The pace of evolution is typically measured in millions of years, as random, individual mutations accumulate over generations, but researchers at Cornell and Bar-Ilan Universities have uncovered a new mechanism for mutation in primates that is rapid, coordinated, and aggressive. The discovery raises questions about the accuracy of using the more typical mutation process as an estimate to date when two species diverged, as well as the extent to which this and related enzymes played a role in primate evolution.
Alon Keinan, associate professor of Biological Statistics and Computational Biology at Cornell, and Erez Levanon, co-senior author and an associate professor with the Mina and Everard Goodman Faculty of Life Sciences at Bar-Ilan University in Israel, describe the novel, and rare, process triggered by a member of the APOBEC family of virus-fighting enzymes in the journal *Genome Research*. As primates evolved—including chimpanzees, Neanderthals, and modern humans—the number of types of viruses tailored for targeting primates multiplied. APOBECs in our cells mount a vigorous defense, bombarding the viral genome with clusters of mutations to render them unable to continue an infection. However, having such a mutation-based defense is risky for cells, since "friendly fire" could wreak havoc on our genome as well. Indeed, the enzymes have been shown to cause mutations in the tumor cells of breast and other cancers.

"For several years, my collaborator, Erez Levanon, has been trying to convince me that we should test whether 'friendly fire' events might be passed on to subsequent generations," said Keinan. "More recently, with the mounting evidence of their role in cancer and hints of being expressed in the cells that produce sperm and eggs, we were ready to test whether the inheritance of such events has left an evolutionary impact."

The discovery is particularly significant because the enzyme has a tendency to alter regions of the genome that code for proteins as well as the areas responsible for their regulation. It's a vestige of their primary function in viral defense: Many viruses are composed of single stranded DNA or RNA, and DNA being actively used as a template for proteins is temporarily single stranded and unwound from the double helix. To the enzyme, they look the same.

The researchers looked for the signature of past mutations in humans and our closest hominid relatives, focusing on one of the enzymes in the APOBEC family, APOBEC3, since it has expanded into several
subtypes during primate evolution, each with unique mutational signatures.

They knew that the enzyme recognizes a specific motif in the DNA and it targets only one of the DNA bases for mutation. Another telltale sign: multiple mutations occurring close together. Using conservative criteria, they identified thousands of such instances unique to primate genomes and, as negative control, did not identify any in other vertebrates such as mice that lack many of the APOBEC3 genes.

"What is appealing is that it's an accelerated evolutionary mechanism that could generate a large change in a gene in a single generation," said Levanon. "It's like playing the lottery—it could not have an impact, or it could have a major one."

"These events potentially mutate dozens of DNA bases in a small region less than the size of a gene. It is reasonable to think that most of these mega-mutations will be deleterious and will disappear in evolutionary time, but we do see a large number that survived," added Keinan. "Importantly, those that survived are overrepresented in functionally important parts of the genome, which suggests that some of these mutations have been maintained by natural selection because they conferred an advantage."

Provided by Cornell University

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