Epigenetic programming contributes to resistance to *M. tuberculosis*

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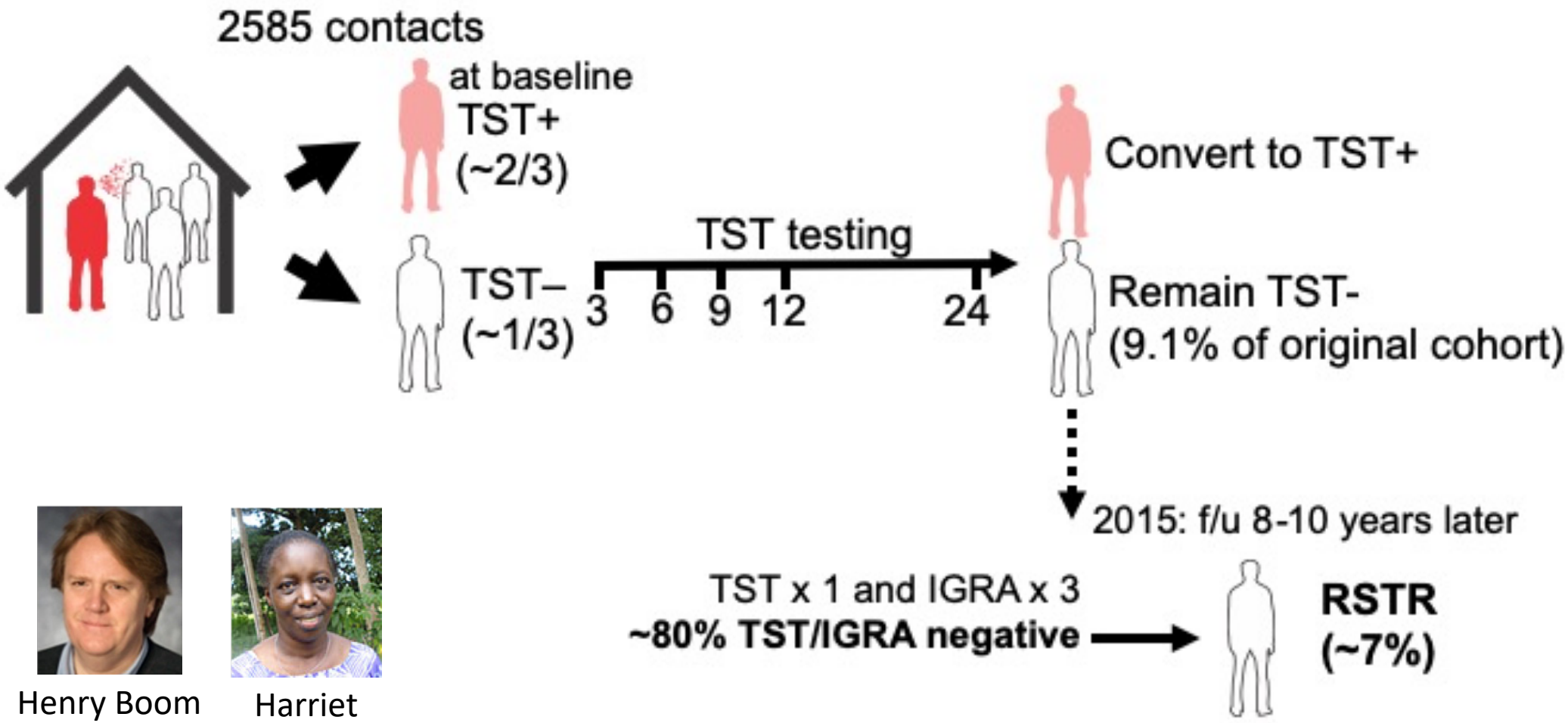
Hawn lab · Jan 29, 2021

Tuberculosis is the leading cause of infectious disease death worldwide

How do we better treat and prevent TB infection?

Uganda household contact study



Cathy Stein

Henry Boom

Harriet Mayanja-Kizza

Case Western

Makerere U

RSTR: Resister

- highly exposed to TB but by available measures, remains uninfected for many years

