Egyptian fruit bat genome yields clues about bats' ability to harbor and transmit deadly pathogens without getting sick

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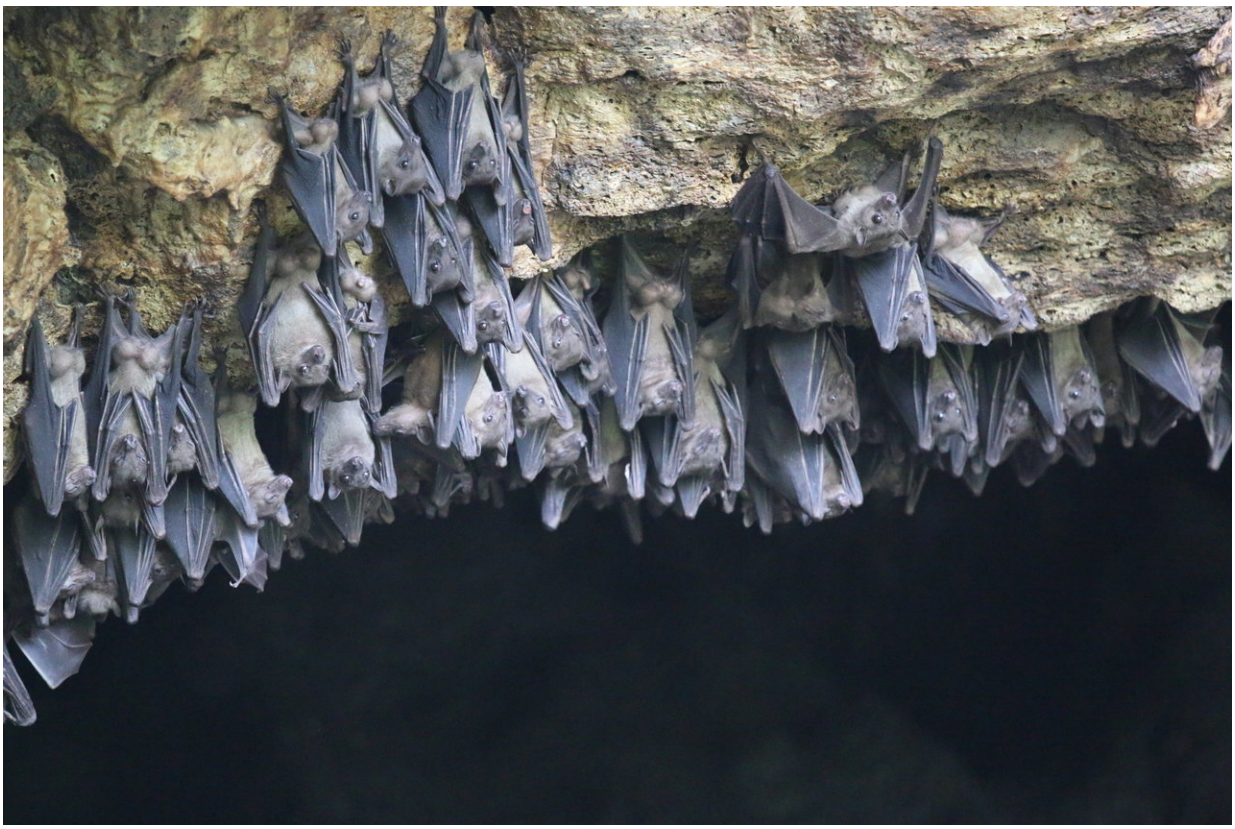

Egyptian fruit bats at Python Cave, Uganda. Bats from Python Cave caused two cases of Marburg virus disease in 2007 and 2008, one of which was fatal. Credit: Jonathan Towner

Boston University researchers, Thomas Kepler, professor of microbiology; Stephanie Pavlovich, an MD/PhD student; and Elke Mühlberger, director, Biomolecule Production Core, National Emerging Infectious Diseases Laboratories (NEIDL); in collaboration with the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) and the Centers for Disease Control and Prevention's (CDC) Viral Special Pathogens Branch, today released new research about bats' ability to harbor and transmit deadly pathogens, like Marburg virus, without getting sick themselves.

