Mycobacterium tuberculosis genetic features associated with pulmonary tuberculosis severity

Charlotte Genestet1,2, Elisabeth Hodille1,2, Guislaine Refrégier5, Alexa Barbry1,2, Emilie Westeel1,6, Jean-Luc Berland1,2, Gérard Lina1,2, Florence Adler1,2, Laurent Jacob10, Stéphane Dray19, François Massol1,4, Samuel Venner18, Oana Dumitrescu12,14 on behalf of the Lyon TB study group

Background
➢ Wide spectrum of tuberculosis (TB) clinical presentations and wide spectrum of severity symptoms
➢ To date, no proven Mycobacterium tuberculosis (Mtb) genetic determinants of these clinical presentations
➢ Next Generation Sequencing (NGS): discerning micro-diversity within patient isolates

Objectives
What are the Mtb genetic features associated with pulmonary TB severity?
Focus on Mtb genomic diversity within hosts

Method

Inclusion of 234 pulmonary TB patients diagnosed at the Lyon University Hospital

Patients stratification according to the Bandim TBscore (severity score based on pulmonary TB symptoms)
➢ 123 Mild grade (TBscore ≤4)
➢ 111 Moderate/Severe grade (TBscore ≥5)

WGS of Mtb clinical isolates, including identification of Mtb micro-diversity through unfixed mutations
➢ Distribution of unfixed mutations according to functional categories
➢ Genome wide association study (GWAS)

Results

TB severity and within-host Mtb diversity

Correlation between TB severity and detection of micro-diversity within clinical isolates

Distribution of unfixed mutations according to their functional categories

- Mild grade: Cell wall and cell processes
- Lipid metabolism
- Moderate/severe grade: Regulatory proteins

Mutation identified by GWAS

<table>
<thead>
<tr>
<th>Location</th>
<th>Mild grade</th>
<th>Moderate/Severe grade</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>espR promoter</td>
<td>4/123</td>
<td>15/111</td>
<td>p=0.007</td>
</tr>
</tbody>
</table>

SNP located one nucleotide downstream of the transcriptional start site of espR
EspR: transcriptional regulator of ESX-1 secretion system

- Moderate/severe grade: global adaptation through regulatory proteins

Conclusion
➢ Correlation between TB severity and detection of diversity within Mtb clinical isolates
➢ Mild grade: adaptation to host-pathogen interaction
➢ Moderate/severe grade: global adaptation through regulatory proteins

Potential prognosis marker?

Contacts:
charlotte.genestet@gmail.com
oana.dumitrescu@chu-lyon.fr

Declaration of Interests
The authors declare no competing interests.