

## 10. RPOB S450L MUTATION AND TRANSMISSION FEATURES OF MDR MYCOBACTERIUM TUBERCULOSIS STRAINS IN THE REPUBLIC OF MOLDOVA



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**Introduction.** The Republic of Moldova (RM) faces a significant challenge with a high prevalence of multidrug-resistant tuberculosis (MDR-TB).

**Aim of study.** This study aims to explore the potential impact of rpoB S450L mutations on the phylogenetic features of MDR Mycobacterium tuberculosis strains in RM.

**Methods and materials.** We randomly selected MTB isolates from the biobank of the National Reference Tuberculosis Laboratory in RM, covering the period 2013-2018. After extracting MTB DNA, whole-genome sequencing (WGS) was performed. On the sequencing data a phylogenetic tree for the studied strains was generated, with consequent assessment of the impact of rpoB gene mutations on tree distribution.

**Results.** All 288 strains included in the study had at least one resistant mutation in the rpoB gene. Clustering rate in the sequenced strains was (51,7%). It was higher in lineage 4 (L4) than in lineage 2 (L2) strains (63% for L4 vs 36.3% for L2,  $p < 0,001$ ). In our study, 86.4% of MDR MTB strains exhibited the S450L mutation in the rpoB gene, with a frequency of 43% in lineage L2 and 57% in L4. Strains harboring the rpoB S450L mutation had a higher clustering rate (55,8% vs 25.6%,  $p=0.0005$ ). As well, among L4 strains with rpoB S450L mutations clustering rate was higher than in those without it (66% vs 31.8%,  $p=0.0016$ ). However, the difference in clustering rate in L2 strains with and without rpoB S450L was statistically insignificant (39.2% vs 17.6%,  $p=0.1068$ ). Compensatory mutations were found in 93.2% of strains with mutations in rpoB S450L, of which 83.9% were in the rpoC gene and 9.2% in the rpoB gene, whereas strains without the S450L mutation had a lower rate (38,4%) of compensatory mutation, of which in the rpoC (5.1%) and rpoB gene (33.3%).

**Conclusion.** The rpoB S450L mutation appears linked to the evolution of resistance and transmission dynamics of distinct MTB lineages in the Republic of Moldova.