

Biological Heterogeneity of *Mycobacterium tuberculosis* Lineages and Its Impact on Drug Response and Treatment Outcomes in Ethiopia

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Tuberculosis (TB) remains a major public health challenge in Ethiopia, where diverse *Mycobacterium tuberculosis* (Mtb) lineages co-circulate and contribute to variable treatment responses. This study investigated the phenotypic, genomic, and transcriptomic characteristics of clinically prevalent Ethiopian Mtb strains, with particular emphasis on dominant Lineage 4 sub-lineages. In vitro growth kinetics and drug susceptibility testing revealed significant lineage-dependent differences, with sub-lineage 4.2.2.2 exhibiting accelerated growth and minimum inhibitory concentration (MIC) values approaching WHO critical concentrations despite phenotypic susceptibility. Integrated RNA sequencing and whole-genome analyses identified significant downregulation of several non-canonical resistance-associated genes, including Rv0096, Rv2780, Rv3136, Rv3136A, Rv3137, and Rv3230c, suggesting alternative mechanisms of drug adaptation. In addition, discordance between genotypic resistance markers and phenotypic susceptibility was observed, as classic mutations such as rpoB p.Ser450Leu and katG p.Ser315Thr were detected in isolates without corresponding phenotypic resistance. Collectively, these findings demonstrate that lineage-specific genomic and transcriptional variation influences bacterial fitness, stress adaptation, and drug response. Integrating phenotypic testing with multi-omics approaches provides valuable insights into treatment heterogeneity and supports the development of precision-oriented TB diagnostics and therapeutic strategies in Ethiopia and other high-burden settings.

Biography

Tesfaye Gebreyohannis Hailemariam, PhD, is a pharmacologist and infectious disease researcher specializing in tuberculosis biology, antimicrobial resistance, translational genomics and Pharmacogenomics. He is affiliated with the Armauer Hansen Research Institute (AHRI) in Ethiopia. Dr. Tesfaye's research integrates phenotypic drug susceptibility testing, whole-genome sequencing, and transcriptomics to investigate lineage-specific variation in *Mycobacterium tuberculosis*, with a particular focus on sub-lineage 4.2.2.2 prevalent in Ethiopia. His work explores how bacterial heterogeneity influences drug response, resistance evolution, and treatment outcomes in high-burden settings. Through multidisciplinary collaborations, he aims to advance precision-oriented TB diagnostics and therapeutic strategies to improve global TB control efforts.