Study suggests genetic connection between short stature and arthritis

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Common genetic variants linked to arthritis may also play a role in human height, a new study shows. The international study was co-led by the University of Michigan School of Public Health. The journal *Nature Genetics* will publish the findings online Jan. 13.

The new study confirms observations by health professionals of a connection between decreased height and increased risk of osteoarthritis, the most common form of arthritis. Researchers speculate that both extremes of height may be associated with osteoarthritis for different reasons. Shorter bones and/or less cartilage may render the joints more susceptible to damage, while longer bones may produce greater levels of damaging stress on the joints.

The findings are exciting for several reasons, said Gonçalo Abecasis, assistant professor in the School of Public Health. For one, there are many genes that control height, but only a few associated with osteoarthritis, he said.

"In this case the gene we picked also is important in osteoarthritis and it's actually quite hard to find genes for osteoarthritis," said Abecasis, who co-directed the study with Karen Mohlke of the University of North Carolina. "One of the things we were excited about is you could study (height) in many people, and once you've done that you have a short list of genes that you can then study for what they do in terms of osteoarthritis."

The findings also add to the general understanding of height.

"It is useful to know all genes responsible for height variation, so we are reassured if our baby is shorter than others because he has a collection of "short" alleles on his DNA, and not because he has something wrong, like a metabolism disorder," said Serena Sanna, co-author who worked on the paper as a post-doctoral student in Abecasis' group and who is now at the National Research Council di Cagliari in Italy. Anne Jackson, a research specialist at U-M, is also a co-author.

To arrive at their findings, researchers from the United States and Europe analyzed the genomes of more than 35,000 people. If there were average height differences for individuals with certain genetic variants, this indicated that something in that genomic region containing the variants likely influenced height. In this particular study, researchers initially examined the effects of more than 2 million genetic variants.

The new variant accounts for less than 1 percent of the genetic basis of height, and is associated with an average difference in height of about 0.4 centimeters, or a little more than an eighth of an inch. The range went from 0.3 cm to 1.4 cm, depending on the population and whether an individual had one or two copies of the so-called taller version of the variant. A variety of factors, including genetics, diet and prenatal environment, interact to determine how tall someone grows. It is currently thought that genetic factors are responsible for at least 80 percent of the variation in height among people.

The variants most strongly associated with height lie in a region of the human genome thought to influence expression of a gene for growth differentiation factor 5, called GDF5, which is a protein involved in the development of cartilage in the legs and other long bones. Rare variants in the GDF5 gene have been associated with disorders of skeletal development, and more common variants recently have been tied to

susceptibility to osteoarthritis of the hip and knees in Asian and European populations.

The completion of the map of human genetic variation, or HapMap, has fueled a surge in this type of genome-wide association study, with most of the growth coming in the past 10 months. Researchers around the globe have now associated more than 60 common DNA variants with the risk of more than 20 common diseases or related traits.

Source: University of Michigan