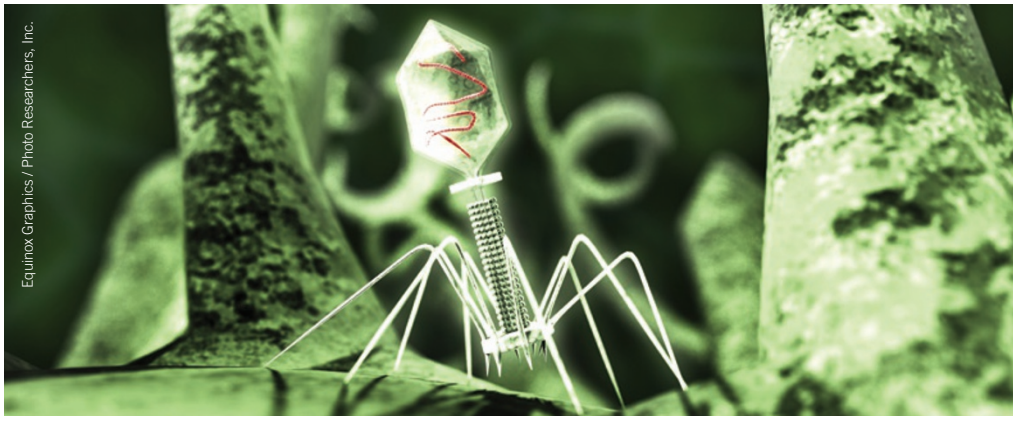
Sequencing reveals suite of commensal and pathogenic viruses



Feather in your capsid: Researchers make headway sequencing the human virome.

VANCOUVER, CANADA — After coming to realize that symbiotic bacteria play a large part in running our bodies, scientists are slowly beginning to appreciate the importance of our viral communities, too. As researchers discussed here last month at the International Human Microbiome Congress, new sequencing techniques are revealing that these viruses—collectively called the 'virome'—often differ significantly between healthy and diseased individuals.

"There's no question that these viral populations are affecting human health," says Frederic Bushman, a molecular virologist at the University of Pennsylvania School of Medicine in Philadelphia. "But we're just at an early stage in figuring out who's there and what they're doing. Well down the road we'll be asking how to engineer [the virome] to affect health outcomes."

Metagenomic studies of viral communities trace their roots back to 2003 when Forest Rohwer and his colleagues at San Diego State University first sequenced the bacteriophage viruses living in a single human fecal sample (*J. Bacteriol.* **185**, 6220–6223, 2003). Since then, newer high-throughput sequencing methods have started to produce vastly more data on many more samples, yet the applications of virome studies to disease are only just starting to be worked out.

To better understand the links between viruses and diet, for example, Bushman and his colleagues placed five people on either a high-fat or a low-fat diet and then sequenced their stool samples over a ten-day period. Reporting at the March meeting, Bushman showed that the bacteriophage populations of people on the same diets grew more similar as the experiment proceeded, raising the possibility that viral communities could be engineered to combat obesity.

At the meeting, Kristine Wylie from the Genome Center at Washington University in St. Louis also presented viral sequence data isolated from nasal swabs and blood samples taken from children with fevers of unknown cause. This analysis showed that many DNA and RNA viruses, particularly mastadenoviruses, are more common in feverish kids compared to health controls. "This is suggesting that these fevers of unknown origin may have a viral cause," says Wylie.

Notably, Wylie's analysis flagged two recently discovered viruses that had never before been linked to fevers: an astrovirus called MLB2 characterized from stool samples taken from diarrhea sufferers in India (*Virol J.* **6**, 161, 2009) and the HRV-QPM rhinovirus first found in infants around the world with acute respiratory infections (*J. Clin. Virol.* **39**, 67–75, 2007). "If we can find new agents and demonstrate that they're linked to diseases, then perhaps interventions could be developed," says Dave Wang, a medicinal virologist at the Washington University School of Medicine in St. Louis who discovered MLB2.

Vital viruses

These recently presented studies add to a burgeoning body of evidence about the importance of the human virome in healthy and diseased individuals. For example, Rohwer and his colleagues have described viral communities from people with cystic fibrosis (*PLoS One* **4**, e7370, 2009) and, more recently, in the mouths of healthy people (*Proc. Natl. Acad. Sci. USA*, **108**, supplement 1, 4547–4553, 2011).

Last year, Rohwer, in collaboration with microbiologist Jeffrey Gordon from the Washington University School of Medicine, also characterized all the bacteriophages living in the feces of four sets of identical twins and their mothers. Unlike gut bacteria, which show a high degree of similarity between related individuals, the researchers found that the viral phage populations were unique to each person and remained relatively constant over the span of a year (*Nature* **466**, 334–338, 2010). "These phages are an indicator of our individuality," Gordon says.

Viral metagenomic studies are still in their infancy. But Eric Delwart, director of molecular virology at the Blood Systems Research Institute in San Francisco, contends that all these emerging viral sequence data should soon translate to the clinic. "Finding new viruses and showing that they're pathogens is a precursor to having a medical impact," he says. "Once you've identified viruses as pathogens, then you know where to aim your diagnostics, treatments and vaccines."

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announcement "indicates a political will to continue in the same direction" as the 2005–2008 plan, she notes.

But three of the major rare disease advocacy groups, which the government describes as partners for the plan, were initially worried. In a joint statement, the French Association against Myopathies (AFM), the European Organization for Rare Diseases (EURORDIS) and the French Rare Diseases Alliance described the eagerly awaited plan as "low-key," with insufficient attention paid to areas of therapeutic development and the organization of patient care.

Since then, however, Health Minister Xavier Bertrand has given his assurance that their demands will be met. In particular, he promised that a rare diseases coordinator would be appointed in each of France's 26 regions, says Christel Nourissier, general secretary of EURORDIS. "This is vital now that the French health service has been decentralized, because rare diseases are never a priority in the [country's] regions," she told *Nature Medicine*.

Nourissier also welcomes Bertrand's assurances that France will resume a leading role in promoting the rare disease cause at the EU level. "No country has enough resources on its own, so we all need to share our know-how," she says.

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