LTBI: latent TB infection

- infected with TB but not actively manifesting symptoms

Epigenetics

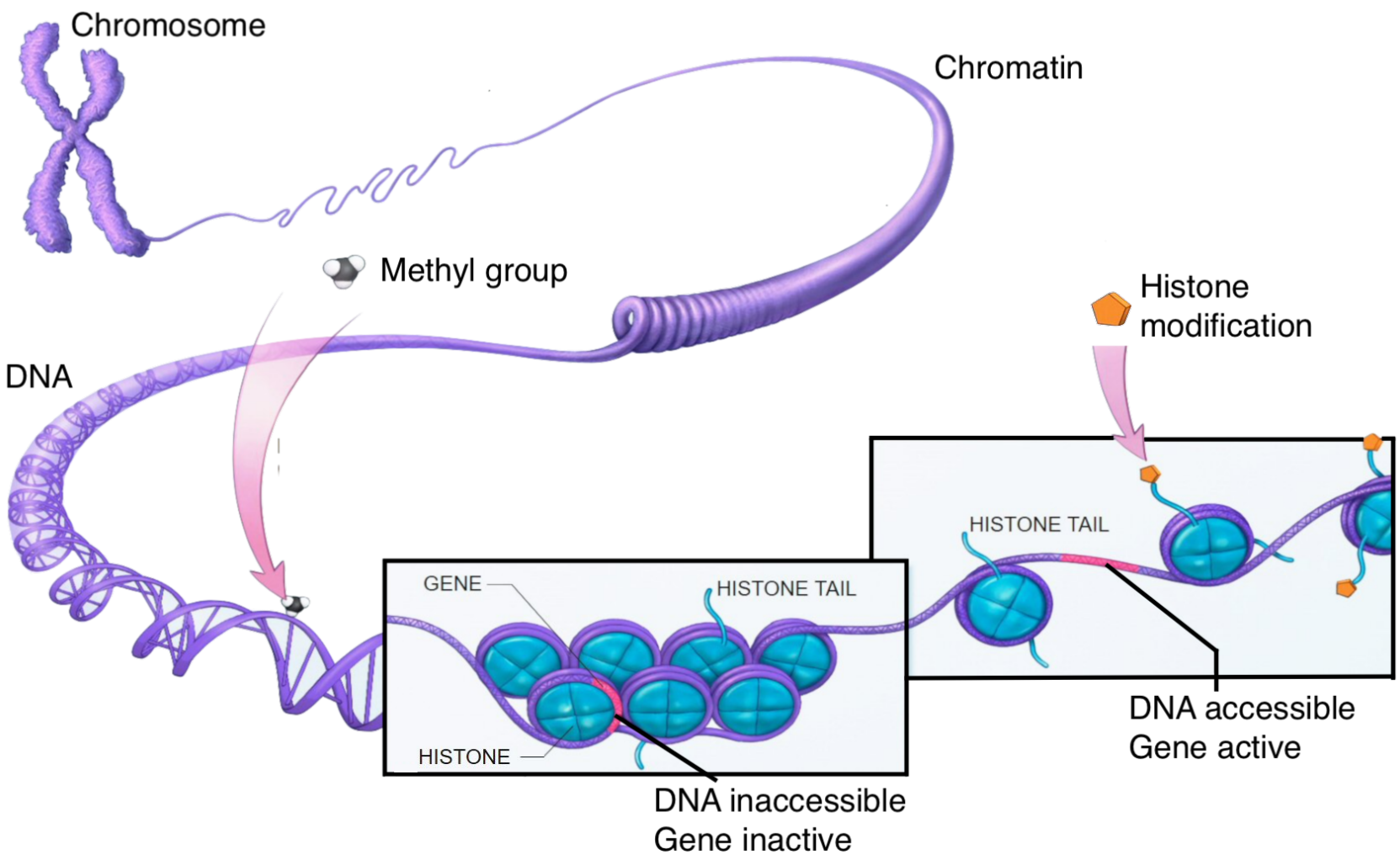
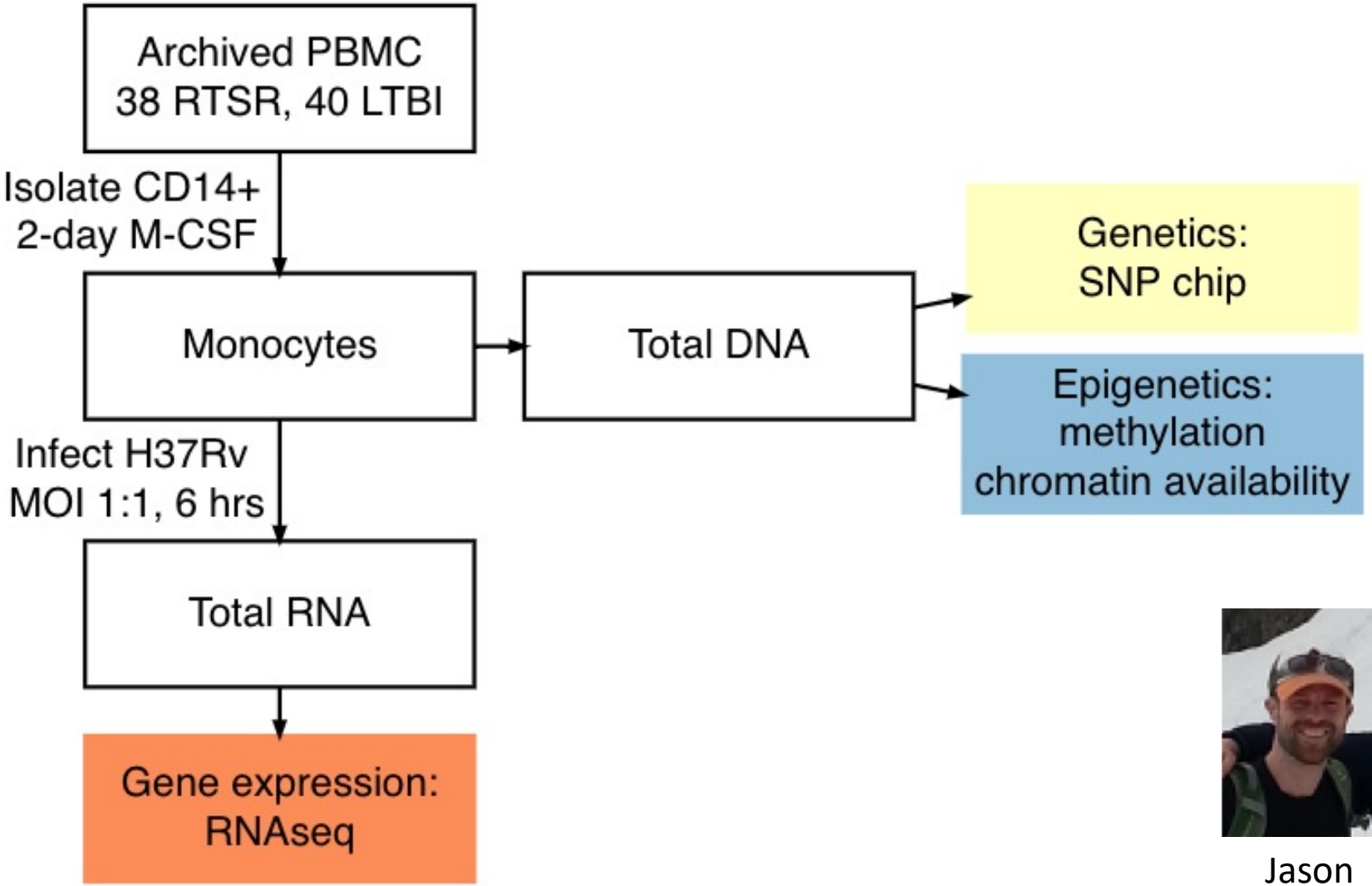


