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Kanji, A; Hasan, R; Zaver, A; Ali, A; Imtiaz, K; Ashraf, M; Clark, TG; McNerney, R; Shafiq, S; Hasan, Z (2016) Alternate efflux pump mechanism may contribute to drug resistance in extensively drug-resistant isolates of *Mycobacterium tuberculosis*. *International journal of mycobacteriology*, 5 Suppl 1. S97-S98. ISSN 2212-5531 DOI: 10.1016/j.ijmyco.2016.09.064

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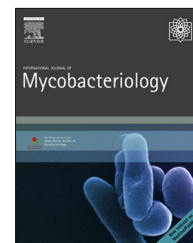


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Alternate efflux pump mechanism may contribute to drug resistance in extensively drug-resistant isolates of *Mycobacterium tuberculosis*

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ARTICLE INFO

Article history:

Received 5 September 2016

Accepted 14 September 2016

Available online 22 November 2016

Keywords:

Efflux pumps

XDR

MTB

ABSTRACT

Introduction: Extensively drug-resistant tuberculosis (XDR-TB) has emerged as one of the biggest threats to public health and TB control programs worldwide. XDR-TB is caused by *Mycobacterium tuberculosis* (MTB) strains resistant to rifampin and isoniazid, as well as to a fluoroquinolone and to at least one injectable aminoglycoside. Drug resistance in MTB has primarily been associated with single nucleotide polymorphisms (SNPs) in particular genes. However, it has also been shown that efflux pumps may play a role in resistance of MTB. Upregulation of drug efflux pumps can decrease the intracellular concentration of drugs and reduce their efficacy.

Methods: Whole genome sequencing was performed on 32 XDR-TB clinical isolates. Sequence data were used to investigate SNPs in efflux pump genes as compared with the H37Rv reference genome.

Results: Of the XDR MTB strains, eight (21.62%) were wild type for *rpsL*, *rrs* (500 region), and *gidB* genes, but had non-synonymous (ns) SNPs (aspartic acid to histidine) in the *drmA* efflux pump gene at position 3273138. Three of eight (37.5%) XDR MTB strains, wild type for *rpsL*, *rrs* (500 region), *gidB*, and *gyrB* genes were phenotypically streptomycin sensitive and five (62.5%) XDR MTB strains were streptomycin resistant, while all XDR MTB strains, wild type for *rpsL*, *rrs*, *gidB*, and *gyrB* genes were resistant to fluoroquinolone (ofloxacin) and ethambutol. In addition, three XDR MTB strains wild type for *rpsL*, *rrs*, *gidB*, and *drmA* genes showed nsSNPs (isoleucine to valine) in the major facilitator superfamily, Rv1634 efflux pump gene at position 1839306.

Conclusion: Our data show an nsSNP in the *drmA* efflux pump gene that may result in upregulation of drug efflux mechanisms in MTB strains. It is therefore imperative to

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Peer review under responsibility of Asian African Society for Mycobacteriology.

<http://dx.doi.org/10.1016/j.ijmyco.2016.09.064>

understand the mechanism of efflux and its role in drug resistance, which will enable the identification of new drug targets and development of new drug regimens to counteract the drug efflux mechanism of MTB.

Conflict of interest

The authors state that they have no conflict of interest.