Comparative genomics of members of the *Mycobacterium tuberculosis* complex are of great help to get new insights into the evolution of the tubercle bacilli and uncover the molecular mechanisms involved in their pathogenicity. Phylogenetic analysis based on genomic regions of difference (RD) led to a complete revision of our understanding of the evolutionary pathway of the tubercle bacilli, and suggests that *M. tuberculosis* is closer related to the common ancestor of the tubercle bacilli than *Mycobacterium bovis*, long time thought to be the progenitor of these bacteria. Recent analyses of very rare strains showing smooth colony morphology that were isolated from tuberculosis patients in Djibouti-East-Africa further extended these results, and allowed a progenitor species (*Mycobacterium prototuberculosis*) to be proposed. These isolates, which include *M. canetti* strains, share many properties of MTBC members, but radically differ in terms of a more diversified population structure and obvious traces of horizontal gene transfer (HGT). These features suggest that the smooth MTBs are extant representatives of a much broader and older progenitor species. Genomic and phenotypic analyses of these tubercle bacilli in comparison with other members of the *M. tuberculosis* complex have the potential to provide novel insights into the genetic background and molecular mechanisms that have contributed to the outstanding evolutionary success of certain lineages of the *M. tuberculosis* complex.