

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)

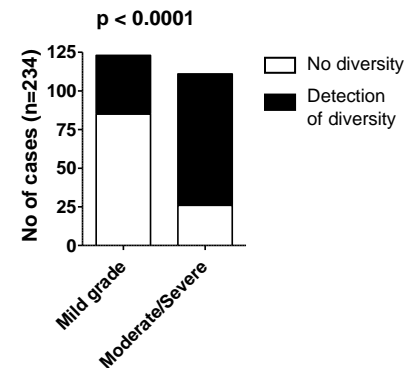
- **123 Mild grade** (TBscore ≤4)
- **111 Moderate/Severe grade** (TBscore ≥5)

WGS of Mtb clinical isolates, including identification of **Mtb micro-diversity** through unfixed mutations

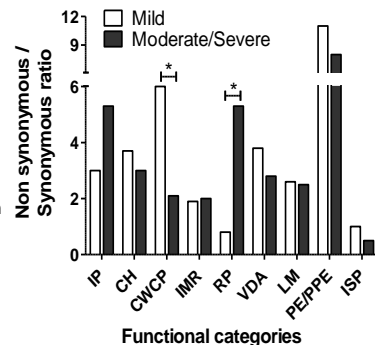
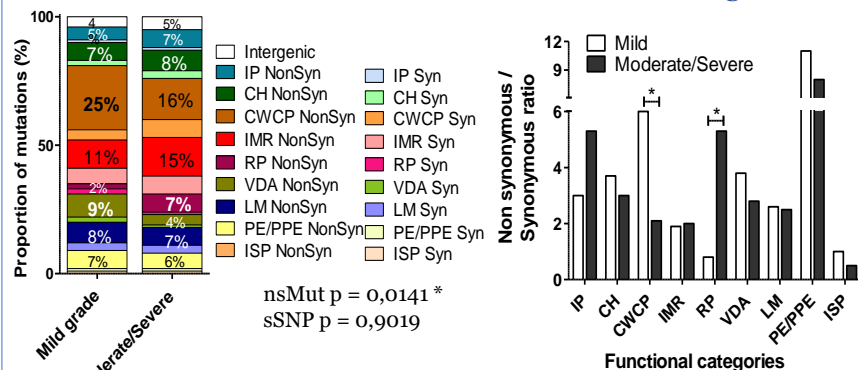
- Distribution of unfixed mutations according to **functional categories**
- Genome wide association study (**GWAS**)

Results

TB severity and within-host Mtb diversity



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

Location	Mild grade	Moderate /Severe grade	p-value
<i>espR</i> promoter	4/123	15/111	p=0.007

SNP located one nucleotide downstream the transcriptional start site of *espR*

EspR: transcriptional regulator of ESX-1 secretion system

➤ **Moderate/severe grade:**
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 ?

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

IP: Information pathways; CH: Conserved hypotheticals; CWCP: Cell wall and cell processes; IMR: Intermediary metabolism and respiration; RP: Regulatory proteins; VDA: Virulence, detoxification, adaptation; LM: Lipid metabolism; ISP: Insertion seqs and phages; NonSyn: Nonsynonymous mutations; Syn: Synonymous SNP. n=457 mutations analysed. Fisher exact or χ^2 test was used to compare mild grade and moderate/severe grade groups, where appropriate.