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Evolutionary History of SARS Supports Bats as Virus Source

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Scientists who have studied the genome of the virus that caused severe acute respiratory syndrome (SARS) say their comparisons to related viruses offer new evidence that the virus infecting humans originated in bats.

Newswise — Scientists who have studied the genome of the virus that caused severe acute respiratory syndrome (SARS) say their comparisons to related viruses offer new evidence that the virus infecting humans originated in bats.

The analysis tracing the viruses' paths through human and animal hosts counters assertions that SARS was eradicated in 2004 when thousands of palm civet cats in China were identified as the original source and killed in an effort to eliminate the risk of new outbreaks.

According to this new analysis, humans actually appear to be the source of the virus found in those civets, a wild game animal considered a delicacy in southern China.

SARS infected more than 8,000 and killed more than 900 people worldwide during a nine-month outbreak that ended in the summer of 2003, according to the World Health Organization. No human infections have been reported since early 2004.

Finding the origin of SARS is key to fully understanding how the global outbreak occurred, and it is critical to worldwide efforts aimed at preventing future illnesses that could infect and kill millions of people, said Daniel Janies, lead author of the study and an assistant professor of biomedical informatics at Ohio State University.

"Certainly, there are undiscovered viruses closely related to SARS and these viruses have novel associations with host animals that remain unknown. Our lack of knowledge of viral and host diversity around the world is a source of concern for the re-emergence of a SARS-like disease," Janies said.

To further illustrate the speed of the SARS outbreak as part of the investigation, Janies and colleagues also designed an interactive map that traces the genetic, geographic and evolutionary history of SARS. The map also shows when and where the virus shifted from animal to human hosts. The map is projected onto a virtual globe using Google Earth and can be downloaded at: <http://supramap.osu.edu/cov/janiesetal2008covsars.kmz>.

The research appears in the online early edition of the journal *Cladistics*.

The rapid transmission of SARS from Asia to North America prompted a collaborative scientific and medical response to halt human infections and to share data about the virus's genetic characteristics. Despite the shared data, scientists have not reached agreement in identifying the animal source of the coronavirus that caused SARS in humans, a virus known as SARS-CoV.

Coronaviruses primarily infect the upper respiratory and gastrointestinal tracts of mammals and birds, and just a few are known to infect humans. Before SARS, attempts to understand coronaviruses were confined primarily to agricultural and veterinary circles. The rapid transmission of SARS among humans moved coronavirus study into the realm of human infectious diseases and comparative genomics.

Janies and his colleagues are not the first scientists to suggest bats were the source of SARS – two research teams identified several species of Chinese bats as the natural viral reservoir in 2005 using a couple of genes from a few viruses. But Janies said he has put those findings to the test with the largest and most comprehensive analysis of coronavirus origins, using whole genomes from hundreds of viruses.

His group reconstructed the history of the disease, applying basic evolutionary theory to the study of virology. He said the genomic data put to rest any notion that civets were the cause of SARS.

"The real story is that civets were not the animal reservoir of SARS. But it's a messy story," Janies said. "Bats harbor a strain of SARS that is our best example of the virus before it infected humans – but we still see missing links in the history of the transfers of SARS from animals to humans because we don't know that much about coronavirus diversity. If you look at the way the bat virus works, it doesn't interact well with human cells, so at present there's no clear explanation about how the virus shifted from bat to human hosts. There must be other SARS-CoV in other animals that served as intermediate hosts.

"With the data at hand, we see how the virus used different hosts, moving from bat to human to civet, in that order. So the civets actually got SARS from humans. We see this evolutionary sequence of events, but other biochemical reports of the poor interaction of bat viruses and human cells suggest that there remains a missing link in the wild."

To arrive at these conclusions, Janies and colleagues secured genetic data of hundreds of different isolates of the SARS-CoV virus that had been found in humans, various bats, civets, raccoon badgers and pigs. Using the same equipment that was originally developed for the Human Genome Project, scientists determined the nucleotide sequence of each of the viruses. Bioinformatics came into play as the researchers linked many computers together to be able to analyze the massive amounts of data, comparing the viral genomes and building what is called a phylogenetic tree by searching for shared mutations. Phylogenetics is the study of the evolutionary relationships among various biological species, or in this case, viruses, believed to have a common ancestor.

The resulting tree is a branching diagram that illustrates the interrelationship of various viruses. The phylogenetic tree also shows the timeline of the travels and mutations of various strains of SARS as they jumped between host species. In this tree, the SARS-CoV virus traveled from bat hosts to humans, from humans to civets and pigs, and, in rare cases late in the outbreak, back to humans.

Janies' lab took the analysis many steps further, using genomes from coronaviruses that are relatives of SARS-CoV that have been isolated in humans, cows, rats, cats, dogs, mice, turkeys and pigs. Adding these additional "outgroups" to the evolutionary analysis provided a broader context under which to trace SARS-CoV as a way of ruling out other possible coronavirus sources that hadn't been considered, Janies said. In essence, including the outgroup viruses was a way of being sure he didn't miss the root of the SARS-CoV tree.

"You need to search outside of the viruses involved in the outbreak to create a baseline so you have a point of reference, and then from that root of the tree you can read the entire history of the exchange of the virus among hosts," Janies said.

Such contextual analysis had not been done before with the SARS-CoV virus, he said. "Showing where these other coronaviruses connect with SARS-CoV provides an undisputed and unbiased way of discovering the host origins of SARS-CoV and the direction of viral exchanges among various animal and human hosts."

There remains a shortage of publicly available genetic data on coronaviruses, and Janies said only through the discovery and sequencing of even more viruses can the complete SARS story be told.

"We don't fully understand SARS and whether or not it will come out of the wild again. SARS has opened our eyes to other kinds of viruses. Sequencing of more coronaviruses in exotic animals will teach us about their potential for disease," he said.

Janies said the interactive map of the SARS-CoV virus's travels could help guide researchers to geographic hotspots that appear most likely to be home to animals with coronaviruses that have the potential to jump to human hosts.

This research was supported by Ohio State's Department of Biomedical Informatics in the College of Medicine and School of Biomedical Sciences, the National Aeronautics and Space Administration, the Defense Applied Research Projects Agency, the National Science Foundation, the Hewlett Packard Corp. and the Ohio Supercomputer Center.

The study was co-authored by Farhat Habib and Boyan Alexandrov of Ohio State's Department of Biomedical Informatics, Andrew Hill of the University of Colorado and Diego Pol of Ohio State's Mathematical Biosciences Institute.

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