

A Roadmap of The Human Body Resistome

Lucia Maestre-Carballa

University of Alicante: Universitat d'Alacant

Vicente Navarro

Hospital de Vinalopó: Hospital Universitario del Vinalopó

Manuel Martinez-Garcia (✉ m.martinez@ua.es)

Universitat d'Alacant <https://orcid.org/0000-0001-5056-1525>

Research

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Abstract

Background

In response to the global antibiotic resistance crisis, efforts have been focused on gaining a better understanding of resistomes (sets of antibiotic resistance genes (ARGs)) and the dispersion of ARGs in nature. A comprehensive metagenomic characterization of the human body resistome is paramount for laying the foundation to develop a better strategy to address this health concern. Here, we study the resistomes of 771 samples from five major body parts of healthy subjects from the Human Microbiome Project (HMP). In line with the One Health concept (WHO), we also investigated the presence of ARGs from the HMP in 272 pristine environments.

Results

Of all the detected HMP genes/proteins ($9.17E+07$), 40,816 were ARGs showing high interindividual and inter-body-site abundance variability. Nares had the highest ARG abundance (2.18 ± 2.64 ARGs/Mb; ≈ 5.5 ARG per bacterial genome), while the gut (0.34 ± 0.34 ARGs/Mb; ≈ 1.3 ARG per bacterial genome), which also showed the highest richness of different ARG types, had the lowest abundance. Fluoroquinolone resistance genes were the most abundant antibiotic resistance gene family, followed by MLS or tetracycline resistance genes, depending on the body site. From all the detected ARGs, we found 366 different ARG types, with *parC R* (fluoroquinolone resistance) being the most abundant in the oral cavity, *mprF* (peptide antibiotic resistance) in the skin and nares, and *tetQ* (tetracycline resistance) in the gut and vagina. Most of the ARGs belonged to common bacterial commensals, and many of them were also multidrug resistance genes and were more abundant in the nares and vagina.

The total number of ARGs from the HMP data ($n=34$) detected in pristine environments (266 samples) was negligible, and most of them (73%) were classified as housekeeping genes in autochthonous bacteria having known mutations conferring antibiotic resistance (natural reservoirs). A significant fraction of ARGs (24%) in pristine environments were actually from exogenous contaminants. The detection of identical HMP ARGs in autochthonous bacteria was extremely infrequent (3%).

Conclusions

Our results comprehensively reveal the resistomes from all body parts and HMP samples that can serve as a baseline for comparison for long-term survey and monitoring of human resistome variations. Finally, our data provide hope, since the spread of common ARGs from the HMP data to pristine environments thus far remains very unlikely.

