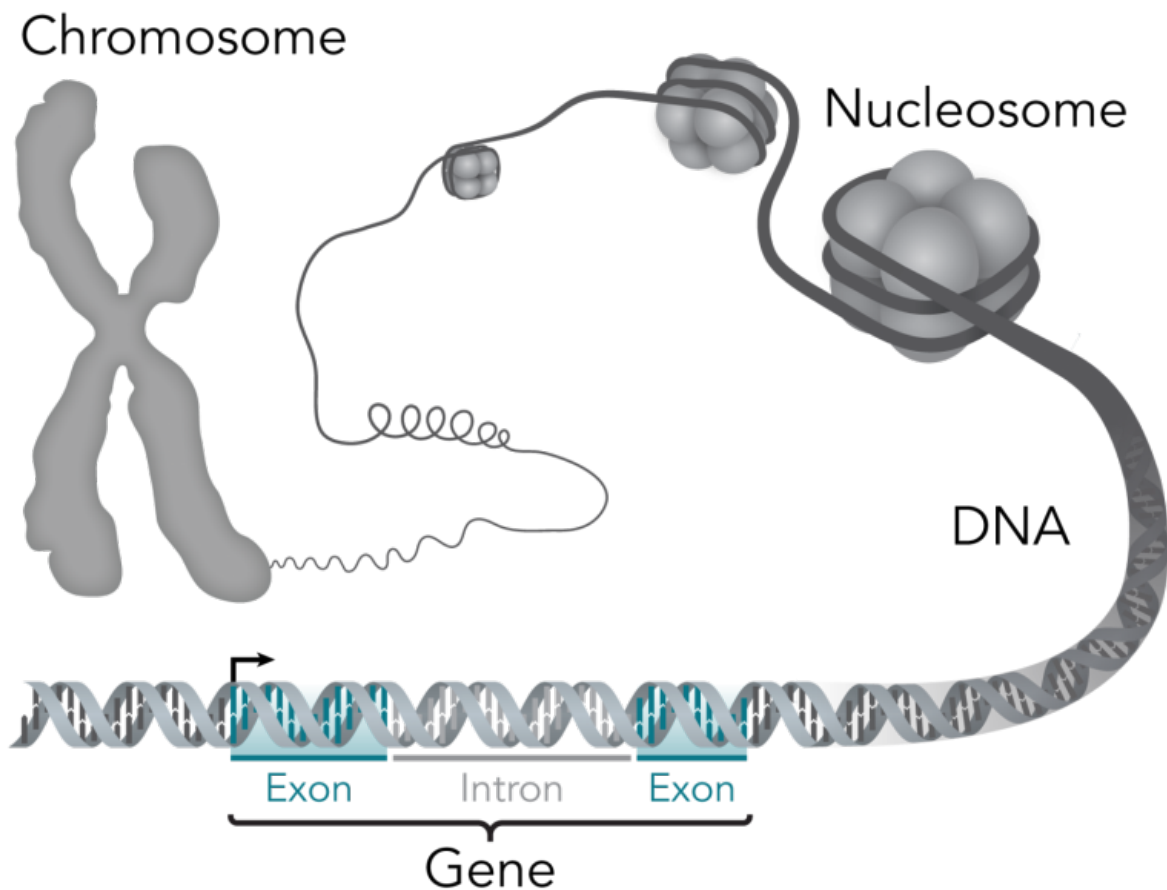


Tweak in gene expression may have helped humans walk upright, researchers say

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This stylistic diagram shows a gene in relation to the double helix structure of DNA and to a chromosome (right). The chromosome is X-shaped because it is dividing. Introns are regions often found in eukaryote genes that are removed in the splicing process (after the DNA is transcribed into RNA): Only the exons encode the protein. The diagram labels a region of only 55 or so bases as a gene. In reality, most genes are hundreds of times longer. Credit: Thomas

Consider the engineering marvel that is your foot. Be it hairy or homely, without its solid support you'd be hard-pressed to walk or jump normally.

Now, researchers at the Stanford University School of Medicine and the HudsonAlpha Institute for Biotechnology in Huntsville, Alabama, have identified a change in gene expression between humans and primates that may have helped give us this edge when it comes to walking upright. And they did it by studying a tiny fish called the threespine stickleback that has evolved radically different skeletal structures to match environments around the world.

