Epigenetics and resistance to tuberculosis

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Tuberculosis is
the leading cause of infectious disease
death worldwide

Estimated TB incidence rates, 2017

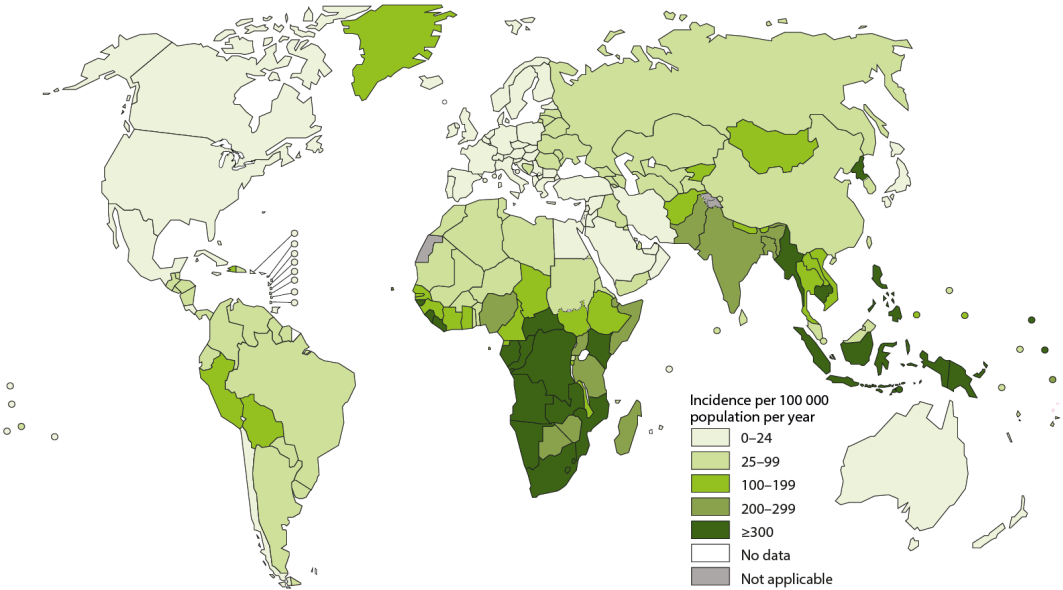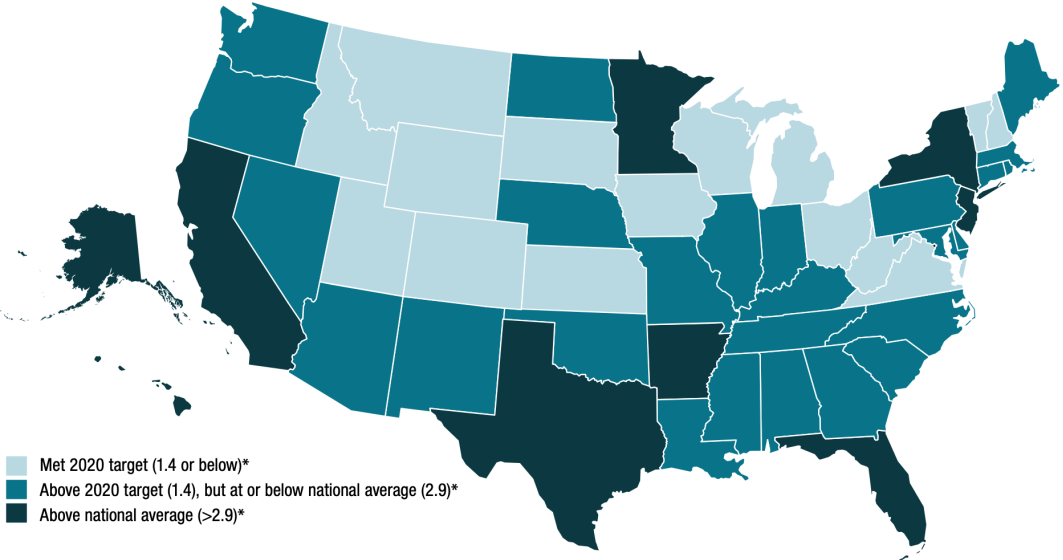Incidence per 100 000
population per year