Funded by the Defense Threat Reduction Agency, the study examined the genome of *Rousettus aegyptiacus*, the Egyptian fruit bat, and found larger-than-expected families of genes related to the mammalian immune system. Specifically, researchers found large families of interferon and natural killer genes that differed dramatically from their counterparts in other mammals. The finding, published online and featured in the May 2018 print edition of *Cell*, may eventually lead to a deeper understanding of virus transmission, and better treatments for humans who become infected.

"What we learn from bats may help us in the development of pharmacological agents," says Thomas Kepler. "And more importantly, it may help us understand zoonotic transmission—how animals host a virus without being symptomatic, and pass it to humans. Exactly what is going on in that transmission? What does an animal gain by hosting a virus for a very long time, for coevolving with the virus, so that when it's transferred, it's highly virulent in the spillover host?"

Bats are now known to carry several deadly pathogens, including Marburg and a SARS-like coronavirus, and transmit disease via bite or exposure to saliva, feces, or urine.

Jonathan Towner, a scientist with the CDC's Viral Special Pathogens

Branch, decided to investigate a colony of Egyptian fruit bats implicated in a Marburg fatality in Uganda. Towner traveled to Uganda, captured uninfected bats and brought them back to the CDC. There, scientists extracted DNA from a single bat, and sent it to colleagues at USAMRIID for initial sequencing. The USAMRIID scientists sent their data to Stephanie Pavlovich, student in Thomas Kepler's lab at Boston University.

It took two years for Pavlovich, working with her colleague Sean Lovett at USAMRIID, to assemble the genome. Then they compared their Egyptian fruit bat genome to the genomes of other mammals, including a handful of other bats, humans, and guinea pigs. They looked broadly at first, and then focused specifically on areas known to be associated with the mammalian immune system.

"We were looking for gene families that had grown either much larger or much smaller than was expected, given the evolutionary history of this bat," says Pavlovich, who is lead author on the *Cell* paper. They also looked for genes with evidence of "positive selection," the evolutionary process that propels new, useful genetic variants throughout a population. "That allowed us to find a number of genes that were evolving at a faster rate in this bat, and then also a number of gene families that were much larger than we expected."

The two gene families near the top of the "larger than expected" list were type 1 interferon genes, which are often called "the first line of defense" against viruses and have been implicated in the disease course of filoviruses like Marburg and Ebola, and natural killer—or "NK"—cell receptors. Natural killer cells are a critical part of the human immune system, able to quickly recognize and respond to virus-infected cells.

Finding them in the Egyptian fruit bat was a surprise, says Pavlovich. "Folks had previously looked at a number of bat genomes and not been

able to find any traditional NK cell receptors," she says. "And so, when we saw these genes, it turns out that actually, yes, bats do have NK cell receptors, and it's a specific unusual group." This prompted Pavlovich to take a second look at previously sequenced bat genomes, and, using different tools, she was able to find natural killer cell receptors there, too.

Kepler notes that these initial results point to the possibility of what he calls "soft protection" from the bat immune system. "Activation and inhibition are much more intermingled in the bat than they are in most other organisms," he says, regarding the NK cell receptors. "The bat may be assuaging the virus for a short period of time, trying to prevent the virus' growth without making a full-on attack. There's something really interesting going on here."

Pavlovich and Kepler note that the findings, while intriguing, are just a first step to better understanding bats' special immunity to deadly viruses. "The next step is figuring out: 'Do these extra genes actually do anything?'" asks Pavlovich, who is now doing follow-up work on cell lines in the lab of Elke Mühlberger. "I would like to know if there's an advantage to having so many, or if they just happen to be there."

More information: Stephanie S. Pavlovich et al, The Egyptian Rousette Genome Reveals Unexpected Features of Bat Antiviral Immunity, *Cell* (2018). DOI: 10.1016/j.cell.2018.03.070 , dx.doi.org/10.1016/j.cell.2018.03.070

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https://phys.org/news/2018-04-egyptian-fruit-genome-yields-clues.html