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Reaching consensus on drug resistance conferring mutations

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ABSTRACT

Objective/background: Molecular-based, rapid drug-susceptibility tests are needed to guide the appropriate use of new drugs and new therapeutic regimens at the programmatic level, and to prevent a further increase in the incidence of drug-resistant tuberculosis (TB). Experts have recognized the need for a global, curated, and standardized analysis and data-sharing platform that provides a one-stop data source for clinically relevant genotypic and phenotypic information on *Mycobacterium tuberculosis*.

Methods: To this purpose, the Relational Sequencing TB Data Platform (ReSeqTB) consortium has critically reviewed the most inclusive set of published data on mutations associated with drug resistance in *M. tuberculosis* to date, and has graded a comprehensive list of globally prevalent mutations based on the strength of their association with drug resistance.

Results and Conclusions: ReSeqTB serves as a single repository for the compilation, curation, and validation of existing and newly created sequences and metadata on *M. tuberculosis* strains and will use the currently reviewed data set, validated by international experts, as a starting point until sufficient new sequence data are accumulated. This initiative is supported by a global partnership of academic institutions, public health agencies, and nongovernmental organizations including the Critical Path Institute, FIND, the World Health Organization, the New Diagnostics Working Group, the U.S. Centers for Disease Control and Prevention, and the National Institute of Allergy and Infectious Diseases and it is financially supported by the Bill & Melinda Gates Foundation.

Key strengths of the ReSeqTB Database include the following:

- A user-friendly interface designed for nonexpert or expert operability.
- A standardized and validated analysis pipeline for variant analyses of *M. tuberculosis* next-generation sequencing (NGS) data.
- Access to data beyond the published literature with dynamic and iterative updates of new data generated by global surveillance and clinical trials.
- A well-developed legal structure to ensure intellectual property rights and data ownership remain with contributors.
- A structured data-sharing architecture to restrict access to sensitive or unpublished data sets.
- Metadata standardization using CDISC: supports global, platform-independent data standards that enable information system interoperability.
- An emphasis on data quality and rigorous, expert curation with multiple quality control checks for whole-genome sequencing and other metadata.

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- Validation of NGS analysis output by an expert committee with grading of resistance conferring mutations based on rigorous statistical standards.
- Regulatory-compliant analysis pipeline and database architecture.

Successful execution of such an extensive database platform requires substantial collaboration from scientists investigating the genetic basis for drug resistance worldwide, and from developers with expertise in database design and implementation.

Conflicts of interest

All authors declare no conflicts of interest.

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