Sequence analysis of the embB gene for identification of mutations associated with resistance of multidrug-resistant Mycobacterium tuberculosis strains to ethambutol

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One of the greatest challenges in the fight against tuberculosis (TB) has been the emergence and spread of drug-resistant (DR), and multidrug-resistant (MDR) strains of Mycobacterium tuberculosis.

Ethambutol (EMB) is a first-line drug for the treatment of tuberculosis that targets the cell wall of tubercle bacilli through interfering with arabinosyl transferases, encoded by the genes of the embCAB operon and involved in the biosynthesis of arabinogalactan and lipoarabinomannan, the key structural components of the mycobacterial cell wall. Mutations in the embB gene, and those within its conserved EMB resistance determining region (ERDR) in particular, have been associated with resistance to EMB in Mycobacterium tuberculosis. Analysis of mutations in the embB gene in M. tuberculosis strains may contribute to the development of new tests for rapid detection of EMB resistance.

BACKGROUND

The aim of this study was to examine the mutational “hot spots” in the embB gene, including the ERDR, among multidrug-resistant (MDR) M. tuberculosis clinical isolates and to find a possible association between embB mutations and resistance to EMB.

METHODS

A 863-bp region of the embB gene of 48 clinical isolates of M. tuberculosis (21 EMB-resistant, 27 EMB-susceptible), recovered from as many MDR-TB patients in Poland in 2004 was sequenced and screened for mutations linked to EMB resistance. Mutations in the embB gene were detected by comparing the assembled sequences with the corresponding sequences of a wild-type reference laboratory strain M. tuberculosis H37Rv. The obtained results were interpreted in the context of EMB susceptibility profile of the strains tested.

RESULTS

• Eight embB mutation types were detected in 6 distinct codons in 26 (54.2%) M. tuberculosis strains
• Only 10 (38.5%) of those strains were EMB-resistant and had mutations either in codon 306 (7 strains) or 406 (3 strains)
• None of the two mutation types were found exclusively in EMB-resistant strains
• Analysis of other genetic loci is needed for the identification of more specific mutations associated with EMB resistance

CONCLUSIONS