Genome-wide association study of inflammatory proteins in ALSPAC Mothers and offspring

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University of BRISTOL

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Background

- pQTL - protein Quantitative Trait Loci, which are robust connections between a gene variant and the levels of a protein
- 2 main proteomic platforms – Olink and Somalogic

somalogic

Olink

- UKBB – 3,000 proteins; 54,219 participants (Olink)

Plasma proteomic associations with genetics and health in the UK Biobank

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Most studies have just looked at one timepoint in adults

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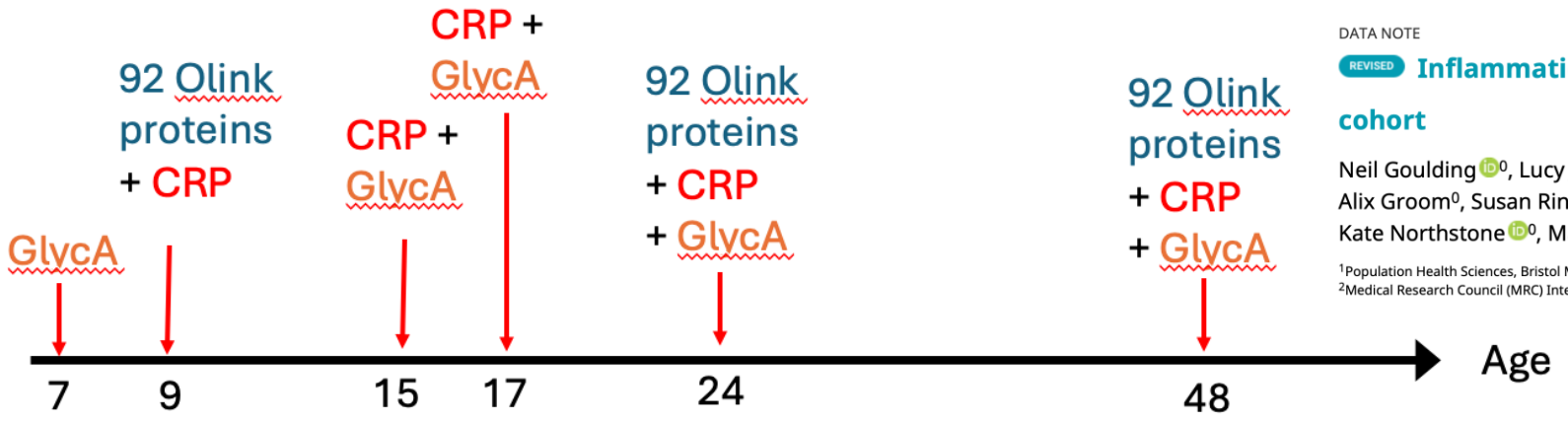
ALSPAC

- Avon Longitudinal Study of Parents and Children – also known as Children of the 90s
- Genetics - dataset contains > 8 million SNPs
- Proteomics - 3000 mothers, 3000 9-year-olds and 3000 24-year-olds
- 92 inflammatory proteins - Olink target 96 inflammatory panel



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Check for updates

DATA NOTE

REVISED **Inflammation proteomics datasets in the ALSPAC cohort**

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Aims

1. Identify pQTL across the lifecourse (ages 9, 24 and 48)
2. Which pQTL are robust across the lifecourse?
3. What proportion of UK Biobank pQTLs replicate at each of the three ALSPAC timepoints?
4. Investigate the relationship of pQTL with downstream phenotypes (e.g. asthma) at each timepoint

