Molecular epidemiology of MDRTB in Portugal

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In Portugal, the majority of multidrug resistant (MDR) strains of *Mycobacterium tuberculosis* (Mtb) circulating in Lisbon Health Region belong to the genetically related family Lisboa. Genotyping by Restriction Fragment Length Polymorphism (RFLP-IS6110) has identified this family in the 90's as being involved in an outbreak occurring mainly among HIV seropositive patients. Since then the strains have spread beyond Lisbon to other regions of the country.

Over the past years, we have been characterizing the genetic diversity of Mtb strains circulating in Lisbon, and evaluated continuously the prevalence of family Lisboa strains. Our most recent studies show that the prevalence of this family among MDR-TB cases is now 88%, with about 50% XDR-TB cases, the highest XDR-TB rate ever reported. XDR-TB strains are clustered in two different, but highly related profiles (defined by MIRU-VNTR genotyping method), Lisboa3 and Q1, and are probably a result of more than 15 years of family Lisboa MDR-TB strains circulating in Portugal. These two major clusters in Lisbon Health Region appear to be highly endemic to Portugal and unique from a genotyping standpoint, showing a high degree of success for transmission in the community. For several decades, it has been assumed that MDR strains are less prone to expansion in the general population. However, such an assumption has been proved untrue, as the epidemic potential of MDR/XDR-TB strains has been largely demonstrated.

Understandings of the genomic variability among Mtb isolates results in a deeper understanding of the TB biology, as well as facilitate the barcoding and

monitoring of emergent drug resistant strains. Recent innovations in sequencing technology turn possible to carry out whole-genome sequencing (WGS) of Mtb isolates on a large scale, thereby making it feasible to conduct large genomic epidemiological (diversity and association) studies, as well as track their evolution over time and space. Combining this powerful new tool with detailed epidemiology, allowed us to identify genetic variations and genome dynamics that can be correlated with the variability in the outcome of exposure and the success of particular clones, like the Lisboa family strains. Whole-genome sequencing of several Mtb isolates allowed the construction of a genome-wide SNP-based phylogeny showing that Lisboa3 and Q1 isolates form two distinct and unique monophyletic clades. Further genome analysis led to the identification of putative rifampicin resistance compensatory mutations and the identification of clade-specific genomic structural variants.

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