Image modified from NIH

Design



Jason Simmons

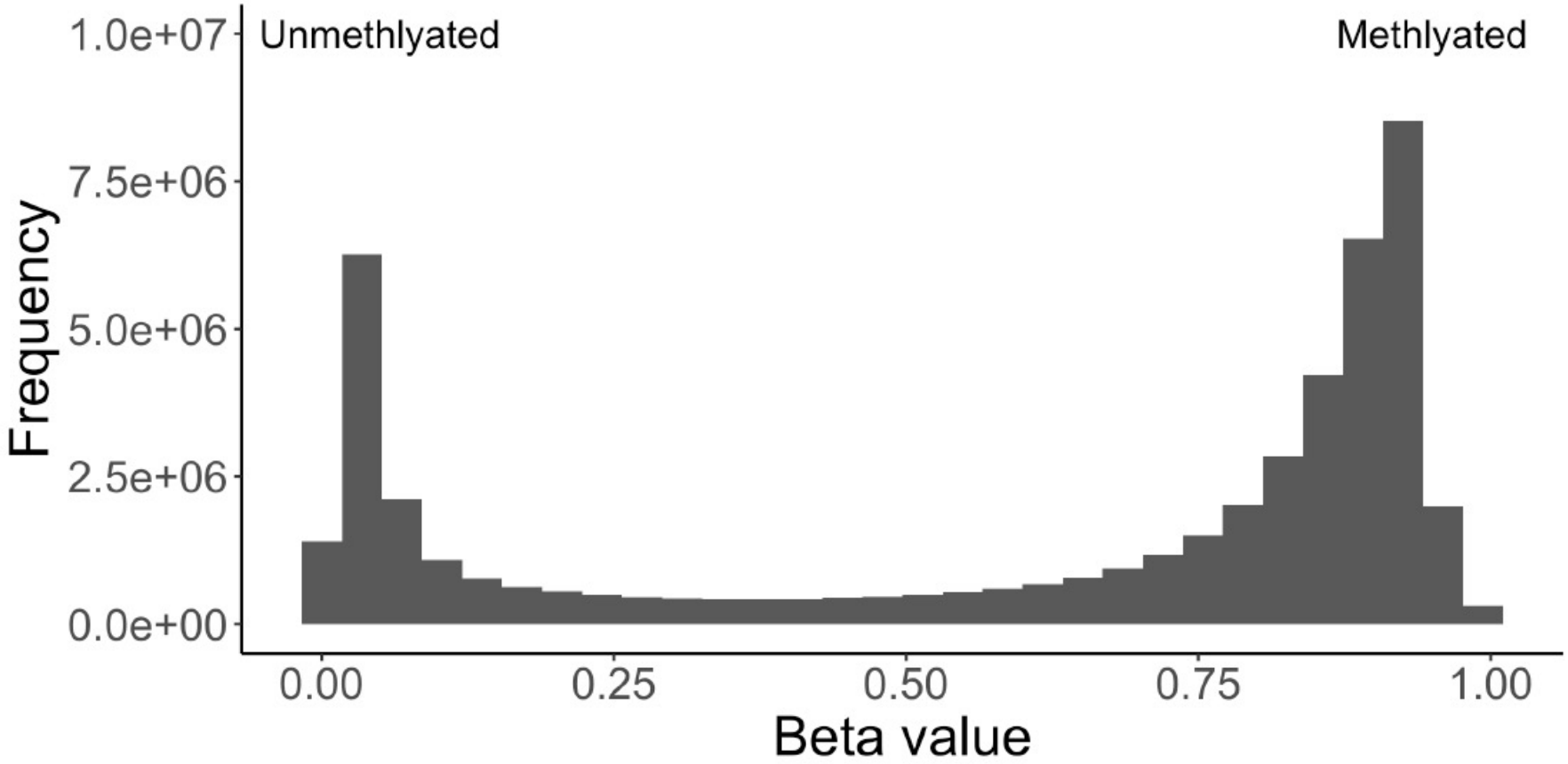
Glenna Peterson

Methylation data

- Illumina Infinium MethylationEPIC arrays I and II

- 865,918 probes across genome
  - CpG sites and CpG islands
  - Differentially methylated sites identified in tumor versus normal
  - FANTOM5 enhancers
  - ENCODE open chromatin and enhancers
  - DNase hypersensitive sites
  - miRNA promoter regions

