



## GENOME WATCH

# Metagenomics for surveillance of respiratory pathogens

Victoria R. Carr  and Chrispin Chaguz

This month's Genome Watch highlights how metagenomics can be used for surveillance and studying infections with respiratory pathogens.

High-throughput sequencing of single isolate genomes has enabled us to explore the phylogeny and track the aetiology of known pathogens. However, this approach relies on culturing the pathogen, limiting rapid discovery of novel and unculturable species. Metagenomic sequencing has been making waves in discovering new microorganisms and directing our understanding of the compositions and interactions within microbial communities. Here, we refer to metagenomic sequencing as only whole or shotgun sequencing, and not including amplicon sequencing.

An early metagenomic study of nasopharyngeal sites detected seven human viral species known to cause respiratory illness, one of which was a human coronavirus genome that had been discovered previously but was still uncharacterized at that time<sup>1</sup>. Recent advances in next-generation sequencing and the advent of third-generation sequencing enabled the discovery and characterization of novel pathogens from whole metagenomes. In fact, the novel SARS-CoV-2 coronavirus was first identified and characterized from RNA metagenomes of the lower respiratory tract of infected patients using a combination of Illumina and Oxford Nanopore sequencing<sup>2</sup>. The metagenomic reads were assembled into longer contiguous sequences, and the gaps were filled with PCR to resolve the complete genome.

Charalampous et al. showed that metagenomic detection was highly sensitive to bacterial and viral pathogens in 40 patients with suspected lower respiratory tract infections, but was not as specific without performing a complementary standard molecular test and pathobiont-specific gene analyses<sup>3</sup>. Thus, more rapid and cheaper nanopore technologies could be feasible diagnostics of respiratory infections of known and unknown aetiology.

Metagenomics have also been applied to study the ecology of microbial environments and compositions of microbial genomes within them. Most studies focused on the gut microbiota, possibly as it was minimally invasive to collect stool samples, and because the higher yield of microbial material in stool samples made it easier to extract microbial DNA than from respiratory tract flora. As DNA and RNA extraction techniques are constantly improving, researchers have become better equipped at profiling metagenomes from the respiratory system. However, due to the invasive process of sampling the respiratory tract, especially in the lower regions, there are fewer opportunities to collect samples from healthy participants or patients with acute infections. This has possibly influenced a study bias towards sampling individuals with chronic respiratory illnesses, such as cystic fibrosis, as patients who visit the clinic frequently are likely to undergo invasive sample collections directly from the lungs.

Chronic infection of *Pseudomonas aeruginosa* in the airways of patients with cystic fibrosis is strongly associated with microbial 'dysbiosis'. The dynamics of the microbiota

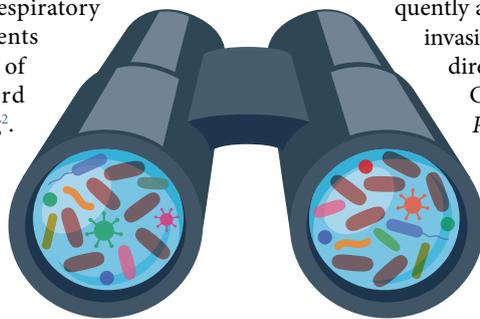
composition and its interaction with the host immune system are unique to individuals. A whole metagenome study by Bacci et al. comparing individuals with cystic fibrosis showed that they had heterogeneous microbiota compositions that were dynamic short-term between clinical statuses, but shared core gene profiles, including antimicrobial resistance genes<sup>4</sup>. As well as labelling the presence of respiratory pathogens as markers for infections, the influence of host–microbiome interactions on clinical outcomes of respiratory diseases should be investigated using metagenomic methods.

Better extraction protocols and sequencing depths have helped characterize and untangle interactions between pathogens, commensals and pathobionts from complex microbial communities, and antimicrobial resistance and virulence traits in the human microbiome. Not only has metagenomic sequencing become crucial in discovering emergent respiratory pathogens, but it has potential to guide our understanding of how microbial interactions within a given environment influence the aetiology and course of respiratory infections.

Victoria R. Carr  and Chrispin Chaguz   
Parasites and Microbes, Wellcome Sanger Institute,  
Wellcome Genome Campus, Hinxton, UK  
✉e-mail: [vc11@sanger.ac.uk](mailto:vc11@sanger.ac.uk); [cc19@sanger.ac.uk](mailto:cc19@sanger.ac.uk)  
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**Competing interests**  
The authors declare no competing interests.



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