- 0–24
- 25–99
- 100–199
- 200–299
- ≥300
- No data
- Not applicable

image: WHO Global Tuberculosis Report 2018

Estimated TB incidence rates, 2016

- Met 2020 target (1.4 or below)*
- Above 2020 target (1.4), but at or below national average (2.9)*
- Above national average (>2.9)*

*Cases per 100,000 persons

image: CDC National TB Surveillance Systems

How do we better treat and prevent TB infection?

Uganda household contact study

- 2002 – 2012 in Kampala, Uganda
- 872 Index Cases with culture confirmed pulmonary TB
- 2585 contacts of Index Cases
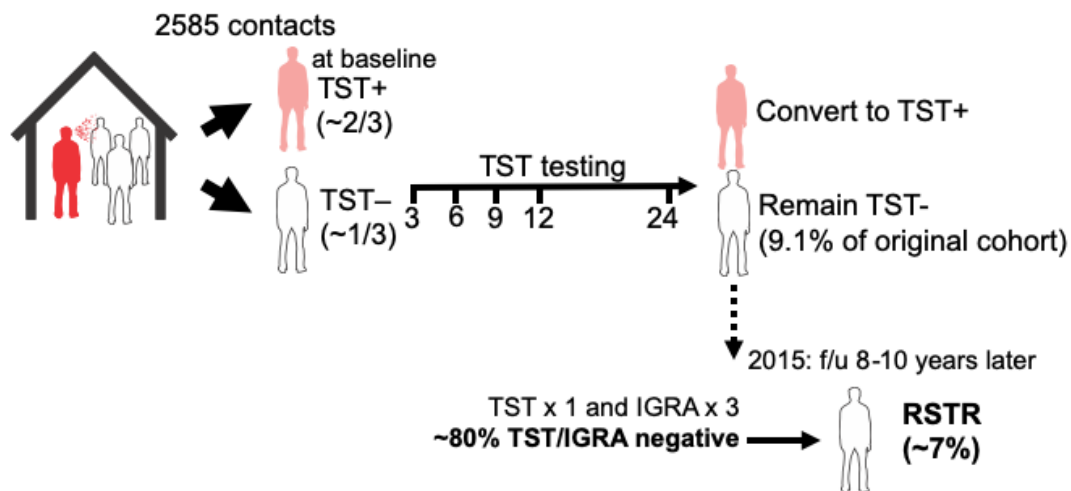
Thomas Hawn   Henry Boom   Cathy Stein   Harriet Mayanja-Kizza

Ma N *et al* 2014 doi: 10.1186/1471-2334-14-352
Stein C *et al* 2018 doi: 10.1093/aje/kwx380

Uganda household contact study

Slide courtesy T Hawn

- TST: Tuberculin skin test
- IGRA: Interferon-gamma release assay

RSTR: Resister

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

LTBI: latent TB infection

- infected* with TB but not actively manifesting symptoms

TB: pulmonary TB

- infected with TB in lungs and actively manifesting symptoms

What makes resisters resistant?