Methylation data



Proportion of reads from methylated beads

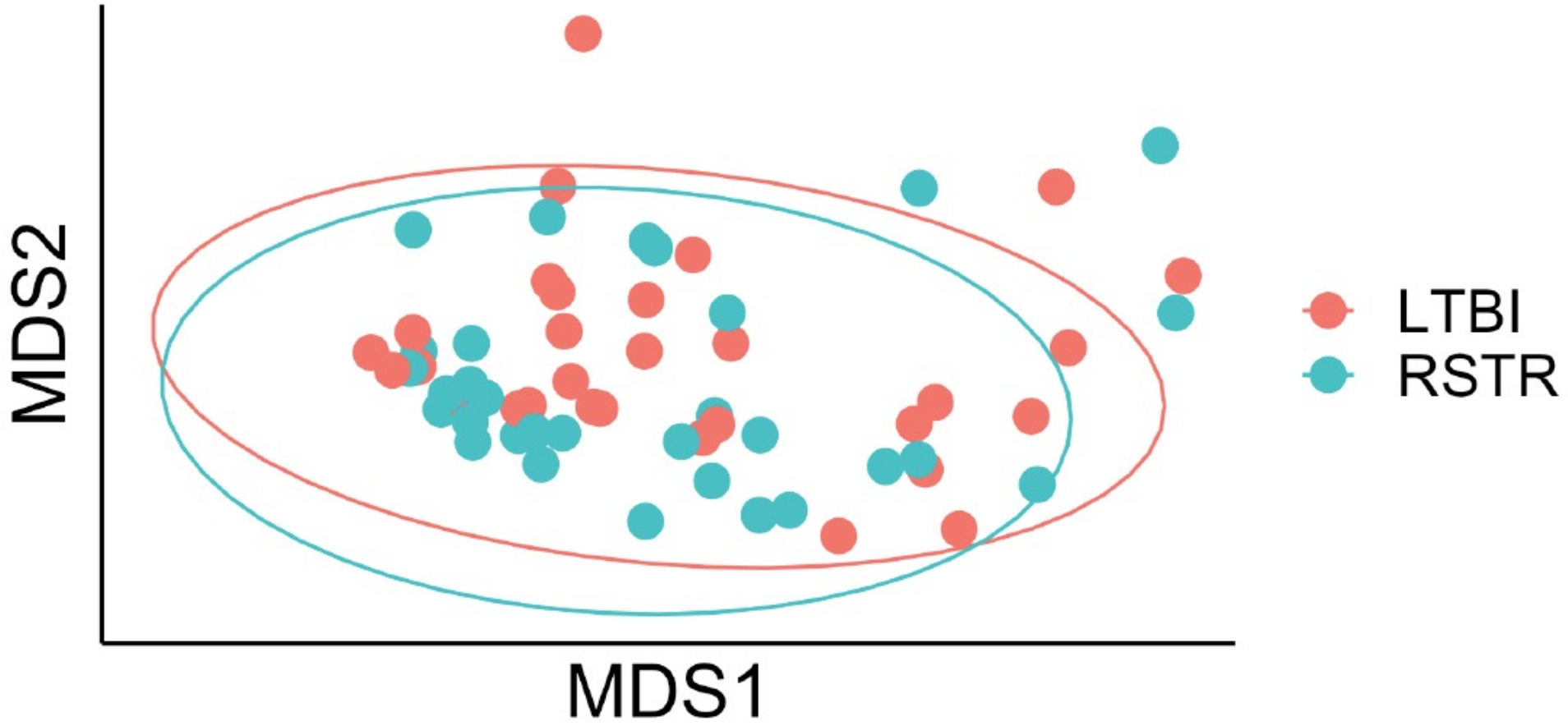
Methylation data

1. Data cleaning
   - Quality-filter (N = 728,380)
   - Normalize, log2 transform

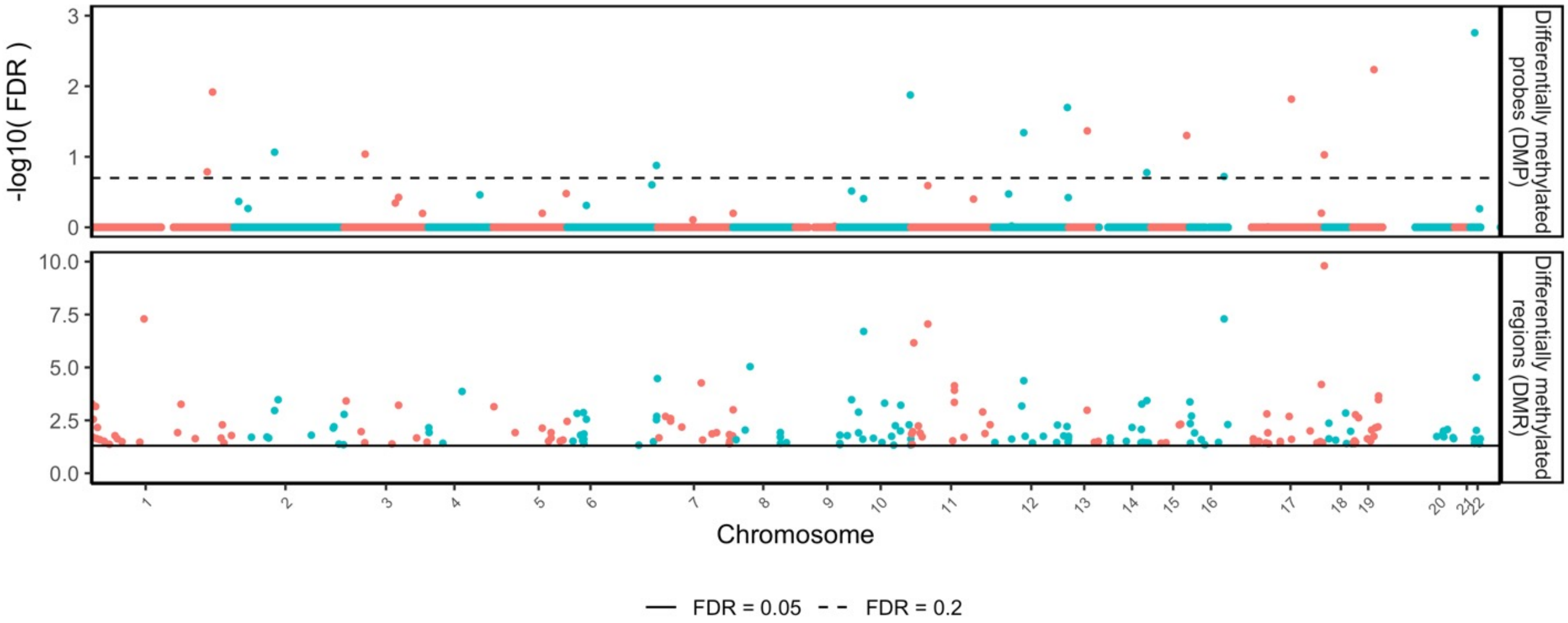
2. Model selection
   - Co-variates age, sex, BMI, TB risk, BCG, family blocks, kinship
   - `~ RSTR + age + sex + kinship + (1 | donor)`

Do overall methylation profiles differ between RSTR and LTBI?

