

## Substantial Molecular Evolution In Prolonged Latent *Mycobacterium Tuberculosis* Infections In Humans - DTU Orbit (08/11/2017)

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**Introduction:** Despite its central role as a reservoir for active tuberculosis disease (TB), latent *Mycobacterium tuberculosis* (*Mtb*) infections and the underlying persistence mechanisms are poorly understood. The *Mtb* genome in latently infected individuals may hold the key to understanding the processes that lead to reactivation and progression to clinical disease. **Methods:** We studied genomic relationships among 14 isolates of *Mtb* from historical and recent Danish clinical strain collections, spanning more than three decades, to investigate 6 putative cases of *Mtb* reactivation, inferred from IS6110 profiles. Single-nucleotide polymorphism (SNPs) patterns were analyzed to identify true cases of TB re-activation, as well as the underlying mutational patterns. **Results:** Two parallel cases of latent TB reactivation were identified. We found an average mutation rate of 0.2 – 0.3 over 33 years, as well as evidence for distinct processes such as oxidative damage or natural selection having contributed to mutation accumulation. **Conclusions:** Our study shows that distinct processes can shape *Mtb* genomes during latent infection. Most importantly, we document substantial molecular evolution of *Mtb* over three decades, with mutation rates similar to observations from cases of active disease. Our study thus emphasizes the importance of identifying and controlling latent cases.

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