

# How did the giraffe get its long neck? Clues now revealed by new genome sequencing

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A bachelor group of adult male Masai giraffes at Ndarakwai West Kilimanjaro, Tanzania. Credit: Doug Cavener

For the first time, the genomes of the giraffe and its closest living relative, the reclusive okapi of the African rainforest, have been sequenced—revealing the first clues about the genetic changes that led to the evolution of the giraffe's exceptionally long neck and its record-holding ranking as the world's tallest land species. The research will be published in the scientific journal *Nature Communications* on May 17, 2016.

"The giraffe's stature, dominated by its long neck and legs and an overall height that can reach 19 feet (~ 6 m), is an extraordinary feat of evolution that has inspired awe and wonder for at least 8,000 years—as far back as the famous rock carvings at Dabous in the Republic of Niger," said Douglas Cavener of Penn State University, who led the research team with Morris Agaba of the Nelson Mandela African Institute for Science and Technology in Tanzania.

"The evolutionary changes required to build the giraffe's imposing structure and to equip it with the necessary modifications for its high-speed sprinting and powerful cardiovascular functions have remained a source of scientific mystery since the 1800s, when Charles Darwin first puzzled over the giraffe's evolutionary origins," said Cavener, a professor of biology and the Verne M. Willaman Dean of the Eberly College of Science at Penn State. The giraffe's heart, for example, must pump blood two meters straight up in order to provide an ample blood supply to its brain. This feat is possible because the giraffe's heart has evolved to have an unusually large left ventricle, and the species also has blood pressure that is twice as high as other mammals.

To identify [genetic changes](#) likely to be responsible for the giraffe's unique characteristics, including sprints that can reach 37 miles per hour (60 km/h), Cavener and Agaba compared the gene-coding sequences of the giraffe and the okapi to more than forty other mammals including the cow, sheep, goat, camel, and human. "Okapi's gene sequences are

very similar to the giraffe's because the okapi and giraffe diverged from a common ancestor only 11-to-12 million years ago - relatively recently on an evolution timescale," Cavener said. "In spite of this close evolutionary relationship, the okapi looks more like a zebra and it lacks the giraffe's imposing height and impressive cardiovascular capabilities. For these two reasons, Okapi's genome sequence provides a powerful screen that we have used to identify some of the giraffe's unique genetic changes."

Using a battery of comparative tests to study the genome sequences of the giraffe and the okapi, the scientists discovered 70 genes that showed multiple signs of adaptations. "These adaptations include unique amino-acid-sequence substitutions that are predicted to alter protein function, protein-sequence divergence, and positive natural selection," Cavener said. Over half of the 70 genes code for proteins that are known to regulate development and physiology of the skeletal, cardiovascular, and nervous system - just the type of genes predicted to be necessary for driving the development of the giraffe's unique characteristics.

Among the research team's discoveries are that several genes known to either to regulate the development of the cardiovascular system or to control blood pressure are among the genes showing multiple signs of adaptation in the giraffe. Some of these genes control both cardiovascular development and skeletal development, suggesting the intriguing possibility that the giraffe's stature and turbocharged cardiovascular system evolved in concert through changes in a small number of genes.



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The scientists also discovered genetic clues to the evolution of the

giraffe's long neck and legs, which have the same number of bones as the neck and legs of humans and other mammals. "To achieve their extraordinary length, giraffe cervical vertebrae and leg bones have evolved to be greatly extended," Cavener said. "At least two genes are required - one gene to specify the region of the skeleton to grow more and another gene to stimulate increased growth." Among the 70 genes that the team's research revealed are markedly different in the giraffe, the scientists identified genes that are known to regulate both of these functions.

"The most intriguing of these genes is *FGFRL1*, which has a cluster of amino acid substitutions unique to giraffe that are located in the part of the protein that binds fibroblast growth factors—a family of regulators involved in regulating many processes including embryo development," Cavener said. This fibroblast-growth-factor pathway plays a crucial role in controlling development, beginning in early development of the embryo and extending through the bone-growth phase after the giraffe is born. In humans and also in mice, severe skeletal and cardiovascular defects are associated with debilitating mutations in this gene.

The scientists also identified four homeobox genes—the kind involved in the development of body structures—which are known to specify the regions of the spine and legs. Cavener speculates, "The combination of changes in these homeobox genes and the *FGFRL1* gene might provide two of the required ingredients for the evolution of the giraffe's long neck and legs."

Agaba first noticed a group of genes regulating metabolism and growth that were diverged in giraffe as compared to okapi. One of these genes encodes the receptor for folic acid, which is an essential B vitamin necessary for normal growth and development. Other metabolic genes that the scientists found to be significantly changed in giraffe are those involved in the metabolism of the volatile fatty acids that are generated

by the fermentation of ingested plants—the major source of energy for the giraffe and other ruminants like cattle and goats. The giraffe has an unusual diet of acacia leaves and seedpods, which are highly nutritious but also are toxic to other animals. The scientists speculate that the genes responsible for metabolizing acacia leaves may have evolved in the giraffe in order to circumvent this toxicity.

Cavener and Agaba, both experimental geneticists, say they are anxious to test the function of some of the identified [genes](#) that they believe may be responsible for the giraffe's unique characteristics. Their research team currently is testing the potential effect of the unique differences of the giraffe's FGFR1 gene by introducing these changes into mice using the new CRISPR gene-editing methods. Substituting the giraffe's FGFR1 gene into mouse is not expected to make a long-necked mouse. However, the scientists are hoping to see how the giraffe's FGFR1 gene may affect differential growth of the spine and legs of the mice that is predictive of the giraffe's unique features.

"We hope that the publication of the giraffe genome and clues to its unique biology will draw attention to this species in light of the recent precipitous decline in giraffe populations," Cavener said. "While the plight of the elephant—giraffe's shorter companion in the African savannah—has received the lions share of attention, giraffe populations have declined by 40 percent over the past 15 years due to poaching and [habitat loss](#). At this rate of decline, the number of [giraffes](#) in the wild will fall below 10,000 by the end of this century. Some giraffe subspecies already are teetering on the edge of extinction."

**More information:** *Nature Communications*, [DOI: 10.1038/ncomms11519](#)

Provided by Pennsylvania State University

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