A standardised method for interpreting the association between mutations and phenotypic drug resistance in Mycobacterium tuberculosis

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Author(s) Miotto, Paolo; Tessema, Belay; Tagliani, Elisa; Chindelevitch, Leonid; Starks, Angela M.; Emerson, Claudia; Hanna, Debra; Kim, Peter S.; Liwski, Richard; Zignol, Matteo; Gilpin, Christopher; Niemann, Stefan; Denkinger, Claudia M.; Fleming, Joy; Warren, Robin M.; Crook, Derrick; Posey, James; Gagneux, Sebastien; Hoffner, Sven; Rodrigues, Camilla; Comas, Iñaki; Engelthaler, David M.; Murray, Megan; Alland, David; Rigouts, Leen; Lange, Christoph; Dheda, Keertan; Hasan, Rumina; Ranganathan, Uma Devi K.; McNerney, Ruth; Ezewudo, Matthew; Cirillo, Daniela M.; Schito, Marco; Köser, Claudio U.; Rodwell, Timothy C.
Author(s) at UniBasel Gagneux, Sebastien ;
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A clear understanding of the genetic basis of antibiotic resistance in Mycobacterium tuberculosis is required to accelerate the development of rapid drug susceptibility testing methods based on genetic sequence.Raw genotype-phenotype correlation data were extracted as part of a comprehensive systematic review to develop a standardised analytical approach for interpreting resistance associated mutations for rifampicin, isoniazid, ofloxacin/levofloxacin, moxifloxacin, amikacin, kanamycin, capreomycin, streptomycin, ethionamide/prothionamide and pyrazinamide. Mutation frequencies in resistant and susceptible isolates were calculated, together with novel statistical measures to classify mutations as high, moderate, minimal or indeterminate confidence for predicting resistance.We identified 286 confidence-graded mutations associated with resistance. Compared to phenotypic methods, sensitivity (95% CI) for rifampicin was 90.3% (89.6-90.9%), while for isoniazid it was 78.2% (77.4-79.0%) and their specificities were 96.3% (95.7-96.8%) and 94.4% (93.1-95.5%), respectively. For second-line drugs, sensitivity varied from 67.4% (64.1-70.6%) for capreomycin to 88.2% (85.1-90.9%) for moxifloxacin, with specificity ranging from 90.0% (87.1-92.5%) for moxifloxacin to 99.5% (99.0-99.8%) for amikacin.This study provides a standardised and comprehensive approach for the interpretation of mutations as predictors of M. tuberculosis drug-resistant phenotypes. These data have implications for the clinical interpretation of molecular diagnostics and next-generation sequencing as well as efficient individualised therapy for patients with drug-resistant tuberculosis.
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