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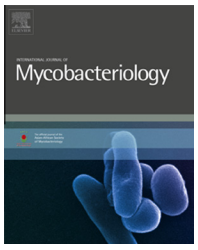

Evaluation of genetic mutations associated with mycobacterium tuberculosis resistance to isoniazid, rifampicin (MTBDR plus), fluoroquinolone and injectable second-line drugs (MTBDRsl)

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ABSTRACT

Aims and objectives: Tuberculosis (TB) is one of the major public health problems in Armenia. In 2009, TB incidence in Armenia was reported to be as high as 45.5 per 100,000 population, and TB mortality was 3.9 per 100,000 population. Only 35% of estimated new sputum smear-positive pulmonary TB patients are notified annually. From 1729 TB cases notified in 2010, only 329 patients were sputum smear-positive. The treatment success rate of new sputum smear-positive pulmonary TB patients was 76%, which is below the WHO target of 85%. Poor treatment outcome is partially explained by the high prevalence of drug resistant forms of TB. According to the 2007 drug resistance survey, MDR-TB among never-treated patients was 9.4% and 43.2% among previously treated cases with 4% of XDR cases. This represents an enormous public health challenge for Armenia; early identification and effective treatment of patients with MDR-TB is crucial to prevent further spread of the disease.

Methods: A total of 583 specimens are sent to the NRL Armenia being either acid-fast bacterium positive or negative, but culture positive. Rifampin and isoniazid resistance was performed on 77 out of the 583 specimens of DR TB clinical isolates to analyze resistance for FQL, AM/CP and EMB.

The DNA preparation method used was as described and recommended by the manufacturer (MTBDR plus version 1.0 and MTBDR sl version 2.0 Hain Lifescience, Nehren).

For 99 (88.4%) and 160 (76.2%) strains, the mutations causing rifampicin and isoniazid resistance were located in the codon of rpoB S531L and katG S315T 1, respectively. Regarding isoniazid, 14 (6.6%) strains have a mutation in the inhA regulatory region (C15T) and 31 (14.7%) in both katG and InhA.

Mutations detected in the FQ, EMB and rrs-resistant respectively are: 13 (16.9%) strains with the majority of mutations (10 [13%]) in the codon of 94 of the gyrA gen; 20 (26%) strains, with the majority of mutations (7 [9.1%]) in the codon of 306 of the EMB gen; and 13 (16.8%) strains with the majority of mutations (9 [11.6%]) in the codon of 1401 of the rrs gen.

Comparing with phenotypically DST sensitivity and specificity for RMP was 97.6% (69 strains) and 100%, respectively. False resistance was detected for 2 strains containing

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missed bands of rpoB (W6, 7, 8) and 1 strain W7. Sensitivity and specificity for INH was 98.33%, 87.5% (69 strains). From 2 strains, 1 was false resistant (missing of WT 1, 2 bands) and 1 false sensitive results for INH. The sensitivity and specificity for AM/CM was 80%, 100%, and for the FQL 85.7%, 96.72%, respectively (69 strains).

Conclusion: Rapid and accurate detection of resistance to first- and second-line anti-TB drugs is the key to successful therapy and interruption of the transmission chain of MDRTB strains. In summary, this data represent an important addition to the rare epidemiological data concerning resistance patterns of MTB in Armenia and showed that the application of the GenoType MTBDRplus and GenoType MTBDRsl assays might be useful additional tools to allow for a rapid and safe diagnosis of MDR and XDR TB. In mutations associated with katG, high dosages of isoniazid in future will be considered for treatment.