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Study identifies hundreds of genetic 'switches' that effect height

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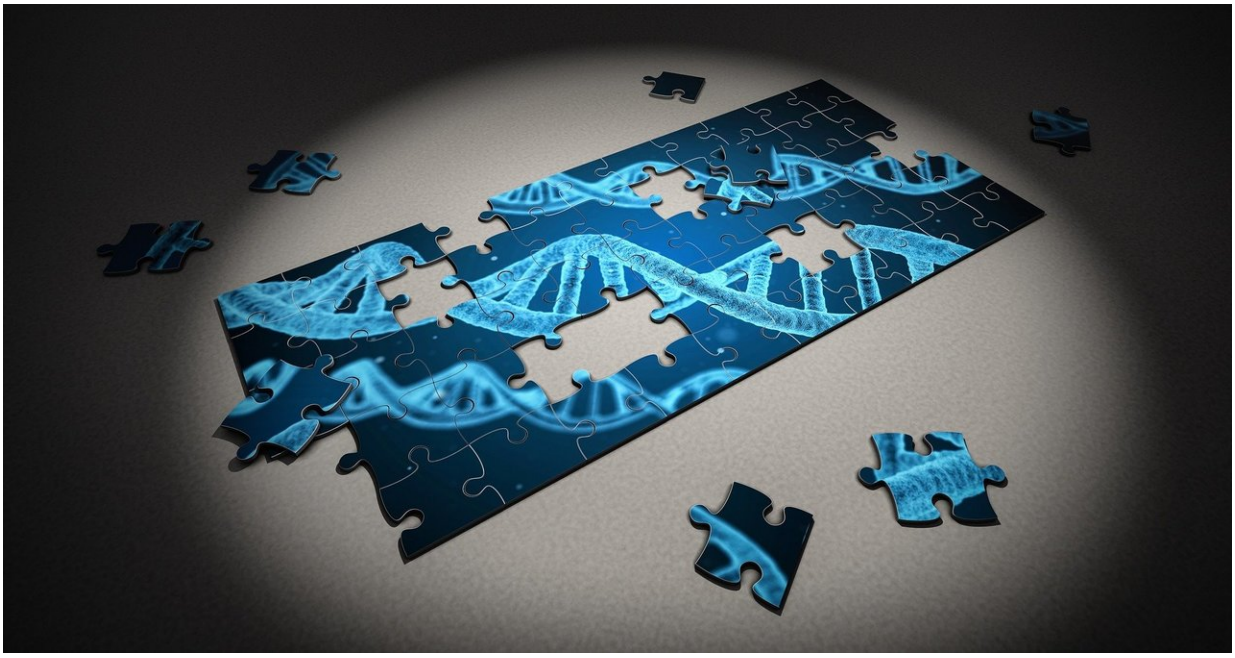

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It's been understood for decades that a host of factors - everything from pre- and post-natal health, nutrition, and genetics - play a role in determining height, but efforts to untangle the complex web of factors that contribute to height have long been stymied.

That picture, however, is becoming clearer, thanks to the work of

Harvard scientists.

Led by Associate Professor of Human Evolutionary Biology Terence D. Capellini, a team of researchers discovered hundreds of genetic "switches" that have an influence on height and performed functional tests that demonstrated precisely how one such switch alters the function of a key gene involved in height differences. The study is described in a December 5 paper published in *eLife*.

"Large genome-wide association studies on upwards of 250,000 people found about 700 genetic regions associated with height," Capellini said. "But within each region there could be many single DNA variants linked together, so there are potentially tens of thousands of variants spanning those regions. The question is how do you whittle that number down to those specific variants that influence height?"

The first step, Capellini said, was to filter the list of more than 60,000 genetic variants to those that are likely functional in the cartilage growth plates of bones. To do this they identified in the femurs of developing mice regions of the DNA that act as regulatory "switches" - that is, sequences of DNA that cause nearby genes to turn on or off. As part of that search, Capellini and colleagues focused on areas where the genome was "open," or available for transcription using a technique called ATAC-seq.

The problem, however, is that process identifies every switch in the growth plate cartilage cell, many of which may not be involved in bone growth but rather basic cellular processes. To separate those "general" switches from those related to bone growth and thus likely height, the team performed the same test again, but on a different cell type, and identified sequences that were open in both. "If we find a common sequence that's open in a brain cell and in a cartilage cell, we can say it likely turns on some gene that may be important for cells to live,"

Capellini said. "So we filtered those out, but we didn't ignore them completely, because they may actually be important. While we first concentrated on the bone-specific switches, we know there are a lot of inputs to height - it's about the length of our bones, but we also know hormones trigger height, malnutrition can impact height, among other inputs so there may be general genetic factors that influence height."

As part of that work, Capellini said, researchers also performed a number of "quality control" tests to ensure the unique switches they identified were actually involved in bone and cartilage development as well as height.

After performing those tests and filters, Michael Guo, an author on the study, was next able to determine how many of the 60,000 variants associated with height actually reside in on/off switches for bone. This resulted in a list of about 900 genetic variants.

To make sure that this process generated unique height signals, Capellini and colleagues performed additional analyses. "We took genome-wide analyses from other studies that had nothing to do with height and looked to see if we saw the same signal, and we didn't, which makes sense," he said. "We also looked at switches from other cell types to see if these genetic variants appeared, and they didn't. That really suggests to us that the signals we're seeing are very strong, it's not just a property of the genome or a property of identifying these switches."

The team then chose one on/off switch, associated with a gene known as Chondroitin Sulfate Synthase 1, or CHSY1, which plays a key role in how cartilage cells create the extra-cellular matrix that hardens into bone. In turn, the gene influences femur length in mice and humans.

"We did some tests to find out how this switch effects CHSY1 activity, and found that both versions - for taller height and shorter height - act as

repressors on the gene," Capellini said. "But surprisingly the height-increasing variant isn't as strong."

To verify that the switch indeed acts in a repressive manner, using CRISPR tools, researchers removed the switch or the variant altogether from human cartilage cells, and saw a very strong increase in the expression of the gene.

Going forward, Capellini and colleagues hope to use high-throughput functional methods to understand the role each variant plays in human height, and to develop other methods to test all 60,000-plus variants in order to study height in a more unbiased manner.

In addition to providing a new understanding of a complex human trait, the study may ultimately demonstrate how genetic tools might be used to understand other conditions - like macular degeneration, diabetes or even heart disease - that are tied to both environmental and genetic factors.

"For any disease or trait, being able to say here is a switch that turns a gene on or off, and here is the mutation in that switch that can effect it dramatically...that's pretty powerful," Capellini said. "That will allow us figure out what are the biological pathways that are worth targeting. The future of personalized medicine will rely on knowing what specific pieces of DNA are doing in the body, and this is one way to do that."

Provided by Harvard University