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Hunting Fossil Viruses in Human DNA

By CARL ZIMMER

The borna virus is at once obscure and grotesque. It can infect mammals and birds, but scientists know little about its effects on its victims. In some species it seems to be harmless, but it can drive horses into wild fits. The horses sometimes kill themselves by smashing in their skulls. In other cases, they starve themselves to death. Some scientists have even claimed that borna viruses alter human behavior, playing a role in schizophrenia and bipolar disorder, although others say there is no solid evidence of a link.

The virus now turns out to have an intimate bond with every person on Earth. In the latest issue of Nature, a team of Japanese and American scientists report that the human genome contains borna virus genes. The virus infected our monkey-like ancestors 40 million years ago, and its genes have been passed down ever since.

Borna viruses are not the only viruses lurking in our genome. Scientists have found about 100,000 elements of human DNA that probably came from viruses. But the borna virus belongs to a kind of virus that has never been found in the human genome before. Its discovery raises the possibility that many more viruses are left to be found.

Scientists who hunt for these viruses think of themselves as paleontologists searching for fossils. Just as animals get buried in rock, these viruses become trapped in the genomes of their hosts. While their free-living relatives continue to evolve, fossil viruses are effectively frozen in time.

“We can really dig fossils out of the genome and literally put them back together,” said Cédric Feschotte, a genome biologist at the University of Texas, Arlington. “It’s like putting a hominid back together and asking it if it can walk upright.”

When scientists sequenced the human genome in 2001, they noticed many segments that bore a striking resemblance to genes in retroviruses, a class of viruses that includes H.I.V.

Retroviruses carry their genetic material in a single-stranded version of DNA, called RNA. To make new viruses, they make DNA versions of their genes, which are inserted into a host cell’s genome. The cell then reads the retrovirus’s genes as if they were its own, and manufactures new retroviruses.

Scientists speculated that every now and then a retrovirus inserted itself into a host cell and then failed to turn it into a virus factory. If the trapped retrovirus happened to be in sperm or egg cells, its DNA might be passed down to the host’s descendants. From generation to generation, the virus’s DNA would mutate. It would lose its ability to produce normal viruses.

For a while it might be able to make new viruses that could re-infect the same cell, but over enough time, the viruses would become disabled.

In recent years, scientists have found several lines of evidence to support this idea. . Koala retroviruses, for example, appear to be in the middle of the journey. The viruses can move from one koala to another. But in some populations of koalas, the virus's DNA is permanently lodged in their genomes.

Thierry Heidmann of the Gustave Roussy Institute in France and his colleagues put the fossil virus hypothesis to a spectacular test: they tried to resurrect a dead retrovirus. They first identified a number of copies of the same virus-like stretch of DNA in the human genome. Each version had its own set of mutations that it acquired after the virus had invaded our ancestors.

By comparing the copies, Dr. Heidmann and his colleagues were able to figure out what the original sequence of the virus's genes had been. When they synthesized the genes from scratch and injected the genetic material into cells, the cells produced new viruses.

"It was a tour-de-force of an experiment," said John Coffin, an expert on fossil viruses at Tufts University.

Now fossil virus hunters are moving beyond the human genome. They're taking advantage of the growing number of mammal genomes piling up in online databases and helping to flesh out the evolutionary history of viruses, reaching back tens of millions of years. Aris Katzourakis, an evolutionary biologist at the University of Oxford, and his colleagues recently went on a hunt for fossils of foamy viruses in mammals. Foamy viruses infect some mammals, including monkeys and apes. Primate foamy viruses can infect humans harmlessly, but researchers fear they may evolve to become dangerous. Dr. Katzourakis and his colleagues discovered hundreds of foamy virus copies in the DNA of the two-toed sloth. They then found the same virus lurking in the genome of the three-toed sloth. Before Dr. Katzourakis's fossil hunt, scientists had never found a foamy virus infecting any sloths, or any of their relatives like armadillos and anteaters.

