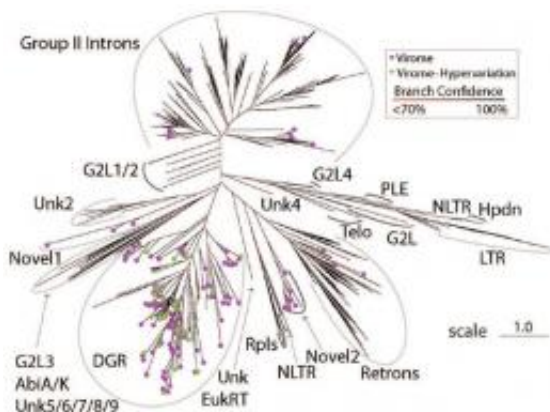


Genetic variation in human gut viruses could be raw material for inner evolution

March 19 2012, By Karen Kreeger



Phylogenetic tree of reverse transcriptase sequences. Credit: Samuel Minot, Perelman School of Medicine, University of Pennsylvania, PNAS

(PhysOrg.com) -- A growing body of evidence underscores the importance of human gut bacteria in modulating human health, metabolism, and disease. Yet bacteria are only part of the story. Viruses that infect those bacteria also shape who we are. Frederic D. Bushman, PhD, professor of Microbiology at the Perelman School of Medicine at the University of Pennsylvania, led a study published this month in the [Proceedings of the National Academy of Sciences](#) that sequenced the DNA of viruses -- the virome -- present in the gut of healthy people.

Nearly 48 billion bases of DNA, the [genetic building blocks](#), were collected in the stools of 12 individuals. The researchers then assembled

the blocks like puzzle pieces to recreate whole virus genomes. Hundreds to thousands of likely distinct viruses were assembled per individual, of which all but one type were bacteriophages — [viruses](#) that infect bacteria -- which the team expected. The other was a human pathogen, a human papillomavirus found in a single individual. Bacteriophages are responsible for the toxic effects of many bacteria, but their role in the human microbiome has only recently started to be studied.

To assess variability in the viral populations among the 12 individuals studied, Bushman's team, led by graduate student Samuel Minot, looked for stretches of bases that varied the most.

Their survey identified 51 hypervariable regions among the 12 people studied, which, to the team's surprise, were associated with reverse transcriptase genes. Reverse transcriptase enzymes, more commonly associated with replication of retroviruses such as HIV, copy RNA into [DNA](#). Of the 51 regions, 29 bore sequence and structural similarity to one well-studied reverse transcriptase, a hypervariable region in the Bordetella bacteriophage BPP-1. Bordetella is the microbe that causes kennel cough in dogs.

BPP-1 uses reverse transcriptase and an error-prone copying mechanism to modify a protein to aid in entering and reproducing in a wide array of viral targets. Bushman and colleagues speculate that the newly discovered hypervariable regions could serve a similar function in the human virome, and microbiome, by extension.

"It appears there's natural selective pressure for rapid variation for these classes of bacteriophages, which implies there's a corresponding rapidly changing environmental factor that the phage must be able to quickly adapt to," says Minot. Possible reasons for change, say the authors, include evading the immune system and keeping abreast of ever-evolving bacterial hosts — a kind of mutation-based host-pathogen arms

race. Whatever the case, Minot says, such variability may be helping to drive evolution of the gut microbiome: "The substrate of evolution is mutation."

Evolutionary analysis of the 185 reverse transcriptases discovered in this study population suggests that a large fraction of these enzymes are primarily involved in generating diversity. Now, Minot says, the challenge is to determine the function of the newly discovered hypervariable regions, and understand how their variability changes over time and in relationship to disease.

"This method opens a whole new world of 'diversity-generating' biology to discover what these clearly important systems are actually doing," he says.

In addition to Bushman and Minot, co-authors are Stephanie Grunberg (Department of [Microbiology](#)); Gary Wu (Division of Gastroenterology); and James Lewis (Department of Biostatistics and Epidemiology), all from Penn.

Provided by University of Pennsylvania School of Medicine

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