Gene Mutation Turned West Nile Virus Into Killer Disease Among Crows

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A gene mutation that appears to be responsible for changing relatively mild forms of the West Nile virus into a highly virulent and deadly disease in American crows has been identified by a team of scientists led by a researcher at the University of California, Davis.

Because it is highly susceptible to West Nile virus, the American crow has served as the major sentinel species, playing an important role in alerting scientists and health professionals to the movement of the disease across North America.

The results of the study will be reported in the Aug. 12 online issue of the journal *Nature Genetics*.

"The findings from this study highlight the potential for viruses like West Nile to rapidly adapt to changing environments when introduced to new geographic regions," said Aaron C. Brault, a virologist at the Center for Vectorborne Diseases in the Department of Pathology, Microbiology and Immunology of the UC Davis School of Veterinary Medicine.

"The study also suggests that the genetic mutations that create such adaptive changes may result in viral strains that have unexpected symptoms and patterns of transmission," Brault said.

About West Nile virus

West Nile virus, which is passed back and forth between birds and mosquitoes and transmitted to humans via mosquito bites, was first identified in 1937 in Uganda. Although it was recognized as a cause of severe encephalitis and meningitis (inflammation of the brain and spinal cord, respectively) during a 1957 outbreak in Israel, it has been primarily associated with mild infections accompanied by fevers in humans in Africa and the Middle East.

In 1996, West Nile virus caused an outbreak of encephalitis in Romania, moving on to cause similar outbreaks throughout the next several years in Israel, Tunisia and Russia.

In 1999, the virus was first recognized in North America and has since been reported in humans, birds, horses and mosquitoes in Canada and in all of the contiguous U.S. states. It has become the leading cause of encephalitis from a virus transmitted by arthropods, a group of invertebrates that includes insects, spiders and ticks.

West Nile in birds

A variety of North American bird species, including billed gulls, house finches, crows and black-billed magpies, are extremely susceptible to West Nile virus. In fact, a hallmark of the West Nile virus in North America has been how deadly the virus has been among wild and captive birds. Particularly vulnerable to West Nile virus is the American crow, which is common in urban and suburban areas as well as in all natural habitats except the Southwestern deserts.

Because the American crow is so common and so highly susceptible to West Nile virus, it has served as the sentinel species in North America. Epidemiological studies have found that deaths of American crows due to West Nile virus are associated with higher rates of infection among mosquito populations and clusters of the disease in humans.

Although scientists and health professionals have thoroughly described how West Nile virus spreads through both human and animal populations in North America, it has been unclear just how the virus emerged to cause such serious disease in birds, particularly the American crow.

Pinpointing the gene mutation site

To identify how West Nile virus developed into such a deadly disease for birds, the research team looked to the genetic makeup of the virus. West Nile virus is an RNA virus -- its genetic material being composed of RNA, rather than DNA. Although RNA and DNA molecules differ somewhat in structure and function, both play key roles in enabling cells to build the proteins necessary for reproducing and carry out the cells' functions.

The researchers analyzed the evolutionary relationships of the West Nile virus genomes, or entire collections of genes, for 21 different strains of West Nile viruses that had been sampled globally in recent years, including strains from North America. Analysis of genetic patterns indicated a disproportionate rate of change at a particular amino acid within one of the viral genes.

Onto this genome "tree" for the various strains of West Nile virus, they mapped the mutational changes in the same gene region mentioned above. They found that the same amino acid change had occurred three different times and that the resulting virus had been associated with human disease outbreaks.

In order to determine if this mutation was associated with the increased virulence of the West Nile virus in birds and its subsequent ability to spread to humans, the researchers introduced the mutation independently into the low-virulence virus. They also removed that mutation from the highly virulent North American strain.

At that location, the researchers made changes in the amino acids, which they suspected might change a relatively mild West Nile virus strain from Kenya into a much more virulent strain and, conversely, could weaken the more potent New York strain.

Then they inoculated American crows with either a parent virus or one of the newly created recombinant viruses in order to observe the viruses' activity.

As expected, they found that the parent virus from the relatively mild Kenya strain did not become detectable in the crows' bloodstream until two to three days after the birds were infected. However, the new recombinant form of that viral strain quickly became detectable in the crows' bloodstream, and by the third day was present at 10,000 times the concentration of the parent virus from which it was developed, killing nearly all.

The researchers then made the reciprocal amino acid change in the parent virus of the virulent New York strain of West Nile virus, drastically reducing its deadliness in crows. This weakened New York strain was comparable to the relatively mild parent virus from Kenya in terms of detectable levels in the bloodstream and its deadliness among the inoculated crows.

"It appears that the naturally occurring changes in the amino acids at this particular gene site have played an important role in increasing the virulence of West Nile virus in birds before it appeared in North America," Brault said. "Furthermore, these data indicate how much West Nile virus relies on replicating to high levels in birds for efficient transmission of the virus, potentially leading to human disease outbreaks."

Source: UC Davis