Human Genetics of Mycobacterial Infections
Implications for immunotherapeutic strategies
# The genus *Mycobacterium*

<table>
<thead>
<tr>
<th>‘Virulent’</th>
<th>‘Weakly virulent’</th>
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</table>
| *M. tuberculosis* complex | > 80 species (e.g. *M. avium*, *M. marinum*, *M. fortuitum*…)
| *M. leprae* | Environmental transmission |
| Human transmission (airborne) | (water, soil, air…)

<table>
<thead>
<tr>
<th><em>M. ulcerans</em> (Buruli ulcer)</th>
<th>BCG vaccine</th>
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<tbody>
<tr>
<td>Aquatic bug transmission?</td>
<td>Injection transmission</td>
</tr>
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</table>
Human genetics in mycobacterial diseases?

1. Concept
2. Epidemiological observations
3. Experimental models
4. Mendelian genetics
5. Genetic epidemiology
6. Proof of concept
TB: Individual variability in clinical outcomes

Accidental inoculation with *M. tuberculosis* 251 infants

- Death by year 1 77 infants
- Various signs of infection 127 infants
- No sign of infection 47 infants

**TB: Individual variability in response to infection**

- The Lübeck disaster in 1926
Epidemiological observations $\rightarrow$ inter-individual variability

MYCOBACTERIA

EXPOSURE FACTORS

VIRULENCE FACTORS

MYCOBACTERIA

INFECTION

CLINICAL PHENOTYPES

HOST

NON-GENETIC FACTORS

GENETIC FACTORS
### Methods of investigation in humans

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Rare</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(disseminated forms)</td>
<td>(TB, Leprosy)</td>
</tr>
<tr>
<td>Causality</td>
<td>monogenic</td>
<td>complex</td>
</tr>
<tr>
<td>Tools</td>
<td>Mendelian Genetics</td>
<td>Genetic Epidemiology</td>
</tr>
<tr>
<td>Sample</td>
<td>Small</td>
<td>Large</td>
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</table>

- Rare mutation
- Strong effect
- Common polymorphism
- Modest effect
MENDELIAN AND COMPLEX INHERITANCE

HYPOTHESIS TESTING
(Candidate gene approach)

ANIMAL  HUMAN

CANDIDATE GENES

VARIANT DETECTION

‘RARE’ MUTATIONS  ‘COMMON’ POLYMORPHISMS

ASSOCIATION STUDIES
(Replications)

FUNCTIONAL STUDIES

HYPOTHESIS GENERATING
(Genome-wide approach)

LINKAGE  EXPRESSION  ASSOCIATION  SEQUENCE
Mendelian susceptibility to mycobacterial diseases (MSMD)

* Infections by BCG and environmental Mycobacteria

* Otherwise healthy individuals

* Very rare ($10^{-5} - 10^{-6}$) but often familial (consanguinity)
MSMD: 6 genes, 13 genetic diseases

Mycobacteria

Macrophage/Dendritic Cell

→ Specific antimycobacterial pathway in natura (IL12/IFN-γ)
→ Immunotherapy (IFN-γ treatment)
→ From BCG/EM to M. tuberculosis
**IL12R-β1 deficiency and tuberculosis**

MSMD  
*IL12RB1* mutation: R213W

Abdominal TB  
*IL12RB1* mutation: R213W

Severe TB  
*IL12RB1* mutation: 1721+2T→G

**Complete IL12R-β1 deficiency** : No cellular responses to IL-12

→ **Mendelian tuberculosis**
The proportion of Mendelian TB in disseminated forms of children could be far from negligible.
Complex predisposition to common mycobacterial diseases

**Tuberculosis**
*(M. tuberculosis)*

- ~8 millions new cases per year
- ~90% of infected subjects do not develop the disease

**Leprosy**
*(M. leprae)*

- ~400,000 new cases per year
- ~95% of infected subjects do not develop the disease

*Very large spectrum of clinical manifestations*
HYPOTHESIS TESTING
(Candidate gene approach)

