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A genome wide insight into the molecular events accompanying the emergence and expansion of a multidrug-resistant *Mycobacterium tuberculosis* outbreak strain

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Because drug-resistance conferring mutations are generally associated with a fitness cost, basically multidrug-resistant (MDR) *Mycobacterium tuberculosis* strains are less prone to expand in the general population. However, multidrug-resistant tuberculosis (MDR-TB) outbreak involving 51 non institutionalized, apparently immune-competent, young individuals has been identified in Tunisia since 2001, suggesting its increased transmissibility potential. To get a genome-wide insight into the molecular events accompanying the emergence of the Tunisian MDR-TB outbreak strain, we sequenced and compared the genomes of two MDR outbreak strains and their drug sensitive parental strain.

With regard to the genome of the *M. tuberculosis* reference strain H37Rv, the 3 clinical strains shared 786 single nucleotide polymorphisms (SNPs) and 85 insertions/deletions (indels), thus confirming their genetic relationships. The putative drug sensitive parental strain proved phylogenetically distant from its two MDR outbreak progenies and accumulated a consistent number of specific SNPs and indels, suggesting that it could not be the immediate progenitor. Furthermore, and despite the fact that the two MDR outbreak strains display identical MIRU-VNTR24 patterns and differed only by one IS6110 copy, they could be differentiated by 49 SNPs and 97 indels, a finding that may indicate a high level of genomic instability during the outbreak expansion. Strikingly, some deletion events in functionally important genes shared by all MDR outbreak-associated strains were absent from the genome of the parental drug sensitive strain, and could thus have contributed to the emergence of the outbreak.

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