The RSTR phenotype

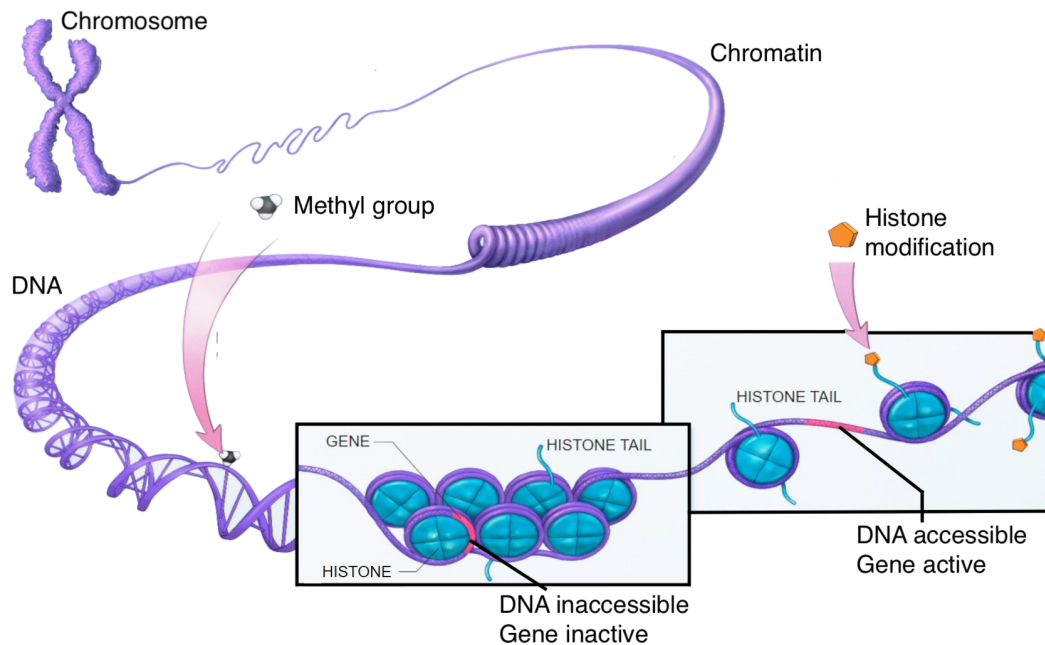- Genetics?

- Epigenetics?

- Environment?

Epigenetics

image modified from National Institutes of Health

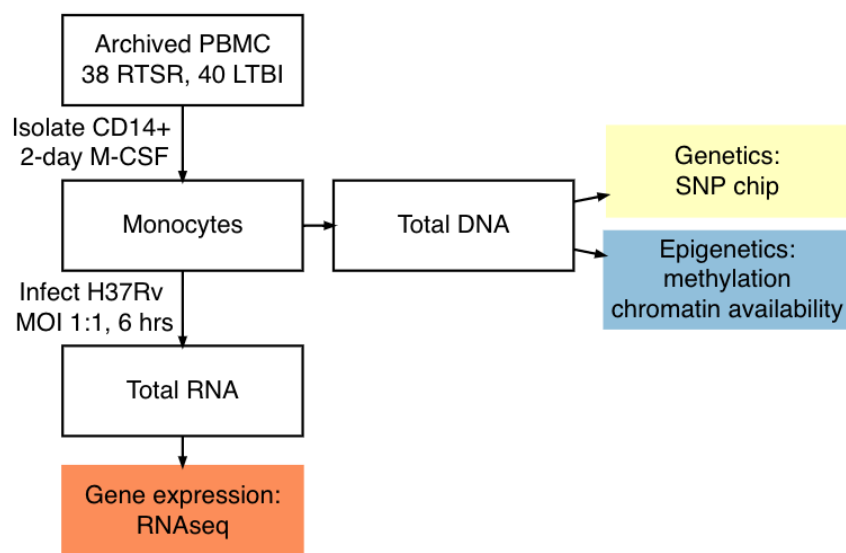# Why epigenetics in RSTR?

