# Infectious disease may have shaped human origins, study says

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*Escherichia coli* bacteria, like these in a false-color scanning electron micrograph by Thomas Deerinck at UC San Diego's National Center for Microscopy and Imaging Research, cause a variety of often life-threatening conditions, particularly among the young. Varki and colleagues suggest a genetic change 100,000 or so years ago conferred improved protection from these microbes, and likely altered human evolutionary development. Credit: Thomas Deerinck at UC San Diego's National Center for Microscopy and Imaging Research

An international team of researchers, led by scientists at the University of California, San Diego School of Medicine, suggest that inactivation of two specific genes related to the immune system may have conferred selected ancestors of modern humans with improved protection from some pathogenic bacterial strains, such as Escherichia coli K1 and Group B Streptococci, the leading causes of sepsis and meningitis in

human fetuses, newborns and infants.

Roughly 100,000 years ago, human evolution reached a mysterious bottleneck: Our ancestors had been reduced to perhaps five to ten thousand individuals living in Africa. In time, "behaviorally modern" humans would emerge from this population, expanding dramatically in both number and range, and replacing all other co-existing evolutionary cousins, such as the Neanderthals.

The cause of the bottleneck remains unsolved, with proposed answers ranging from gene mutations to cultural developments like language to climate-altering events, among them a massive volcanic eruption.

Add another possible factor: infectious disease.

In a paper published in the June 4, 2012 online Early Edition of *The* Proceedings of the National Academy of Sciences, an international team of researchers, led by scientists at the University of California, San Diego School of Medicine, suggest that inactivation of two specific genes related to the immune system may have conferred selected ancestors of modern humans with improved protection from some pathogenic bacterial strains, such as Escherichia coli K1 and Group B Streptococci, the leading causes of sepsis and meningitis in human fetuses, newborns and infants.

"In a small, restricted population, a single mutation can have a big effect, a rare allele can get to high frequency," said senior author Ajit Varki, MD, professor of medicine and cellular and molecular medicine and co-director of the Center for Academic Research and Training in Anthropogeny at UC San Diego. "We've found two genes that are non-functional in humans, but not in related primates, which could have been targets for bacterial pathogens particularly lethal to newborns and infants. Killing the very young can have a major impact upon

reproductive fitness. Species survival can then depend upon either resisting the pathogen or on eliminating the target proteins it uses to gain the upper hand."

In this case, Varki, who is also director of the UC San Diego Glycobiology Research and Training Center, and colleagues in the United States, Japan and Italy, propose that the latter occurred. Specifically, they point to inactivation of two sialic acid-recognized signaling receptors (siglecs) that modulate immune responses and are part of a larger family of genes believed to have been very active in human evolution.

Working with Victor Nizet, MD, professor of pediatrics and pharmacy, Varki's group had previously shown that some pathogens can exploit siglecs to alter the host immune responses in favor of the microbe. In the latest study, the scientists found that the gene for Siglec-13 was no longer part of the modern human genome, though it remains intact and functional in chimpanzees, our closest evolutionary cousins. The other siglec gene – for Siglec-17 – was still expressed in humans, but it had been slightly tweaked to make a short, inactive protein of no use to invasive pathogens.

"Genome sequencing can provide powerful insights into how organisms evolve, including humans," said co-author Eric D. Green, MD, PhD, director of the National Human Genome Research Institute at the National Institutes of Health.

In a novel experiment, the scientists "resurrected" these "molecular fossils" and found that the proteins were recognized by current pathogenic strains of *E. coli* and Group B Streptococci. "The modern bugs can still bind and could potentially have altered immune reactions," Varki said.

Though it is impossible to discern exactly what happened during evolution, the investigators studied molecular signatures surrounding these genes to hypothesize that predecessors of modern humans grappled with a massive pathogenic menace between 100,000 and 200,000 years ago. This presumed "selective sweep" would have devastated their numbers. Only individuals with certain gene mutations survived – the tiny, emergent population of anatomically modern humans that would result in everyone alive today possessing a non-functional Siglec-17 gene and a missing Siglec-13 gene.

Varki said it's probable that humanity's evolutionary bottleneck was the complex result of multiple, interacting factors. "Speciation (the process of evolving new species from existing ones) is driven by many things," he said. "We think infectious agents are one of them."

Provided by University of California - San Diego