Sloths and their relatives branched off from all other placental mammals about 100 million years ago. Dr. Katzourakis's discovery thus reveals the great antiquity of foamy viruses. They were already infecting the common ancestor of all placental mammals back when dinosaurs ruled the Earth.

These fossils are also offering clues to how viruses evolved. Dr. Katzourakis and his colleagues have found fossil viruses that are helping shed light on the deep history of H.I.V., for example.

H.I.V. evolved about a century ago from a chimpanzee virus known as simian immunodeficiency virus, or S.I.V. Many apes and monkeys carry their own strain of S.I.V, but it's not clear how long the viruses have been infecting primates.

In 2008, Dr. Katzourakis and his colleagues discovered fossil S.I.V. in the genome of the gray lemur, a primate that lives in Madagascar. Last May, Dr. Feschotte and his colleagues reported that they had found the same fossil virus in the fat-tailed lemur.

Scientists had never before found S.I.V. in lemurs, which branched off from all other living primates some 50 million years ago. The fossil virus is also missing one of the genes found in all other forms of S.I.V. and H.I.V. It may be a transitional form of the virus, akin to the fossils paleontologists have found of feathered dinosaurs that couldn't fly.

Fossil viruses are also illuminating human evolution. Scientists estimate that 8.3 percent of the human genome can be traced back to retrovirus infections. To put that in perspective, that's seven times more DNA than is found in all the 20,000 protein-coding genes in the human genome.

But that figure may be too low, according to Dr. Katzourakis. "The measurable diversity of viruses may go up, and the true diversity may be much higher," he said.

For one thing, some viruses may be too well hidden for scientists to see. The discovery of borna viruses in the human genome is another reason to wonder if we're actually more viral than we know. All fossil viruses discovered until now have been retroviruses, but borna viruses are not.

Unlike retroviruses, borna viruses do not insert themselves into host genomes. Instead, they take up residence inside the nucleus, the chamber that holds our DNA. There, they manipulate the cell's proteins to make new copies of themselves.

Keizo Tomonaga, a virologist at Osaka University, discovered the borna virus DNA by accident. He had been comparing the virus genes with human genes to see if the virus might have evolved to mimic our own proteins. Instead, he discovered four segments of human DNA that clearly had descended from a borna virus gene. "I was surprised when I found them," Dr. Tomonaga said.

He and his colleagues found the same borna virus DNA in apes and monkeys. In other words, borna virus first invaded the common ancestor of humans, apes and monkeys about 40 million years ago. But primates were not the only targets for borna viruses. Dr. Tomonaga and his colleagues have found independent invasions in other mammals, including ground squirrels, guinea pigs and elephants.

Dr. Tomonaga and his colleagues suspect that borna viruses didn't actually invade mammal genomes. Instead, the genomes kidnapped them.

Mammal genomes contain thousands of stretches of DNA called LINEs. LINEs sometimes make copies of themselves that get reinserted back into the genome. Dr. Tomonaga's research indicates that LINEs grabbed the genes of borna viruses and pulled them into their genome.

The discovery raises the possibility that LINEs have kidnapped other viruses floating near their host's DNA, like flu viruses.

Two of the four copies of the borna virus gene carry crippling mutations. It's impossible for our cells to make proteins from them. But the other two genes look remarkably intact, perhaps suggesting that our bodies use them for our own benefit. Exactly what they do isn't clear though.

Studies on other captive viruses have revealed that some help ward off viral invasions. One virus protein, syncytin, is essential for our being born at all.

“The only place it’s expressed is in the placenta,” Dr. Heidmann said. To understand its function, he and his colleagues disabled the gene in mice. Without syncytin, mice developed deformed placentas, and their embryos died.

Syncytin started as a surface protein on retroviruses that fused them to cells. When mammals captured the gene, they used it in the placenta to create a layer of fused cells through which mothers can send nutrients to their embryos.