- ANIMAL
- HUMAN

HYPOTHESIS GENERATING
(Genome-wide approach)

- LINKAGE
- EXPRESSION
- ASSOCIATION?
- SEQUENCE

CANDIDATE GENES

VARIANT DETECTION

- ‘RARE’ MUTATIONS
- ‘COMMON’ POLYMORPHISMS

ASSOCIATION STUDIES (Replications)

FUNCTIONAL STUDIES

Examples: NRAMP1, HLA-DR, DC-SIGN…
PULMONARY TB

HYPOTHESIS TESTING (Candidate gene approach)

- ANIMAL
- HUMAN

HYPOTHESIS GENERATING (Genome-wide approach)

- LINKAGE
- EXPRESSION
- ASSOCIATION
- SEQUENCE

CANDIDATE REGION

VARIANT DETECTION

- ‘RARE’ MUTATIONS
- ‘COMMON’ POLYMORPHISMS

ASSOCIATION STUDIES (Replications)

FUNCTIONAL STUDIES
TUBERCULOSIS: Genome-wide screen

96 multiplex families

<table>
<thead>
<tr>
<th># affected offspring</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td># families</td>
<td>68</td>
<td>21</td>
<td>7</td>
</tr>
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</table>

Total of 227 offspring (92%>15 years, 90%<40 years) with positive pulmonary TB

Linkage to chromosome 8q12-q13

Consistent with dominant inheritance

39 families with affected parent
All 96 families

Linkage disequilibrium mapping is ongoing

p<0.00002
p<0.00007

5.6e+07 5.7e+07 5.8e+07 5.9e+07 6.0e+07 6.1e+07
Two successful positional clonings in leprosy

6p22 (Lod=2.6)

→ LTA +80 variant
(Alcaïs et al, Nat Genet, 2007)

6q25 (Lod=4.3)

→ PARK2/PACRG variants
Genetic predisposition to mycobacterial infections

→ continuous spectrum

- **Mendelian mutations with causal role demonstrated**
  - direct clinical and therapeutic implications (disseminated TB of children)
  - information on immunological pathways (→ candidate genes)

- **Intermediate major gene effects**
  - in specific populations, phenotypes, age class (LTA and leprosy) …
  - implications ~ Mendelian

- **Common polymorphisms with moderate effect**
  - molecular basis difficult to validate (same pathway, interest of GWAS)
  - may have strong attributable risk at the population level
Genetic spectrum depends on age

Origin of genetic cases (%)

Mendelian

Major gene

Polygenic

Age

Primary infection

Reinfection/reactivation
Mortality per 100,000

- Generalized TB
- Pulmonary TB

Years:
- 0-1
- 1-2
- 3-5
- 6-10
- 11-15
- 16-20
- 21-30
- 31-40
- 41-50
- 51-60
- 61-70

Mortality per 100,000
What are the critical pathways in natural conditions of infection?

- Identification of
  - pathways to boost (vaccination) or rescue (treatment)
  - correlates of protective immunity (to assess early vaccine efficacy)
Vaccine/Treatment implications for TB

→ Who are the individuals at risk?

\[ M. \text{tuberculosis} \xrightarrow{\sim80-90\%} \text{Infection} \quad \xrightarrow{\sim5\%} \quad \text{Primary} \]
\[ \xrightarrow{\sim95\%} \quad \text{Extrapulmonary} \]
\[ \xrightarrow{\sim5\%} \quad \text{Latency} \quad \xrightarrow{\sim5\%} \quad \text{Reactivation} \]
\[ \xrightarrow{\sim5\%} \quad \text{Pulmonary} \]

\( \{ \text{TB} \)  

\~90\% of individuals are naturally resistant \( \rightarrow \) major confounding factor in any vaccine trials

Some individuals are highly susceptible to mycobacteria \( \rightarrow \) avoiding major side effects of candidate vaccines (live vaccines)
Laboratory of Human Genetics of Infectious Diseases

**Mycobacteria**
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