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Saving Malaysia's **Fruit Bats**

*Research group
led by former
BCI student
scholar promotes
education and
coexistence*

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(*Phyllostomus discolor*)

Photo: Jose Gabriel Martinez-Fonseca

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Protecting Malaysia's bats by providing education to farmers and tourists.

Photo: Sanjitpaal Singh / Jitspics.com

Out of the Dark



Big leaps in bat genomics illuminate the animals' most closely held biological secrets



By Christie Wilcox

In 1990, an international group of geneticists began what was, at the time, an astonishingly challenging endeavor. Their goal: to sequence the human genome, all 3 billion base pairs. It took dozens of researchers from 20 institutions in six countries longer than a decade and cost more than \$2.5 billion, but they ultimately succeeded. In the ensuing years, genomes for other animals have followed. Most are still incomplete, but researchers have unveiled six complete bat genomes.

Published in *Nature* in July, the six complete bat genomes are the first to come from the ambitious Bat1K global genome consortium, which aims to sequence the genome of every single bat species. Achieving this lofty goal would allow

unprecedented comparisons between species with different abilities or ecological roles, which, in turn, would help researchers unravel the mysteries of bat evolution, including how they took to the skies.

The ultimate goal, though, reaches far beyond illuminating bat biology. “Both humans and bats are mammals, and that means that we also have something in common in terms of our overall physiology,” explains Dr. Sharlene Santana, an evolutionary biologist with the University of Washington and the curator of mammals at the Burke Museum of Natural History and Culture in Seattle. “So, understanding how bats’ physiology works may eventually help us understand how we, ourselves, might fight disease or live longer.”

fitness



Unprecedented insights

Before this new batch, genomes from a little more than 125 of the roughly 6,500 species of mammals had been constructed. Only 13 of those were bats, even though the Chiroptera account for about one-fifth of all mammals.

“Bats represent a large amount of the diversity of mammals,” Dr. Santana says. “So, just understanding the diversity, not only their external features but also their genomes, that tells us a lot about how they became survivors.”

“Genomics is really powerful,” says Dr. Hannah Frank, an evolutionary ecologist with Tulane University. Because all living things can trace back to a single common ancestor, comparing genome

sequences can help scientists figure out how species split into the ones alive today. It can also tell us how those splits occurred by revealing what genes changed the most or the least—signatures of strong evolutionary selection.

Such comparative analyses will provide researchers novel insights into the origins of quintessential bat traits like echolocation and flight. But even more so, Dr. Frank says, “we hope that, by looking at their immune systems and looking in their genomes, we will perhaps see how they’re tolerating or fighting disease, and then maybe apply some of that to ourselves.”

Even before the new set, previous bat genomes had deepened our understanding of immunology,

says Dr. Stephanie Pavlovich, a clinical researcher and medical resident at the University of North Carolina School of Medicine. For her Ph.D., she helped construct a draft genome of the Egyptian fruit bat (*Rousettus aegyptiacus*)—a species known to harbor the deadly Marburg virus without showing signs of illness. That genome revealed that the animals have a much larger number of type one interferon genes—proteins essential for the body’s initial attack on invading viruses—than we do. The discovery meant researchers could now perform the kind of experiments that tease out what role each of those genes plays in the bat’s immune system.

“Understanding how bats’ physiology works may eventually help us understand how we, ourselves, might fight disease or live longer.”
— Dr. Sharlene Santana

“Having more genomic information is always helpful in terms of asking the right evolutionary questions,” she says. The new genomes not only expand the number of species we can mine for similar insights, but they also provide richer data on previous species genomes that can be used to deepen our understanding of previous discoveries. “There are always genes that you’ve missed, spaces that you need to go back and fill in with additional sequencing,” Dr. Pavlovich says. She is hopeful the new, more complete Egyptian fruit bat genome, one of the six, can help fill in some of the blanks her team may have missed. And looking forward, she says having these diverse genomes—which represent both of the major lineages of bats, as well as bats with different geographic ranges, traits, and ecological roles—will help improve the process of sequencing genomes for other species.

Size matters

The researchers refer to their genomes as “reference-quality” because they’re much more complete than the previous bat genomes—in many cases, by orders of magnitude. But obtaining the six incredibly complete genomes was no simple feat. Though genome sequencing has become a lot cheaper and faster in the 30 years since the Human Genome Project began, putting together a high-quality genome remains a challenge. There are trade-offs to consider when it comes to your method of sequencing, explains Dr. Frank.