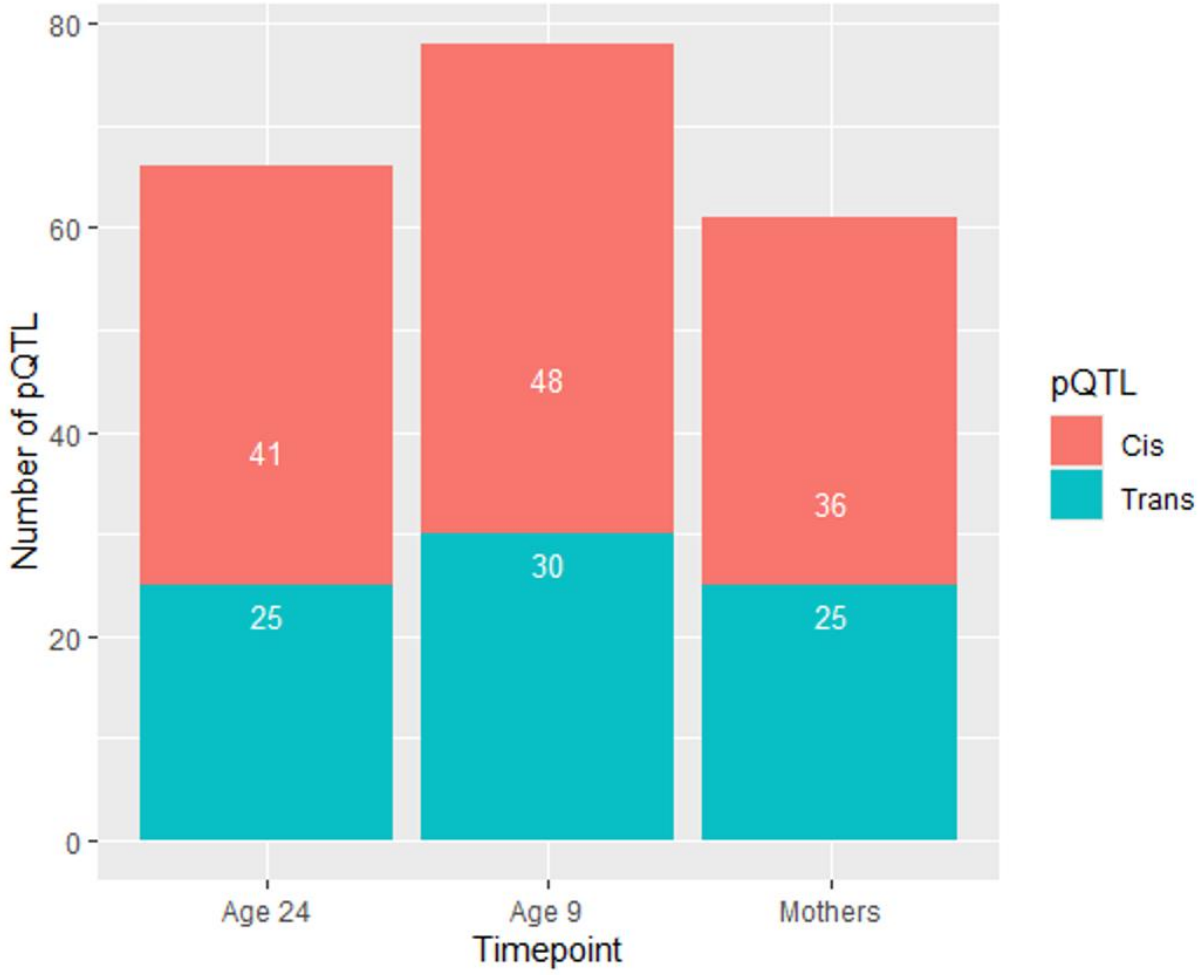
- **This talk will focus on aims 1 and 2**

Methods

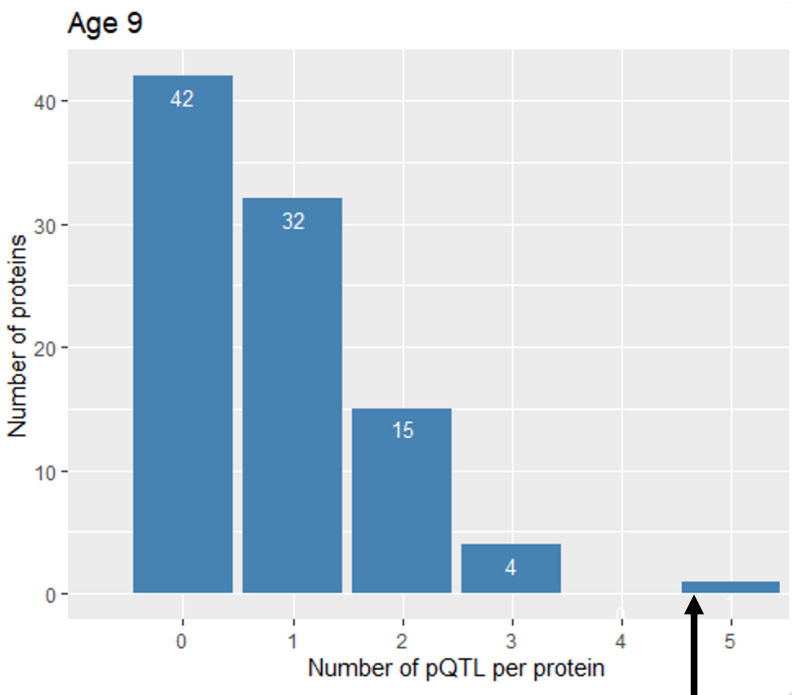
- Genome-wide testing performed using PLINK 2.3, fitting linear regression models between protein levels and 1000 Genomes imputed SNPs.
- Adjusted for age, sex and the top 10 genetic principal components.
- Extracted pQTLs with $p < 5.3 \times 10^{-10}$, which is the threshold of genome-wide significance (5×10^{-8}) adjusted for multiple testing (94 proteins).
- For each of the proteins there is a protein-coding gene. We defined associations with independent SNPs within 1 million base pairs (1 Mb) window of the gene boundaries of the protein-coding gene as *cis*-signals, and otherwise in *trans* (***except GlycA***)
- Clumped $\pm$ 1MB around leading variants using PLINK