· Transcription of histone deacetylase (HDAC) genes associated with RSTR-derived PBMCs (monocytes) infected with *Mycobacterium tuberculosis*

· Genetic variation in HDAC genes associated with RSTRs

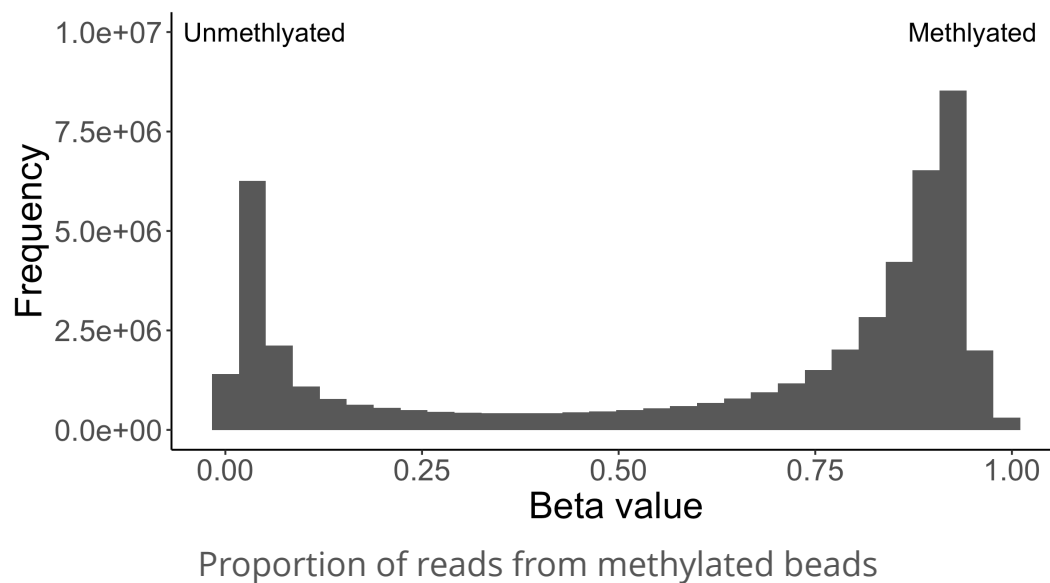· HDAC3 inhibitor treatment decreased *M. tuberculosis* replication in macrophages

Experimental design

Measuring methylation

- Only occurs at CpG sites

- Array-type (as opposed to whole genome)

- Illumina Infinium MethylationEPIC arrays I and II
- 865,918 probes across genome

Measuring methylation

Proportion of reads from methylated beads

Why isn't it 0:1?

Technical

- Sample processing
- EPIC array error

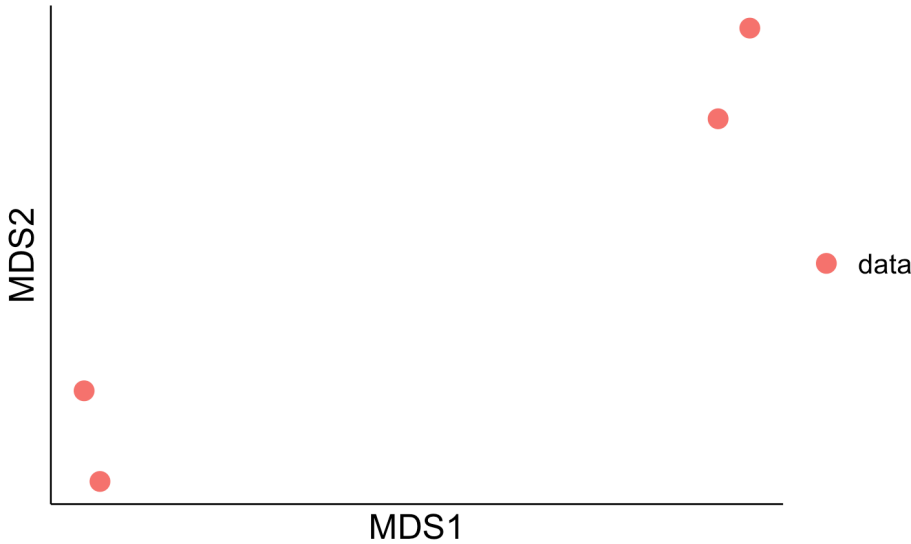**Biological**
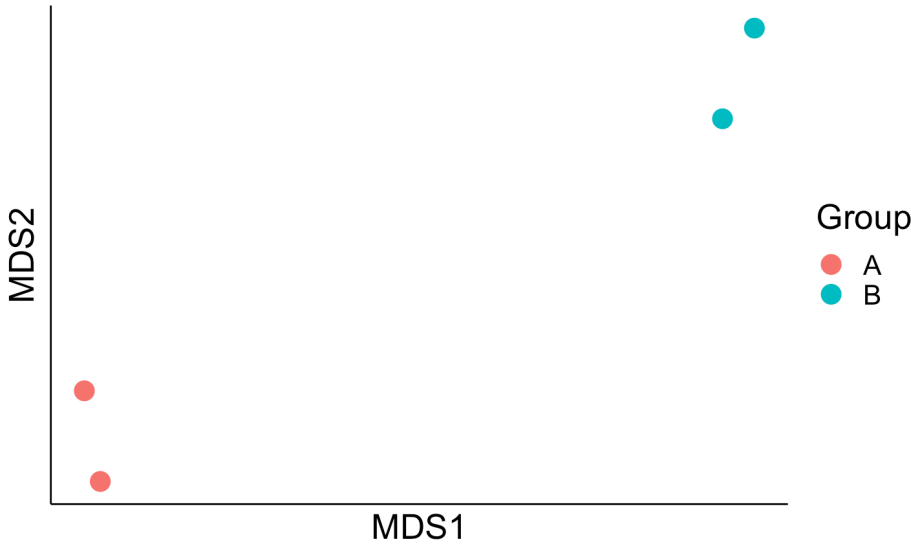
- Heterogeneous genes
- Heterogeneous cell population

