Trends in
Microbiology

CellPress
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Spotlight

Antimicrobial susceptibility prediction from genomes: a dream come true?

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Genome-based diagnostics provides relevant information to guide patient treatment and support pathogen and resistance surveillance. Recently, Coll *et al*. introduced a curated database for predicting antimicrobial resistance (AMR) from *Enterococcus faecium* genomics data, offering excellent predictive values for susceptibility to important antimicrobials. Challenges to predict resistance to last-resort antimicrobials remain.

Antimicrobials are the most effective weapon against bacterial infections; however, resistance is increasing worldwide and its burden is estimated to cause ten million deaths annually by 2050 [1]. Rapid identification of the infectious disease agent and its antimicrobial susceptibility profile is essential to administer a successful treatment, and so is the need to monitor the emergence of AMR through surveillance programs. Classic methods to determine antimicrobial susceptibility rely on culture-based procedures that, although standardized and validated, can be time-consuming and laborious. The prediction of antimicrobial susceptibility from bacterial whole-genome data represents a groundbreaking stride in the battle against infectious diseases. By scrutinizing the presence of resistance genes, mutations, and other genetic markers within the bacterial genome, experts can predict with increasing accuracy the likelihood of a strain being phenotypically resistant to antimicrobials [2,3]. This approach not only aids in identifying potential threats via surveillance programs but also facilitates the implementation of tailored therapeutic strategies, promoting more effective and personalized treatment plans. The integration of genomics into the study of AMR heralds a promising era in the field of infectious diseases, guiding clinicians towards more informed decisions for patient care and public health, for the continuous monitoring of susceptibility trends, and for dealing with the emergence of new threats [4].

As a commensal, *E. faecium* naturally inhabits the human gastrointestinal tract. However, under certain circumstances, it can become a pathogen and cause infections, particularly in immunocompromised individuals or those with underlying health conditions. Factors that contribute to the pathogenicity of *E. faecium* include the ability to acquire and transfer AMR genes, the production of virulence factors, the capacity to persist in the hospital environment, and the potential to withstand host immune responses. Understanding the genetic mechanisms leading to AMR in *E. faecium* can help to build a catalog of acquired genes and mutations predictive of AMR. In their article in *Lancet Microbe*, Coll and collaborators [5] compared phenotypic and genotypic data of the largest *E. faecium* dataset to date (n = 4382). A list of genes and mutations predictive of AMR in this species was compiled, consisting of 228 genetic markers involved in resistance to 12 antimicrobials. The diagnostic accuracy of genotypic predictions was obtained by comparing the genotypic predicted AMR and the phenotypically determined susceptibility data. The authors developed a new AMR prediction pipeline to process sequencing reads, identify genetic determinants associated with AMR, and report genotypic resistance. The database and the scripts are publicly available ([5] https://github.com/francesccoll/amr_efm_wgs).

Very accurate genotypic predictions were obtained for clinically relevant AMRs, including ampicillin, ciprofloxacin, vancomycin, and the last-resort option linezolid. High sensitivity was obtained for tetracycline, teicoplanin, and high-level resistance to aminoglycosides (streptomycin and gentamicin), although at lower specificity. Sensitivity was low for the last-resort antimicrobials daptomycin and tigecycline, for which the genetic basis of resistance is not fully described. This newly curated database improved sensitivity and specificity for detecting resistance to a number of antimicrobials, compared with existing AMR detection tools and databases, paving the way for the adoption of whole-genome sequencing (WGS) for diagnosis and surveillance of AMR in *E. faecium*.

Admittedly, this is not the first article describing genotype-to-phenotype predictions of AMR from WGS data. The novelty here is the introduction of a highly curated AMR marker database based on evidence in the scientific literature and the use of phenotypic categories defined by determination of the minimum inhibitory concentrations (MICs), as recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). From a legal perspective, proper antimicrobial therapy requires determination of an MIC or an equivalent phenotypic result, so efforts to determine the MIC based on genotypic data are highly desirable [6]. Time is essential, especially in invasive cases where time to initiate adequate treatment directly correlates with survival rate [7].

It is interesting to observe how MIC distributions for the isolates differed substantially between antimicrobials, with the presence of certain AMR markers correlating close to 100% with the clinical breakpoints for resistance to ampicillin, ciprofloxacin, and vancomycin. For linezolid, however, quite a high number of phenotypically susceptible isolates carried genotypic resistance markers lowering its positive predictive

value (PPV). Conversely, several phenotypically daptomycin-resistant isolates had no genetic determinant identified. The authors clearly address difficulties in identifying and/or validating genetic resistance markers to last-resort antimicrobials, an aspect widely ignored in previous studies. These are often multifactorial, partly, or even widely unknown, and are further complicated by the fact that phenotypic testing for these antimicrobials is often challenging as well. This is especially intriguing since administration of these compounds should be done properly, based on valid diagnostics and according to strict guidelines. Efforts should be made to elucidate relevant mechanisms and to be able to predict the basis for the development of resistance more validly. Next steps could involve machine learning-based AMR predictions for complicated and unknown resistances [8].

The benefit of genome-based diagnostics is obvious; it offers relevant information to initiate and guide individual patient treatment and the possibility to support infection prevention and control using a single method. Recent point-of-care applications of next-generation sequencing technologies, resulting in faster WGS protocols, real-time processing of raw data, and real-time bioinformatics analyses, have increased the chances of obtaining a reliable genome-based taxonomic and resistance prediction [9]. However, as described by Coll and coworkers [7], for certain antimicrobials the genetic underpinnings of resistance are not fully characterized, causing challenges in data interpretation. In addition, a well-curated and constantly updated AMR database for each bacterial species is key for optimal use. The method employed by Coll and colleagues should now be extended to other pathogens of clinical significance and should be endorsed by key stakeholders, such as the World Health Organization (WHO), similarly to what has been done for *Mycobacterium tuberculosis* (https://www.who.int/publications/i/item/9789240082410). The ultimate scenario is direct sample sequencing enabling real-time, point-of-care species identification and resistance prediction to guide individual patient therapy and support pathogen and resistance surveillance [8–10].

Acknowledgments

This manuscript is endorsed by the ESCMID Study Groups for Epidemiological Markers (ESGEM) and for Genomic and Molecular Diagnostics (ESGMD).

Declaration of interests

All authors declare no conflict of interest.

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https://doi.org/10.1016/j.tim.2024.02.012

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