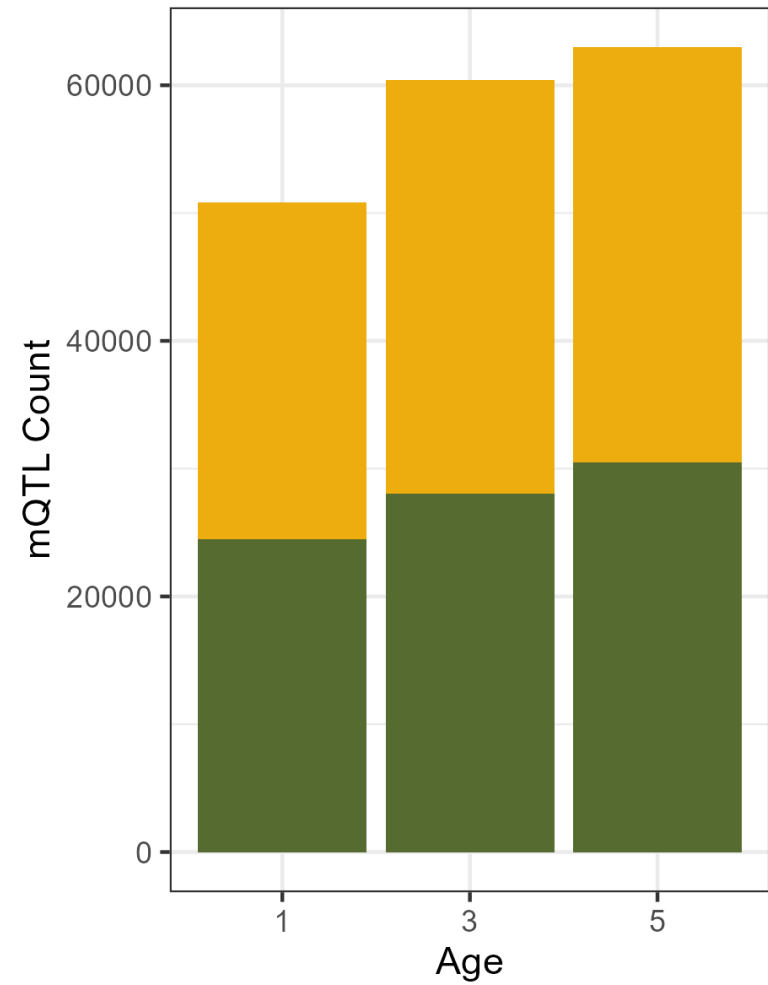
Where the residual beta value for each individual  $i$  is  $r_i = y_i - \hat{y}_i$ .

## 2. Association test

$$r_{ei} = \beta_0 + \beta_1 x_{gi} + \epsilon_{egi}$$

Where for each CpG site  $e$ , the residual beta value  $r_{ei}$  in individual  $i$ , is regressed against each SNP,  $g$ .

