A high genomic mutation rate underpins the successful spread of a multidrug-resistant Mycobacterium tuberculosis Lineage 4 Haarlem genotype

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Understanding how multidrug-resistant tuberculosis (MDR-TB) emerge and spread, particularly in an HIV-negative context, could help deciphering the contributing factors inherent to the bacillus. Here we explored thoroughly the population structure of the *Mycobacterium tuberculosis* lineage 4 (L4)-Haarlem genotype in Northern Tunisia, where it caused from the very outset a major MDR-TB outbreak among HIV-negative young individuals. For this purpose, we ensured an 11-year full coverage of the Haarlem genotype in the epidemic region by analyzing all M. *tuberculosis* isolates displaying the Haarlem spoligotype signature (N = 253). We performed 24-loci MIRU-VNTR (multiple interspersed repetitive unit-variable-number tandem repeat) typing and whole-genome sequenced 94 representative isolates. Various population genetics and evolutionary analyses were then carried out. We disclosed the propensity of the Haarlem genotype to undergo an epidemic spread, irrespective of the drug susceptibility pattern (83% overall recent transmission rate). The overall MDR-TB epidemic was linked to a single drug-susceptible progenitor clone, whose existence was dated back 124 years. Strikingly, an overall high mutation rate close to that of the globally spread L2-Beijing sublineage was estimated, a finding in line with the almost concurrent acquisition of multi-drug resistance and compensatory mutations. Such a high mutation rate also explains the elevated number of nucleotide differences between the genomes of isolates from patients with established epidemiologic direct links. In conclusion, our data uncovered the relative high mutation rate of the Haarlem genotype evolving in Northern Tunisia, an inherent hallmark that most likely contributed to the emergence of successfully transmitted MDR clones through rapid acquisition of compensatory mutations. If not contained, this rapidly evolving Haarlem clone, which at present remains geographically confined, could represent a threat to the Euro Mediterranean space.

Biography

Helmi Mardassi, a Doctor in Veterinary Medicine (DVM), has carried out his PhD in Virology-Immunology at the Institut Armand-Frappier, University of Quebec. Currently, he is leading a research laboratory at the Institut Pasteur de Tunis, focusing on the delineation of the molecular mechanisms underlying emergence of TB outbreaks, the success of particular *Mycobacterium tuberculosis* clones, and the impact of drug resistance on fitness. For this purpose, his group is applying various approaches based on molecular typing, targeted mutagenesis, whole genome sequencing, etc.

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