When you chop the DNA up into smaller pieces, the sequences are more accurate, but they’re harder to piece together—hard enough that genes or even sections of chromosomes can get left out on accident. Longer strings give you a better sense of the overall architecture of the genome, but they’re also more prone to error.

The “big breakthrough” for the Bat1K team was using both, says Dr. Liliana Dávalos, an evolutionary biologist with Stony Brook University, BCI science advisory committee member, and one of the researchers involved in constructing the six genomes. By combining multiple technologies, especially newer ones that sequence longer strings of DNA, they ensured the genome was both accurate and complete.

“The only genomes that are better, in terms of completeness, than the bat genomes in the paper, are actually the ones from mouse and human,” Dr. Dávalos says. And because they’re so accurate, they will allow scientists to do something really new: to learn more about ourselves.



The 6 Sequenced Species



Greater horseshoe bat
(*Rhinolophus ferrumequinum*)
Range: Northern Africa, Europe, and Eastern and Central Asia
Family: Rhinolophidae
Echolocation: Yes
Diet: Insectivore, especially moths
Previously sequenced? No



Egyptian fruit bat
(*Rousettus aegyptiacus*)
Range: Parts of Africa and the Middle East
Family: Pteropodidae
Echolocation: No (uses tongue clicks)
Diet: Frugivore
Previously sequenced? Yes



Pale spear-nosed bat
(*Phyllostomus discolor*)
Range: South America into Central America
Family: Phyllostomidae
Echolocation: Yes
Diet: Omnivore
Previously sequenced? No

Photos by Yushi & Keiko Osawa; Steve Gestler/Minden Pictures; Jose Gabriel Martinez Fonseca

Which Came First: Echolocation or Fruit Bats?

Apart from flight, perhaps the most impressive bat feature is their ability to “see” with sound by using echolocation. But fruit bats in the family Pteropodidae (flying foxes) lack this sonic superpower, and that sets up two possible scenarios for the trait’s evolution: either it arose separately in the close cousins of these fruit bats and all other bats, or the ancestor of all bats could echolocate, and these fruit bats lost the ability. “This has been a long-standing question in bat biology,” explains Dr. Santana—one that these six genomes may have finally answered.

Comparing physical features and genetic ones has yielded different answers in the past, Dr. Santana explains, but the six highly complete genomes were able to provide clearer insights. Instead of having to zero in on known genes and compare them between species, the BatIK team was able to compare whole genomes and look for areas that differ between the various bats. That allowed them to uncover mutations present only in echolocating bats, including a tiny duplication in part of a hearing-related gene that no one had noticed before.

Since these genetic features were identical in all echolocating bats—including in previously published genomes—they concluded that two independent origins for echolocation was extremely unlikely.

It’s one thing to sequence a genome, and a whole other to decipher what that sequence really means. And, to date, all other animal genome sequences have relied heavily on the human and mouse genomes to infer what different genes do, a process called annotating. Because of this, other animal genomes struggle to provide novel insights into how human genes work. But now, because the six bat genomes are “on the level of the human and the mouse genomes,” Dr. Dávalos thinks these animals will start teaching us a few things.

Bats are sometimes known for their ability to survive and not even seem ill when infected with viruses that are lethal in humans. Now that we have their genomes, we can dive deep into the nitty-gritty of how bats pull that off. Dr. Dávalos envisions a not-too-distant future where experimental work in bats and in cultured bat cells reveals essential information about how our immune system works—or why it doesn’t always work.

Such studies could pinpoint genes that bats have that we don’t, or ones that bats turn on at different times or in different amounts, for instance—all of which might provide clues to boosting our own anti-virus systems. “It’s a very exciting time,” she says. 🦇

“We hope that, by looking at [bats’] immune systems and looking in their genomes, we will perhaps see how they’re tolerating or fighting disease, and then maybe apply some of that to ourselves.”

– Dr. Hannah Frank

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Greater mouse-eared bat (*Myotis myotis*)

Range: Europe into Asia

Family: Vespertilionidae

Echolocation: Yes

Diet: Insectivore

Previously sequenced? No



Kuhl's pipistrelle (*Pipistrellus kuhlii*)

Range: Europe, Northern Africa, and parts of Asia

Family: Vespertilionidae

Echolocation: Yes

Diet: Insectivore

Previously sequenced? No



Velvety free-tailed bat (*Molossus molossus*)

Range: South America into Central America

Family: Molossidae

Echolocation: Yes

Diet: Insectivore

Previously sequenced? No