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Applications Note

OXFORD

Sequence analysis

ResistoMap—online visualization of human gut microbiota antibiotic resistome

Konstantin S. Yarygin[1,2,*], Boris A. Kovarsky[2], Tatyana S. Bibikova[3], Damir S. Melnikov[3], Alexander V. Tyakht[1,2] and Dmitry G. Alexeev[1,2]

[1]Moscow Institute of Physics and Technology (MIPT), 9 Institutskiy per, Dolgoprudny, Moscow Region 141700, Russian Federation, [2]Federal Research and Clinical Centre of Physical-Chemical Medicine (FRCC PCM), Malaya Pirogovskaya 1a, Moscow 119435, Russian Federation and [3]Data Laboratory, Kostycheva 64-12, Bryansk 241037, Russian Federation

*To whom correspondence should be addressed.

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Abstract

We created ResistoMap—a Web-based interactive visualization of the presence of genetic determinants conferring resistance to antibiotics, biocides and heavy metals in human gut microbiota. ResistoMap displays the data on more than 1500 published gut metagenomes of world populations including both healthy subjects and patients. Multiparameter display filters allow visual assessment of the associations between the meta-data and proportions of resistome. The geographic map navigation layer allows to state hypotheses regarding the global trends of antibiotic resistance and correlates the gut resistome variations with the national clinical guidelines on antibiotics application.

Availability and Implementation: ResistoMap was implemented using AngularJS, CoffeeScript, D3.js and TopoJSON. The tool is publicly available at http://resistomap.rcpcm.org.

Contact: yarygin@phystech.edu

Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Microbial drug resistance is a global healthcare problem caused by the extensive uncontrolled use of antibiotics in medicine and agriculture. It is predicted that toward 2050 around 10 million people will die annually for reasons connected with drug resistance (O'Neill, 2016). Although resistant pathogens are the main concern, the global microbial channels of gene exchange existing between unrelated microbial taxa allow commensal microbes to share resistance genes with opportunists.

Human gut microbiota is increasingly viewed as a clinically important reservoir of drug resistance (Willmann and Peter, 2017). Among other human-associated communities, this one is the largest and most intimately involved in host health. The pool of antibiotic resistance (AR) genes that increases in abundance during antibiotic treatment becomes a 'tinderbox': the transmission of these genes to a pathogen has dire consequences for both the patient and society.

Semi-quantitative analysis of the functional composition of microbiota using 'shotgun' metagenomics allows the assessment of relative abundance of AR genes in human microbiota and thus provides a personalized prediction for the capacity of microbiota to contribute to the onset of resistant pathogens. Vast volumes of metagenomes have been published that provide the opportunity to estimate the variation of resistome between the subjects, healthy populations of the world as well as the clinical cohorts. However, there is a lack of visual tools for exploratory analysis of such data; moreover, there is no integrated database of gut resistome profiles.

Here we present ResistoMap, an interactive tool for comprehensive visualization of the gut resistome in populations of the world. The displayed features include the relative abundance of AR genes, AR-conferring mutations as well as genes conferring resistance to biocides and heavy metals. ResistoMap is a perspective tool for exploring the global landscape of gut resistome in order to identify national

traits in antibiotic intake, correlating the resistome composition with various external factors and generate biomedical hypotheses that can help to control the drug resistance on a global scale.

2 Implementation

2.1 Navigation

ResistoMap contains two main interactive work fields—a geographic map and a heatmap. The heatmap displays the median relative levels of determinants conferring resistance to each of the antibiotic groups (columns) in each selected cohort of subjects (rows). The values were precomputed by classifying the gut metagenomic reads from 12 publicly available studies (see section 2.2). The number of metagenomes included in the cohort is displayed on the left from the heatmap below the colour key.

The heatmap contains four vertical sections corresponding to different types of resistome quantification:

1. levels of AR-conferring genes
2. levels of mutations in target genes
3. levels of genes conferring resistance to biocides (total)
4. levels of genes conferring resistance to heavy metal (total)

Using the drop-down lists at the top of the screen, users can choose the antibiotic group of interest, the study(-ies) and/or the country (-ies) to be displayed on the heatmap. To filter the cohort, users can use 'Pool by' checkboxes that allow the stratification of cohorts by country of origin, gender, age and diagnosis (where applicable). It is possible to sort the rows of the heatmap by the number of samples and resistance level (by mean value or a selected antibiotic). For convenience of comparison between close values, clicking on a cell 'freezes'/'unfreezes' the displayed abundance value on the right.

2.2 Metagenomic data

The datasets for the analysis of resistome included 1593 gut metagenomes from the individuals from 12 studies covering 15 countries (Clemente *et al.*, 2015; Consortium *et al.*, 2012; Karlsson *et al.*, 2013; Nielsen *et al.*, 2014; Nishijima *et al.*, 2016; Obregon-Tito *et al.*, 2015; Qin *et al.*, 2012; Rampelli *et al.*, 2015; Tyakht *et al.*, 2013; Yap *et al.*, 2013; Zeevi *et al.*, 2015; Zeller *et al.*, 2014). For each metagenome, additional factors including country of origin, gender, age and clinical status were considered (where available).

Using ResistoMap, one can estimate the global landscape of resistance potential to different groups of antibiotics as well as infer associations between specific drugs and clinical meta-data. It is important to provide a diverse reference database of the resistance genes in order to draw adequate conclusions from metagenomic data; such databases are constantly expanding, and already, using current data we have discovered a number of interesting patterns, some of which are in agreement with available epidemiological data while others are non-intuitive and await interpretations from a clinical perspective (see Supplementary Material). Although the precision of the resistome profile comparison between different studies may be limited due to variations in sample preparation protocols, the exploratory analysis of global gut resistome using ResistoMap shows global trends that will gain new insights and contribute to the spread of antibiotic stewardship and rational use of antimicrobial substances in agriculture.

2.3 User contributions

It is possible to contribute published datasets to ResistoMap by following the instructions on the site ("Add your data" button).

3 Data processing

The relative abundance of resistance-conferring genes was evaluated by mapping the metagenomic reads to the CARD database v.1.0.5 (McArthur *et al.*, 2013) and normalizing the gene coverage. The potential resistance-conferring mutations were analyzed using the published list of such mutations (Elbehery *et al.*, 2016) and PATRIC database (Wattam *et al.*, 2013). The levels of resistance to heavy metals and biocides were assessed using the BacMet database (Pal *et al.*, 2014). Details of these steps are described in the Supplementary Data.

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