Full Text

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Figures

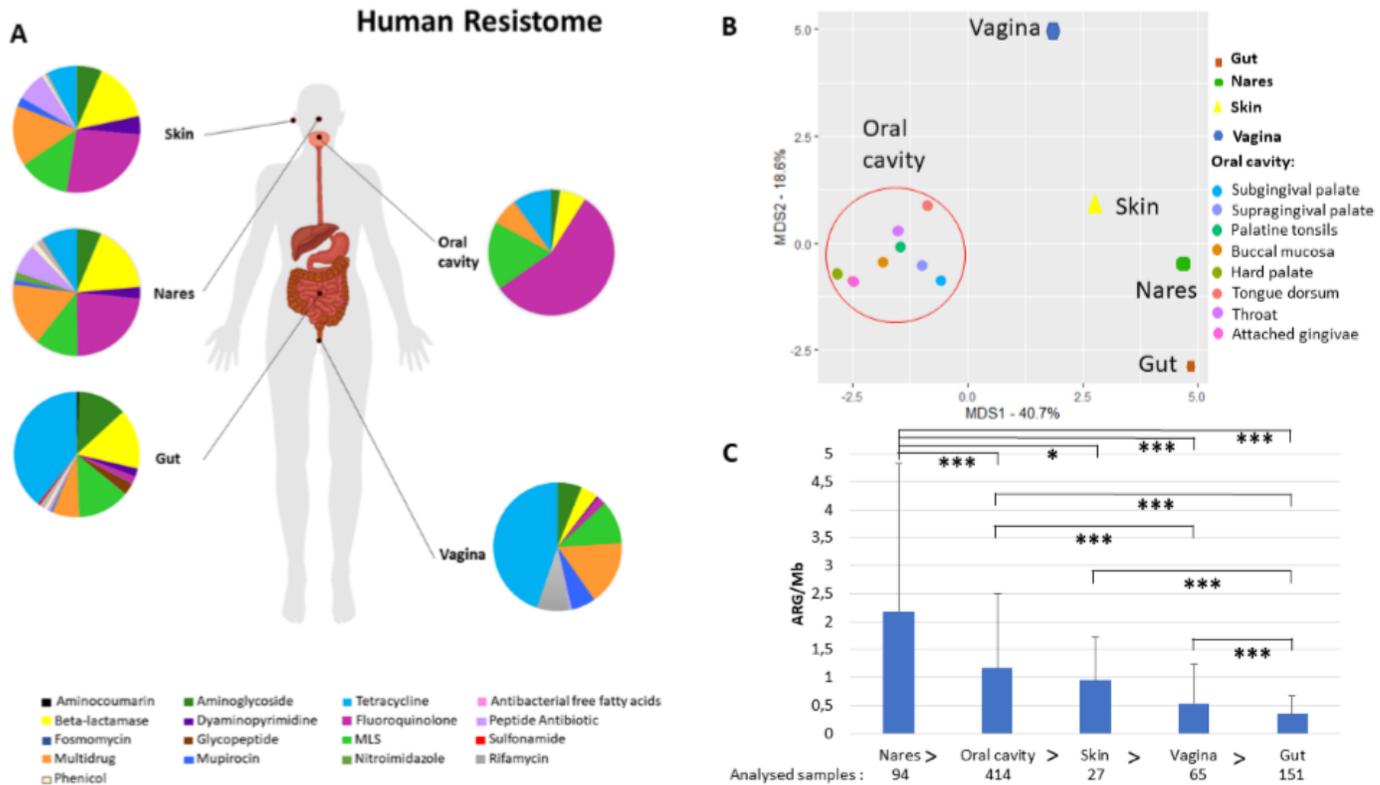


Figure 1

Human Resistome. Human atlas of the ARGs grouped by AR families present in different body parts. The body groups studied were the gut, the skin (retroauricular crease), vagina (posterior-fornix, mid vagina and vagina intraotus), the nares and the oral cavity (hard palate, buccal mucosa, saliva, subgingival plaque, attached gingivae, tongue dorsum, throat, palatine tonsils, and supragingival plaque) (A). PCoA analysis of the different body sites distributed according to their relative abundance of AR families (B). The samples included in the group oral cavity (hard palate, buccal mucosa, saliva, subgingival plaque, attached gingivae, tongue dorsum, throat, palatine tonsils, and supragingival plaque-shaped as a circle)-gathered and separately from the other body sites analysed. Abundance of antibiotic resistance genes calculated as ARGs hits per assembled Mb and number of samples included in each body group (C). Welch test was performed to compare ARG abundances between different body sites. All paired samples showed statistically significant differences but the oral cavity and the skin and the vagina and the skin. P-values (P) considered as significant were indicated with an asterisk: $P \leq 0.05$ *, $P \leq 0.01$ **, $P \leq 0.001$ ***.

