

A single gene mutation may have helped humans become optimal long-distance runners

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Two to three million years ago, the functional loss of a single gene triggered a series of significant changes in what would eventually

become the modern human species, altering everything from fertility rates to increasing cancer risk from eating red meat.

In a new paper, published in the September 12 issue of the *Proceedings of the Royal Society B*, researchers at University of California San Diego School of Medicine report on studies of mice engineered to lack the same gene, called *CMAH*, and resulting data that suggest the lost gene may also have contributed to humanity's well-documented claim to be among the best long-distance runners in the animal kingdom.

At roughly the same time as the *CMAH* mutation took hold, human ancestors were transitioning from forest dwellers to life primarily upon the arid savannahs of Africa. While they were already walking upright, the bodies and abilities of these early hominids were evolving dramatically, in particular major changes in skeletal biomechanics and physiology that resulted in long, springy legs, big feet, powerful gluteal muscles and an expansive system of sweat glands able to dissipate heat much more effectively than other larger mammals.

Such changes, say scientists, helped fuel the emergence of the human ability to run long distances relatively tirelessly, allowing ancestors to hunt in the heat of the day when other carnivores were resting and to pursue prey to their point of exhaustion, a technique called persistence hunting.

"We discovered this first clear [genetic difference](#) between humans and our closest living evolutionary relatives, the chimpanzees, more than 20 years ago," said senior author Ajit Varki, MD, Distinguished Professor of Medicine and Cellular and Molecular Medicine at UC San Diego School of Medicine and co-director of the UC San Diego/Salk Center for Academic Research and Training in Anthropogeny.

Given the approximate timing of the mutation and its documented

impact on fertility in a mouse model with the same mutation, Varki and Pascal Gagneux, Ph.D., professor of anthropology and pathology, began investigating how the genetic difference might have contributed to the origin of *Homo*, the genus that includes modern *Homo sapiens* and extinct species like *Homo habilis* and *Homo erectus*.

"Since the mice were also more prone to muscle dystrophy, I had a hunch that there was a connection to the increased long distance running and endurance of *Homo*," said Varki, "but I had no expertise on the issue and could not convince anyone in my lab to organize this long-shot experiment."

Ultimately, a graduate student named Jon Okerblom took up the task, building mouse running wheels and borrowing a mouse treadmill. "We evaluated the exercise capacity (of mice lacking the *CMAH* gene), and noted an increased performance during treadmill testing and after 15 days of voluntary wheel running," said Okerblom, the study's first author. The researchers then consulted Ellen Breen, Ph.D., a research scientist in the division of physiology, part of the Department of Medicine in the UC San Diego School of Medicine, who added observations that the mice displayed greater resistance to fatigue, increased mitochondrial respiration and hind-limb muscle, with more capillaries to increase blood and oxygen supply.

Taken together, Varki said the data suggest *CMAH* loss contributed to improved skeletal muscle capacity for oxygen utilization. "And if the findings translate to humans, they may have provided early hominids with a selective advantage in their move from trees to becoming permanent hunter-gatherers on the open range."

When the *CMAH* gene mutated in the genus *Homo* two to three million years ago, perhaps in response to evolutionary pressures caused by an ancient pathogen, it altered how subsequent hominids and modern

humans used sialic acids—a family of sugar molecules that coat the surfaces of all animal cells, where they serve as vital contact points for interaction with other cells and with the surrounding environment.

The human mutation causes loss of a sialic acid called *N*-glycolylneuraminic acid (Neu5Gc), and accumulation of its precursor, called *N*-acetylneuraminic acid or Neu5Ac, which differs by only a single oxygen atom.

This seemingly minor difference affects almost every cell type in the human body—and has proved to be a mixed blessing. Varki and others have linked the loss of the *CMAH* gene and sialic acids to not just improved long-distance running ability, but also enhanced innate immunity in [early hominids](#). Sialic acids may also be a biomarker for [cancer risk](#).

Conversely, they have also reported that certain sialic acids are associated with increased risk of type 2 diabetes; may contribute to elevated cancer risk associated with red meat consumption; and trigger inflammation.

"They are a double-edged sword," said Varki. "The consequence of a single lost gene and a small molecular change that appears to have profoundly altered human biology and abilities going back to our origins."

More information: Human-like *Cmah* Inactivation in Mice Increases Running Endurance and Decreases Muscle Fatigability: Implications for Human Evolution, *Proceedings of the Royal Society B*, rspb.royalsocietypublishing.org/doi/10.1098/rspb.2018.1656

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