Results – total number of pQTLs

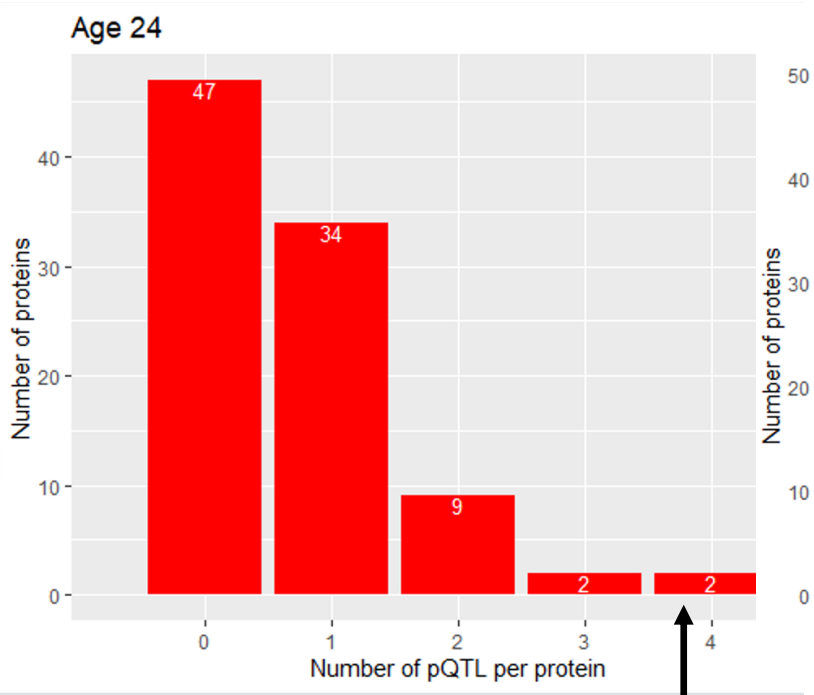
- After clumping – 205 pQTL in total across all 3 timepoints (61% cis)
- Most pQTLs at age 9
- 59%-61% cis-pQTL at each timepoint
- N = 2426 (age 9)
- N = 2170 (age 24)
- N = 2120 (mothers)