Overall methylation



Do individual methylation sites differ between RSTR and LTBI?



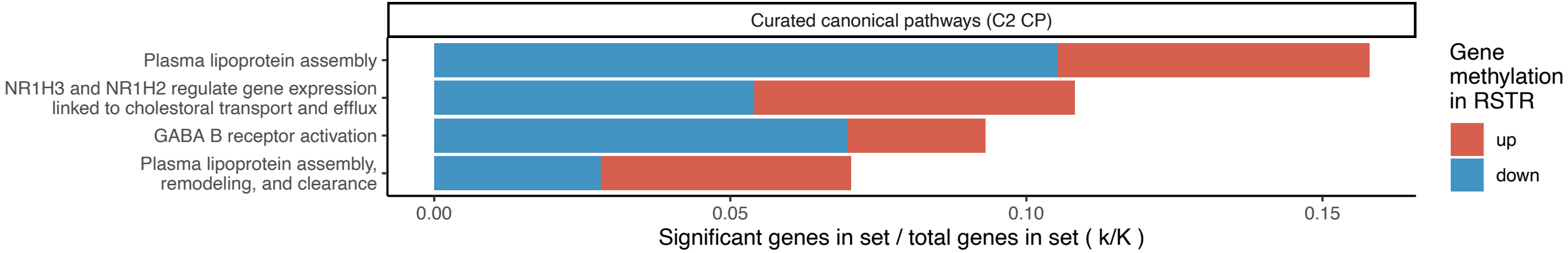
DMRcate https://doi.org/10.1186/1756-8935-8-6

Significant genes

	Hits	Unique genes*	Unique genes in HGNC	Unique genes in ENTREZ	Unique genes in STRING
DMP + DMR	16 + 221	305	261	253	157

*Annotations include intron, exon, untranslated region (UTR), or promoter as defined as within 1500 bp of the transcription start site (TSS)