Dr. Heidmann and his colleagues have discovered that over the past 100 million years, mammals have repeatedly harnessed viruses to make syncytin. “Wherever we search for them, we find them,” Dr. Heidmann said.

But the syncytin genes we use today may have actually replaced an ancestral one that a virus bequeathed to the very first placental mammals. In fact, that infection may have made the placenta possible in the first place. “It was a major event for animal evolution,” Dr. Heidmann said.

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Viruses: Infecting mammals for 100 million years

Viruses have been infecting mammals for over 100 million years, says a new study in *Science*. The study hints that mammals did not start being infected with viruses recently, but that the two have been evolving together for millions of years.

The researchers from the University of Oxford, Imperial College London and the Copenhagen University discovered a virus strain, a type of retrovirus that currently infects many mammals, in the two-toed sloth. Because retroviruses insert their genetic information into their host's genome, they leave a "fossil record" of their evolution. The virus had not been previously detected in the records of mammals.

The researchers screened a variety of mammals, but only found the insertions from the virus in two-toed sloths, members of the oldest known mammalian group.

Traces of the virus in the sloth appear as far back as 39 million years ago, says the study. At that time, sloths were geographically isolated in South America. Primates and rodents did not arrive in the area until 30 million years ago, so the two groups could not have brought over the virus.

The retrovirus often mutates and changes quickly, but it has changed very little in the two-toed sloth. The few changes support the idea that the genetic makeup of viruses can remain the same over millions of years through limits placed on evolution, the study says.

By Lindsey Anderson
Photo: A baby two-toed sloth sits on its mother. (Matt Rourke, AP)

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Retroviral Remnants in Sloth Genome Offer Clues to Viral-Mammalian Co-Divergence

September 17, 2009
By a GenomeWeb staff reporter

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NEW YORK (GenomeWeb News) – Retroviral footprints in the two-toed sloth genome hint at co-divergence between these viruses and mammals.

A team of British and Danish researchers used genomic, phylogenetic, and biogeographic analyses to track the evolutionary history of a type of retroviruses called foamy viruses in mammals. They found many foamy virus-like sequences in the genome of the two-toed sloth, *Choloepus hoffmanni* that they believe go back more than 100 million years. The research, which appears online today in *Science*, suggests mammals did not start being infected with foamy viruses recently, but co-diverged with these viruses.

"The descendants of foamy viruses that infected ancestral mammals … have persisted in a surprisingly unchanged form until today," senior author Oliver Pybus, a zoology researcher at the University of Oxford, and his co-authors wrote, "supporting the idea that evolutionary constraint can maintain viral genomic conservation over many millions of years despite exceptionally high short-term rates of mutation."

Retroviruses, in general, are RNA viruses that are reverse-transcribed to DNA before being integrated into their host's genome. Because they insert themselves into the genetic code, these viruses can leave traces in the host genome, the researchers explained.

Pybus and his co-workers focused on foamy viruses, which were not previously detected in the viral "fossil records" of mammalian genomes. The team screened as many mammalian genomes as they could get their hands on. But they only found foamy virus insertions in one genome: that of the two-toed sloth.

The team dubbed the viral sequences "sloth endogenous foamy virus," or SloEFV. Their analysis uncovered hundreds of these elements in the two-toed sloth genome, though just 72 of these still had 1,000 or more bases of coding sequences. And the coding regions that remained were rife with stop codons, insertions, deletions, and frame shift mutations.

The SloEFV grouped phylogenetically with modern-day foamy viruses, the team noted. When the researchers came up with a 11,500 or so base consensus genome for SloEFV, they also found that it aligned — and shared characteristic features — with current foamy viruses.

Because the sloth belongs to a basal mammalian group that diverged from other mammals roughly 105 million years ago, the researchers estimate that foamy viruses were present in mammalian ancestors for more than 100 million years.