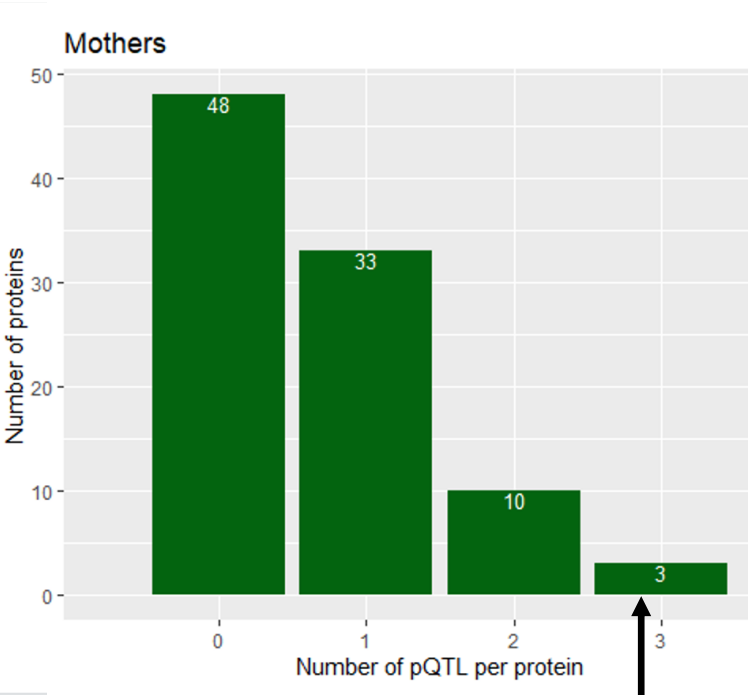
Number of pQTLs per protein



CCL25



CCL25, MMP1



CCL25, CD8A, MCP4

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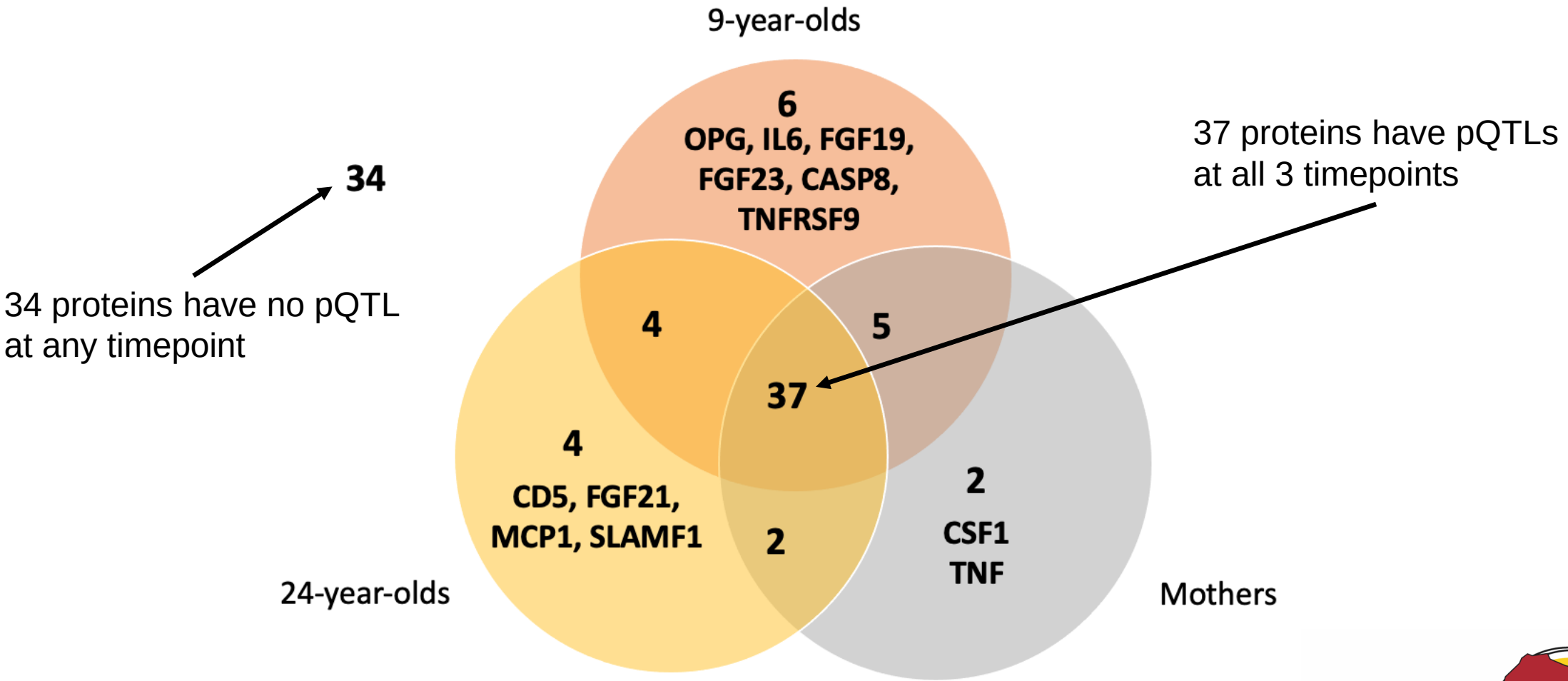
Results 3



Venn diagram of proteins that have pQTLs at each timepoint

Conclusions and Further Work

- Many of the proteins have pQTL that are robust across the lifecourse
- We have also found pQTL unique to each time point
- Is genetic architecture across development more complicated than initially thought?
- Next step - replication in UKBB
- Investigate the relationship of pQTL with downstream phenotypes (e.g. asthma) at each timepoint

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