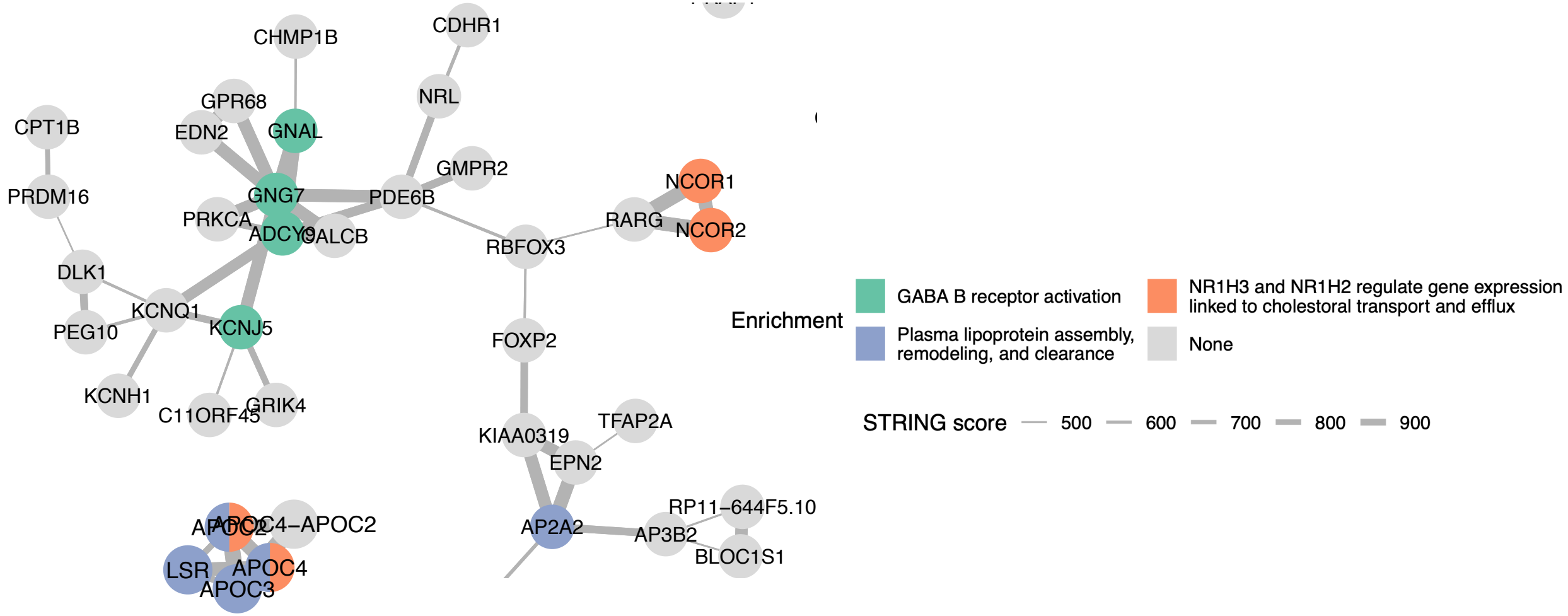
Significant gene enrichment



- Hypergeometric enrichment of Broad gene sets
  - hallmark, canonical pathways, gene ontology

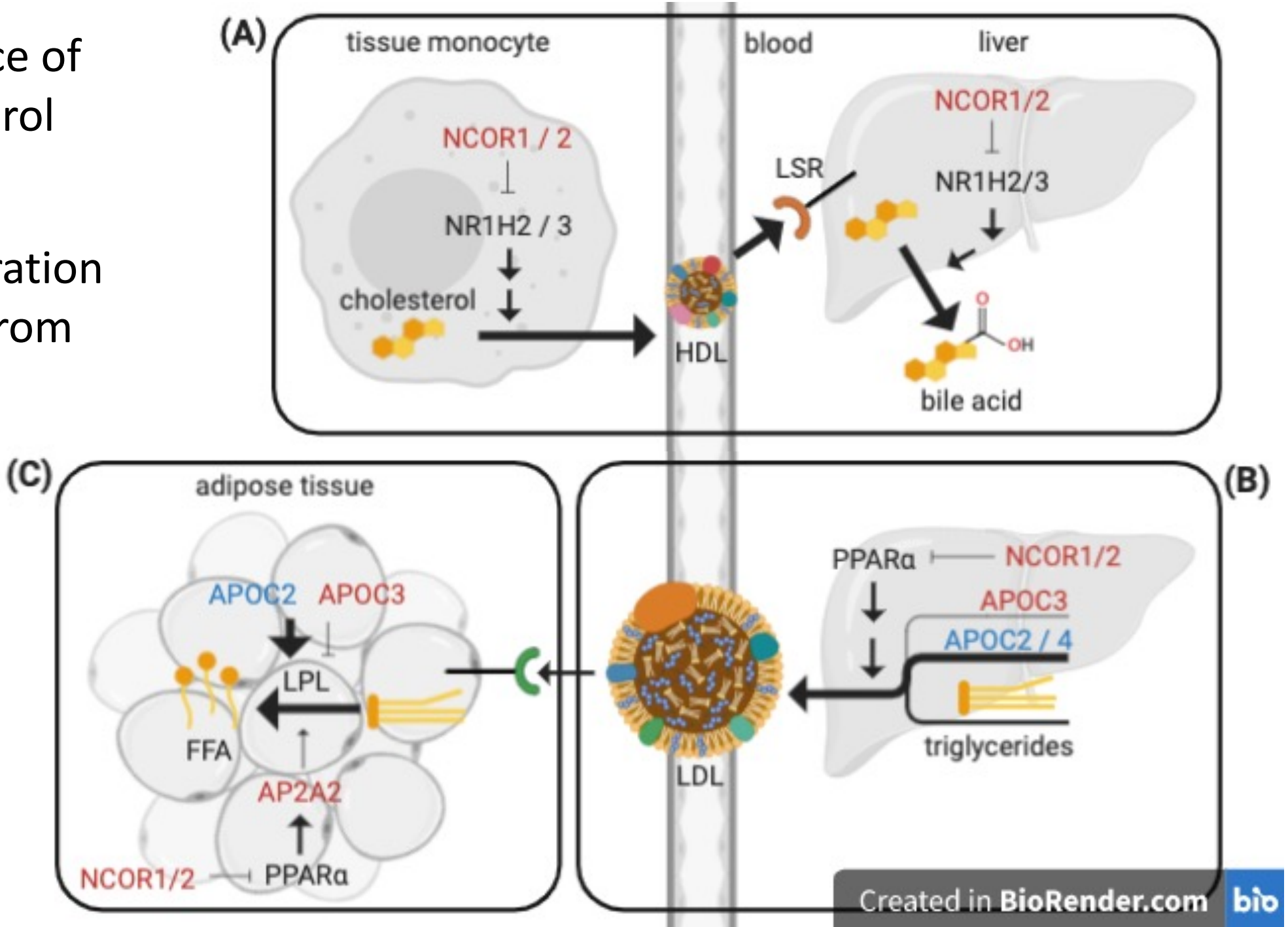
- k = proportion of genes in a Broad set that overlap with DMP or DMR genes
- K = total genes in Broad gene set

