

Scientists identify genes linked to Western African Pygmies' small stature

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If Pygmies are known for one trait, it is their short stature: Pygmy men stand just 4'11" on average. But the reason why these groups are so short and neighboring groups are not remains unclear. Scientists have proposed various theories based on natural selection, including that Pygmies' reduced size lowered nutritional requirements, helped them better handle hot climates, or allowed them to reach sexual maturity at an earlier age.

Now a new study of the Western African Pygmies in Cameroon, led by geneticists from the University of Pennsylvania, identifies genes that may be responsible for the Pygmies' relatively small size.

The work also provides evidence based on genetic signatures of [natural selection](#) to suggest why these groups evolved to be small, with signs pointing to hormonal pathways and immune system regulation as possible drivers.

"There's been a longstanding debate about why Pygmies are so short and whether it is an adaptation to living in a tropical environment," said Sarah Tishkoff, senior author on the study and a Penn Integrates Knowledge professor with appointments in the genetics department of the Perelman School of Medicine and in the biology department of the School of Arts and Sciences. "I think our findings are telling us that the [genetic basis](#) of complex traits like height may be very different in globally diverse populations."

While hundreds of studies have sought and identified genes that play a role in height variations in European populations — nearly 180 such genes have been pinpointed — this is the first genome-wide study of genes that contribute to stature in African Pygmy populations.

"By performing a detailed genetic analysis, Dr. Tishkoff and her colleagues have identified many candidate genes that have played an adaptive role in Pygmy populations, including several related to stature," said Irene Eckstrand, who oversees evolutionary-biology grants at the National Institutes of Health's National Institute of General Medical Sciences, which partially funded the work. "This research illustrates the value of studying human traits in their evolutionary and ecological contexts for understanding how humans adapted to their local environments."

Tishkoff led the study with Joseph Jarvis, a Penn postdoctoral researcher at the time the study was conducted and now a senior research scientist at the Coriell Institute for Medical Research. Other Penn contributors included Laura Scheinfeldt, Sameer Soi, Charla Lambert, Bart Ferwerda and William Beggs of the Department of Genetics.

The Penn researchers collaborated with Larsson Omberg, Gabriel Hoffman and Jason Mezey of Cornell University; Alain Froment of the Musée de l'Homme in France; and Jean-Marie Bodo of the Ministère de la Recherche Scientifique et de l'Innovation in Cameroon.

Their paper will be published in the journal *PLoS Genetics* on April 26.

Africa is the birthplace of humankind and remains a continent rife with examples of the variation within our species, including variation in body size, ranging from short-statured Pygmy hunter-gatherers to tall-statured East African pastoralists. Individuals in one of these unique groups, Western African Pygmies, are 17 centimeters shorter on average than

their Bantu-speaking neighbors.

These two groups diverged genetically 60-70,000 years ago. But roughly 4-5,000 years ago, Bantu-speaking groups expanded into the tropical forests where Pygmies' ancestors lived. The resulting contacts led to population mixing, typically Bantu men reproducing with Pygmy women. Their children would return to Pygmy villages; therefore Pygmies' genomes reflect the contributions of Bantus, while Bantu genomes contain little to no input from Pygmies.

Using a variety of analyses, Tishkoff's team took advantage of the stature differences and history of genetic exchange between the Bantus and Pygmies to seek candidate genes responsible for the Pygmies' small size.

The geneticists scanned the genomes of 67 Pygmies and 58 Bantus for particular mutations — known as single nucleotide polymorphisms, or SNPs — that provide information about individuals' ancestry. They confirmed that height differences had a genetic component, as the more Bantu ancestry a Pygmy had, the taller that individual tended to be.

Although in general Pygmy genomes were heavily mixed with Bantu genomes from thousands of years of genetic exchange, the researchers identified a region of chromosome 3 that tended to have stretches of DNA that were distinctly different between Bantus and Pygmies. The same region also turned up when the [geneticists](#) searched the study subjects' genomes for signals of natural selection. And it came up again when they sought a correlation with height.

"Using all of these different approaches we kept seeing a lot of them highlight that region in chromosome 3," Tishkoff said. "It just seemed like a hot spot for selection and for very high differentiation and, as it turns out, very strong association with height as well."

This uniqueness drew their attention, so they zoomed in to look closer at the genes encoded in this area.

Among those that stood out were DOCK3 and CISH. DOCK3 is a gene that is expressed in the brain and has been linked to height variation in [European populations](#). And CISH, located a relatively close 63,000 base pairs down the DNA strand from DOCK3, encodes a protein involved in a molecular signaling pathway that regulates human growth hormone. Mice that overexpress CISH are small in size.

CISH has also been implicated in susceptibility to infectious disease, a potentially meaningful finding since Pygmies, living in a tropical forest climate, shoulder heavy burdens of parasites and other disease-causing agents.

In a final set of analyses, the researchers took SNPs in Pygmies that showed strong signs of being under natural selection — that is, mutations that appeared to confer an evolutionary advantage and were thus passed down through generations — and searched for genes located nearby in the DNA. They also pulled out SNPs with the strongest association with height.

The biological pathways in which these identified mutations may be involved include those having to do with reproductive hormone activation, thyroid hormone activation, [immune system](#) function and insulin and growth hormone regulation.

"We kept seeing enrichment of genes involved in oxytocin, serotonin and thyrotropin-releasing hormone receptor signaling pathways in our genome-wide scans for natural selection," Tishkoff said. "Genes in those pathways are important in reproduction and metabolism and that was intriguing in light of the hypothesis that the reason Pygmies are short is so that they can reach reproductive maturity early."

Early reproduction could be a significant advantage in Pygmies, whose life spans average between 15 and 24 years, Tishkoff added.

"By contrast, genes enriched for association with height included those involved in the growth hormone and insulin signaling pathways, adding strength to physiologic studies indicating that alterations to these pathways play an important role in the short stature of [Pygmies](#)."

Tishkoff said the results also raise the possibility that [short stature](#) itself was not even the trait under selection but instead arose because [genes](#) related to height might also have other functions, such as those that boost immunity.

Jarvis noted that the multi-faceted approach the team used is likely to be useful in the future when seeking the genetic basis of complex traits that involve more than one gene in their expression, traits such as height or even increased risk of heritable diseases like diabetes or cancer.

"Our approach relied on multiple analyses and on the integration of the multiple signals we discovered," Jarvis said. "The evolutionary process is incredibly complicated and rarely produces obvious genetic signatures, so it's very important to be sensitive to subtle patterns. Ultimately our analyses repeatedly highlighted similar regions of the genome, and that overlap is what suggests that something interesting is going on."

More information: Jarvis JP, Scheinfeldt LB, Soi S, Lambert C, Omberg L, et al. (2012) Patterns of Ancestry, Signatures of Natural Selection, and Genetic Association with Stature in Western African Pygmies. *PLoS Genet* 8(4): e1002641.
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