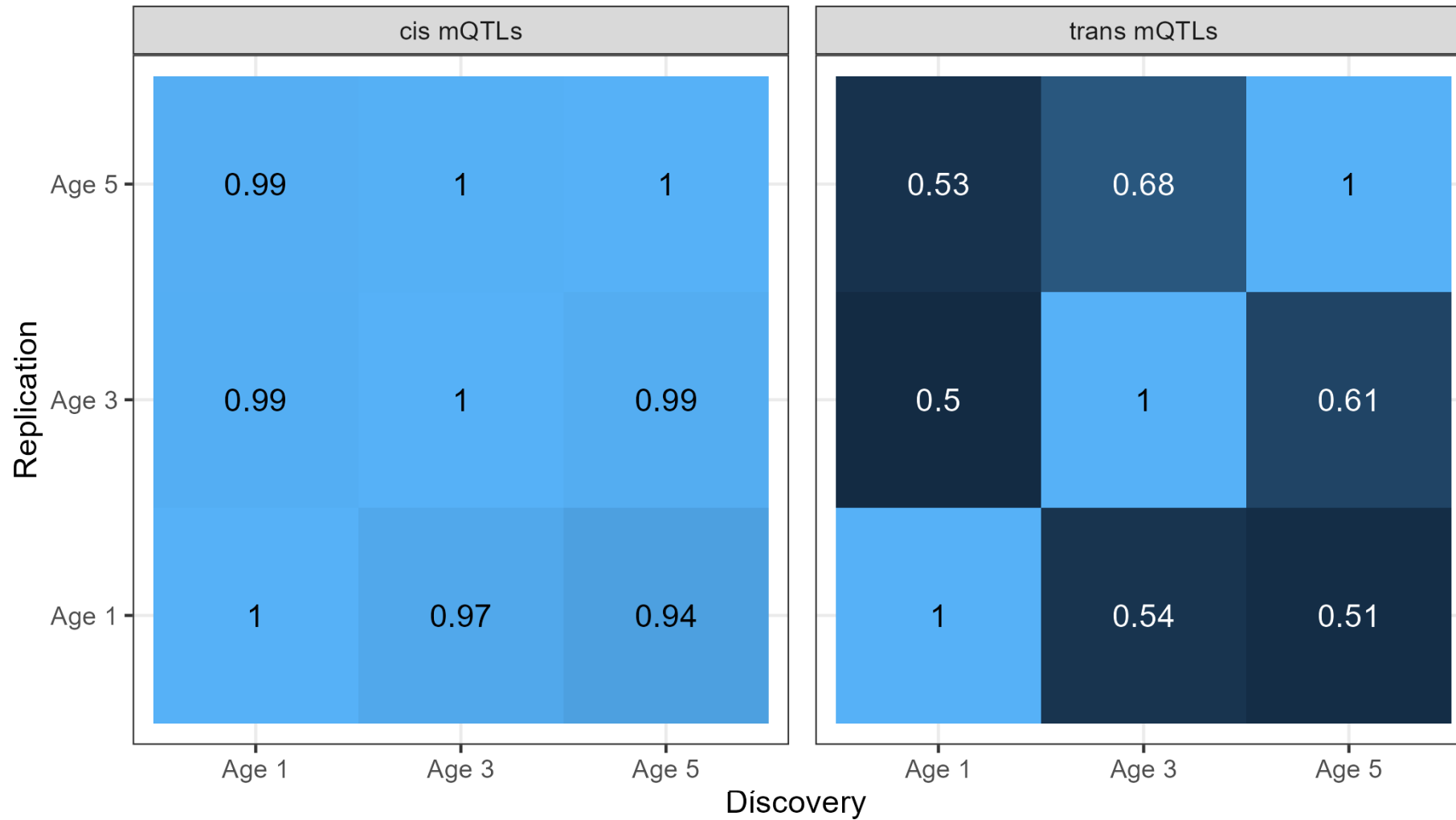
# Identifying *cis*- and *trans*-mQTL associations across timepoints



Conditionally independent SNP-CpG pairs with p value  $< 1e-14$



# Replicating *cis*- and *trans*-mQTL associations across timepoints



**Age-specific effects**  
in trans-mQTLs?

Replication in additional time points with  $p$  value  $< 1e-7$





## Conclusions

- ❖ **cis-mQTL** effects appear **mostly stable** throughout early development
- ❖ A high proportion of **trans-mQTLs** shows **age-specific effects** throughout early development

## Next..

- ❖ Further **characterizing** stable and age-specific mQTL effects
- ❖ Investigating **longitudinal mQTL effects**
- ❖ Creating a publicly available **DCHS mQTL database**



# Thank you!



**Prof Dr Andrew J. Simpkin** | University of Galway, Ireland

**Prof Dr Erin C. Dunn** | Purdue University, IN, USA

**Dr Alexandre A. Lussier** | Massachusetts General Hospital, MA, USA  
& the whole R01 team!

**Dan J. Stein, Heather J. Zar, Marilyn Lake** & the whole DCHS team!

CRT for Genomics Data Science, Ireland



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Some figures in this presentation were created with BioRender.com.