Based on such findings, the team speculated that mammals and foamy viruses have been co-evolving since the first mammalian species, co-diverging "across an entire geological era."

"Our analysis highlights the role of evolutionary constraint in maintaining viral genome structure and indicates that accessory genes and mammalian mechanisms of innate immunity are the products of macroevolutionary conflict played out over a geological time scale," they wrote.

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Did Evolution Cause Rapid Changes or Just the Opposite in Sloth Virus?

by Brian Thomas, M.S. *

Researchers have recently focused on DNA sequences as a means for determining the evolutionary history of both viruses and their host organisms. To discover when mammals were first infected by them, a team of scientists scanned the genomes of all mammals. They searched for common DNA sequences that they interpret as having come from a retrovirus that entered mammals long ago. What they found, however, was evidence that confutes not only the evolutionary dates, but also the mechanism that supposedly drives evolution.

The team found a particular DNA sequence that looks like a retrovirus, named SloEFV, embedded in the sloth genome.[1] Retroviruses have been said to be part of "junk DNA," considered by many to be genetic leftovers from an evolutionary past. These viruses operate by inserting their DNA into the genome of the host organism. Many retroviruses, and viruses in general, are species-specific.[2]

In their study published in *Science*, the researchers correlated the evolutionary time of "divergence" for SloEFV (i.e., the time when it supposedly split off from its ancestor virus) with the assumed evolutionary date of divergence of its sloth host, along with several other hand-picked mammals, citing this correlation as evidence that the SloEFV evolved at least "39 million years" ago.[1] However, this age was entirely dependent on tying the molecular data to the evolutionary timeline presumed to exist in the related fossil data—an example of circular reasoning that actually proves nothing.

For example, the technical background provided with the study stated, "We estimated a neutral evolutionary rate for Xenarthan nuclear genes using a previously published alignment

of three nuclear genes."[3] Xenarthans are a group of mammals that include sloths. The observable data is merely gene sequences, which can be aligned for comparison. These were then dated based on an assumed evolutionary history. But many differences between similar sequences might well reflect an original design that has since been altered, rather than divergence from some hypothetical common ancestor.

However, even if the time of divergence is accepted as accurate, for the sake of argument, it leads to a disturbing conclusion. The viral genetic sequence (SloEFV) changed only a tiny amount over those supposed 39 million years. The same SloEFV sequence has "persisted in a surprisingly unchanged form until today, supporting the idea that evolutionary constraint can maintain viral genomic conservation over many millions of years despite exceptionally high short-term rates of mutation."[1]

In other words, these researchers want to have their cake and eat it, too. They espouse that evolution explains why gene sequences like SloEFV change rapidly over time, as well as why SloEFV in particular has changed hardly at all. Which is it?

The persistence of such extremely similar sequences in sloths and a modern retrovirus that infects sloths does not necessarily support the idea that evolution can maintain sequence integrity over eons. On the contrary, the rapid rate of change known by observation to take place in retroviral genomes, together with the similarities found in them today, supports the idea that the evolutionary time scale is "many millions of years" in error because the origin of both sloth and virus looks recent.

References

1. Katzourakis, A. et al. 2009. Macroevolution of Complex Retroviruses. *Science*. 325 (5947): 1512.
2. Many genetic sequences that look like they were derived from retroviruses have been found to provide essential regulatory functions within those animals. Therefore, it is possible that SloEFV, though it shares features in common with sequences derived from retroviruses, actually was engineered into the sloth genome from the beginning. See Doyle, S. 2008. Large scale function for 'endogenous retroviruses.' *Journal of Creation*. 22 (3): 16.
3. Katzourakis, A., et al. 2009. Macroevolution of Complex Retroviruses. *Science*. 325 (5947): 1512. Supporting online material, posted on sciencemag.org in conjunction with the article.

* *Mr. Thomas is Science Writer at the Institute for Creation Research.*

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