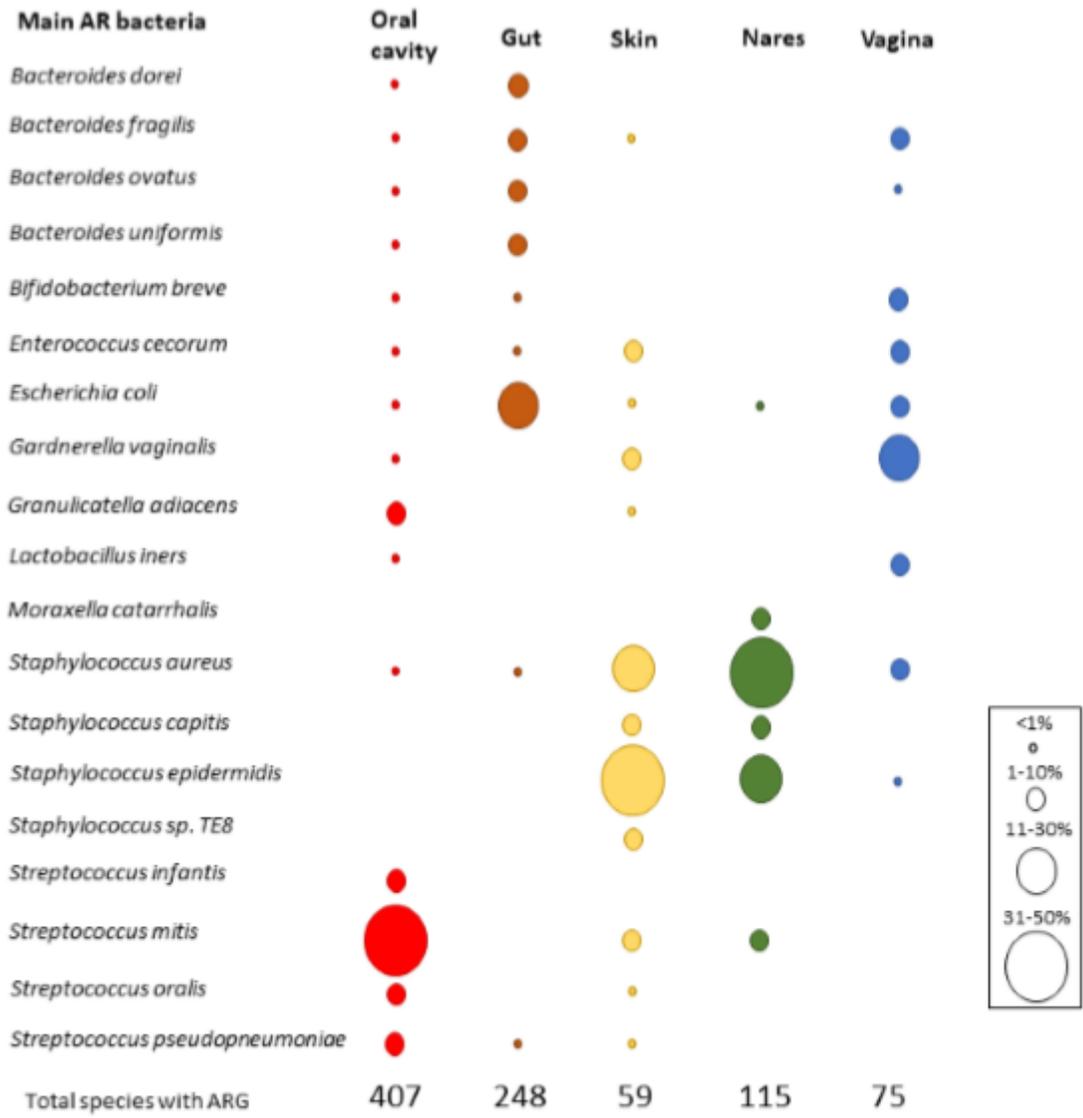


Figure 2

Main antibiotic resistant bacteria in HMP dataset. Relative abundance of the most abundant resistant bacteria. Top five bacteria were chosen in each body part and then the graphic was completed with the relative frequency of all the chosen bacteria in all body parts. Circle sizes were different to determine the relative abundance of each species and colours were used to differentiate the body parts (red-oral cavity, brown-gut, skin-yellow,green-nares,blue-vagina). At the bottom of the graphic the number of different species that carried ARGs is shown.

