Contribution of katG, ahpC and inhA mutations to the detection of isoniazid-resistant Mycobacterium tuberculosis isolates from Lebanon and Syria

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ARTICLE INFO

Article history:
Received 9 November 2014
Accepted 10 November 2014
Available online 23 December 2014

Keywords:
M. tuberculosis
katG
ahpC
inhA
Lebanon
Syria

ABSTRACT

Aims and objectives: In Lebanon, the trend of tuberculosis (TB) incidence had been declining until the year 2011. In 2012, the National TB Program (NTP) observed that 48% of all notified cases were among the Syrian refugee population. As of August 2013, according to the NTP, 100 Syrian refugees have been diagnosed with TB in Lebanon, including 3 cases of MDR (multidrug-resistant) TB.

Resistance-associated point mutations have already been described for commonly used anti-TB drugs. The widespread use of Isoniazid (INH), a cornerstone drug for treating TB, has seen treatment failures due to increasing resistance to the drug. Clinical resistance to INH is widely known to be caused by mutations within katG, inhA and ahpC genes. The objective of this study is to determine by pyrosequencing the prevalence of mutations on the codon 315 of the katG gene, on the inhA promoter and on the ahpC-oxyR intergenic region in 14 and 52 INH-resistant MTB isolates recovered from TB patients in Lebanon and Syria, respectively.

Methods: The clinical isolates were provided by the Medical Biotechnology Section of the National Commission for Biotechnology in Syria and the Health and Environment Microbiology Laboratory at the Azm Center for Research in Biotechnology at the Lebanese University. The isolates were derived from 52 Syrian and 14 Lebanese patients between July 2003 and October 2005 from all Syrian and Lebanese provinces. The identification of point mutations on katG, inhA and ahpC-oxyR intergenic region was performed by pyrosequencing, and sequences from clinical isolates were compared with that of wild-type MTB ATCC 25177.

Results: The results showed that among the 52 Syrian isolates, 22 (42.3%) had the aa 315 mutation in the katG gene, while 6 of the 14 Lebanese strains (42.8%) had this mutation. The most common mutation was Ser315Thr (92.8%). Mutations in the inhA promoter region were responsible for INH resistance in 14 Syrian strains (26.9%) of the isolates. The most common inhA promoter mutation was −15 C-T and was present in 13 of the 14 inhA mutations. Screening for mutations on the ahpC-oxyR intergenic region revealed the presence of

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http://dx.doi.org/10.1016/j.ijmyco.2014.11.006
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6 mutated Syrian strains (11.5%) with 46 G-A the most common mutation (4 of 6 strains). It is interesting to note that 4 strains had mutations in katG in addition to ahpC-oxyR mutations and 1 strain had both katG and inhA mutations.

None of the Lebanese strains had mutations on inhA or ahpC-oxyR implying that these mutations do not contribute to the detection of INH-resistant MTB in the Lebanese strains.

Conclusions: This study showed that the pyrosequencing applied to katG, inhA promoter and ahpC-oxyR intergenic region was able to detect a relatively large proportion of Syrian INH-resistant MTB isolates (80.7%) in Syria. This strategy may be inappropriate for Lebanese strains, as the genetic mechanisms of resistance remain unidentified for approximately half of the isolates, so it is quite possible to detect the presence of other mechanisms of resistance.

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