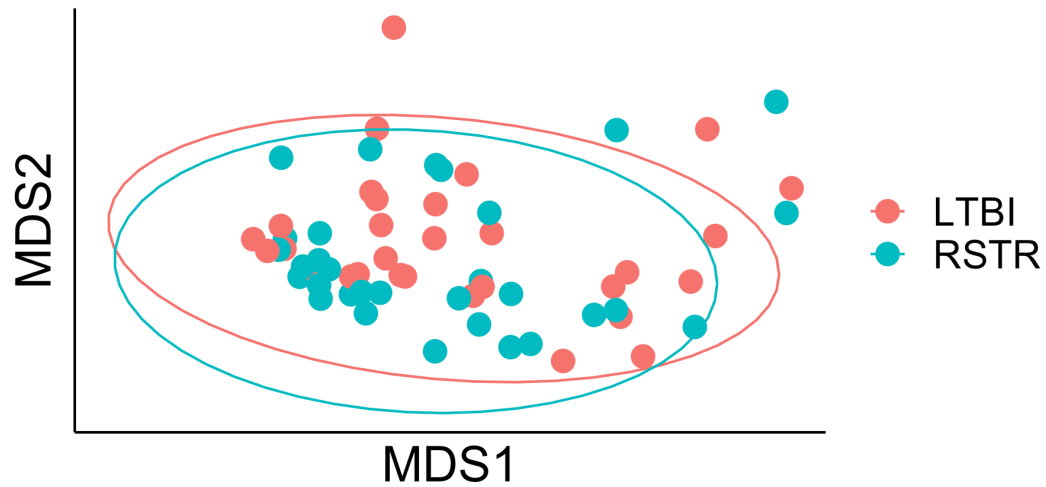# Do overall methylation profiles differ between RSTR and LTBI?