"It's somewhat unusual to have a research project that spans from fish all the way to humans, but it's clear that tweaking the expression levels of molecules called bone morphogenetic proteins can result in significant changes not just in the skeletal armor of the stickleback, but also in the hind-limb development of humans and primates," said David Kingsley, PhD, professor of developmental biology at Stanford. "This change is likely part of the reason why we've evolved from having a grasping hind foot like a chimp to a weight-bearing structure that allows us to walk on two legs."

Kingsley, who is also a Howard Hughes Medical Institute investigator, is the senior author of a paper describing the work that will be published online Jan. 7 in *Cell*. The lead author is former Stanford postdoctoral scholar Vahan Indjeian, PhD, now head of a research group at Imperial College London.

Adapting to different environments

The threespine stickleback is remarkable in that it has evolved to have many different body structures to equip it for life in different parts of the world. It sports an exterior of bony plates and spines that act as armor to protect it from predators. In marine environments, the plates are large and thick; in freshwater, the fish have evolved to have smaller, lighter-weight plates, perhaps to enhance buoyancy, increase body flexibility and better slip out of the grasp of large, hungry insects. Kingsley and his colleagues wanted to identify the regions of the fish's genome responsible for the skeletal differences that have evolved in natural populations.

The researchers identified the area of the genome responsible for controlling armor plate size, and then looked for differences there in 11 pairs of marine and freshwater fish with varying armor-plate sizes. They homed in on a region that includes the gene for a [bone morphogenetic protein](#) family member called GDF6. Due to changes in the regulatory DNA sequence near this gene, freshwater sticklebacks express higher levels of GDF6, while their saltwater cousins express less. Strikingly, marine fish genetically engineered to contain the regulatory sequence of freshwater fish expressed higher levels of GDF6 and developed smaller armor plates, the researchers found.

Regulatory regions in humans vs. chimps

Kingsley and his colleagues wondered whether changes in GDF6 expression levels might also have contributed to critical skeletal modifications during human evolution. The possibility was not as far-fetched as it might seem. Other studies by evolutionary biologists, including Kingsley, have shown that small changes in the [regulatory regions](#) of key developmental genes can have profound effects in many vertebrates.

They began by working with colleagues in the laboratory of Gill Bejerano, PhD, Stanford associate professor of developmental biology, of computer science and of pediatrics, to compare differences in the genomes of chimps and humans. In previous surveys, they found over 500 places in which humans have lost regulatory regions that are conserved from chimps and many other mammals. Two of these occur near the GDF6 gene. They homed in on one in particular.

"This regulatory information was shared through about 100 million years of evolution," said Kingsley. "And yet, surprisingly, this region is missing in humans."

To learn more about what the GDF6 regulatory region might be controlling, the researchers used the chimp regulatory DNA to control the production of a protein that is easy to visualize in mice. Laboratory mice with the chimp regulatory DNA coupled to the reporter protein strongly and specifically expressed the protein in their hind limbs, but not their forelimbs, and in their lateral toes, but not the big toes of the hind limbs. Mice genetically engineered to lack the ability to produce GDF6 in any part of their bodies had skull bones that were smaller than normal and their toes were shorter than those of their peers. Together, these findings gave the researchers a clue that GDF6 might play a critical role in limb development and evolution.

The big toe: an explanation

The fact that humans are missing the hind-limb-regulatory region probably means that we express less of the gene in our legs and feet during development, but comparable amounts in our nascent arms, hands and skulls. Loss of this particular regulatory sequence would also shorten lateral toes but not the first toe of feet. This may help explain why the big toe is aligned with other short, lateral toes in humans. Such a modification would create a more sturdy foot with which to walk

upright.

"These bone morphogenetic proteins are strong signals for bone and cartilage growth in all types of animals," said Kingsley.

"You can evolve new skeletal structures by changing where and when the signals are expressed, and it's very satisfying to see similar regulatory principles in action whether you are changing the armor of a stickleback, or changing specific hind-limb structures during human evolution."

Provided by Stanford University Medical Center

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