Prediction of the intestinal resistome by a three-dimensional structure-based method

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Background. The gut microbiota harbours an allegedly vast diversity of antibiotic resistance determinants (ARDs) yet their census (i.e. the resistome) has not been previously determined. Indeed, bioinformatic tools are stymied by the identity gap between known ARDs and those of bacteria from the gut microbiota. Thus, whether subjects can be stratified according to their resistome remains unanswered. Here, we used a new 3-dimensional modeling based approach to accurately identify ARDs. We then stratified MetaHIT subjects with regards to their gut resistome.
Methods. We developed a new method of functional annotation named pairwise comparative modelling (PCM). Homology modeling of candidates with templates (PDB) identified as (i) reference on one hand, and (ii) negative on the other hand are compared. Scores generated by the two modeling paths were compared and the candidates classified into the most appropriate category. When tested with an external functional metagenomic dataset, ARD predictions by were 99.1% (1,380/1,391) true. We then queried the 3.9M MetaHIT gene catalogue for ARDs belonging to 20 classes, conferring resistance to nine major antibiotic families. We attempted to stratify 663 subjects from the MetaHIT cohort according to their ARDs class distributions, and assessed the possible connexions between gut resistome, richness and enterotypes.
Results. Using the PCM, we identified 6,095 ARDs candidates among which half had an amino-acid identity below 30%. ARDs candidates were assigned to Firmicutes (49%), Bacteroidetes (14%) and Proteobacteria (4%) phyla, while 29% remained unassigned. The distribution of phyla varied according to the ARD family: aminoglycosides-modifying enzymes (AMEs) and class B beta-lactamases (bla) were enriched in Firmicutes while class A bla and Sul were enriched in Bacteroidetes. Of note, we predicted four ARDs in Methanobrevibacter and three in Methanoculleus. A chromosomal localization was suggested for 59.9% of ARDs. Mapping reads frequencies ranged from 0.18% to 0.52% per metagenomes. Six ARD clusters, using distribution patterns of ARDs classes, were detected. We observed that ARDs richness was positively correlated with overall gene richness and that ARDs clusters were associated with enterotypes: *Bacteroides* driven enterotype was associated with two ARD clusters enriched in class D beta-lactamases and tetracycline resistance conferring Tet(X), while Clostridiales driven enterotype was associated with three ARD clusters enriched in AMEs and *Prevotella* driven enterotype with a class B1-bla enriched cluster.
Conclusions. The human gut resistome was associated with gene richness and enterotypes. Our findings open perspectives in deciphering the variable response of the gut microbiota to antibiotics.
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