Compensatory mutations in multidrug-resistant Mycobacterium tuberculosis complex isolates from Kazakhstan

P-01.3-02

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Kazakhstan is one of the 30 countries with the highest burden of multidrug-resistant tuberculosis. A recent expansion of drug-resistant isolates in the country is linked to the spread of Central Asian/Russian sublineage of *Mycobacterium tuberculosis* Beijing genotype. We studied a random sample of 11 multidrug-resistant Central Asian/Russian isolates of *M. tuberculosis* from the two most populated cities in Kazakhstan, namely, Nur-Sultan and Almaty. We utilized whole-genome sequencing to differentiate the isolates and to look for the adaptive compensatory mechanisms lowering the fitness-cost of mutations causing resistance to Rifampicin. According to genomic analysis, nine isolates belong to K-2 (Central Asia outbreak) clade and two belong to the K-1 (Central Asia) clade of Central Asian/Russian sublineage. All the studied isolates had sigE gene codon 98 CTG>CTA polymorphism that is specific for the Central Asian/Russian sublineage. The mutations previously associated with fitness-compensatory mechanisms were found in the *rpoC* gene (V431M, Q435H, L449V, V483G, V483A, D943N, and S1100A) of seven isolates. One compensatory SNP was found in the *rpoA* gene (T187A) in a single isolate. One SNP was found in the *rpoB* gene (Q980R) of another isolate. Two phenotypically resistant isolates have harbored neither compensatory SNPs nor resistance mutations to Rifampicin, despite positive phenotypic drug susceptibility testing. In conclusion, the acquisition of compensatory mechanisms, in addition to accumulated resistance-associated mutations, makes Central Asian/Russian sublineage a clear threat to global health. This work was funded by grant AP09058045 from the Ministry of Education and Science of the Republic of Kazakhstan.