Extensive characterisation of the gut resistome yields new insights about the microbiome

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Abstract

Background: The gut resistome (harbors an allegedly vast density of antibiotic resistance determinants (ARDs)) yet remains largely uncharacterized. Although bacterial taxa can be assigned to 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 open, and this was now studied by functional metagenomic similarity (MetaHIT) technology. Our Methods: We developed a new method of functional metagenomic similarity (MetaHIT) technology, using the functional resistome of metagenomes (CARD) and CARD-MERGETAG, which allowed us to identify ARDs. We then quantified the MetaHIT sites, and we searched for ARDs in the CARD database. We then enumerated the ARDs in each sample and compared them between subjects. The results of the MetaHIT technology were compared with those of the CARD database, which served as a reference. Results: We identified 1727 ARDs, and we found that the MetaHIT sites were highly correlated with the CARD database. Conclusions: This study provides insights into the relationship between the resistome and the microbiome.

Materials and Methods

• Pairwise comparative modeling (PCM) is a method based on a comparison between two modeling paths of one candidate: one path uses a reference template, the other uses negative reference templates that do not share the function but some sequence identity with candidate (Figure 1).

• PCM is first applied on reference ARD and negative references to build a model by logistic regression (Figure 2). Then, the modeling and alignment scores of the candidates are submitted to the model and a confidence score (the percentage of times the candidates has been classified as an ARD) is obtained.

Results/discussion

• 10077 ARD candidates were identified: 6095 were predicted as ARD with >50% confidence (Figure 3). 28% of the predicted ARDs could not be assigned a phylum (Figure 4). PCM showed 99.1% sensitivity (Figure 5). Predicted ARDs richness appeared to be positively correlated with the overall richness among subjects of MetaHIT1 cohort (Figure 7).

Conclusion

• PCM appears to be efficient in predicting ARDs, even when aminoacid identity is low and to be more sensitive than conventional one-dimensional methods.

• The Human resistome was associated with gene richness and enterotypes. Our findings open perspectives in deciphering the variable response of the gut microbiota to antibiotics.