Host Genetics of Tuberculosis

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Tuberculosis Pathogenesis

1. Resistance to infection (no entry into latency)
2. Primary TB (clinical TB without latency)
3. Latent TB infection (LTBI) (no overt clinical symptoms)
   Reactivation TB (Pulmonary symptoms)
Host Genetics of TB?

TB is an infectious disease caused by *Mycobacterium tuberculosis*:

No *M. tuberculosis* = No TB!

Is TB a genetic disease? NO!

Host Genetics of TB?

Phenylketonuria (PKU) is a metabolic disease that is caused by phenylalanine:

No phenylalanine = No PKU!

Is PKU a genetic disease? YES!
Host Genetics of TB?

"It is not the microbe that is transmitted from the parents to the offspring, but the predisposition to disease"

Louis Pasteur

*In ‘Etudes sur la maladie des vers à soie. La pébrine et la flacherie (tome I)’ Gauthier-Villars eds; 1870*

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**The Lübeck Accident**

<table>
<thead>
<tr>
<th>Virulence level</th>
<th>Number</th>
<th>Disease severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>death</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>93</td>
<td>6 = 6.5%</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
<td>18 = 21.7%</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>53 = 71.6%</td>
</tr>
</tbody>
</table>

**Totals**

<table>
<thead>
<tr>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>251</td>
</tr>
<tr>
<td>77</td>
</tr>
<tr>
<td>61</td>
</tr>
<tr>
<td>112</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

Twin studies

DZ TWINS

2 fertilizations

Share 50% of genetic background

MZ TWINS

1 fertilization

Share 100% of genetic background

Twin studies

Concordance

<table>
<thead>
<tr>
<th>Monozygous twins</th>
<th>Dizygous twins</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>65%</td>
<td>25%</td>
<td>Diehl and Von Verschuer, Beitr. Klin Kunsch 92: 275, 1936</td>
</tr>
<tr>
<td>62%</td>
<td>18%</td>
<td>Kallmann and Reisner, Am Rev Respir Dis 47, 549, 1942</td>
</tr>
<tr>
<td>32%</td>
<td>14%</td>
<td>Comstock, Am Rev Respir Dis 117, 621, 1978</td>
</tr>
</tbody>
</table>

Significant excess of concordance among monozygous twins demonstrates the importance of host genetic factors
Host genetics of tuberculosis

Only few TB susceptibility genes have been convincingly identified.

Why do we have difficulties in identifying host susceptibility genes?

TB pathogenesis is more than “disease”

(i) age
(ii) host x pathogen interaction (M. tuberculosis strain)
(iii) gene x environment interactions (exposure history)

Max Lurie’s Rabbits

Healthy

Infected

Cavitary disease
Mean survival 9.2 months
Lurie M.B. Am Rev Tuberc 1941; 44 (suppl): 1–125

Disseminated disease
Mean survival 4.8 months

Innate resistance

20-40% no disease
85% Tuberculin test negative
11-19 months of exposure

Werneck-Barroso E. Int J Tuberc Lung Dis 1999;3:166-68
Latent *M. tuberculosis* infection

How do we measure infection?

No “gold standard”

Three types of assays

*In vivo* tuberculin skin test (TST)

*In vitro* production of antigen-specific IFN\(\gamma\) production (ELISA)

*In vitro* determination of frequency/number of antigen-specific T-cells

(ELISpot/FACS)

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**Tuberculin Skin Test**

<table>
<thead>
<tr>
<th>Tuberculin (PPD)</th>
<th>Delayed Type Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Tuberculin Image" /></td>
<td><img src="image2.png" alt="Hypersensitivity Image" /></td>
</tr>
</tbody>
</table>

**Detection of people infected by *M. tuberculosis***

<table>
<thead>
<tr>
<th>Public Health</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 5 mm (Immun-)</td>
<td></td>
</tr>
<tr>
<td>≥ 10 mm (no BCG)</td>
<td></td>
</tr>
<tr>
<td>≥ 15 mm (BCG)</td>
<td></td>
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</table>

**Intrinsically a quantitative measure**

High heritability in endemic area (70 to 90%)
Study Setting: Cape Town, South Africa

- During subject enrolment period:
- Highest TB incidence worldwide
- Pediatric HIV < 1%
- BCG at birth

TST reactivity is bi-modal

Gallant et al Chest 137:1071, 2010
Age has a strong effect on TST

Two phenotypes – Two linkage analyses

TST= 0 vs. Non 0

TST-BIN

TST-QTL

Pearson residuals

Tobit residuals

**TST1** ⇒ T-cell-independent resistance to *M. tuberculosis*

Linkage disequilibrium mapping

**TST2** ⇒ intensity of T-cell mediated DTH to tuberculin

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