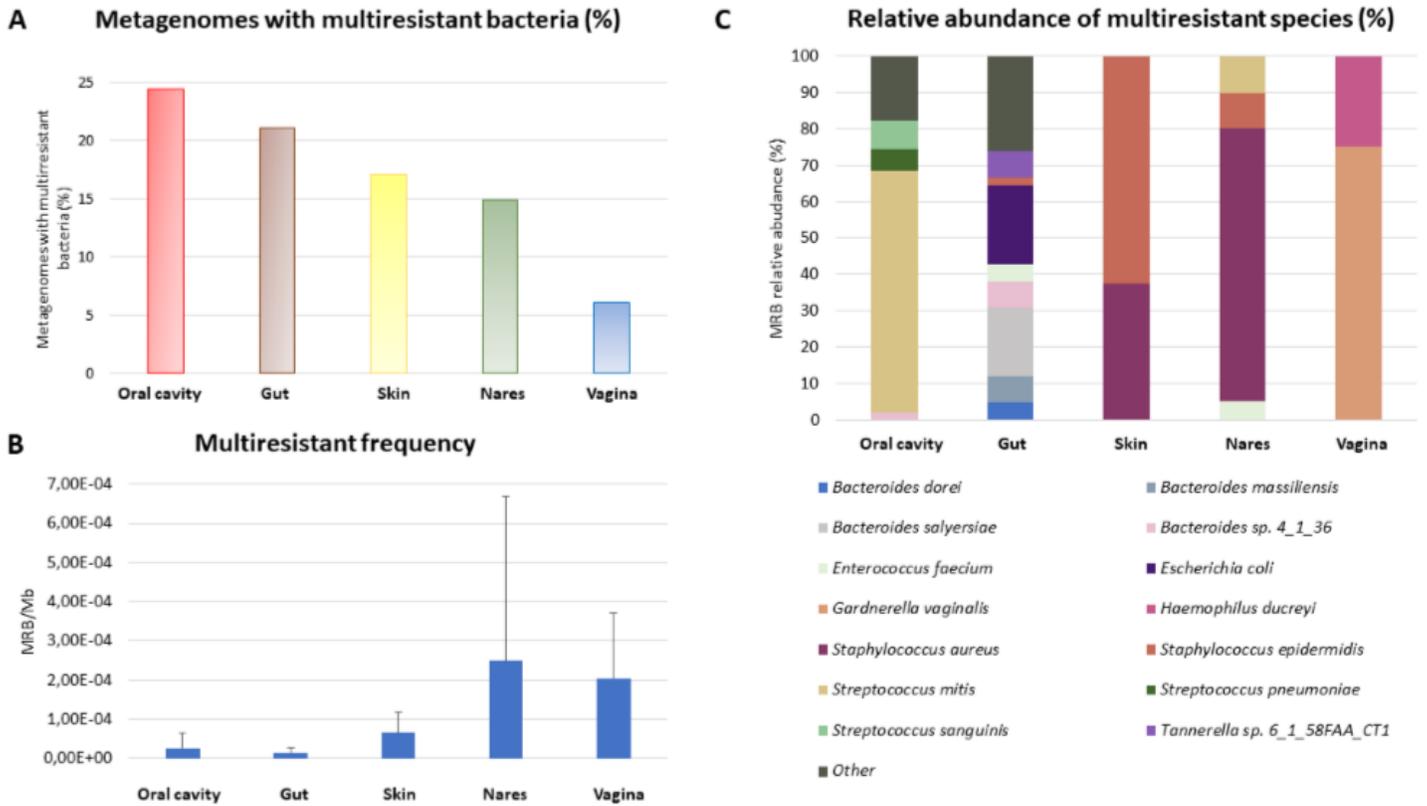


Figure 3

Multiresistance in the human body. Those assembled genome fragments (i.e. contigs) that had more than one ARG conferring resistance to at least 2 different antibiotic families were considered as multiresistant (MR). Percentage of metagenomes with multiresistant contigs compared with all the metagenomes studied from the same HMP sample (A). Study of the multiresistant contigs frequency (B), to compare the different samples, the number of multiresistant contigs was divided by the assembled Mb. Standard deviation is shown in the graphic. Relative abundance of the most abundant MR (C). Only MR whose relative abundance was, at least in one body site, equal or greater than 5% were represented.

