GENOME WATCH

Beyond the census of human gut dwellers

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This month's Genome Watch highlights the use of genome-centric approaches to further our understanding of the human gut microbiome.

The human gastrointestinal tract microbiota has moved increasingly into the spotlight as we have realized that our trillions of gut residents affect our health and well-being. Numerous studies have associated changes in the gut microbiome with disease phenotypes, including type 2 diabetes, obesity, liver diseases, cancer and even neurodegenerative and cardiovascular diseases. These studies have largely focused on 16S ribosomal RNA gene amplicon-based or gene-centric microbial community analyses. Moving beyond such census approaches, a genome-centric approach has been featured in a recent burst of publications.

Zou et al.¹ generated more than 1,500 reference genomes from faecal isolates derived from healthy individuals from China. These were selected from >6,000 cultures and cover most core genera of the gut microbiota. With this new reference catalogue, dubbed the Culturable Genome Reference (CGR), the authors improved sequence mapping of faecal shotgun metagenomes and further highlighted its usefulness in calling SNPs and pan-genome analysis. Predicting the functional potential of the gut isolates revealed proteobacterial genes encoding proteins for xenobiotic degradation, which might have implications for drug therapies.

Forster et al.² sequenced the genomes of over 700 bacteria isolated from faeces of individuals in North America and the United Kingdom. Combined with >600 genomes of human gut microorganisms, the resulting global Human Gastrointestinal Bacteria Genome Collection (HGG) — like the CGR — improved taxonomic classification of faecal metagenome sequences, here bins, by more than 60%. Remarkably, when mapping metagenome contigs to HGG, subspecies level

assignment was achieved for more than 40% of the sequences.

Two additional recent studies by Almeida et al.³ and Nayfach et al.⁴ used genome-resolved metagenomics to investigate the gut microbiome, and a third study more broadly spanned various human body sites⁵. Almeida and colleagues extracted 92,143 bacterial metagenome-assembled genomes (MAGs) from faecal microbiomes of primarily North American and European origin, representing nearly 2,000 candidate bacterial species. These MAGs increased phylogenetic diversity by more than 280-fold compared with known human gut bacterial lineages. As in previous studies, metagenome read assignments were improved, most considerably in data sets from Africa and South America, underscoring the need to sample the gut microbiota at geographic breadth. A comparison of the functional profiles of MAGs and isolate genomes revealed a depletion of genes encoding antioxidant and redox functions in MAGs, which is suggestive of lower tolerance to reactive oxygen species, which could impede their cultivability.

Nayfach and colleagues, through a similar approach, reconstructed >60,000 bacterial and archaeal MAGs from a geographically and host phenotypically diverse set of human faecal metagenomes, which yielded >2,000 novel candidate species. The authors used host clinical metadata to associate MAG-derived gut species and disease. A striking example was the depletion of a novel candidate species of Negativicutes in patients with ankylosing spondylitis, as compared with their healthy counterparts. Nayfach et al. also compared the functional profiles of MAGs and their cultivated relatives, which likewise revealed trends suggestive of higher sensitivity of uncultivated bacteria to oxygen.

These studies highlight the critical importance of quality reference genomic catalogues

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derived from both cultivated and uncultivated community members and from diverse data sets. Such catalogues enhance taxonomic assignment to improve metagenome data interpretation, provide a tracking system for polymorphisms in gut microbial communities and facilitate the quantitative characterization of meta-omic data. These efforts provide great strides towards an improved understanding of how our microbial gut dwellers affect health and disease, which may ultimately facilitate the development of novel microbiome-based therapeutics.

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Competing interests

The author declares no competing interests.