Significant gene enrichment



Higher clearance of excess cholesterol by RSTR?

Better sequestration of lipids away from M.tb in RSTR?



Lipoprotein next steps

Collaboration with Tomas Vaisar, Andy Hoofnagle, Daniel Raftery

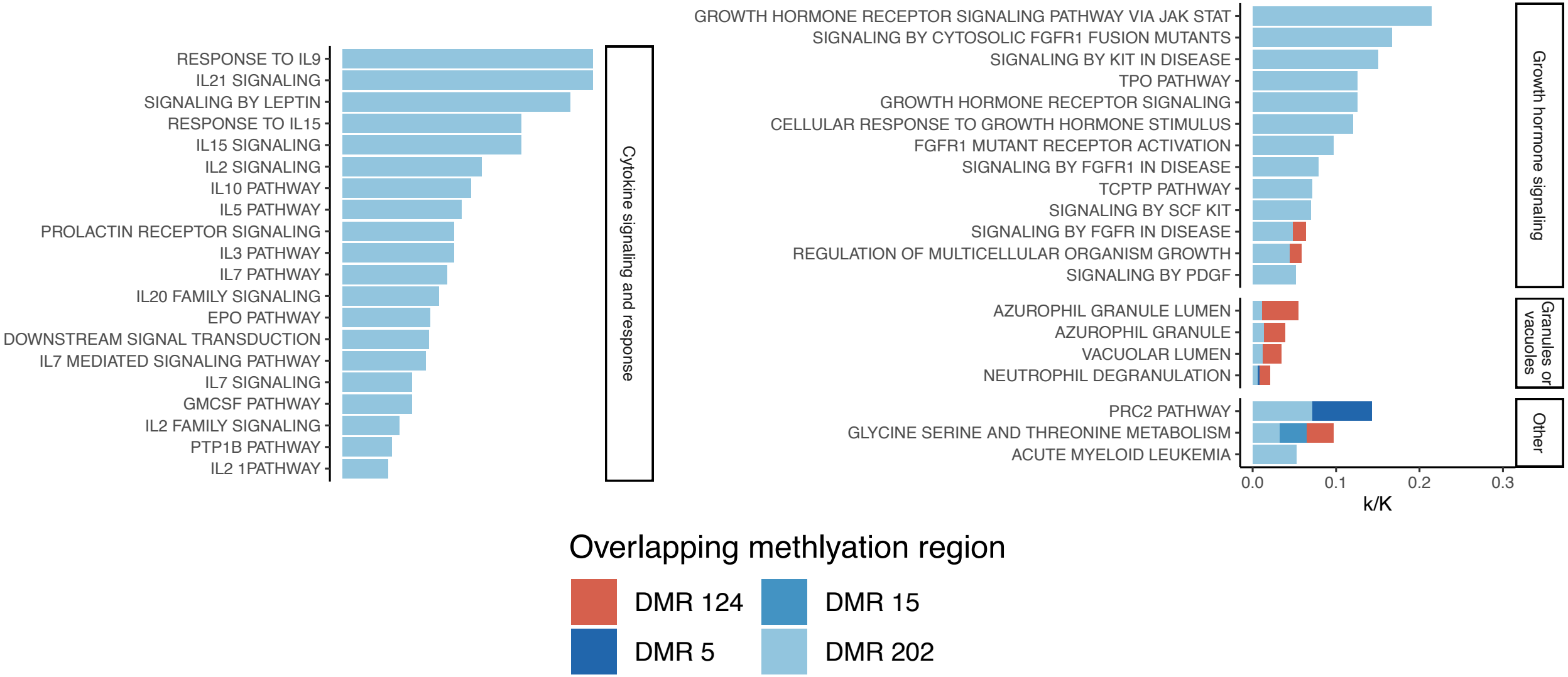
RSTR vs LTBI serum

- Proteomics and lipidomics of high-density lipoproteins (HDL)
- Cholesterol efflux capacity