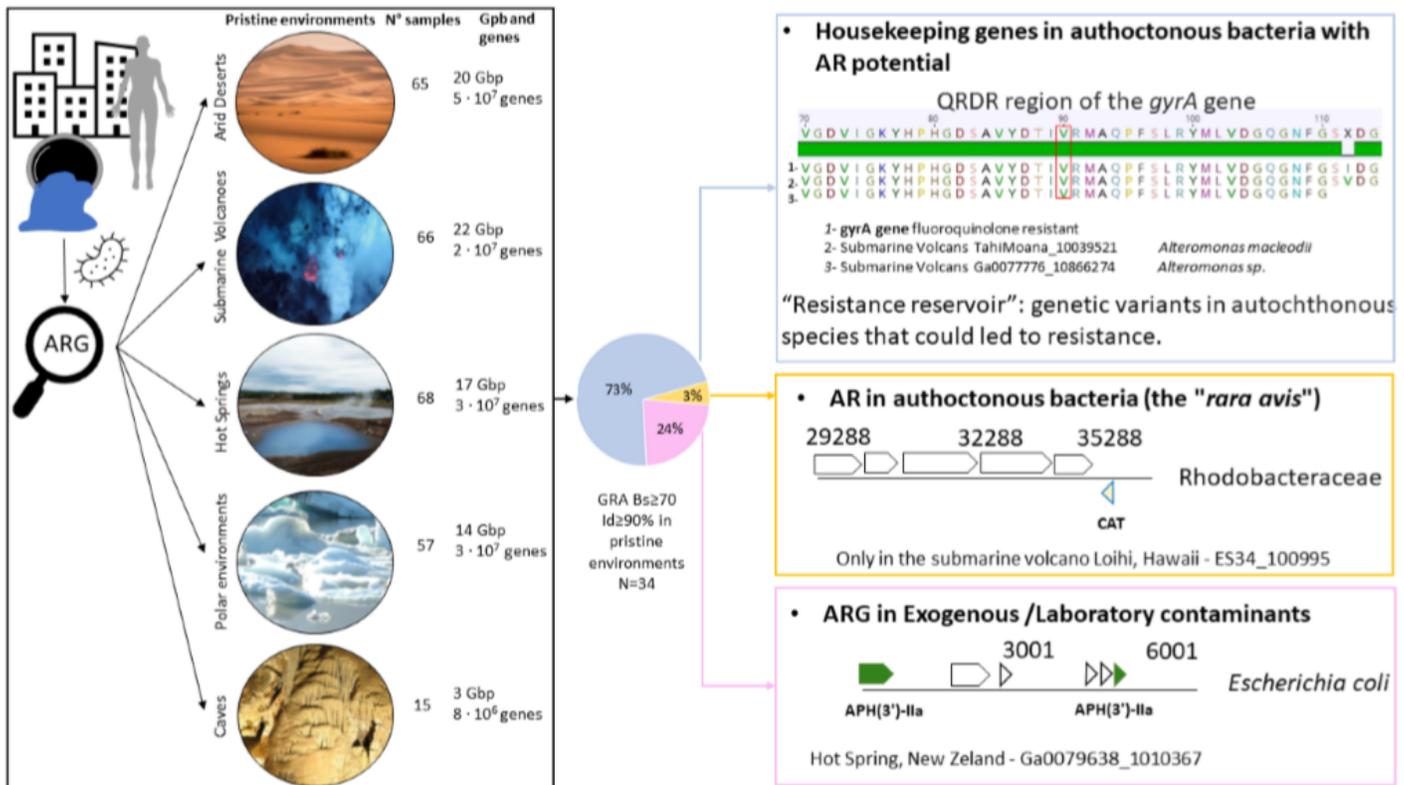


Figure 4

Detection of ARGs from Human Microbiome Project dataset in pristine environments. The dispersion of ARGs found in the HMP samples analysed was analyzed in 5 different types of pristine environments. Those environments were classified as arid deserts (n=65), submarine volcanoes (n=66), hot springs (n=68), polar environment (n=57) and caves (n=15). Only 35 genes were found in those environments in contigs with at least 4 proteins, an amino acid identity of 90% and a bit-score of 70 compared with the HMP antibiotic resistance genes. The found genes could be divided in three groups: housekeeping genes with mutations that could lead to resistance, genes that belonged to exogenous or laboratory contaminants and ARGs present in autochthonous bacteria, which was the less frequent case. Desert photo taken from Boris Ulzibat (PEXELS). Submarine volcano photograph courtesy of NOAA / NSF / WHOI page (<https://oceanexplorer.noaa.gov/facts/volcanoes.html>).