Evolution of *Mycobacterium tuberculosis*

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No disclosures

Relevant financial relationships
Off-label/ investigational use
Overview/ Learning Objectives

• Why study *M.tb* evolution?
• Scales of evolution
• Within-host evolution
• Evolution during transmission
• The global scale
TB: A global public health emergency

WHO (2011):
- 3 billion infections
- 8-9 million incident cases/y
- 1-2 million deaths/y
Scales of adaptation
The world within each host

- Small inoculum (~10-30)
- 10 billion bacterial cells
- Dynamic
- Harsh
Adaptation within and between hosts

• Within-host
  – Pooled WGS
  – 3 patients
  – Serial samples
  – Drug R
  – China

• Between-host
  – WGS
  – 201 *M. tb* isolates
  – Drug susceptible
  – Global

• Diversity:
  – \( \pi, \theta \)

• Selection:
  – Tajima’s D
  – \( \piN/\piS \)
  – F_{ST} outliers
  – Convergent SNPs
## Diversity

<table>
<thead>
<tr>
<th>Population</th>
<th>$\pi$</th>
<th>$\Theta_w$</th>
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<tbody>
<tr>
<td><strong>Between-host</strong></td>
<td><strong>$n$</strong></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>201</td>
<td>$3.71 \times 10^{-4}$</td>
</tr>
<tr>
<td>Lineage 2</td>
<td>37</td>
<td>$1.07 \times 10^{-4}$</td>
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<tr>
<td>EAS</td>
<td>18</td>
<td>$2.39 \times 10^{-4}$</td>
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<tr>
<td>China</td>
<td>14</td>
<td>$2.57 \times 10^{-4}$</td>
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<td><strong>Within-host</strong></td>
<td><strong>COV</strong></td>
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</tr>
<tr>
<td>a1</td>
<td>50X</td>
<td>$7.78 \times 10^{-5}$</td>
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<tr>
<td>a2</td>
<td>50X</td>
<td>$1.24 \times 10^{-4}$</td>
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<td>a3</td>
<td>50X</td>
<td>$1.33 \times 10^{-4}$</td>
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<td>b2</td>
<td>50X</td>
<td>$2.70 \times 10^{-4}$</td>
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<tr>
<td>c1</td>
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<tr>
<td>c2</td>
<td>50X</td>
<td>$1.46 \times 10^{-4}$</td>
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### Functional Category

**Tuberculist**
- Conserved hypotheticals
- Lipid metabolism
- Virulence, detoxification, adaptation
- Cell wall and cell processes
- Information pathways
- Regulatory proteins
- Intermediary metabolism and respiration

**Targets of independent mutation (drug resistance association)**
- Nonessential
- *in vivo* essential
- *in vitro* essential

**Clusters of Orthologous Groups (COG)**
- Q - Secondary metabolites biosynthesis, transport and catabolism
- L - Replication, recombination and repair
- T - Signal transduction mechanisms
- V - Defense mechanisms
- G - Carbohydrate transport and metabolism
- E - Amino acid transport and metabolism
- C - Energy production and conversion
- O - Posttranslational modification, protein turnover, chaperones
- P - Inorganic ion transport and metabolism
- R - General function prediction only
- U - Intracellular trafficking, secretion, and vesicular transport
- H - Coenzyme transport and metabolism
- K - Transcription
- M - Cell wall/membrane/envelope biogenesis
- S - Function unknown
- I - Lipid transport and metabolism
- J - Translation, ribosomal structure and metabolism
- F - Nucleotide transport and metabolism
- D - Cell cycle control, cell division, chromosome partitioning

### Enrichment (q-value)

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**WH**

**BH**
The MDR pandemic

Kalmykia, Russia
> 20% new cases = MDR
50% re-treatment cases = MDR

Map showing the proportion of Multidrug-Resistance among Reported TB Cases:
- > 6%
- 3% - 6%
- < 3%
- No Data
Phylogeography of TB in Kalmykia, Russia

Use *M.tb* WGS data to infer TB dispersal patterns

Barriers between TB micro-epidemics are evident in *M.tb* genetic data

Pepperell et al, *MBE* 2010

How best to tailor TB control policy to these micro-epidemics?
The Big Picture

- Pandemic TB ~ 500y
- Pathological & historical evidence of TB from > 6,000y B.P.
- Has *M.tb* been evolving with us for 6,000+ y?
- Was ancient “TB” due to *M.tb*?
- Is pandemic TB due to recently emerged – fit – clone of *M.tb*?

Mummified remains w/ *M.tb* DNA; Donoghue *Lancet ID* 2004
The out-of-Africa hypothesis

Out-of-Africa migration and Neolithic coexpansion of *Mycobacterium tuberculosis* with modern humans

Used calibration points from human evolution to estimate rates of *M.tb* evolution

Found qualitative evidence of parallel histories of *M.tb* and humans over the past 70,000 years
An opposing perspective

Calibration of *M. tb* evolution using historical events (fur trade)

Estimate rates of *M. tb* evolution

Origin of extant *M. tb*

Pepperell et al *PNAS* 2011

Pepperell et al *PLoS Pathogens* 2013
Parallel recent demography of humans & *M.tb*

25-fold expansion of global *M.tb* population

Human pop. (billions)

Pepperell et al *PLoS Path* 2013
How to settle this question?

• Origin extant *M.tb* = human migration out of Africa 70,000y ago

• *VS*

• Alternatives

• **Answer**: analysis of ancient *M.tb* DNA
Blame the seals?

Pre–Columbian mycobacterial genomes reveal seals as a source of New World human tuberculosis

Kirsten I. Bos1*, Kelly M. Harkins2*, Alexander Herbig1,3*, Mireia Coscolla4,5*, Nico Weber3, Iñaki Comas6,7, Stephen A. Forrest1, Josephine M. Bryant8, Simon R. Harris8, Verena J. Schuenemann1, Tessa J. Campbell9, Kerrtu Majander1, Alicia K. Wilbur2, Ricardo A. Guichon10, Dawnie L. Wolfe Steadman11, Della Collins Cook12, Stefan Niemann13,14, Marcel A. Behr15, Martin Zumarraga16, Ricardo Bastida17, Daniel Huson3, Kay Nieselt3, Douglas Young18,19, Julian Parkhill8, Jane E. Buikstra2, Sebastien Gagneux4,5, Anne C. Stone2 & Johannes Krause1,20,21
Analyses of ancient *M.tb* DNA do not support out-of-Africa

Eighteenth-century genomes show that mixed infections were common at time of peak tuberculosis in Europe

Gemma L. Kay¹,*, Martin J. Sergeant¹,*, Zhemin Zhou¹,*, Jacqueline Z.-M. Chan¹, Andrew Millard¹, Joshua Quick², Ildikó Szikossy³, Ildikó Pap³, Mark Spigelman⁴,⁵, Nicholas J. Loman², Mark Achtman¹, Helen D. Donoghue⁵ & Mark J. Pallen¹
Summary

• Evolution of *M. tb* occurs at distinct scales
  – Within-hosts, Between-hosts, Global
• Within-host evolution appears highly dynamic
• Between-host evolution shaped by architecture of human populations
• Debate on “the story of TB”