Mutations in gyra and gyrb among fluoroquinolone- and multidrug-resistant Mycobacterium tuberculosis isolates

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Background: For multidrug-resistant Mycobacterium tuberculosis (MDR-TB) isolates, it is unclear whether resistance-associated mutations outside the QRDR of gyra and gyrb are associated with fluoroquinolone (FQ) resistance.

Material/methods: Drug susceptibility of the isolates was tested using modified proportional disk elution methods. DNA sequencing of the entire gyra and gyrb genes were amplified with 8 primer sets. Genotyping (spoligotyping and 24-locus mycobacterial interspersed repetitive-unit-variable-number tandem-repeat (MIRU-VNTR genotyping) was performed as previously described.

Results: A total of 111 MDR-TB isolates were categorized into ofloxacin (OFX)-susceptible (minimum inhibitory concentrations, MIC ≤2 μg/ml), low- (MIC 4-8 μg/ml) and high-level (MIC ≥16 μg/ml) OFX-resistant isolates, and moxifloxacin (MFX)-susceptible (MIC ≤0.5 μg/ml), low- (MIC 1-2 μg/ml) and high-level (MIC ≥4 μg/ml) MFX-resistant isolates. Resistance-associated mutations inside the gyra gene were found in 30.2% of OFX-susceptible, 72.5% and 72.2% of low- and high-level OFX-resistant isolates, and in 28.6% of MFX-susceptible, 58.1% and 83.9% of low- and high-level MFX-resistant isolates. Compared with OFX-susceptible, low- and high-level OFX-resistant isolates had a significantly higher prevalence of mutations at gyra codons 88–94 (17.0%, 65.0% and 72.2%, respectively; P<0.001) and a higher prevalence of the gyrb G512R mutation (0.0%, 2.5% and 16.7%, respectively; P=0.006). Similarly, compared with MFX-susceptible, low- and high-level MFX-resistant isolates had a significantly higher prevalence of mutations at gyra codons 88–94 (14.3%, 51.6% and 80.6%, respectively; P<0.001) as well as gyrb G512R mutation (0.0%, 0.0% and 12.9%, respectively; P=0.011). D94G and D94N mutations in gyra and the G512R mutation in gyrb were correlated with high-level MFX resistance while the D94A mutation was associated with low-level MFX resistance. The prevalence of those resistance-associated mutations was higher among fluoroquinolone-susceptible East Asian (Beijing) and Indo-Oceanic strains than Euro-American strains.

Conclusions: Our data imply that molecular techniques to detect FQ resistance may be less specific in areas with a high prevalence of FQ-resistant MDR-TB strains.