Overall methylation profiles

Overall methylation profiles

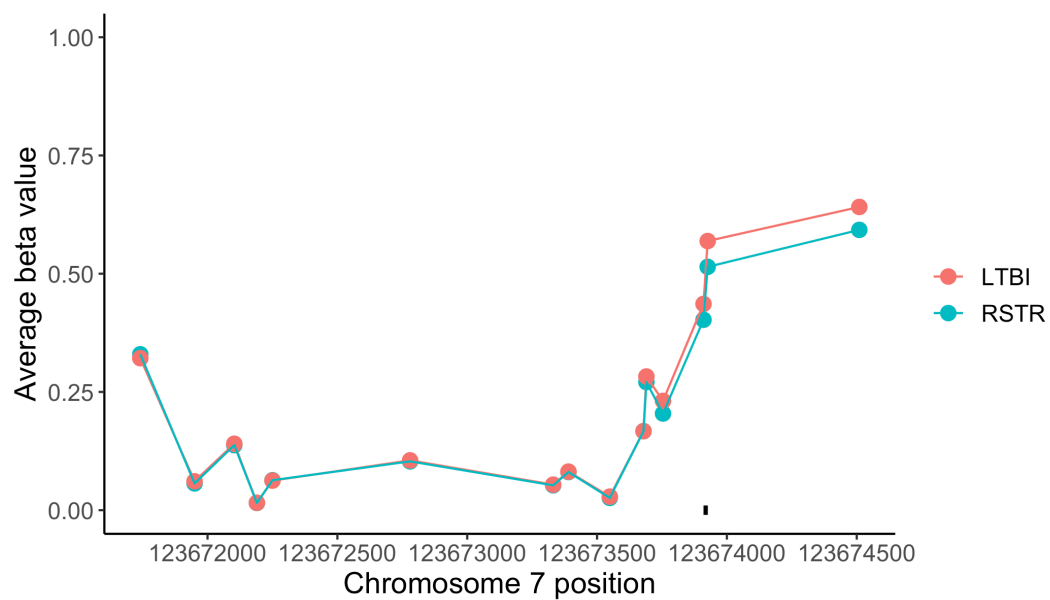# Overall methylation profiles

So… go home?

- MDS (and PCA) do not capture full variability of data

- Human data is messy

- **Not seeing clear separation in MDS/PCA does not indicate that no differences exist.**
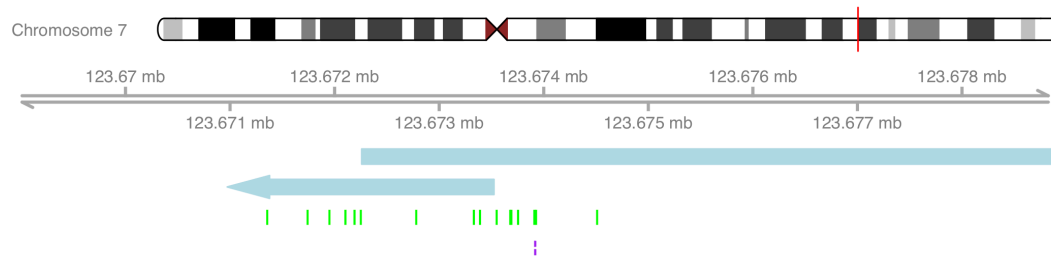
DMR -

Differentially methylated regions

DMR 61 = TMEM229A

DMR 61 = TMEM229A

TMEM229A in RSTR

- Lower methylation in RSTR vs. LTBI (0.91X, FDR = 0.043)
- Higher expression in cells infected with *M. tuberculosis* (1.35X, FDR = 0.158)

- Transmembrane protein

- Associated Broad C7 terms, immunologic signatures
- GSE8921: monocytes treated with *M. tuberculosis* lipopeptide

Identified regions

FDR cutoff	Total regions	Total genes
1e-05	4	4
1e-04	5	5
1e-03	11	10
1e-02	37	32
5e-02	92	69

Future directions

· Integration with SNPs, RNA-seq, chromatin availability

· Refine DMR method

· More complex models including demographics, exposure risk score, etc.

Acknowledgements

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  UW-Medicine

Bioinformatics Interest Group at SLU

- Monthly paired seminar and workshop series

- Coming Winter 2019

- Recruiting executive team members!

For more info:

- UW mail list: slu_bioinformatics
- Website: https://big-slu.github.io/
- Email me: kadm@uw.edu