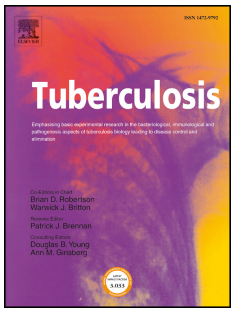
Accepted Manuscript



Genotypic drug resistance using whole-genome sequencing of *Mycobacterium tuberculosis* clinical isolates from North-western Tanzania

Benson R. Kidenya, Stephen E. Mshana, Daniel W. Fitzgerald, Oksana Ocheretina

PII: S1472-9792(17)30353-0

DOI: 10.1016/j.tube.2018.02.004

Reference: YTUBE 1673

To appear in: *Tuberculosis*

Received Date: 22 August 2017

Revised Date: 2 February 2018

Accepted Date: 17 February 2018

Please cite this article as: Kidenya BR, Mshana SE, Fitzgerald DW, Ocheretina O, Genotypic drug resistance using whole-genome sequencing of *Mycobacterium tuberculosis* clinical isolates from North-western Tanzania, *Tuberculosis* (2018), doi: 10.1016/j.tube.2018.02.004.

Genotypic Drug Resistance using Whole-genome Sequencing of *Mycobacterium tuberculosis* Clinical Isolates from North-western Tanzania

Benson R Kidenya[1*], Stephen E Mshana[2], Daniel W Fitzgerald[3], Oksana Ocheretina[3]

1. *Department of Biochemistry and Molecular Biology, Catholic University of Health and Allied Sciences, P.O. Box 1464 Mwanza, Tanzania.*
2. *Department of Medical Microbiology/Immunology, Catholic University of Health and Allied Sciences, Mwanza, Tanzania.*
3. *Center for Global Health, Division of Infectious Diseases, Weill Cornell Medical College, New York, New York, United States of America.*

***Corresponding author:** *benkidenya@yahoo.com*

ABSTRACT

Background: Drug resistant Tuberculosis (TB) is considered a global public health threat. Whole-genome sequencing (WGS) is a new technology for tuberculosis (TB) diagnostics and is capable of providing rapid drug resistance profiles and genotypes for epidemiologic surveillance. Therefore, we used WGS to determine genotypic drug resistance profiles and genetic diversity of drug resistant *Mycobacterium tuberculosis* isolates from Mwanza, North-western Tanzania.

Methods: A cross-sectional study was conducted at the Bugando Medical Centre (BMC) from September 2014 to June 2015. Consecutively, smear-positive newly diagnosed TB patients aged ≥18 years were enrolled. Sputum samples were cultured on Löwenstein-Jensen (LJ) slants. Mycobacterial genomic DNA was extracted for WGS to determine drug resistant mutations for first and second line drugs as well as the spoligotypes.

Results: A total of 78 newly diagnosed patients with pulmonary TB with a median age of 37 [IQR: 30 – 46] years were enrolled. Of these, 57.8% (45/74) were males and 34.6% (27/78) were HIV infected. *Mycobacterium tuberculosis* genomic DNA for WGS was obtained from isolates in 74 (94.9%) patients. Of the 74 isolates, six (8.1%) isolates harbored mutations for resistance to at least one drug. The resistance to the drugs was isoniazid 3/74 (4.1%), rifampicin mono-resistant 2/74 (2.7%), ethambutol 2/74 (2.7%) and streptomycin 1/74 (1.4%). None was isoniazid mono-resistant. Of the 74 only one (1.4%) patient had MDR-TB. The resistance to ethionamide, the second line drug, was detected in one patient (1.4%). None was resistant to pyrazinamide, fluoroquinolones, kanamycin, amikacin, or capreomycin. The mutations detected were *mabA-inhA* promoter region C(-15)T and *katG* Ser513Thr for isoniazid; *rpoB* His526Leu and *rpoB* Ser531Leu for rifampicin; *embB* Met306Val and *embB* Met306Ile for ethambutol; *rpsL* Lys43Arg for streptomycin; and *mabA-inhA* promoter region C(-15)T for ethionamide. The spoligotypes of the drug resistant *Mycobacterium tuberculosis* were distinct to all six isolates and belonged to T1, T2, T3-ETH, CAS1-DELHI, EAI5 and LAM11-ZWE lineages.

Conclusion: The genetic drug resistance profile of *Mycobacterium tuberculosis* isolates from North-western Tanzania comprises of the common previously reported mutations. The prevalence of resistance to first and second line drugs including MDR-TB is low. Six drug