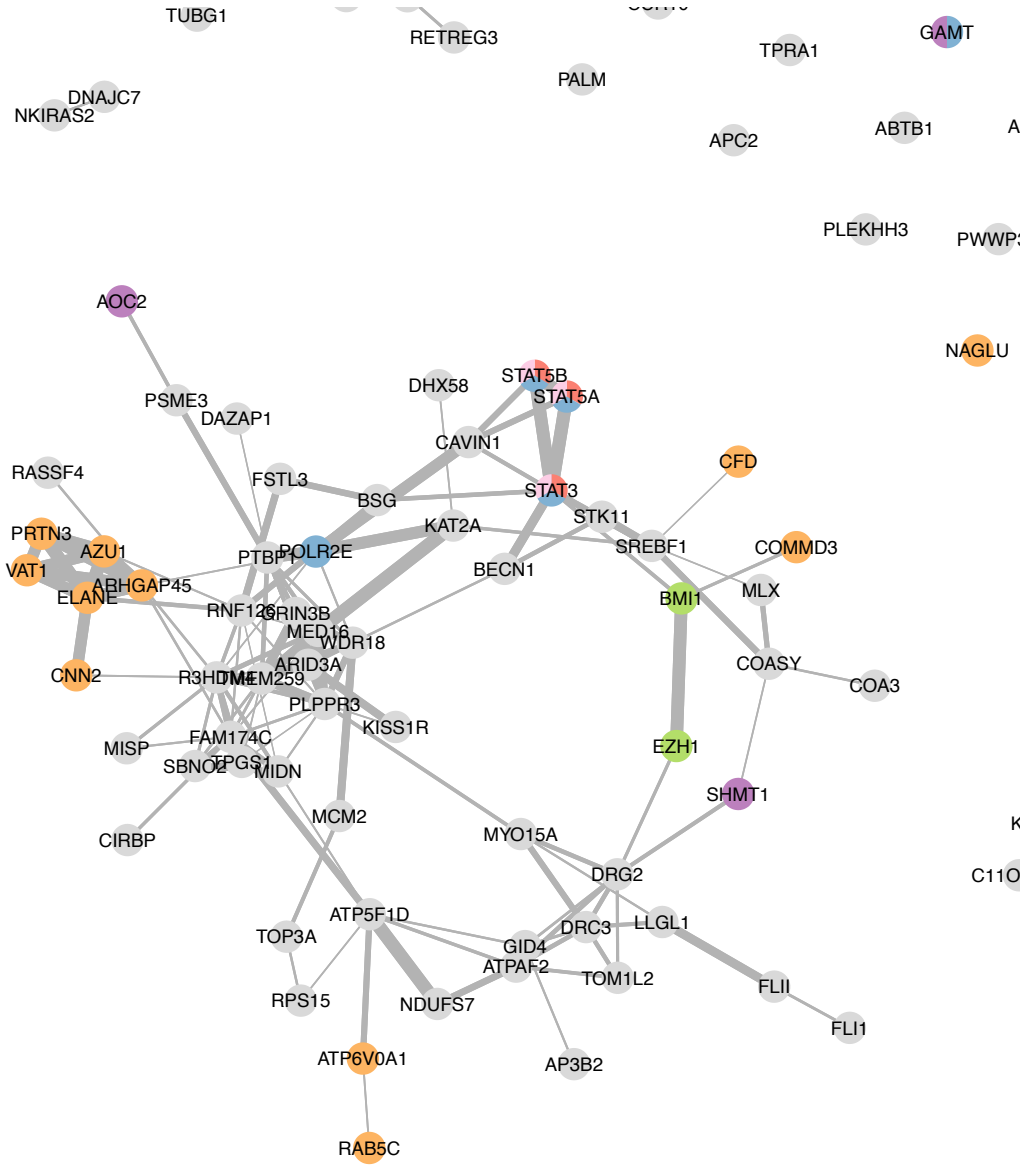
Enhancer regions

- Intergenic regions known to regulate gene expression (Gao *et al* 2016 EnhancerAtlas)
- 10 DMR overlapped with 10 enhancer regions in CD14+ cells
- These enhancer regions correspond to 118 *potentially* regulated genes

Significant enhancer-regulated gene enrichment



Significant enhancer-regulated gene enrichment



Enrichment

- Cytokine signaling and response
- Growth hormone signaling
- Granules or vacuoles
- PRC2 pathway
- Glycine, serine, and threonine metabolism
- Acute myeloid leukemia
- None

STRING score

400 600 800

500 700 900

Acknowledgements

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Statistics

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- Holly Hartman, MS, U Michigan

RSTR project

- Cathy Stein, PhD, Case Western
- Henry Boom, MD, Case Western
- Harriet Mayanja-Kizza, MD, Makerere University
- Chetan Seshadri, MD, UW-Medicine

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Contact me for invite to SLU bioinformatics Slack