Human genetics of the Mitsuda reaction

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Leprosy and Mitsuda test

<table>
<thead>
<tr>
<th>Tuberculoïd</th>
<th>Lepromatous</th>
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<tbody>
<tr>
<td>cellular immunity ++</td>
<td>cellular immunity -</td>
</tr>
<tr>
<td>Mitsuda test</td>
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Borderline
Mitsuda test

- Mitsuda test = delayed (~28 days) skin reaction after intradermal injection of 0.1 ml of heat-killed *M. leprae*

- Positive Mitsuda (>3mm) ⇔ nodular granuloma (epithelioid cells + giant multinucleated cells + lymphocytic infiltrate)

Mitsuda test

- Large inter-individual variability
- Gaussian distribution in healthy populations
- 4 to 40% of negative individuals regardless of the endemicity of leprosy
- Positive reaction can be induced by infection with different microbial agents, including *M. tuberculosis* and BCG

Considerable importance to our understanding of *in vivo* granuloma formation
Genetic mechanisms underlying the Mitsuda reaction

Leprosy polarization

New insight into the immunological control of granulomatous diseases

Complex segregation analysis

Dermatology hospital
Hồ Chí Minh city, Vietnam

168 families (1130 individuals)
≥ 1 affected / family
Distribution of Mitsuda values

Whole population

Healthy population

Distribution of Mitsuda values

Leprosy status

Age (years)
Segregation analysis

Dominant

Recessive

• Incomplete penetrance
• Phenocopies
• Shared environment
• Gene*covariate interaction
• Multiple genes

Complex segregation analysis
Complex Segregation analysis

- Step 1: specify a causal model
- Step 2: derive the corresponding mathematical model
- Step 3: compute how well it explains the data
- Step 4: compare different models and keep the best

Best model: predicted Mitsuda values

Major recessive gene (p<10^{-6}), 12% predisposed to high values
Locate the gene(s) on the genome

Genome-wide linkage analysis
Linkage = co-segregation of marker and phenotype

168 families

20 most informative families
Primary map: genotyping of 388 microsatellites
Fine mapping: 49 additional markers in interesting regions
• Natural Resistance Associated Macrophage Protein 1
• 16 kb, 15 exons, 550 AA
• 90% homology with murine Nramp1
• Murine Nramp1: controls infection by several intracellular pathogens
• Cationic pump influencing the maturation of the phagosome
• Polymorphisms have been associated with onset of TB
17q21-25: numerous candidates

- NOS2A
- STAT3 and STAT5b
- CCL1-5, 7, 8, 11, 13–16, 18, and 23
- MCP-1
- MIP-1 α and β
- RANTES
- etc…

Tuberculosis
Sarcoidosis
2q35 and 17q21-25
Leprosy
Crohn disease
One major message

« The Mitsuda test is a FASCINATING AND EXCITING example to demonstrate how leprosy and its related phenotypes can provide unique insights into the pathogenesis of other common diseases »

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