

## Clinical Microbiology

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#### POLYMORPHISM IN GIDB GENE AS A GENETIC MARKER FOR THE *MYCOBACTERIUM TUBERCULOSIS* Q1 CLUSTER AND IMPLICATIONS FOR THE STREPTOMYCIN RESISTANCE LEVEL

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Development of streptomycin-resistance in *Mycobacterium tuberculosis* is usually associated with mutations in *rpsL* and *rrs* genes, although up to 50% of clinical streptomycin-resistant isolates may present no mutation in either of these genes. The situation in Lisbon Health Region is similar, although mutations in *rrs* gene are only rarely detected. In the present report we investigate the role of *gidB* gene mutations in streptomycin resistance.

We have analyzed 52 streptomycin-resistant and 30 streptomycin-susceptible *Mycobacterium tuberculosis* clinical isolates by sequencing and endonuclease analysis of the *gidB* and *rpsL* genes. All clinical isolates were genotyped by 12-*loci* MIRU-VNTR. Semiquantitative drug susceptibility testing was also performed to a select set of isolates to assess the resistance levels towards streptomycin.

The *gidB* gene of 18 streptomycin-resistant isolates was sequenced and four missense mutations were found: F12L (1/18), L16R (18/18), A80P (4/18) and S100F (18/18). The remaining isolates were screened by endonuclease analysis for mutations A80P in *gidB* and K43R in *rpsL* gene. Overall, mutation A80P in *gidB* gene was found in 7 streptomycin-resistant isolates and 12 streptomycin-susceptible multidrug resistant isolates. Also noteworthy, comparison of the distribution of *gidB*, *rpsL* and *rrs* mutations revealed that *gidB* A80P mutation was only present in isolates without *rpsL* and *rrs* mutations. Moreover, this specific mutation was found among all isolates belonging to genetic cluster Q1.

Streptomycin quantitative drug susceptibility testing showed that isolates carrying the GidB A80P mutation were streptomycin intermediate-level resistant and that standard drug susceptibility testing yielded inconsistent results probably due to borderline resistance. Bioinformatic analysis on the degree of conservation showed that the GidB A80P mutation is predicted to affect protein function.

We conclude that *gidB* mutations may explain the high number of streptomycin-resistant strains with no mutation in *rpsL* or *rrs*. These mutations might occasionally confer undetected streptomycin low-level resistance in regular drug susceptibility testing. Also, GidB A80P mutations may serve as surrogate markers for Q1 cluster isolates that are associated with multidrug/extensively drug-resistant tuberculosis.